Module 20

Case Studies in Longitudinal Data Analysis

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SISCR 2016
July 29, 2016

Learning objectives

- This module will focus on the design of longitudinal studies, exploratory data analysis, and application of regression techniques based on estimating equations and mixed-effects models
- Case studies will be used to discuss analysis strategies, the application of appropriate analysis methods, and the interpretation of results, with examples in R and Stata
- Some theoretical background and details will be provided; our goal is to translate statistical theory into practical application
- At the conclusion of this module, you should be able to apply appropriate exploratory and regression techniques to summarize and generate inference from longitudinal data

Overview

Review: Longitudinal data analysis

Case study: Longitudinal depression scores

Case study: Indonesian Children's Health Study

Case study: Carpal tunnel syndrome

Summary and resources

Overview

Review: Longitudinal data analysis

Case study: Longitudinal depression scores

Case study: Indonesian Children's Health Study

Case study: Carpal tunnel syndrome

Summary and resources

Longitudinal studies

Repeatedly collect information on the same individuals over time

Benefits

- Record incident events
- Ascertain exposure prospectively
- Separate time effects: cohort, period, age
- Distinguish changes over time within individuals
- Offer attractive efficiency gains over cross-sectional studies
- Help establish causal effect of exposure on outcome

Longitudinal studies

Repeatedly collect information on the same individuals over time

Challenges

- Determine causality when covariates vary over time
- Choose exposure lag when covariates vary over time
- Account for incomplete participant follow-up
- Use specialized methods that account for longitudinal correlation

Motivating example

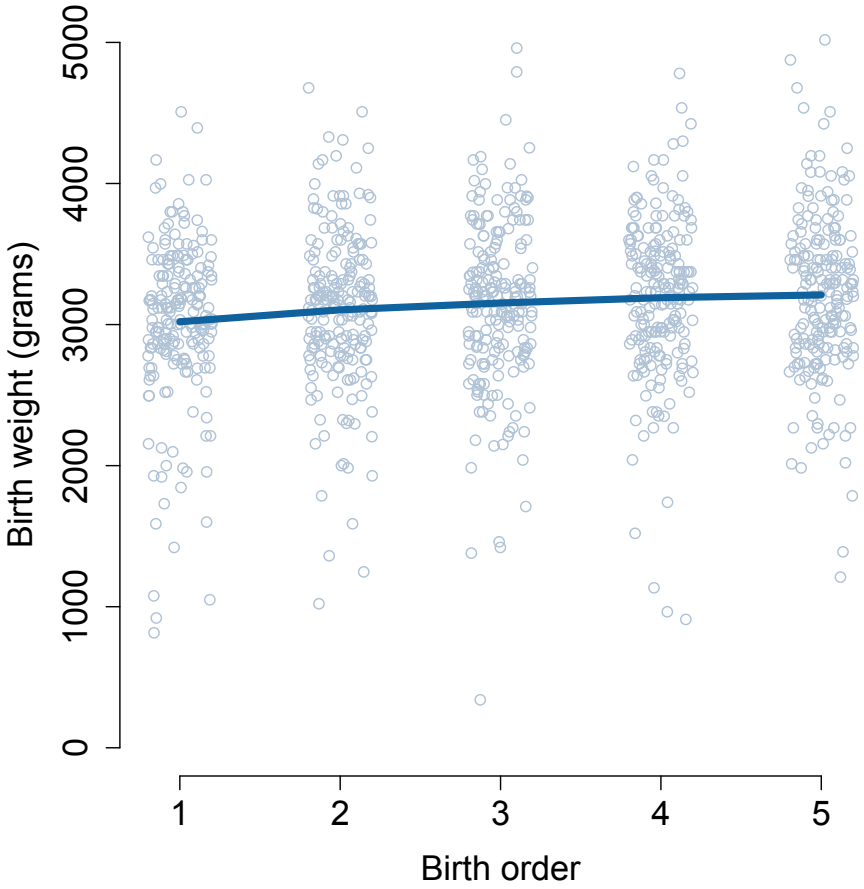
Georgian infant birth weight

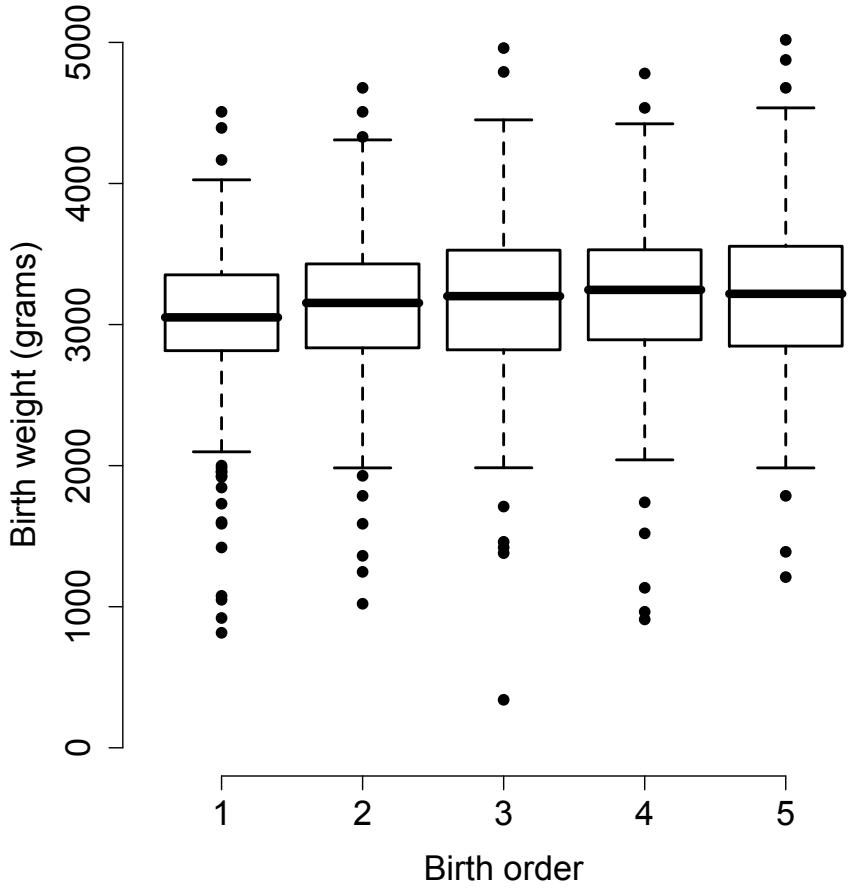
- Birth weight measured for each of $m = 5$ children of $n = 200$ mothers
- Birth weight for infants j comprise repeated measures on mothers i
- Interested in the association between birth order and birth weight
  - Estimate the average time course among all mothers
  - Estimate the time course for individual mothers
  - Quantify the degree of heterogeneity across mothers
- Consider adjustment for mother's initial age (at first birth)

Motivating example

	momid	birthord	bweight	lowbrth	initage
[1]	39	1	3720	0	15
[2]	39	2	3260	0	15
[3]	39	3	3910	0	15
[4]	39	4	3320	0	15
[5]	39	5	2480	1	15
[6]	62	1	2381	1	17
[7]	62	2	2835	1	17
[8]	62	3	2381	1	17
[9]	62	4	2268	1	17
[10]	62	5	2211	1	17

Motivating example





Strategies for analysis of longitudinal data

- **Derived variable**: Collapse the longitudinal series for each subject into a summary statistic, such as a difference (a.k.a. "change score") or regression coefficient, and use methods for independent data

- **Repeated measures**: Include all data in a regression model for the mean response and account for longitudinal and/or cluster correlation

Options for analysis of change

Does mean change differ across groups?

- Consider simple situation with
  - Baseline measurement ($t = 0$)
  - Single follow-up measurement ($t = 1$)
- Analysis options for simple pre-post design
  - Analysis of POST only
  - Analysis of CHANGE (post-pre)
  - Analysis of POST controlling for BASELINE
  - Analysis of CHANGE controlling for BASELINE

Change and randomized studies

- **Key assumption**: groups equivalent at baseline
- Methods that 'adjust' for baseline are generally preferable due to greater precision
  - $\boxed{\rho > 1/2}$ POST $\prec$ CHANGE $\prec$ ANCOVA
  - $\boxed{\rho < 1/2}$ CHANGE $\prec$ POST $\prec$ ANCOVA
  - CHANGE analysis adjusts for baseline by subtracting it from follow-up
  - ANCOVA analysis adjusts for baseline by controlling for it in a model
- Missing data will impact each approach

Change and non-randomized studies

- Baseline equivalence no longer guaranteed
- Methods no longer answer same scientific question
  - POST: How different are groups at follow-up?
  - CHANGE: How different is the change in outcome for the two groups?
  - ANCOVA: What is the expected difference in the mean outcome at follow-up across the two groups, controlling for the baseline value of the outcome?
- CHANGE typically most relevant; multivariable methods to come later characterize CHANGE across multiple timepoints

Strategies for analysis of longitudinal data

- **Derived variable**: Collapse the longitudinal series for each subject into a summary statistic, such as a difference (a.k.a. "change score") or regression coefficient, and use methods for independent data
  - **Example**: birth weight of 2nd child – birth weight of 1st child
  - Might be adequate for two time points and no missing data
- **Repeated measures**: Include all data in a regression model for the mean response and account for longitudinal and/or cluster correlation
  - **Generalized estimating equations** (GEE)
  - **Generalized linear mixed-effects models** (GLMM)

Notation

Define

$$
\begin{aligned}
m_i &= \text{number of observations for subject } i = 1, ..., n \\
Y_{ij} &= \text{outcome for subject } i \text{ at time } j = 1, ..., m_i \\
X_i &= (x_{i1}, x_{i2}, ..., x_{im_i}) \\
x_{ij} &= (x_{ij1}, x_{ij2}, ..., x_{ijp}) \\
&\quad \text{exposure, covariates}
\end{aligned}
$$

Stacks of data for each subject:

$$
Y_i = \begin{bmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \\ Y_{im_i} \end{bmatrix} \qquad X_i = \begin{bmatrix} x_{i11} & x_{i12} & \cdots & x_{i1p} \\ x_{i21} & x_{i22} & \cdots & x_{i2p} \\ \vdots & \vdots & \vdots & \vdots \\ x_{im_i1} & x_{im_i2} & \cdots & x_{im_ip} \end{bmatrix}
$$

Dependence and correlation

Issue Response variables measured on the same subject are correlated

- Observations are **dependent** or **correlated** when one variable predicts the value of another variable
  - The birth weight for a first child is predictive of the birth weight for a second child born to the same mother

- **Variance:** measures average distance that an observation falls away from the mean
- **Covariance:** measures whether, on average, departures in one variable $Y_{ij} - \mu_j$ 'go together with' departures in another variable $Y_{ik} - \mu_k$
- **Correlation:** measure of dependence that takes values from -1 to $+1$

Covariance: Something new to model

$$\text{Cov}(Y_i) = \begin{bmatrix} \text{Var}(Y_{i1}) & \text{Cov}(Y_{i1}, Y_{i2}) & \dots & \text{Cov}(Y_{i1}, Y_{im_i}) \\ \text{Cov}(Y_{i2}, Y_{i1}) & \text{Var}(Y_{i2}) & \dots & \text{Cov}(Y_{i2}, Y_{im_i}) \\ \vdots & \vdots & \vdots & \vdots \\ \text{Cov}(Y_{im_i}, Y_{i1}) & \text{Cov}(Y_{im_i}, Y_{i2}) & \dots & \text{Var}(Y_{im_i}) \end{bmatrix}$$

$$= \begin{bmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho_{12} & \dots & \sigma_1\sigma_{m_i}\rho_{1m_i} \\ \sigma_2\sigma_1\rho_{21} & \sigma_2^2 & \dots & \sigma_2\sigma_{m_i}\rho_{2m_i} \\ \vdots & \vdots & \vdots & \vdots \\ \sigma_{m_i}\sigma_1\rho_{m_i1} & \sigma_{m_i}\sigma_2\rho_{m_i2} & \dots & \sigma_{m_i}^2 \end{bmatrix}$$

Note: $\rho =$ correlation

GEE (Liang and Zeger, 1986)

9145 citations as of July 2016

⋆ Contrast average outcome values across **populations** of individuals defined by covariate values, while accounting for correlation

- Focus on a generalized linear model with regression parameters $\boldsymbol{\beta}$, which characterize the systemic variation in $\boldsymbol{Y}$ across covariates $\boldsymbol{X}$

$$\begin{aligned} Y_i &= (Y_{i1}, Y_{i2}, \ldots, Y_{im_i})^{\mathsf{T}} \\ X_i &= (x_{i1}, x_{i2}, \ldots, x_{im_i})^{\mathsf{T}} \\ x_{ij} &= (x_{ij1}, x_{ij2}, \ldots, x_{ijp}) \\ \beta &= (\beta_1, \beta_2, \ldots, \beta_p)^{\mathsf{T}} \end{aligned}$$

  for $i = 1, \ldots, n$; $j = 1, \ldots, m_i$; and $k = 1, \ldots, p$

- Longitudinal correlation structure is a nuisance feature of the data

Mean model

Assumptions

- Observations are independent across subjects
- Observations could be correlated within subjects

Mean model: Primary focus of the analysis

$$\begin{aligned} \mathrm{E}[Y_{ij} \mid x_{ij}] &= \mu_{ij}(\beta) \\ g(\mu_{ij}) &= x_{ij}\beta \end{aligned}$$

- Corresponds to any generalized linear model with link $g(\cdot)$

Continuous outcome	Count outcome	Binary outcome
$\mathrm{E}[Y_{ij} \mid x_{ij}] = \mu_{ij}$	$\mathrm{E}[Y_{ij} \mid x_{ij}] = \mu_{ij}$	$\mathrm{P}[Y_{ij} = 1 \mid x_{ij}] = \mu_{ij}$
$\mu_{ij} = x_{ij}\beta$	$\log(\mu_{ij}) = x_{ij}\beta$	$\mathrm{logit}(\mu_{ij}) = x_{ij}\beta$

- Characterizes a **marginal** mean regression model

Covariance model

Longitudinal correlation is a nuisance; secondary to mean model of interest

1. Assume a form for **variance** that could depend on μ_{ij}

$$\begin{array}{lrcl} \text{Continuous outcome:} & \text{Var}[Y_{ij} \mid x_{ij}] & = & \sigma^2 \\ \text{Count outcome:} & \text{Var}[Y_{ij} \mid x_{ij}] & = & \mu_{ij} \\ \text{Binary outcome:} & \text{Var}[Y_{ij} \mid x_{ij}] & = & \mu_{ij}(1-\mu_{ij}) \end{array}$$

   which could also include a scale or dispersion parameter $\phi > 0$

2. Select a model for longitudinal **correlation** with parameters α

$$\begin{array}{lrcl} \text{Independence:} & \text{Corr}[Y_{ij}, Y_{ij'} \mid X_i] & = & 0 \\ \text{Exchangeable:} & \text{Corr}[Y_{ij}, Y_{ij'} \mid X_i] & = & \alpha \\ \text{Auto-regressive:} & \text{Corr}[Y_{ij}, Y_{ij'} \mid X_i] & = & \alpha^{|j-j'|} \\ \text{Unstructured:} & \text{Corr}[Y_{ij}, Y_{ij'} \mid X_i] & = & \alpha_{jj'} \end{array}$$

Intuition

$$0 = \sum_{i=1}^{n} \underbrace{D_i^{\mathsf{T}}}_{\boxed{3}} \underbrace{V_i^{-1}}_{\boxed{2}} (\underbrace{Y_i - \hat{\mu}_i}_{\boxed{1}})$$

- $\boxed{1}$ The model for the mean, $\mu_i(\beta)$, is compared to the observed data, Y_i; setting the equations to equal 0 tries to minimize the difference between **observed** and **expected**
- $\boxed{2}$ Estimation uses the inverse of the variance (covariance) to **weight** the data from subject i; more weight is given to differences between observed and expected for subjects who contribute more information
- $\boxed{3}$ Simply a "change of scale" from the scale of the mean, μ_i, to the scale of the regression coefficients (covariates)

Comments

- GEE is specified by a mean model and a correlation model
  1. A regression model for the average outcome, e.g., linear, logistic
  2. A model for longitudinal correlation, e.g., independence, exchangeable
- $\hat{\beta}$ is a consistent estimator for β provided that the mean model is correctly specified, even if the model for longitudinal correlation is incorrectly specified, i.e., $\hat{\beta}$ is 'robust' to correlation model mis-specification
- However, the variance of $\hat{\beta}$ must capture the correlation in the data, either by choosing the correct correlation model, or via an alternative variance estimator
- GEE computes a sandwich variance estimator (aka empirical, robust, or Huber-White variance estimator)
- Empirical variance estimator provides valid standard errors for $\hat{\beta}$ even if the working correlation model is incorrect, but requires $n \geq 40$ (Mancl and DeRouen, 2001)

Variance estimators

- **Independence estimating equation**: An estimation equation with a working independence correlation structure
  - Model-based standard errors are generally not valid
  - Empirical standard errors are valid given large n and $n \gg m$
- **Weighted estimation equation**: An estimation equation with a non-independence working correlation structure
  - Model-based standard errors are valid if correlation model is correct
  - Empirical standard errors are valid given large n and $n \gg m$

	Variance estimator	
Estimating equation	Model-based	Empirical
Independence	$-$	$+/-$
Weighted	$-/+$	$+$

GEE commands

- Stata: `xtset`, then use `xtgee`
- R: `geeglm` in `geepack` library, using `geese` fitter function
- SAS: PROC GENMOD
- **NB**: Order might be important for analysis in software
  - Requires sorting the data by unique subject identifier and time
  - Important for exchangeable and auto-regressive correlation structures

Motivating example

Interested in the association between birth order and birth weight

$$\mathrm{E}[Y_{ij} \mid x_{ij}] = \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2}$$

for $i = 1, \ldots, 200$ and $j = 1, \ldots, 5$ with

- Y_{ij}: Infant birth weight (continuous)
- x_{ij1}: Infant birth order
- x_{ij2}: Mother's initial age

Motivating example: Stata commands

```
* Declare the dataset to be "panel" data, grouped by momid
* with time variable birthord
xtset momid birthord

* Fit a linear model with independence correlation
xtgee bweight birthord initage, corr(ind) robust

* Fit a linear model with exchangeable correlation
xtgee bweight birthord initage, corr(exc) robust
```

Motivating example: Stata output

```
GEE population-averaged model                   Number of obs      =      1000
Group variable:                        momid    Number of groups   =       200
Link:                                identity   Obs per group: min =         5
Family:                              Gaussian                 avg =       5.0
Correlation:                      independent                 max =         5
                                                Wald chi2(2)       =     27.95
Scale parameter:                     324458.3   Prob > chi2        =    0.0000

                                  (Std. Err. adjusted for clustering on momid)
------------------------------------------------------------------------------
             |               Semi-robust
     bweight |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |      46.608   10.02134      4.65   0.000     26.96653    66.24947
     initage |    26.73226    10.1111      2.64   0.008     6.914877    46.54965
       _cons |    2526.622   177.2781     14.25   0.000     2179.164    2874.081
------------------------------------------------------------------------------
```

Motivating example: Stata output

```
GEE population-averaged model                   Number of obs      =      1000
Group variable:                        momid    Number of groups   =       200
Link:                             identity      Obs per group: min =         5
Family:                           Gaussian                     avg =       5.0
Correlation:                  exchangeable                     max =         5
                                               Wald chi2(2)       =     27.95
Scale parameter:                  324458.3     Prob > chi2        =    0.0000

                                  (Std. Err. adjusted for clustering on momid)
------------------------------------------------------------------------------
             |               Semi-robust
     bweight |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
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------------------------------------------------------------------------------
```

Motivating example: Comments

- Difference in mean birth weight between two populations of infants whose birth order differs by one is 46.6 grams, 95% CI: (27.0, 66.2)
- Model-based standard errors are smaller for exchangeable structure, indicating efficiency gain from assuming a correct correlation structure
- In practice, i.e. with real-world data, it's often difficult to tell what the correct correlation structure is from exploratory analyses
- *A priori* scientific knowledge should ultimately guide the decision
- I tend to use working independence with empirical standard errors unless I have a good reason to do otherwise, e.g. large efficiency gain
- Try not to select the structure that gives you the smallest p-value
- Stata labels the standard errors "semi-robust" because the empirical variance estimator protects against mis-specification of the correlation model, but requires correct specification of the mean model

⋆ See `help xtgee` for detailed syntax, other options, and saved results

GEE summary

- In the GEE approach the primary focus of the analysis is a marginal mean regression model that corresponds to any GLM
- Longitudinal correlation is secondary to the mean model of interest and is treated as a nuisance feature of the data
- Requires selection of a 'working' correlation model
- Semi-parametric: Only the mean and correlation models are specified
- The correlation model does not need to be correctly specified to obtain a consistent estimator for β or valid standard errors for $\hat{\beta}$
- Efficiency gains are possible if the correlation model is correct

Issues

- Accommodates only one source of correlation: Longitudinal **or** cluster
- GEE requires that any missing data are missing completely at random
- Issues arise with time-dependent exposures and covariance weighting

Strategies for analysis of longitudinal data

- **Derived variable**: Collapse the longitudinal series for each subject into a summary statistic, such as a difference (a.k.a. "change score") or regression coefficient, and use methods for independent data
  - **Example**: birth weight of 2nd child – birth weight of 1st child
  - Might be adequate for two time points and no missing data
- **Repeated measures**: Include all data in a regression model for the mean response and account for longitudinal and/or cluster correlation
  - **Generalized estimating equations** (GEE): A marginal model for the mean response and a model for longitudinal or cluster correlation

$$g(\mathrm{E}[Y_{ij} \mid x_{ij}]) = x_{ij}\beta \quad \text{and} \quad \mathrm{Corr}[Y_{ij}, Y_{ij'}] = \rho(\alpha)$$

  - **Generalized linear mixed-effects models** (GLMM)

Mixed-effects models (Laird and Ware, 1982)

4515 citations as of July 2016

- ⋆ Contrast outcomes both within and between **individuals**
  - Assume that each subject has a regression model characterized by subject-specific parameters: a combination of **fixed-effects** parameters common to all individuals in the population and **random-effects** parameters unique to each individual subject
  - Although covariates allow for differences across subjects, typically cannot measure all factors that give rise to subject-specific variation
  - Subject-specific random effects induce a correlation structure

Set-up

For subject i the mixed-effects model is characterized by

$$
\begin{aligned}
Y_i &= (Y_{i1}, Y_{i2}, \ldots, Y_{im_i})^{\mathsf{T}} \\
\\
\beta^{\star} &= (\beta_1^{\star}, \beta_2^{\star}, \ldots, \beta_p^{\star})^{\mathsf{T}} && \text{Fixed effects} \\
x_{ij} &= (x_{ij1}, x_{ij2}, \ldots, x_{ijp}) \\
X_i &= (x_{i1}, x_{i2}, \ldots, x_{im_i})^{\mathsf{T}} && \text{Design matrix for fixed effects} \\
\\
\gamma_i &= (\gamma_{1i}, \gamma_{2i}, \ldots, \gamma_{qi})^{\mathsf{T}} && \text{Random effects} \\
z_{ij} &= (z_{ij1}, z_{ij2}, \ldots, z_{ijq}) \\
Z_i &= (z_{i1}, z_{i2}, \ldots, z_{im_i})^{\mathsf{T}} && \text{Design matrix for random effects}
\end{aligned}
$$

for $i = 1, \ldots, n$; $j = 1, \ldots, m_i$; and $k = 1, \ldots, p$ with $q \leq p$

Linear mixed-effects model

Consider a linear mixed-effects model for a continuous outcome Y_{ij}

- **Stage 1**: Model for response given random effects

$$Y_{ij} = x_{ij}\beta + z_{ij}\gamma_i + \epsilon_{ij}$$

with

  - x_{ij} is a vector a covariates
  - z_{ij} is a subset of x_{ij}
  - β is a vector of fixed-effects parameters
  - γ_i is a vector of random-effects parameters
  - ϵ_{ij} is observation-specific measurement error

- **Stage 2**: Model for random effects

$$\begin{aligned} \gamma_i &\sim N(0, G) \\ \epsilon_{ij} &\sim N(0, \sigma^2) \end{aligned}$$

with γ_i and ϵ_{ij} are assumed to be independent

Choices for random effects

Consider the linear mixed-effects models that include

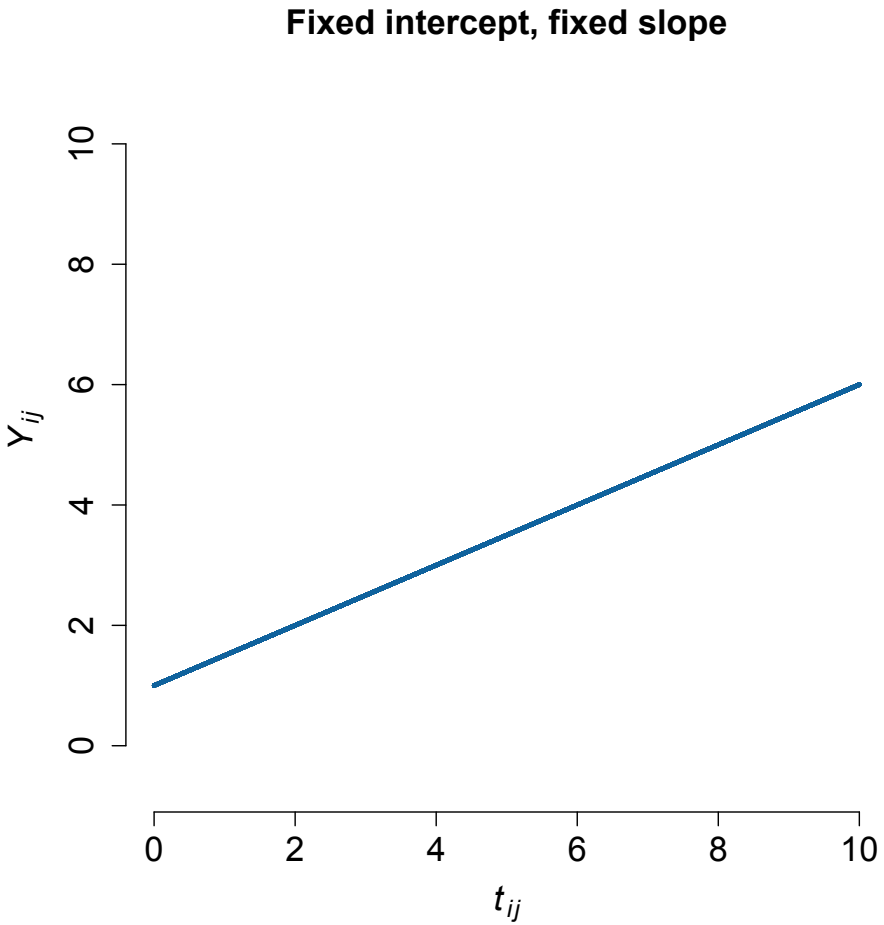
- **Random intercepts**

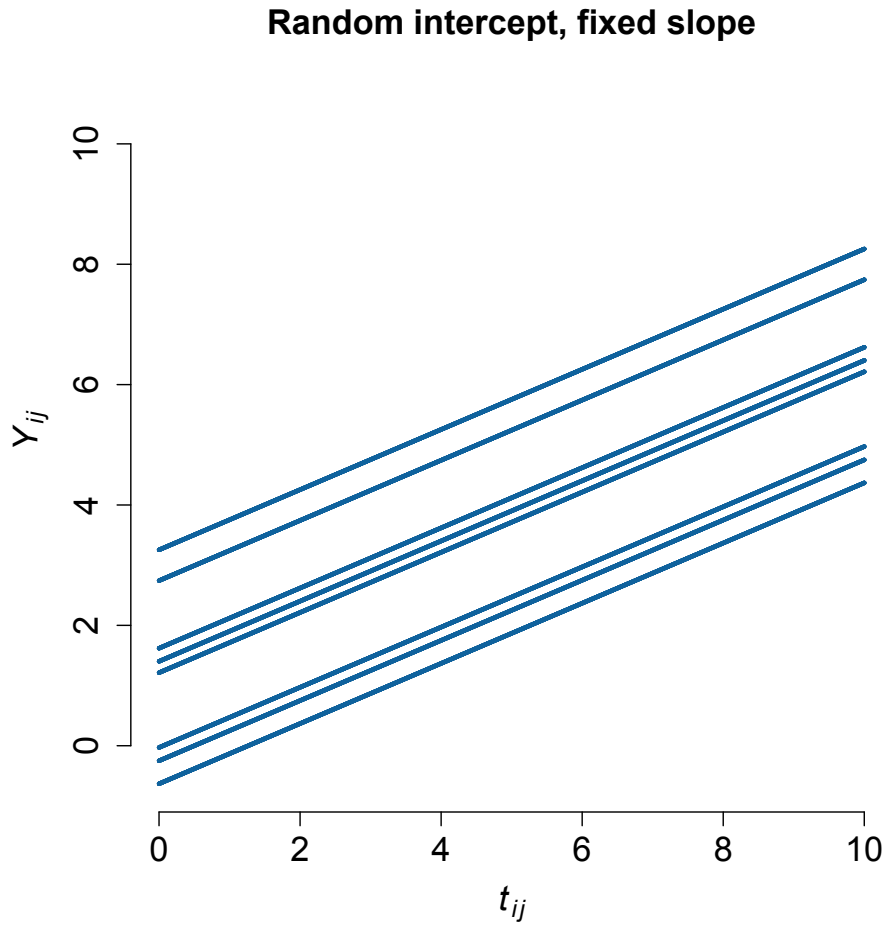
$$\begin{aligned} Y_{ij} &= \beta_0 + \beta_1 t_{ij} + \gamma_{0i} + \epsilon_{ij} \\ &= (\beta_0 + \gamma_{0i}) + \beta_1 t_{ij} + \epsilon_{ij} \end{aligned}$$

- **Random intercepts and slopes**

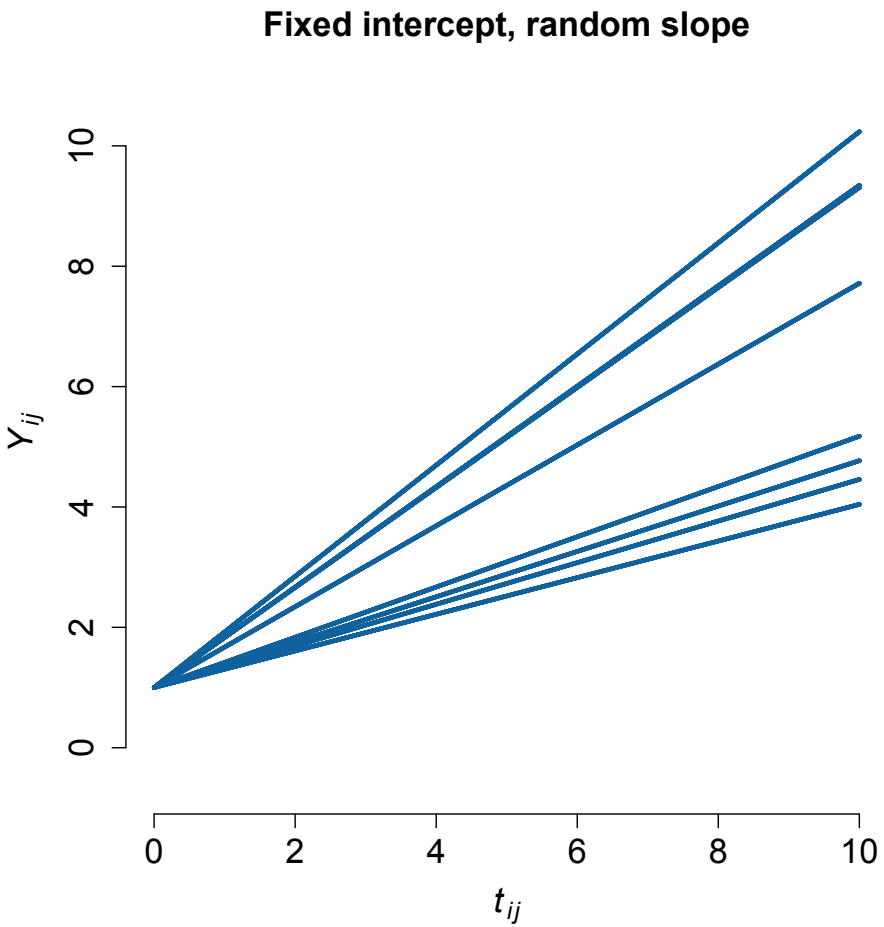
$$\begin{aligned} Y_{ij} &= \beta_0 + \beta_1 t_{ij} + \gamma_{0i} + \gamma_{1i} t_{ij} + \epsilon_{ij} \\ &= (\beta_0 + \gamma_{0i}) + (\beta_1 + \gamma_{1i}) t_{ij} + \epsilon_{ij} \end{aligned}$$

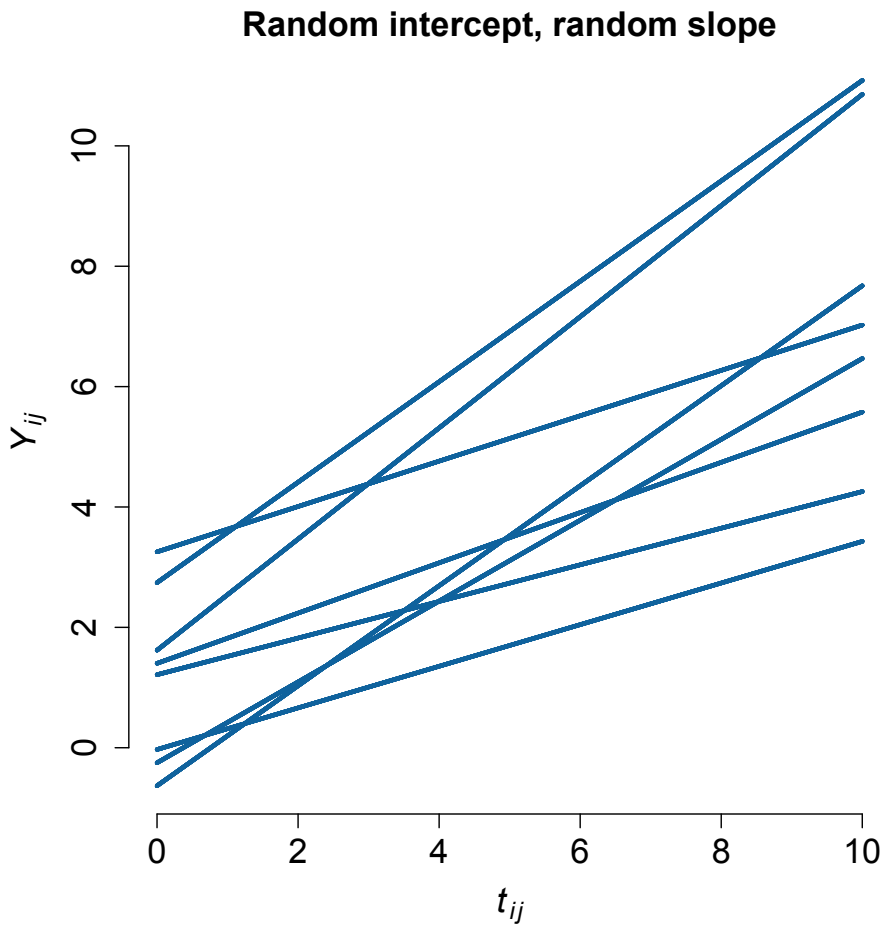
Choices for random effects





Choices for random effects





Choices for random effects: G

G quantifies random variation in trajectories across subjects

$$G = \begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix}$$

- $\sqrt{G_{11}}$ is the typical deviation in the **level** of the response
- $\sqrt{G_{22}}$ is the typical deviation in the **change** in the response
- G_{12} is the covariance between subject-specific intercepts and slopes
  - $G_{12} = 0$ indicates subject-specific intercepts and slopes are uncorrelated
  - $G_{12} > 0$ indicates subjects with **high level** have **high rate** of change
  - $G_{12} < 0$ indicates subjects with **high level** have **low rate** of change

$(G_{12} = G_{21})$

Generalized linear mixed-effects models

A GLMM is defined by **random** and **systematic** components

- **Random**: Conditional on γ_i the outcomes $Y_i = (Y_{i1}, \ldots, Y_{im_i})^{\mathsf{T}}$ are mutually independent and have an exponential family density

$$f(Y_{ij} \mid \beta^\star, \gamma_i, \phi) = \exp\{[Y_{ij}\theta_{ij} - \psi(\theta_{ij})]/\phi + c(Y_{ij}, \phi)\}$$

  for $i = 1, \ldots, n$ and $j = 1, \ldots, m_i$ with a scale parameter $\phi > 0$ and $\theta_{ij} \equiv \theta_{ij}(\beta^\star, \gamma_i)$

Generalized linear mixed-effects models

A GLMM is defined by **random** and **systematic** components

- **Systematic**: $\mu_{ij}^{\star}$ is modeled via a linear predictor containing fixed regression parameters $\beta^{\star}$ common to all individuals in the population and subject-specific random effects γ_i with a known link function $g(\cdot)$

$$g(\mu_{ij}^{\star}) = x_{ij}\beta^{\star} + z_{ij}\gamma_i \Leftrightarrow \mu_{ij}^{\star} = g^{-1}(x_{ij}\beta^{\star} + z_{ij}\gamma_i)$$

  where the random effects γ_i are mutually independent with a common underlying multivariate distribution, typically assumed to be

$$\gamma_i \sim N_q(0, G)$$

  so that G quantifies random variation across subjects

Likelihood-based estimation of β

Requires specification of a complete probability distribution for the data

- Likelihood-based methods are designed for fixed effects, so integrate over the assumed distribution for the random effects

$$\mathcal{L}_Y(\beta, \sigma, G) = \prod_{i=1}^{n} \int f_{Y|\gamma}(Y_i \mid \gamma_i, \beta, \sigma) \times f_\gamma(\gamma_i \mid G) d\gamma_i$$

  where f_γ is typically the density function of a Normal random variable
- For linear models the required integration is straightforward because Y_i and γ_i are both normally distributed (easy to program)
- For non-linear models the integration is difficult and requires either approximation or numerical techniques (hard to program)

Likelihood-based estimation of β

Two likelihood-based approaches to estimation using a GLMM

1. **Conditional likelihood**: Treat the random effects as if they were fixed parameters and **eliminate** them by conditioning on their sufficient statistics; does not require a specified distribution for γ_i
   - `xtreg` and `xtlogit` with `fe` option in Stata
2. **Maximum likelihood**: Treat the random effects as unobserved nuisance variables and **integrate** over their assumed distribution to obtain the marginal likelihood for β; typically assume $\gamma_i \sim N(0, G)$
   - `xtreg` and `xtlogit` with `re` option in Stata
   - `mixed` and `melogit` in Stata
   - `lmer` and `glmer` in R package `lme4`

'Fixed effects' versus 'random effects'

'Fixed-effects' approach provided by conditional likelihood estimation

- Comparisons are made within individuals who act as their own control and differences are averaged across all individuals in the sample
- Could eliminate potentially large sources of bias by controlling for all stable characteristics of the individuals under study $(+)$
- Variation across subjects is ignored, which could provide standard error estimates that are too big; conservative inference $(-)$
- Although controlled for by conditioning, cannot estimate coefficients for covariates that have no within-subject variation $(-/+)$

'Fixed effects' versus 'random effects'

'Random-effects' approach provided by maximum likelihood estimation

- Comparisons are based on within- and between-subject contrasts
- Requires a specified distribution for subject-specific effects; correct specification is required for valid likelihood-based inference $(-/+)$
- Do not control for unmeasured characteristics because random effects are almost always assumed to be uncorrelated with covariates $(-)$
- Can estimate effects of within- and between-subject covariates $(+)$

Assumptions

Valid inference from a linear mixed-effects model relies on

- **Mean model**: As with any regression model for an average outcome, need to correctly specify the functional form of $x_{ij}\beta$ (here also $z_{ij}\gamma_i$)
  - Included important covariates in the model
  - Correctly specified any transformations or interactions
- **Covariance model**: Correct covariance model (random-effects specification) is required for correct standard error estimates for $\hat{\beta}$
- **Normality**: Normality of ϵ_{ij} and γ_i is required for normal likelihood function to be the correct likelihood function for Y_{ij}
- n sufficiently large for **asymptotic inference** to be valid

$\star$ These assumptions must be verified to evaluate any fitted model

Motivating example

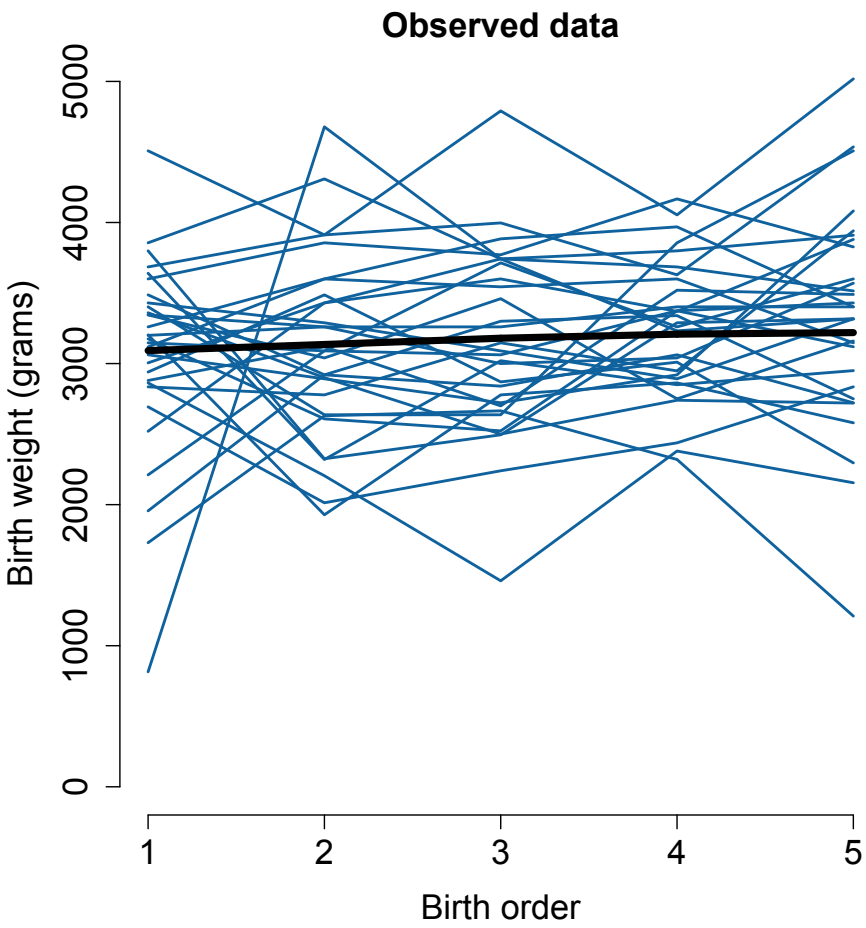
Interested in the association between birth order and birth weight

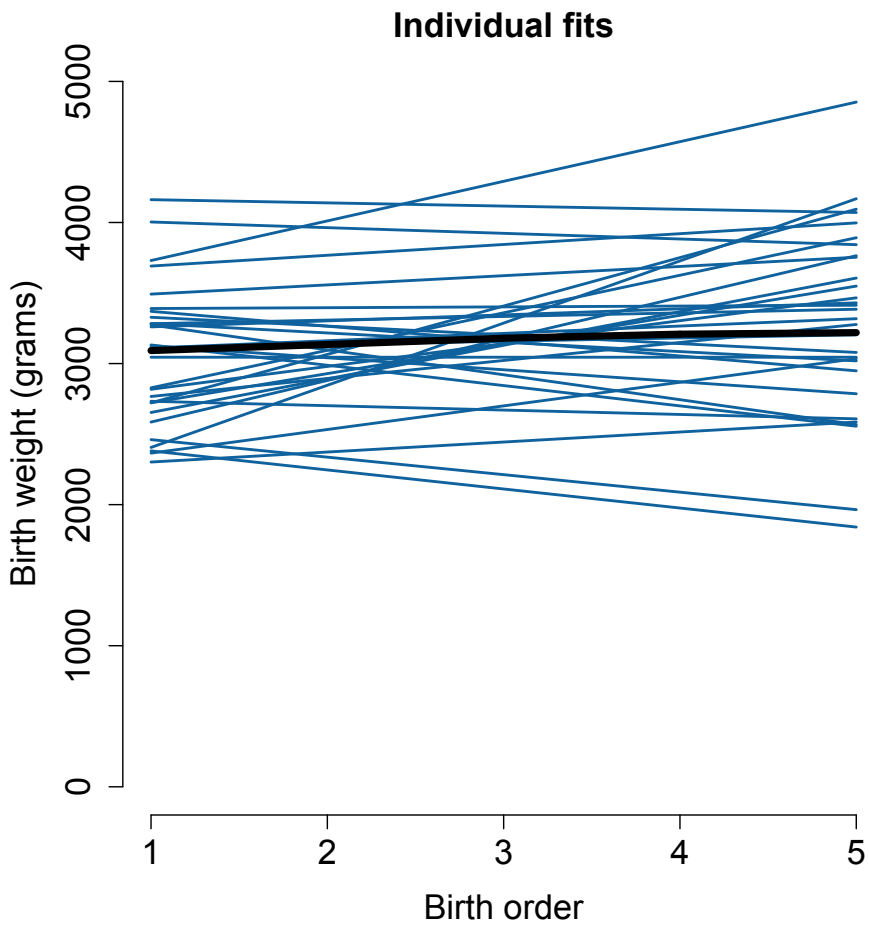
$$\begin{aligned} \mathrm{E}[Y_{ij} \mid x_{ij}, \gamma_i] &= \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \gamma_{0i} \\ \text{or} \quad & \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \gamma_{0i} + \gamma_{1i} x_{ij1} \end{aligned}$$

for $i = 1, \ldots, 200$ and $j = 1, \ldots, 5$ with

- Y_{ij}: Infant birth weight (continuous)
- x_{ij1}: Infant birth order
- x_{ij2}: Mother's initial age

Motivating example





Motivating example: Stata commands

```
* Declare the dataset to be "panel" data, grouped by momid
* with time variable birthord
xtset momid birthord

* Fit a linear model with random intercepts
xtmixed bweight birthord initage || momid:

* Fit a linear model with random intercepts and slopes
xtmixed bweight birthord initage || momid: birthord
```

Motivating example: Stata output

```
Mixed-effects REML regression                   Number of obs      =      1000
Group variable: momid                           Number of groups   =       200

                                                Obs per group: min =         5
                                                               avg =       5.0
                                                               max =         5


                                                Wald chi2(2)       =     30.75
Log restricted-likelihood = -7649.3763          Prob > chi2        =    0.0000

------------------------------------------------------------------------------
     bweight |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |      46.608   9.951014     4.68   0.000     27.10437    66.11163
     initage |   26.73226   9.002678     2.97   0.003      9.08734    44.37719
       _cons |   2526.622   163.3387    15.47   0.000     2206.484     2846.76
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
momid: Identity              |
                   sd(_cons) |   358.1759   23.71804      314.5797    407.8139
-----------------------------+------------------------------------------------
                sd(Residual) |   445.0229   11.13253      423.7298     467.386
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =   209.20 Prob >= chibar2 = 0.0000
```

Motivating example: Stata output

```
Mixed-effects REML regression                   Number of obs      =      1000
Group variable: momid                           Number of groups   =       200

                                                Obs per group: min =         5
                                                               avg =       5.0
                                                               max =         5


                                                Wald chi2(2)       =     29.29
Log restricted-likelihood = -7647.4511          Prob > chi2        =    0.0000

------------------------------------------------------------------------------
     bweight |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |     46.608   10.41108     4.48   0.000     26.20265    67.01335
     initage |   27.06415   8.899505     3.04   0.002     9.621441    44.50686
       _cons |   2520.799   161.1498    15.64   0.000     2204.952    2836.647
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
momid: Independent           |
                sd(birthord) |   49.35226   13.57685      28.78331    84.62007
                   sd(_cons) |   325.7759    29.6488      272.5532    389.3916
-----------------------------+------------------------------------------------
                sd(Residual) |   438.6626   11.43016      416.8224    461.6472
------------------------------------------------------------------------------
LR test vs. linear regression:       chi2(2) =   213.05   Prob > chi2 = 0.0000
```

Motivating example: Comments

- Difference in mean birth weight between two populations of infants whose birth order differs by one is 46.6 grams, 95% CI: (27.0, 66.2)
- Agrees well with GEE point estimate and confidence interval
- $\sqrt{\hat{G}_{00}} = 323$ indicates substantial variability across mothers in the initial level of infant birth weight; $\sqrt{\hat{G}_{11}} = 49$ indicates substantial variability across mothers in the trend of birth weight over time
- **Note**: Typically can specify correlated intercepts and slopes, i.e. $G_{01} \neq 0$, but in this case the model would not converge
- There are options for formal statistical evaluation of two random-effects specifications, but I generally do not recommend an inferential procedure in which a p-value tells you to use a simpler model
- Specification for the random effects should be guided by *a priori* scientific knowledge and exploratory data analysis

GLMM summary

- A GLMM is defined by a random component describing outcomes given subject-specific effects and a systematic component describing the conditional mean given subject-specific effects
- Conditional likelihood for 'fixed effects' eliminates subject-specific effects by conditioning on their sufficient statistics
- Maximum likelihood for 'random effects' integrates over the assumed distribution of the subject-specific effects
- Interpretation of parameter estimates depends on the assumed distribution for the outcome given the subject-specific effects and the specified structure for subject-specific effects

Issues

- GLMM requires that any missing data are missing at random
- Issues arise with time-dependent exposures and covariance weighting

Strategies for analysis of longitudinal data

- **Derived variable**: Collapse the longitudinal series for each subject into a summary statistic, such as a difference (a.k.a. "change score") or regression coefficient, and use methods for independent data
  - **Example**: birth weight of 2nd child – birth weight of 1st child
  - Might be adequate for two time points and no missing data
- **Repeated measures**: Include all data in a regression model for the mean response and account for longitudinal and/or cluster correlation
  - **Generalized estimating equations** (GEE): A marginal model for the mean response and a model for longitudinal or cluster correlation

$$g(\mathrm{E}[Y_{ij} \mid x_{ij}]) = x_{ij}\beta \quad \text{and} \quad \mathrm{Corr}[Y_{ij}, Y_{ij'}] = \rho(\alpha)$$

  - **Generalized linear mixed-effects models** (GLMM): A conditional model for the mean response given subject-specific random effects, which induce a (possibly hierarchical) correlation structure

$$g(\mathrm{E}[Y_{ij} \mid x_{ij}, \gamma_i]) = x_{ij}\beta^\star + z_{ij}\gamma_i$$

Overview

Motivation and design

- Gregoire et al. (1996) published the results of an efficacy study on estrogen patches in treating postnatal depression
- 61 women with major depression, which began within 3 months of childbirth and persisted for up to 18 months postnatally, participated in a double-blind, placebo-controlled study
- Women were randomly assigned to active treatment ($n = 34$) or placebo ($n = 27$)
- Participants attended clinics monthly and at each visit self-ratings of depressive symptoms on the Edinburgh postnatal depression scale (EPDS) were measured
- EPDS is a standardized, validated, self-rating scale consisting of 10 items, each rated on a 4-point scale of 0–3
- **Goal**: Investigate the antidepressant efficacy of treatment with estrogen over time

Data

- Depression scores are assessed across $m = 7$ months for the $n = 61$ subjects in the study
- Depression scores for visit j are the longitudinal components measured on subject i

	subj	group	dep0	dep1	dep2	dep3	dep4	dep5	dep6
1.	1	placebo	18	17	18	15	17	14	15
2.	2	placebo	27	26	23	18	17	12	10
3.	3	placebo	16	17	14	.	.	.	.
4.	4	placebo	17	14	23	17	13	12	12
5.	5	placebo	15	12	10	8	4	5	5
6.	6	placebo	20	19	11.54	9	8	6.82	5.05
7.	7	placebo	16	13	13	9	7	8	7
8.	8	placebo	28	26	27	.	.	.	.
9.	9	placebo	28	26	24	19	13.94	11	9
10.	10	placebo	25	9	12	15	12	13	20

- "Wide" form: A row for each subject
- Note that there are some missing data due to drop-out

Exploratory analyses

1. Summarize the depression scores by visit and treatment group
2. Examine within-person correlations among depression scores, graphically and numerically
3. Graph depression scores over time, by treatment group; include a lowess line (smoother) for each group to summarize trends
4. Plot individual trajectories by treatment group

Regression analyses

5. Consider collapsing the longitudinal series for each subject into a summary statistic between the baseline and sixth depression scores. Use methods for independent data to evaluate the association between change in depression scores and estrogen treatment

6. Reshape the data into long form and evaluate longitudinal associations between depression scores and treatment using GEE
   - Use visit as a linear variable
   - Use visit as a categorical variable
   - Evaluate whether the treatment effect varies over time

Reshape the data

Recall what the data look like in wide form

```
     +-------------------------------------------------------------------+
     | subj      group    dep0    dep1    dep2    dep3    dep4    dep5    dep6 |
     |-------------------------------------------------------------------|
  1. |    1    placebo      18      17      18      15      17      14      15 |
  2. |    2    placebo      27      26      23      18      17      12      10 |
  3. |    3    placebo      16      17      14       .       .       .       . |
  4. |    4    placebo      17      14      23      17      13      12      12 |
  5. |    5    placebo      15      12      10       8       4       5       5 |
     |-------------------------------------------------------------------|
```

For some analyses, reshape the data from wide form to long form

```
. reshape long dep, i(subj) j(visit)
(note: j = 0 1 2 3 4 5 6)

Data                                wide   ->   long
-----------------------------------------------------
Number of obs.                        61   ->      427
Number of variables                    9   ->        4
j variable (7 values)                      ->   visit
xij variables:
                     dep0 dep1 ... dep6    ->   dep
-----------------------------------------------------
```

Reshape the data

"Long" form: A row for each observation

	subj	visit	group	dep
1.	1	0	placebo	18
2.	1	1	placebo	17
3.	1	2	placebo	18
4.	1	3	placebo	15
5.	1	4	placebo	17
6.	1	5	placebo	14
7.	1	6	placebo	15
8.	2	0	placebo	27
9.	2	1	placebo	26
10.	2	2	placebo	23

Answers

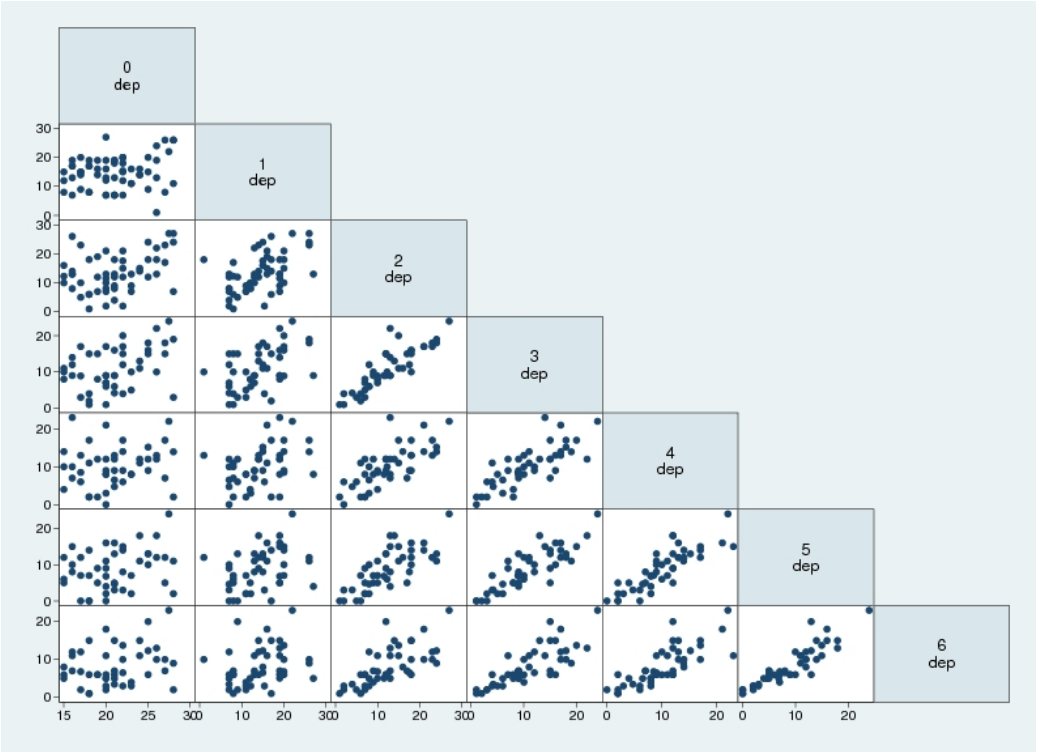
Summaries by group and visit

```
. sort group
. by group: summarize dep0 dep1 dep2 dep3 dep4 dep5 dep6
-------------------------------------------------------------------------------
-> group = placebo
    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
        dep0 |        27    20.77778    3.954874        15         28
        dep1 |        27    16.48148    5.279644         7         26
        dep2 |        22    15.88818    6.124177         4         27
        dep3 |        17    14.12882    4.974648      4.19         22
        dep4 |        17    12.27471    5.848791         2         23
        dep5 |        17    11.40294    4.438702      3.03         18
        dep6 |        17    10.89588     4.68157      3.45         20
-------------------------------------------------------------------------------
-> group = estrogen
    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
        dep0 |        34    21.24882    3.574432        15         28
        dep1 |        34    13.36794    5.556373         1         27
        dep2 |        31    11.73677    6.575079         1         27
        dep3 |        29    9.134138    5.475564         1         24
        dep4 |        28    8.827857    4.666653         0         22
        dep5 |        28    7.309286    5.740988         0         24
        dep6 |        28    6.590714    4.730158         1         23
-------------------------------------------------------------------------------
```

- **Note**: There are fewer observations observed over time

Correlation

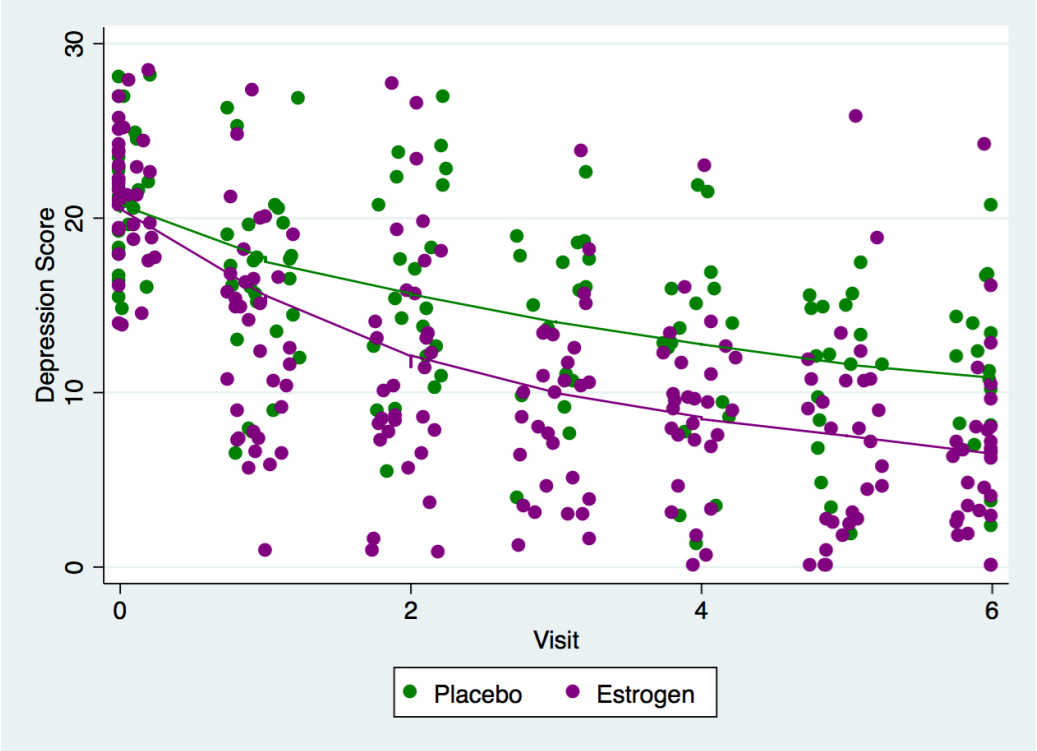
```
. graph matrix dep0 dep1 dep2 dep3 dep4 dep5 dep6, half
```



- All correlations are positive
- Strong correlation between adjacent visits

Depression scores over time

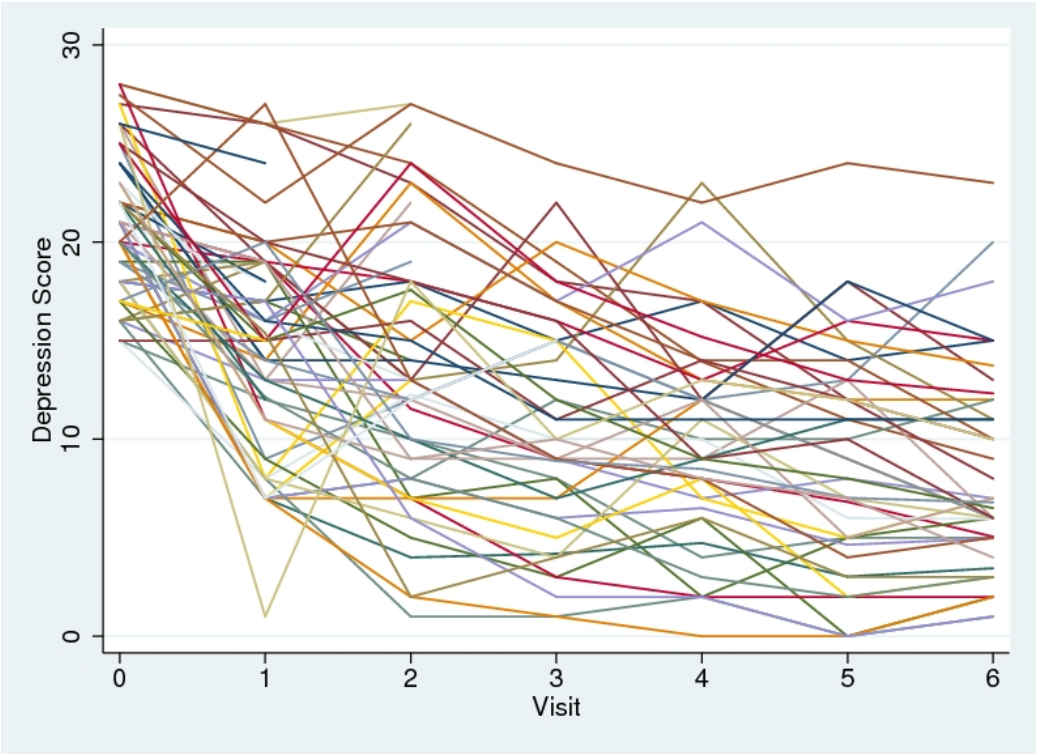
```
. separate dep, by(group)
. graph twoway (scatter dep0 visit, jitter(10) mcolor(green))
  (scatter dep1 visit, jitter(10) mcolor(purple)) ///
  (lowess dep0 visit, lcolor(green)) (lowess dep1 visit, lcolor(purple))
```



- For each treatment arm, mean depression scores decrease over time

Individual trajectories

```
. xtline dep, i(subj) t(visit) overlay legend(off)
    xlab(0(1)6) xtitle("Visit") ytitle("Depression Score")
```



- Reveals the complexity of individual trajectories
- Note that several patients drop out after the second visit

Simple difference

```
. gen diff=dep6-dep0
. ttest diff, by(group) unequal

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 placebo |      17   -9.633529    1.321784    5.449855   -12.43559   -6.831472
estrogen |      28   -14.71143    .8682517    4.594356   -16.49293   -12.92992
---------+--------------------------------------------------------------------
combined |      45   -12.79311    .8158414     5.47283   -14.43733   -11.14889
---------+--------------------------------------------------------------------
    diff |            5.077899    1.581447                1.845991    8.309808
------------------------------------------------------------------------------
    diff = mean(placebo) - mean(estrogen)                         t =   3.2109
Ho: diff = 0                     Satterthwaite's degrees of freedom =  29.5287

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9984         Pr(|T| > |t|) = 0.0032          Pr(T > t) = 0.0016
```

- Clear decreases over time; larger decreases among estrogen group
- Limited to those with complete measurement series

GEE

- A special feature of longitudinal data is that the $m = 7$ observations that are nested within the $n = 61$ subjects are ordered in time
- We can consider *marginal models* to model the within-subject dependence by allowing us to specify the covariance structure across the nested observations
- Parameters describing the covariance must be estimated along with typical regression coefficients
- A variety of options are available to describe the covariance
- Some covariance patterns require more information (i.e., require more parameters to be estimated than others)
- Recall, we identify the data as a "panel" data set using the `xtset` command in Stata

Assumptions

To account for the repeated measures we can use generalized estimating equations which include all of the data over the time points in a marginal model for the mean response and account for the longitudinal correlation

$$g(\mathrm{E}[Y_{ij} \mid x_{ij}]) = x_{ij}\beta \quad \text{and} \quad \mathrm{Corr}[Y_{ij}, Y_{ij'}] = \rho(\alpha)$$

Assumptions

- Observations are independent across subjects
- Observations could be correlated within subjects
- Missing data are missing completely at random

Model

- Using the GEE framework, we consider the "cross-sectional" model where we are interested in the average treatment effect over time

$$\mathrm{E}[Y_{ij} \mid x_{ij}] = \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2}$$

  with
  - Y_{ij}: continuous depression score (`dep`)
  - x_{ij1}: continuous variable for visit (`visit`)
  - x_{ij2}: binary treatment group with 1=estrogen, 0=placebo (`group`)
- For the continuous outcome, we use an identity link, `link(iden)`, in the Gaussian family, `fam(gaus)`; these are the default
- In Stata, `xtgee` allows us to specify various working covariance structures through the `corr` option; the command `estat wcorr` allows us to view the working correlation matrix

Correlation structures

- **Independence**: Observations are assumed to be independent
  - For correlation between any two observations on the same subject we assume that $\text{Corr}[Y_{ij}, Y_{ij'}] = 0$
  - It is unlikely that for any subject, depression scores are independent from one visit to the next
- **Exchangeable**: Correlations are assumed to be constant between any two observations on the same subject; $\text{Corr}[Y_{ij}, Y_{ij'}] = \alpha$
- **AR(1)**: Correlation is assumed to decay as a function of time or distance between observations; $\text{Corr}[Y_{ij}, Y_{ij'}] = \alpha^{|j-j'|}$
  - Likely to be appropriate in cases where there are a reasonable number of repeated measurements over time
  - Given that our data are measured over time, using the AR(1) correlation might help increase efficiency of SE estimation
- **Unstructured**: No relationship is imposed on dependence over time or within subjects; $\text{Corr}[Y_{ij}, Y_{ij'}] = \alpha_{jj'}$

⋆ Robust variance estimator protects against incorrect choice

GEE-independence

```
. xtgee dep visit i.group, corr(ind) robust

GEE population-averaged model                 Number of obs     =        356
Group variable:                      subj     Number of groups  =         61
Link:                              identity   Obs per group:
Family:                            Gaussian                 min =          2
Correlation:                     independent                avg =        5.8
                                                            max =          7
                                              Wald chi2(2)      =     188.72
Scale parameter:                   29.02175   Prob > chi2       =     0.0000

Pearson chi2(356):                 10331.74   Deviance          =   10331.74
Dispersion (Pearson):              29.02175   Dispersion        =   29.02175

                                  (Std. Err. adjusted for clustering on subj)
------------------------------------------------------------------------------
             |               Robust
         dep |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       visit |  -1.921912   .1413007   -13.60   0.000    -2.198857   -1.644968
             |
       group |
   estrogen  |  -3.208912    1.08604    -2.95   0.003    -5.337511   -1.080313
       _cons |   20.19473   .8278936    24.39   0.000     18.57209    21.81737
------------------------------------------------------------------------------
```

GEE-AR(1)

```
. xtgee dep visit i.group, corr(ar1) robust

GEE population-averaged model                   Number of obs     =        356
Group and time vars:                 subj visit Number of groups  =         61
Link:                                  identity Obs per group:
Family:                                Gaussian                min =          2
Correlation:                              AR(1)                avg =        5.8
                                                               max =          7
                                                Wald chi2(2)      =     255.61
Scale parameter:                        29.8609 Prob > chi2       =     0.0000

                                  (Std. Err. adjusted for clustering on subj)
------------------------------------------------------------------------------
             |               Robust
         dep |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       visit |  -2.073222   .1300662   -15.94   0.000    -2.328147   -1.818297
             |
       group |
   estrogen  |  -2.529295   .9610062    -2.63   0.008    -4.412832   -.6457574
       _cons |   21.01002   .7325074    28.68   0.000     19.57433    22.44571
------------------------------------------------------------------------------
```

Working correlation structure

Examine the correlation structure estimated by the model

```
. estat wcorr

Estimated within-subj correlation matrix R:
      |         c1         c2         c3         c4         c5         c6         c7
------+-----------------------------------------------------------------------------
   r1 |          1
   r2 |  .6447567          1
   r3 |  .4157113  .6447567          1
   r4 |  .2680326  .4157113  .6447567          1
   r5 |  .1728158  .2680326  .4157113  .6447567          1
   r6 |  .1114242  .1728158  .2680326  .4157113  .6447567          1
   r7 |  .0718415  .1114242  .1728158  .2680326  .4157113  .6447567          1
```

Compare with simple pairwise correlations

```
. corr dep0 dep1 dep2 dep3 dep4 dep5 dep6
(obs=45)

             |     dep0     dep1     dep2     dep3     dep4     dep5     dep6
-------------+---------------------------------------------------------------
        dep0 |   1.0000
        dep1 |   0.1922   1.0000
        dep2 |   0.3904   0.4982   1.0000
        dep3 |   0.3958   0.5258   0.8672   1.0000
        dep4 |   0.1658   0.3933   0.7357   0.7831   1.0000
        dep5 |   0.2848   0.3674   0.7500   0.8520   0.8449   1.0000
        dep6 |   0.2688   0.2795   0.6900   0.7967   0.7894   0.9014   1.0000
```

Modeling time

- Valid inference from GEE requires that the mean model is correct
- We have two covariates: treatment group is binary, time is ?
- Instead of a continuous variable (or, grouped linear term) for time, consider a categorical variable

$$\begin{aligned} \mathrm{E}[Y_{ij} \mid x_{ij}] = \beta_0 + \beta_2 x_{ij2} + \beta_3 x_{ij3} + \beta_4 x_{ij4} \\ + \beta_5 x_{ij5} + \beta_6 x_{ij6} + \beta_7 x_{ij7} + \beta_8 x_{ij8} \end{aligned}$$

with, in addition to x_{ij2} representing the treatment variable (`group`)

- x_{ij3}: dummy variable for visit 1 compared to visit 0
- x_{ij4}: dummy variable for visit 2 compared to visit 0

  $\vdots$

- x_{ij8}: dummy variable for visit 6 compared to visit 0

GEE-AR(1), categorical time

```
. xtgee dep i.visit i.group, corr(ar1) robust

GEE population-averaged model                   Number of obs     =        356
Group and time vars:                 subj visit Number of groups  =         61
Link:                                  identity Obs per group:
Family:                                Gaussian                min =          2
Correlation:                              AR(1)                avg =        5.8
                                                               max =          7
                                                Wald chi2(7)      =     288.60
Scale parameter:                        26.7531 Prob > chi2       =     0.0000

                                  (Std. Err. adjusted for clustering on subj)
------------------------------------------------------------------------------
             |               Robust
         dep |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       visit |
           1 |  -6.294262   .7775699    -8.09   0.000    -7.818271   -4.770253
           2 |  -7.341596   .8475509    -8.66   0.000    -9.002766   -5.680427
           3 |  -9.258931   .7719962   -11.99   0.000    -10.77202   -7.745847
           4 |  -10.25842   .8352919   -12.28   0.000    -11.89557   -8.621282
           5 |  -11.69253    .807447   -14.48   0.000     -13.2751   -10.10997
           6 |  -12.43824   .7614791   -16.33   0.000    -13.93071   -10.94577
             |
       group |
    estrogen |  -2.593467   .9610867    -2.70   0.007    -4.477163    -.709772
       _cons |   22.48587   .7687195    29.25   0.000      20.9792    23.99253
------------------------------------------------------------------------------
```

Modeling time

- Strong evidence that depression scores vary over time

```
. testparm i.visit

 ( 1)  1.visit = 0
 ( 2)  2.visit = 0
 ( 3)  3.visit = 0
 ( 4)  4.visit = 0
 ( 5)  5.visit = 0
 ( 6)  6.visit = 0

           chi2(  6) =  287.46
         Prob > chi2 =    0.0000
```

- In the model with continuous visit, the difference in mean score between groups was -2.53 and it was highly significant ($p = 0.008$)
- When considering categorical visit, the difference in mean score between groups was -2.59 and it was highly significant ($p = 0.007$)
- Noting that the estimated treatment effect is the same in both models, we opt for the parsimony of the model with continuous visit

Model with interaction

Consider a model that allows the treatment effect to depend on time

- The model of interest becomes

$$\mathrm{E}[Y_{ij} \mid x_{ij}] = \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \beta_3 (x_{ij1} \times x_{ij2})$$

  where Y_{ij} is the continuous depression score, x_{ij1} is a continuous variable for visit, and x_{ij2} is the treatment variable
- Model includes their main effects and the interaction term
- For subjects in the placebo group ($x_{ij2} = 0$), the model is

$$\mathrm{E}[Y_{ij} \mid x_{ij}] = \beta_0 + \beta_1 x_{ij1}$$

- For subjects in the estrogen group ($x_{ij2} = 1$), the model is

$$\mathrm{E}[Y_{ij} \mid x_{ij}] = (\beta_0 + \beta_2) + (\beta_1 + \beta_3) x_{ij1}$$

- Now we can compare whether the mean change in depression score over time differs between treatment groups ("longitudinal" model)

GEE-AR(1), continuous time, interaction

```
. xtgee dep c.visit##i.group, corr(ar1) robust

GEE population-averaged model                   Number of obs     =        356
Group and time vars:                 subj visit Number of groups  =         61
Link:                                  identity Obs per group:
Family:                                Gaussian               min =          2
Correlation:                              AR(1)               avg =        5.8
                                                              max =          7
                                                Wald chi2(3)      =     325.29
Scale parameter:                       29.59602 Prob > chi2       =     0.0000

                                  (Std. Err. adjusted for clustering on subj)
------------------------------------------------------------------------------
             |               Robust
         dep |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       visit |  -1.645136   .2032329    -8.09   0.000    -2.043465   -1.246807
             |
       group |
    estrogen |   -.668246   .9514551    -0.70   0.482    -2.533064    1.196572
             |
group#c.visit |
    estrogen |  -.7209406    .250909    -2.87   0.004    -1.212713   -.2291681
             |
       _cons |    19.9757   .7700831    25.94   0.000     18.46636    21.48503
------------------------------------------------------------------------------
```

Interpretation

- Estimate the change over time for the estrogen group by adding the coefficients for the visit variable and the interaction term

```
. lincom visit + 1.group#c.visit

 ( 1)  visit + 1.group#c.visit = 0

------------------------------------------------------------------------------
         dep |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |  -2.366076   .1471451   -16.08   0.000    -2.654475   -2.077677
------------------------------------------------------------------------------
```

- For a population of women on placebo treatment, mean depression score decreases by approximately 1.65 points for each additional visit, 95% CI: (-2.04, -1.25)
- For a population of women on estrogen treatment, mean depression score decreases by approximately 2.37 points for each additional visit, 95% CI: (-2.65, -2.08)
- Strong evidence that these associations are different ($p = 0.004$)

Summary

- GEE is specified by a mean model and a correlation model
  - We created a linear regression model for the average depression score and modeled the longitudinal correlation using an AR(1) structure
- GEE requires that the mean model is correctly specified
  - We explored different options for modeling temporal trends
- GEE provides valid estimates and standard errors for the regression parameters even under misspecification of the correlation structure, but efficiency gains are possible if the correlation model is correct
  - We chose AR(1) with the robust option
- Model with a group-by-time interaction term facilitated estimation of changes over time within groups and between-group comparisons in temporal trends
  - Contrasted this with a cross-sectional model that compared the mean depression score between groups over all times

Overview

Indonesian Children's Health Study (ICHS)

- Determine the effects of vitamin A deficiency in preschool children
- $n = 275$ children examined for respiratory infection at up to 6 visits
- Xerophthalmia is an ocular manifestation of vitamin A deficiency
- **Goal**: Evaluate association between vitamin A deficiency and risk of respiratory infection

		Age (years)							
Xerophthalmia	Infection	0	1	2	3	4	5	6	7
No	No	77	229	154	196	176	143	65	5
No	Yes	8	30	30	15	9	7	1	0
Yes	No	0	1	9	10	15	8	4	1
Yes	Yes	0	0	4	3	0	0	0	0

Data

```
. list id age time infection xerop gender hfora cost sint
```

	id	age	time	infect~n	xerop	gender	hfora	cost	sint
1.	121013	31	1	0	0	0	-3	-1	0
2.	121013	34	2	0	0	0	-3	0	-1
3.	121013	37	3	0	0	0	-2	1	0
4.	121013	40	4	0	0	0	-2	0	1
5.	121013	43	5	1	0	0	-2	-1	0
6.	121013	46	6	0	0	0	-3	0	-1
7.	121113	-9	1	0	0	1	2	-1	0
8.	121113	-6	2	0	0	1	0	0	-1
9.	121113	-3	3	0	0	1	-1	1	0
10.	121113	0	4	0	0	1	-2	0	1
11.	121113	3	5	1	0	1	-3	-1	0
12.	121113	6	6	0	0	1	-3	0	-1
13.	121114	-26	1	0	0	0	8	-1	0
14.	121114	-23	2	0	0	0	5	0	-1
15.	121114	-20	3	0	0	0	3	1	0
16.	121114	-17	4	1	0	0	0	0	1
17.	121114	-14	5	1	0	0	0	-1	0
18.	121114	-11	6	0	0	0	0	0	-1

Multiple records per person, with age in months, centered at 36 months, and time indicating visit number

Exploratory analyses

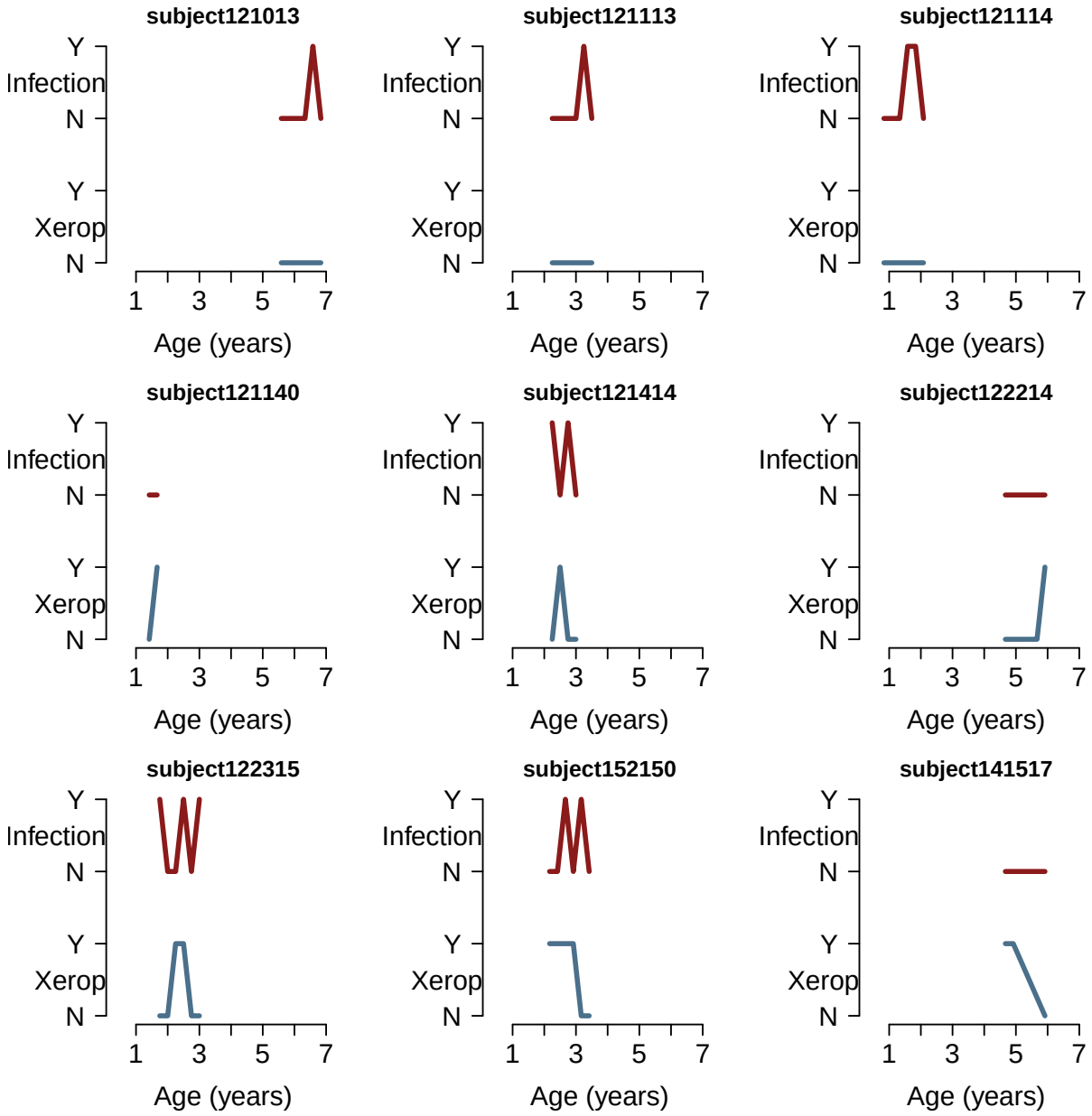
1. Plot vitamin A deficiency and infection status, by age, for a sample of individuals
2. Plot percent with respiratory infection versus age, by presence or absence of vitamin A deficiency
3. Explore correlation structure by visit number, and calculate percent with respiratory infection at each visit

Regression analyses

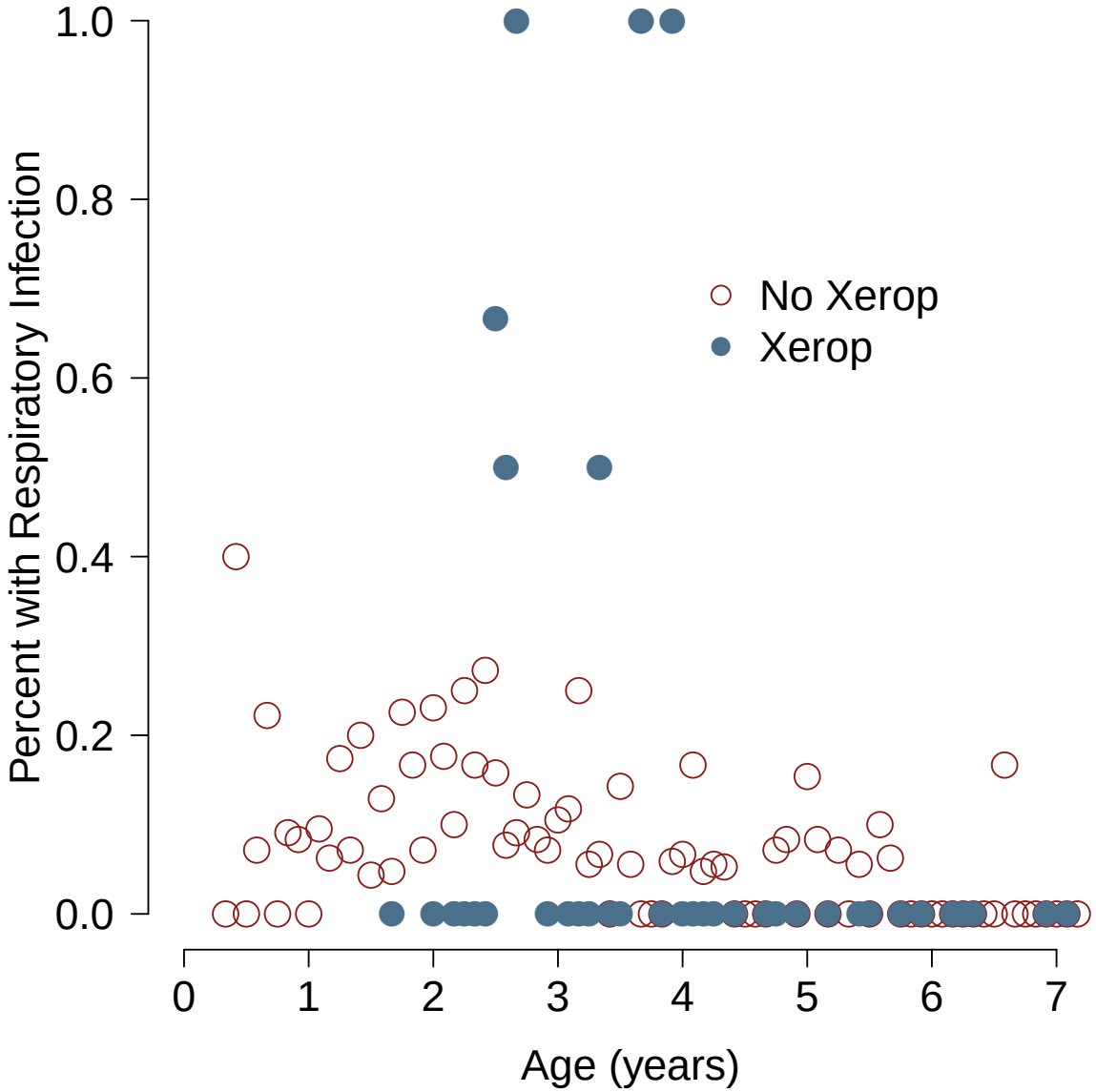
4. Evaluate the association between respiratory infection and vitamin A deficiency using an ordinary logistic regression model
5. Use GEE to estimate the population-averaged odds ratio for respiratory infection, comparing those with vitamin A deficiency to those without, given equivalent values of other covariates. Explore multiple specifications of working correlation
6. Use GLMM to estimate the conditional odds ratio for respiratory infection, comparing a typical individual with vitamin A deficiency to a typical individual without, given equivalent values of other covariates. Estimate the variability in the probability of respiratory infection across individuals

Answers

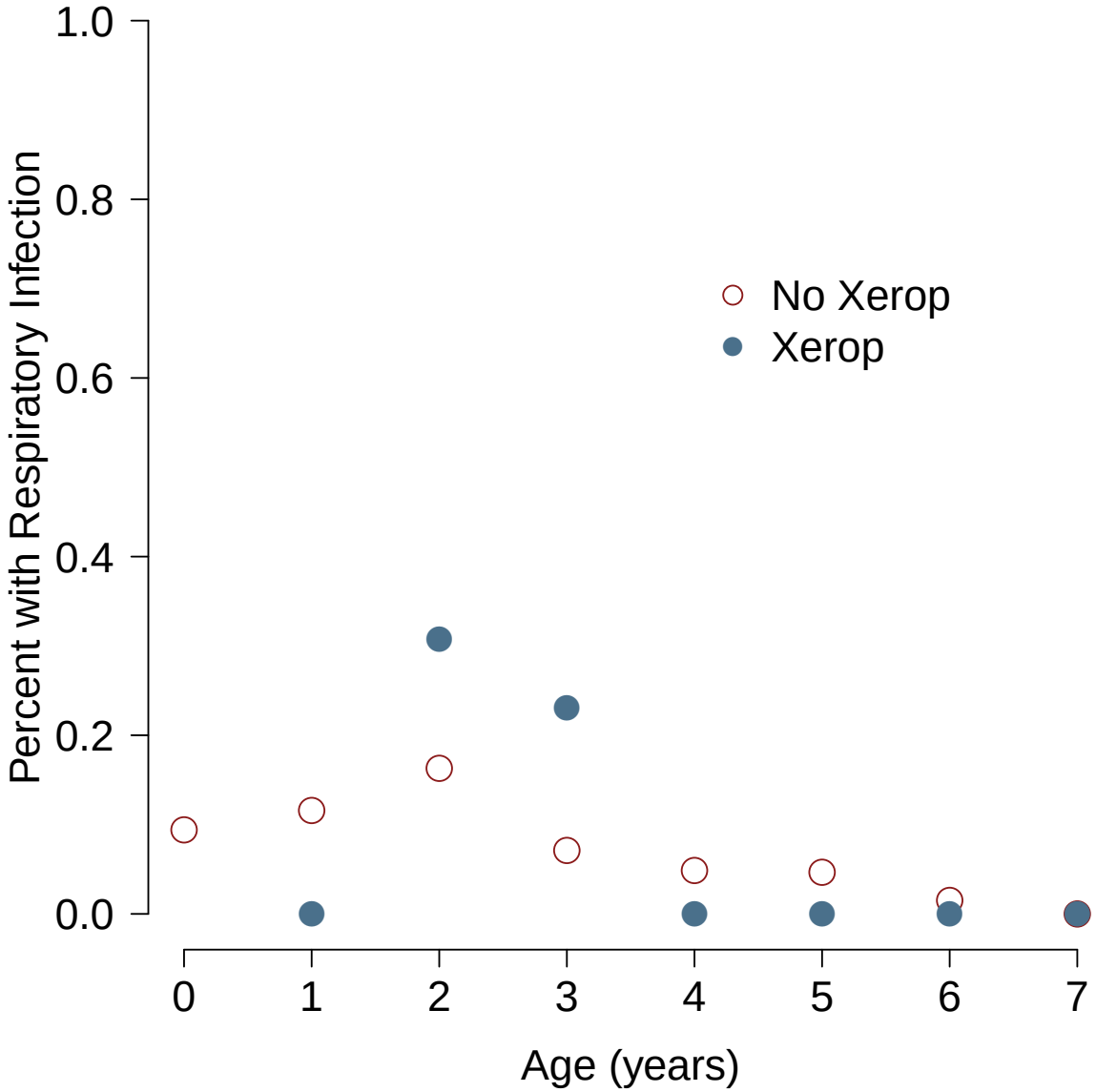
Individual trajectories



Monthly averages



Yearly averages



Logistic regression model

```
> summary(glm(infection ~ xerop + age + gender + hfora + cost + sint,
              data=ichs, family="binomial"))

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -2.42134    0.15920  -15.21  < 2e-16 ***
xerop        0.73148    0.43591    1.68  0.09334 .
age         -0.03188    0.00634   -5.03  4.9e-07 ***
gender      -0.39364    0.21965   -1.79  0.07311 .
hfora       -0.04944    0.02012   -2.46  0.01401 *
cost        -0.58029    0.16722   -3.47  0.00052 ***
sint        -0.16536    0.16851   -0.98  0.32645
```

- $\exp \beta_1 = 2.08$
- 95% CI: (0.88, 4.88)
- Does not take into account within-person correlation

GEE motivation

Do vitamin A deficient children have an increased risk of infection?

$$\begin{aligned} \mu_{ij} &= \mathrm{E}[Y_{ij} \mid x_{ij}] \\ &= \mathrm{P}[Y_{ij} = 1 \mid x_{ij}] \end{aligned}$$

$$\begin{aligned} \operatorname{logit} \mu_{ij} &= \log \frac{\mu_{ij}}{1 - \mu_{ij}} \\ &= \beta_0 + \beta_1 \, \mathrm{Xerophthalmia}_{ij} + \cdots \\ &\approx \log \frac{\mathrm{P}[Y_{ij} = 1 \mid x_{ij}]}{\mathrm{P}[Y_{ij} = 0 \mid x_{ij}]} \end{aligned}$$

- $\exp \beta_1$ represents the ratio of the expected odds of respiratory infection among a population of vitamin A deficient children to that for a population of children replete with vitamin A of the same age, gender, ...
- $\exp \beta_1$ is therefore a **population-averaged** parameter
- Respiratory infection is rare so odds ratio approximates relative risk

Correlations

- Use visit time (not age) to obtain a correlation matrix with $n = 146$–229 observations per cell

	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
Time 1	1					
Time 2	0.06	1				
Time 3	0.07	0.11	1			
Time 4	0.24	-0.03	0.06	1		
Time 5	0.07	0.26	0.19	-0.01	1	
Time 6	0.05	0.12	-0.07	0.06	0.10	1
	13 %	5 %	7 %	4 %	15 %	9 %

Covariance structure

- For a binary outcome, variance depends on mean

$$\text{Var}[Y_{ij}] = \text{E}[Y_{ij}](1 - \text{E}[Y_{ij}])$$

- Correlation also depends (in a somewhat complicated way) on pairwise means
- **NB**
  - With respect to age, data are neither balanced nor complete
  - Even if our analysis will be a function of age, examination of covariance and correlation matrices with respect to visit time is useful
  - Dependence of correlation on pairwise means motivates alternate methods that model odds ratios instead of correlations

Covariance structure

- Odds ratios measure the association between two binary variables
- Here, binary outcomes at two different visit times

	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
Time 1	∞					
Time 2	1.93	∞				
Time 3	2.10	4.62	∞			
Time 4	8.60	0	2.38	∞		
Time 5	1.76	11.9	4.68	0.92	∞	
Time 6	1.63	3.73	0	2.18	2.14	∞

Covariance structure

- Variance model

$$\text{Var}[Y_{ij} \mid x_{ij}] = \mu_{ij}(1 - \mu_{ij})$$

- Consider various specifications for the 'working' correlation structure
  - Independence
  - Exchangeable
  - Auto-regressive

NB: In practice, selection of a working correlation structure should be guided by a priori knowledge and/or exploratory analysis

geepack

- geepack implements estimating equations for β, α, and ϕ
- geeglm
  - Syntax similar to glm; returns an object similar to a glm object
  - An anova method provides multivariate Wald tests for joint hypotheses
  - Calls a fitter function geese to solve the estimating equations
- geese
  - Provides estimation and inference for β, α, and ϕ
  - Model objects are available within geeglm objects

```
names(m1)
names(m1$geese)
m1$geese$vbeta
```

R commands

```
load("ichs.RData")

library(geepack)

m1 <- geeglm(infection ~ xerop + age + gender + hfora + cost + sint,
             id=id, data=ichs, family="binomial", corstr="independence")

m2 <- geeglm(infection ~ xerop + age + gender + hfora + cost + sint,
             id=id, data=ichs, family="binomial", corstr="exchangeable")

m3 <- geeglm(infection ~ xerop + age + gender + hfora + cost + sint,
              id=id, data=ichs, family="binomial", corstr="ar1")
```

GEE-independence

```
> summary(m1)
 Coefficients:
            Estimate  Std.err   Wald Pr(>|W|)
(Intercept) -2.42134  0.16907 205.10  < 2e-16 ***
xerop        0.73148  0.42246   3.00  0.08337 .
age         -0.03188  0.00624  26.08  3.3e-07 ***
gender      -0.39364  0.23571   2.79  0.09492 .
hfora       -0.04944  0.02467   4.01  0.04511 *
cost        -0.58029  0.16928  11.75  0.00061 ***
sint        -0.16536  0.14865   1.24  0.26595
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Estimated Scale Parameters:
            Estimate Std.err
(Intercept)     1.02   0.644

Correlation: Structure = independence
Number of clusters:   275   Maximum cluster size: 6
```

GEE-exchangeable

```
> summary(m2)
 Coefficients:
            Estimate  Std.err   Wald Pr(>|W|)
(Intercept) -2.39852  0.17033 198.30  < 2e-16 ***
xerop        0.62693  0.43618   2.07  0.15063
age         -0.03162  0.00627  25.44  4.6e-07 ***
gender      -0.41887  0.23631   3.14  0.07631 .
hfora       -0.05282  0.02464   4.60  0.03205 *
cost        -0.57171  0.16846  11.52  0.00069 ***
sint        -0.16208  0.14556   1.24  0.26550
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Estimated Scale Parameters:
            Estimate Std.err
(Intercept)     1.02   0.655

Correlation: Structure = exchangeable  Link = identity

Estimated Correlation Parameters:
      Estimate Std.err
alpha   0.0452  0.0449
Number of clusters:   275   Maximum cluster size: 6
```

GEE-AR(1)

```
> summary(m3)
 Coefficients:
            Estimate  Std.err   Wald Pr(>|W|)
(Intercept) -2.41535  0.16926 203.64  < 2e-16 ***
xerop        0.66981  0.44020   2.32  0.12810
age         -0.03197  0.00625  26.13  3.2e-07 ***
gender      -0.39516  0.23579   2.81  0.09376 .
hfora       -0.05095  0.02464   4.28  0.03863 *
cost        -0.57446  0.16839  11.64  0.00065 ***
sint        -0.17108  0.14754   1.34  0.24624
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Estimated Scale Parameters:
            Estimate Std.err
(Intercept)     1.02   0.644

Correlation: Structure = ar1  Link = identity

Estimated Correlation Parameters:
      Estimate Std.err
alpha   0.0526  0.0544
Number of clusters:   275   Maximum cluster size: 6
```

Results

	$\hat{\beta}_1$ (SE)	exp($\hat{\beta}_1$) (95% CI)
Independence	0.73 (0.42)	2.08 (0.91, 4.76)
Exchangeable	0.63 (0.44)	1.87 (0.80, 4.40)
Auto-regressive	0.67 (0.44)	1.95 (0.83, 4.63)

- Vitamin A deficient children have an increased risk of respiratory infection, but confidence interval includes the null-hypothesized value
- geese provides estimation and inference for β, α, and ϕ
- Cannot reject the hypothesis that $\alpha = 0$
- **Note**: Model fit can be evaluated using QIC (Pan, 2001)

Working correlation structures

Exchangeable :

$$\begin{bmatrix} 1 & & & & & \\ 0.045 & 1 & & & & \\ 0.045 & 0.045 & 1 & & & \\ 0.045 & 0.045 & 0.045 & 1 & & \\ 0.045 & 0.045 & 0.045 & 0.045 & 1 & \\ 0.045 & 0.045 & 0.045 & 0.045 & 0.045 & 1 \end{bmatrix}$$

Auto-regressive :

$$\begin{bmatrix} 1 & & & & & \\ 0.053 & 1 & & & & \\ 0.003 & 0.053 & 1 & & & \\ 0.000 & 0.003 & 0.053 & 1 & & \\ 0.000 & 0.000 & 0.003 & 0.053 & 1 & \\ 0.000 & 0.000 & 0.000 & 0.003 & 0.053 & 1 \end{bmatrix}$$

Stata commands

```
* Declare the dataset to be "panel" data, grouped by id
* with time variable time
xtset id time

* Fit models with an exchangeable correlation structure
xtgee infection i.xerop age gender hfora cost sint,
          family(binomial) link(logit) corr(exch) robust

* Examine working correlation structure
estat wcorr
```

GEE-exchangeable

```
GEE population-averaged model                   Number of obs      =      1200
Group variable:                        id       Number of groups   =       275
Link:                               logit       Obs per group: min =         1
Family:                          binomial                      avg =       4.4
Correlation:                 exchangeable                      max =         6
                                                Wald chi2(6)       =     41.27
Scale parameter:                        1       Prob > chi2        =    0.0000

                                  (Std. Err. adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Semi-robust
   infection |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       xerop |   .6269335   .4369803     1.43   0.151    -.2295322    1.483399
         age |  -.0316238    .006281    -5.03   0.000    -.0439343   -.0193133
      gender |  -.4188661   .2367394    -1.77   0.077    -.8828669    .0451347
       hfora |  -.0528237   .0246853    -2.14   0.032    -.1012059   -.0044414
        cost |  -.5717089   .1687711    -3.39   0.001    -.9024942   -.2409237
        sint |   -.162076   .1458239    -1.11   0.266    -.4478856    .1237335
       _cons |   -2.39852   .1706357   -14.06   0.000     -2.73296    -2.06408
------------------------------------------------------------------------------
```

Working correlation structure

```
. estat wcorr

Estimated within-id correlation matrix R:

      |         c1          c2          c3          c4          c5          c6
------+------------------------------------------------------------------------
   r1 |          1
   r2 |  .0451627           1
   r3 |  .0451627   .0451627           1
   r4 |  .0451627   .0451627   .0451627           1
   r5 |  .0451627   .0451627   .0451627   .0451627           1
   r6 |  .0451627   .0451627   .0451627   .0451627   .0451627           1
```

Mixed-effects models

Do vitamin A deficient children have an increased risk of infection?

$$\begin{aligned} \mu_{ij}^{\star} &= \mathrm{E}[Y_{ij} \mid \gamma_{0i}] \\ &= \mathrm{P}[Y_{ij} = 1 \mid \gamma_{0i}] \end{aligned}$$

$$\begin{aligned} \operatorname{logit} \mu_{ij}^{\star} &= \log \frac{\mu_{ij}^{\star}}{1 - \mu_{ij}^{\star}} \\ &= (\beta_0^{\star} + \gamma_{0i}) + \beta_1^{\star} \, \text{Xerophthalmia}_{ij} + \cdots \end{aligned}$$

for $i = 1, \ldots, 275$ and $j = 1, \ldots, m_i$

- $\exp \beta_1^{\star}$ represents the ratio of the expected odds of respiratory infection for a typical individual with vitamin A deficiency to that for a typical individual with a sufficient amount of vitamin A of the same age, gender, ...
- $\exp \beta_1^{\star}$ is therefore a **conditional** parameter
- Respiratory infection is rare so odds ratio approximates relative risk

R commands

- Use the `glmer` command in the `lme4` library

```
library(lme4)
?glmer

m_ri <- glmer(infection ~ (1 | id) + factor(xerop)
              + age + factor(gender) + hfora
              + cost + sint,
              family=binomial, data=ichs, nAGQ=7)

methods(class="merMod")
expit <- function(x){exp(x)/(1+exp(x))}
expit(fixef(m_ri)[1])
expit(fixef(m_ri)[1]-1.96*sqrt(VarCorr(m_ri)$id[[1]]))
expit(fixef(m_ri)[1]+1.96*sqrt(VarCorr(m_ri)$id[[1]]))
```

Random intercepts model

```
> summary(m_ri)

Random effects:
 Groups Name        Variance Std.Dev.
 id     (Intercept) 0.794    0.891
Number of obs: 1200, groups:  id, 275

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)       -2.6931     0.2218  -12.14  < 2e-16 ***
factor(xerop)1     0.6073     0.4863    1.25  0.21173
age               -0.0336     0.0074   -4.54  5.5e-06 ***
factor(gender)1   -0.4403     0.2642   -1.67  0.09564 .
hfora             -0.0555     0.0229   -2.42  0.01553 *
cost              -0.5968     0.1743   -3.42  0.00062 ***
sint              -0.1624     0.1749   -0.93  0.35321
```

Interpreting random effects components

- For continuous outcomes interpreting random effects is 'easy' because their standard deviation is on the scale of the outcome
- For binary outcomes the standard deviation is on the log-odds scale
- Recall for a GLMM with random intercepts

$$\gamma_{0i} \sim N(0,\, G_{11}) \Leftrightarrow (\beta_0^\star + \gamma_{0i}) \sim N(\beta_0^\star,\, G_{11})$$

- In the ICHS analysis the intercept corresponds to the log odds of respiratory infection among females, age 36 months, . . . , with a sufficient amount of vitamin A
- We can use $\hat{\beta}_0^\star$ and $\hat{G}_{11}$ to form an interval to quantify variability in the probability of respiratory infection across these individuals

$$\text{expit}(\hat{\beta}_0^\star \pm 1.96 \times \hat{G}_{11}) = \frac{\exp(\hat{\beta}_0^\star \pm 1.96 \times \hat{G}_{11})}{1 + \exp(\hat{\beta}_0^\star \pm 1.96 \times \hat{G}_{11})},$$

  which is calculated to be 0.06 (0.01, 0.28)
- **NB**: This is **not** a confidence interval for $\beta_0^\star$

Conditional and marginal effects

- Parameter estimates obtained from a **marginal** model (as obtained via a GEE) estimate **population-averaged** contrasts
- Parameter estimates obtained from a **conditional** model (as obtained via a GLMM) estimate **subject-specific** contrasts
- In a linear model for a Gaussian outcome with an identity link these contrasts are equivalent; not the case with non-linear models
  - Depends on the outcome distribution
  - Depends on the specified random effects

Conditional and marginal effects

		Fitted conditional model	
Outcome	Coefficient	Random intercept	Random intercept/slope
Continuous	Intercept	Marginal	Marginal
	Slope	Marginal	Marginal
Count	Intercept	Conditional	Conditional
	Slope	Marginal	Conditional
Binary	Intercept	Conditional	Conditional
	Slope	Conditional	Conditional

⋆ Marginal = population-averaged; conditional = subject-specific

Stata commands

```
* Declare the dataset to be "panel" data, grouped by id
* with time variable time
xtset id time

* Fit a model with random intercepts
help melogit
melogit infection i.xerop age i.gender hfora cost sint || id:

* Obtain predicted probabilities of infection,
* setting the random effects to 0
margins i.xerop, predict(mu fixed)
```

Random intercepts model

```
Mixed-effects logistic regression               Number of obs      =      1200
Group variable:                     id          Number of groups   =       275

                                                Obs per group: min =         1
                                                               avg =       4.4
                                                               max =         6

Integration method: mvaghermite                 Integration points =         7

                                                Wald chi2(6)       =     35.62
Log likelihood = -334.75137                     Prob > chi2        =    0.0000
------------------------------------------------------------------------------
   infection |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
             |
     1.xerop |   .6317689   .4799255     1.32   0.188    -.3088678    1.572406
         age |  -.0336883   .0072704    -4.63   0.000    -.0479379   -.0194386
    1.gender |  -.4357064   .2574121    -1.69   0.091    -.9402248     .068812
       hfora |  -.0547912   .0225386    -2.43   0.015    -.0989661   -.0106164
        cost |   -.598695   .1739193    -3.44   0.001    -.9395706   -.2578193
        sint |  -.1644847   .1746269    -0.94   0.346     -.506747    .1777777
       _cons |  -2.642403   .2120549   -12.46   0.000    -3.058023   -2.226783
------------------------------------------------------------------------------
```

Random intercepts model

```
------------+------------------------------------------------------------
id          |
   var(_cons)|   .6470842   .3492486                      .2246697    1.863704
------------------------------------------------------------------------------
LR test vs. logistic regression: chibar2(01) =     5.52 Prob>=chibar2 = 0.0094


Predictive margins                                Number of obs   =       1200
Model VCE    : OIM

Expression   : Predicted mean, fixed portion only, predict(mu fixed)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       xerop |
          0  |   .0709704   .0106353     6.67   0.000     .0501256    .0918152
          1  |   .1224475   .0496301     2.47   0.014     .0251743    .2197208
------------------------------------------------------------------------------
```

Summary

- Exploratory analysis with binary outcomes is not straightforward
  - Plots of raw data not always useful
  - Aggregated percents (means) can summarize mean response
  - Correlation can be examined using correlations or odds ratios
- GEE provides marginal, population-averaged contrasts
  - Ratio of the expected odds of respiratory infection among a population of vitamin A deficient children to that for a population of children replete with vitamin A of the same age, gender, ...
- GLMM provides conditional, subject-specific contrasts
  - Ratio of the expected odds of respiratory infection for a typical individual with vitamin A deficiency to that for a typical individual with a sufficient amount of vitamin A of the same age, gender, ...
  - Random effects variance components quantify heterogeneity in effects
- Lack of significance likely due to small number of exposed cases

Overview

Carpal tunnel syndrome trial

- Jarvik et al. (2009) compared surgical versus non-surgical treatment for carpal tunnel syndrome (CTS)
- 116 participants were randomized
- Outcomes were assessed using the CTS assessment questionnaire (CTSAQ), every 3 months for 12 months
  - Primary: functional status (low values are favorable)
  - Secondary: symptom severity
- Crossover to surgery was allowed after 3 months
- **Goal**: Determine whether surgery improves functional status

Data (wide format)

```
. list ID idgroup treatassign surgical ctsaqf0 ctsaqf1 ctsaqf2 ctsaqf3 ctsaqf4
```

	ID	idgroup	treata~n	surgical	ctsaqf0	ctsaqf1	ctsaqf2	ctsaqf3	ctsaqf4
1.	11050	2	0	3	1.888889	1.666667	1.888889	1.333333	2.888889
2.	11068	2	0	0	4	4.111111	4.222222	3.777778	4
3.	11071	2	1	1	2	1.571429	1.222222	1	1
4.	11078	2	0	0	1.375	1.5	2.125	2.5	2.333333
5.	11086	2	1	1	3.222222	2.111111	1	1.777778	1
6.	11087	2	1	1	2.555556	1.333333	1.555556	1.222222	1.222222
7.	11098	2	0	4	2	1.555556	1.444444	1.333333	1
8.	11117	2	1	1	2.875	.	2.888889	.	2
9.	12001	4	1	1	3.125	2.75	3.25	2.75	2.75
10.	12004	4	0	3	3.777778	4.333333	4.555555	3.333333	1.888889
11.	12049	4	1	1	2	1	1	1	1.666667
12.	12068	4	1	0	2.444444	3.333333	2.333333	2.333333	2.444444
13.	12093	4	0	0	2.888889	4.222222	.	3.777778	4.222222
14.	12143	4	1	1	2.888889	1.444444	1	1	1
15.	12153	4	0	1	3	3.25	.	.	2.222222
16.	12177	4	1	1	4.555555	3.777778	.	.	.
17.	13001	3	1	0	2	1.222222	1.111111	1.333333	1
18.	13002	3	1	1	2.333333	1.333333	1.444444	1	1
19.	13005	3	0	1	1.888889	1.666667	1.777778	1.444444	1.555556
20.	13006	3	1	1	3.111111	2.333333	1.777778	2	2

```
--more--
```

Variables

- `ID`: unique participant ID
- `idgroup`: study site
  (1 = private, 2 = UW, 3 = VA, 4 = HMC)
- `age`: age in years
- `gender`
  (0 = male, 1 = female)
- `treatassign`: randomized intervention
  (0 = non-surgery, 1 = surgery)
- `surgreported#`: surgery reported at visit #
  (0 = no, 1 = yes)
- `ctsaqf#`: CTSAQ functional status at visit #
- `ctsaqs#`: CTSAQ symptom severity at visit #
- `surgical`: treated surgically during study
  (0 = never, 1 = 0–3 mos, 2 = 3–6 mos, 3 = 6–9 mos, 4 = 9–12 mos)

Exploratory analyses

1. Plot individual trajectories in CTSAQF over time by treatment
2. Plot average CTSAQF over time by treatment
3. Summarize means, variances, and correlations over time by treatment

Regression analyses (intention-to-treat)

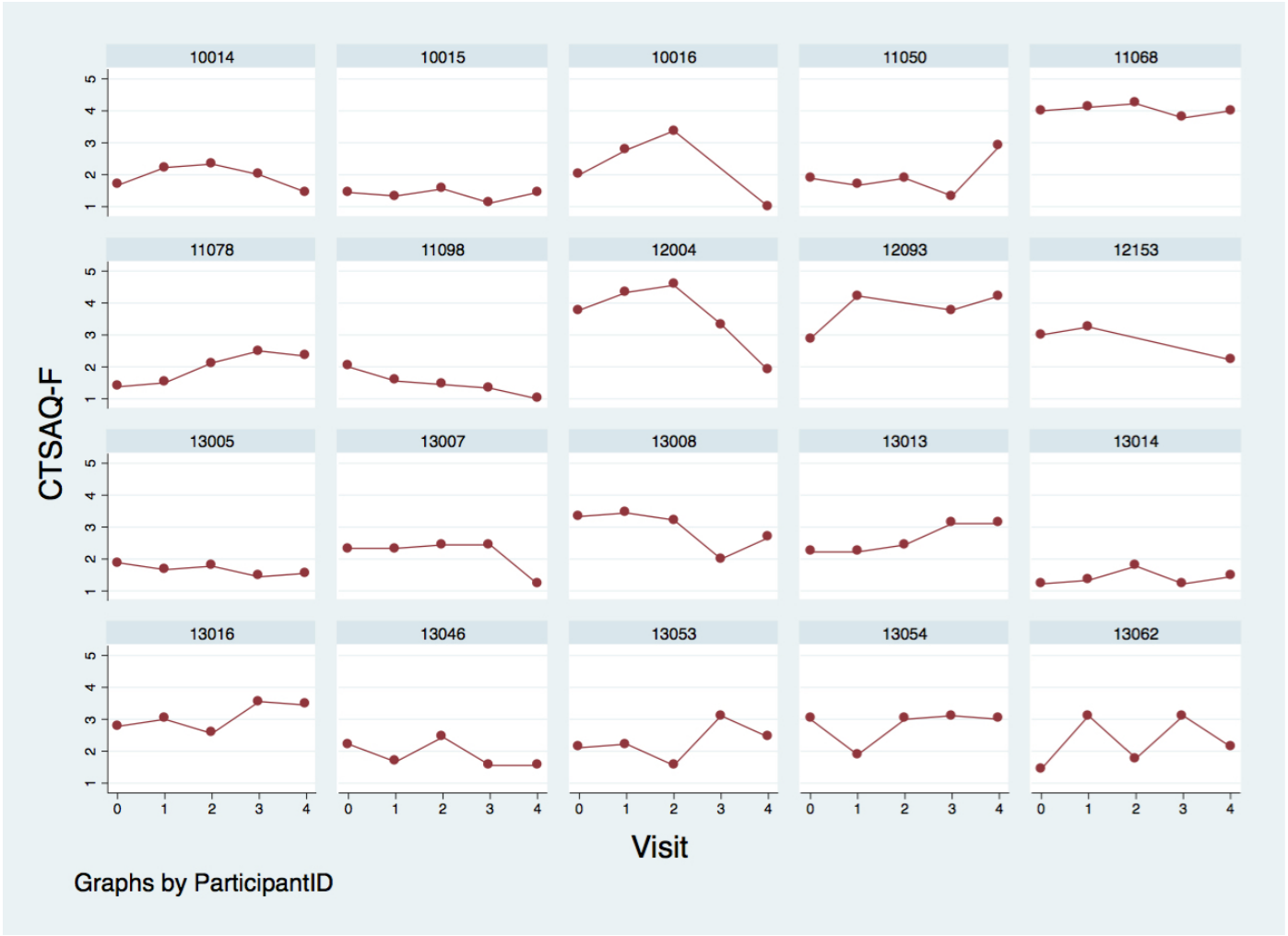
4. Evaluate POST, CHANGE, and ANCOVA models for each timepoint with CTSAQF as outcome
   - POST: follow-up measurement only
   - CHANGE: difference between follow-up and baseline measurement
   - ANCOVA: follow-up measurement controlling for baseline
5. Evaluate difference in mean CTSAQF between treatments at 12 months, adjusted for baseline CTSAQF and study site
6. Using repeated measures regression models, evaluate difference in mean CTSAQF between treatments using all timepoints, adjusted for baseline CTSAQF and study site

Bonus analyses (as treated)

7. Summarize actual treatment patterns by assigned treatment group
8. Plot average CTSAQF by visit. . .
   - For those who received surgery by 3 months versus those who did not
   - For those who received surgery by 9 months versus those who did not
9. Use linear mixed-effects models to estimate differences in mean CTSAQF when exposure is surgery by 3 months and surgery by 9 months instead of assigned treatment group

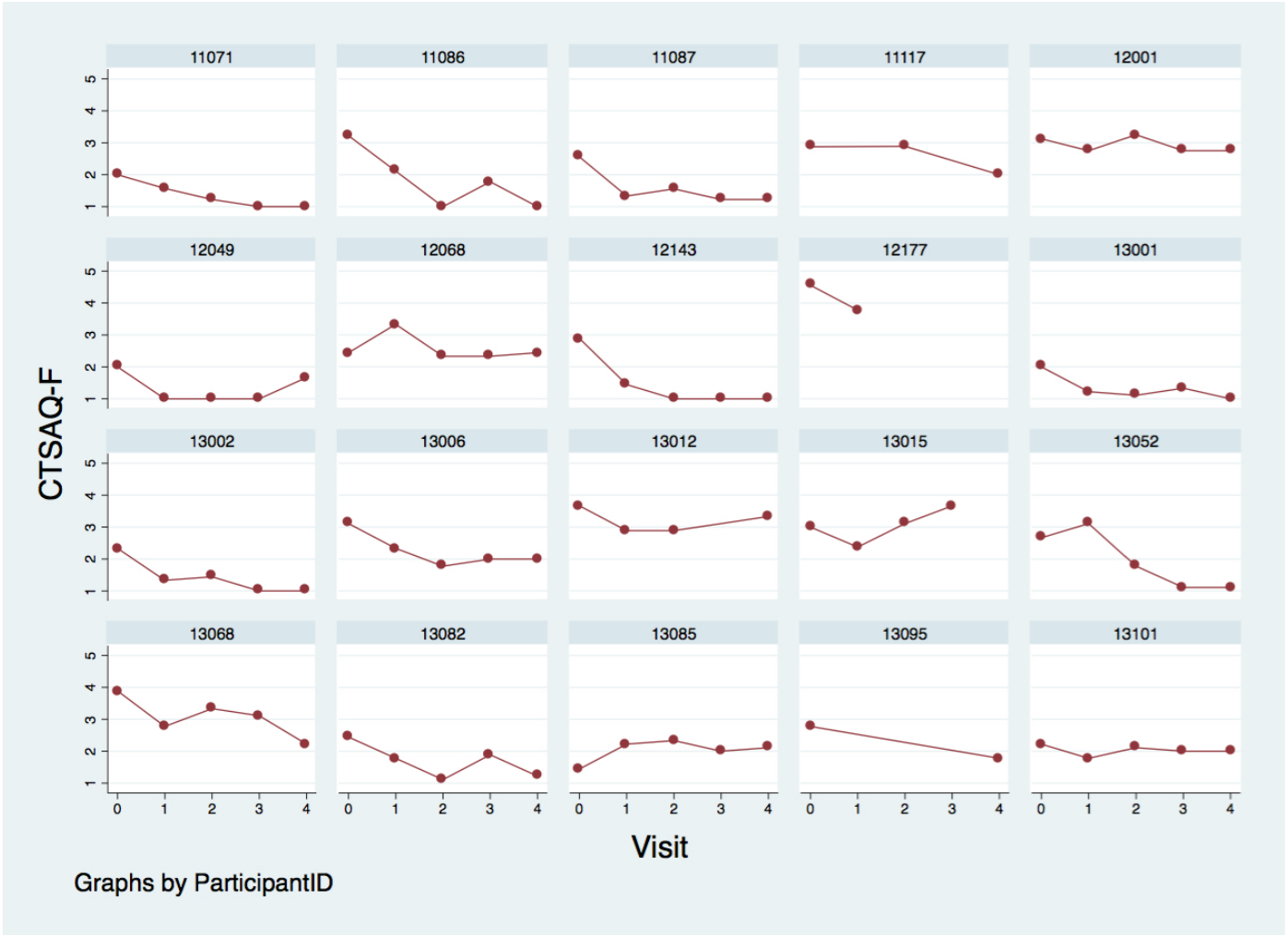
Answers

Individual trajectories, non-surgery arm



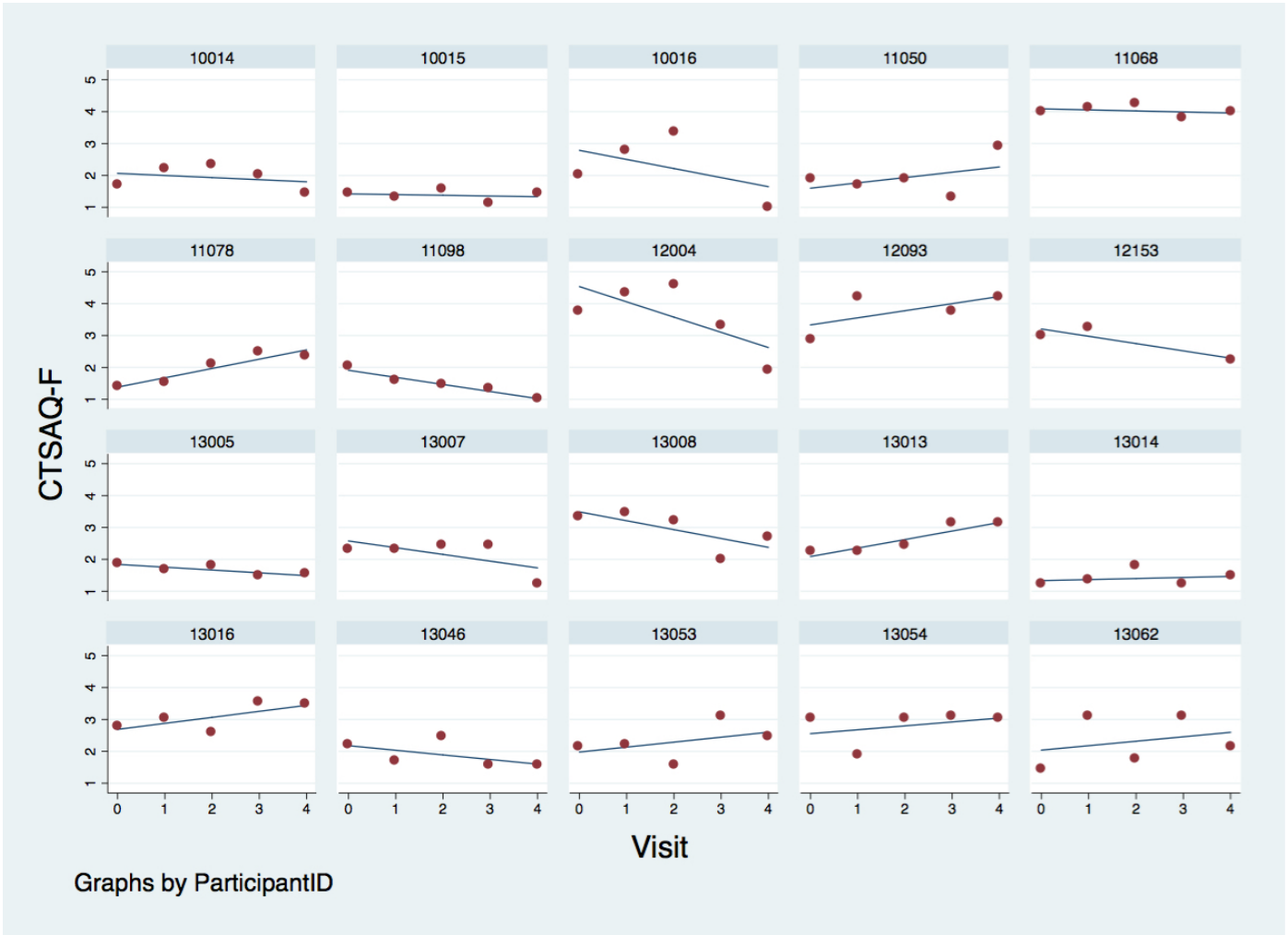

```
graph twoway connected ctsaqf visit if(ID<=13062 & ID!=13009 & treatassign==0),
    by(ID) mcolor(maroon) lcolor(maroon) xtitle("Visit") ytitle("CTSAQ-F")
```

Individual trajectories, surgery arm



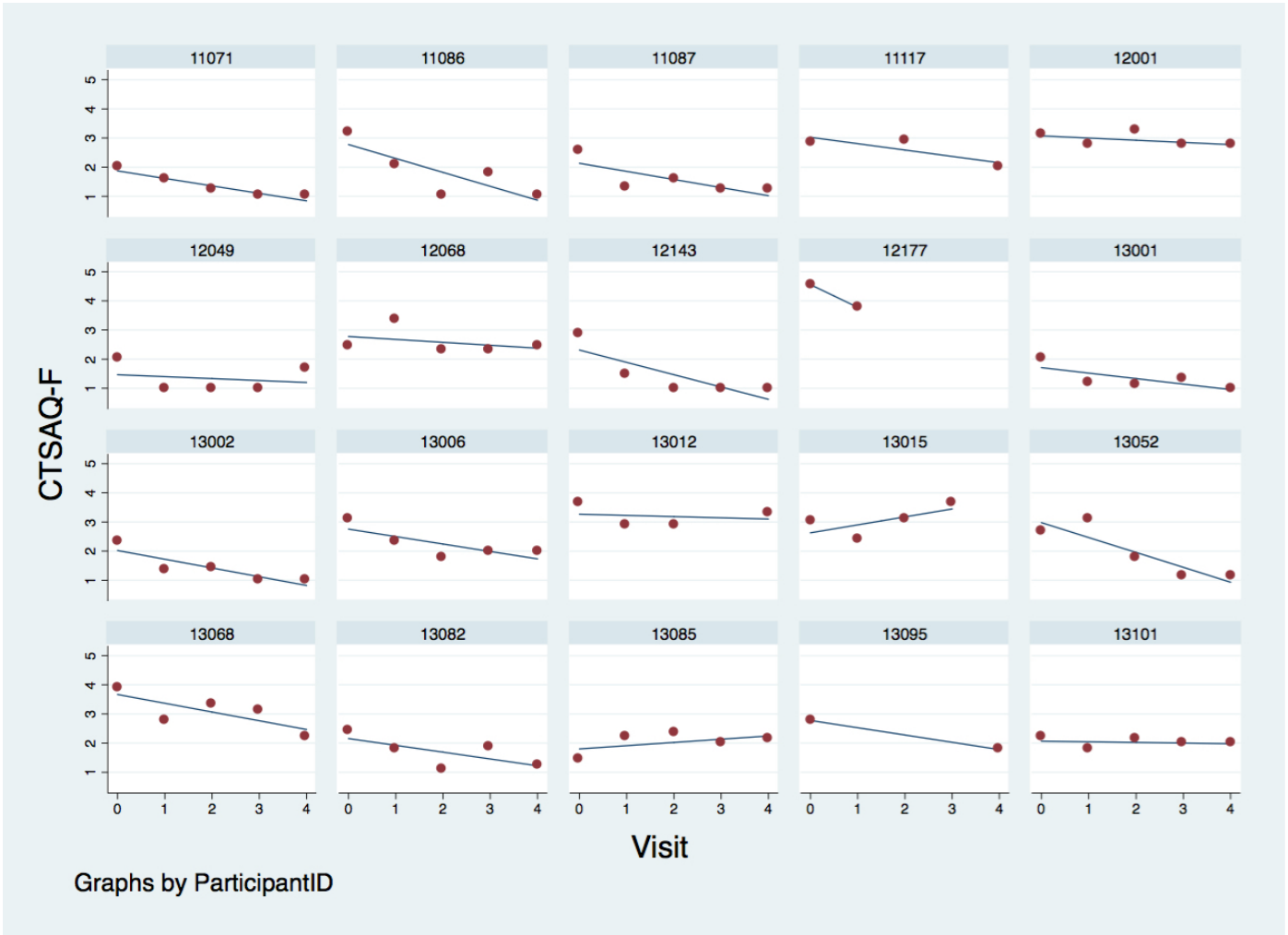

```
graph twoway connected ctsaqf visit if(ID<=13101 & ID!=13009 & treatassign==1),
    by(ID) mcolor(maroon) lcolor(maroon) xtitle("Visit") ytitle("CTSAQ-F")
```

Linear trajectories, non-surgery arm



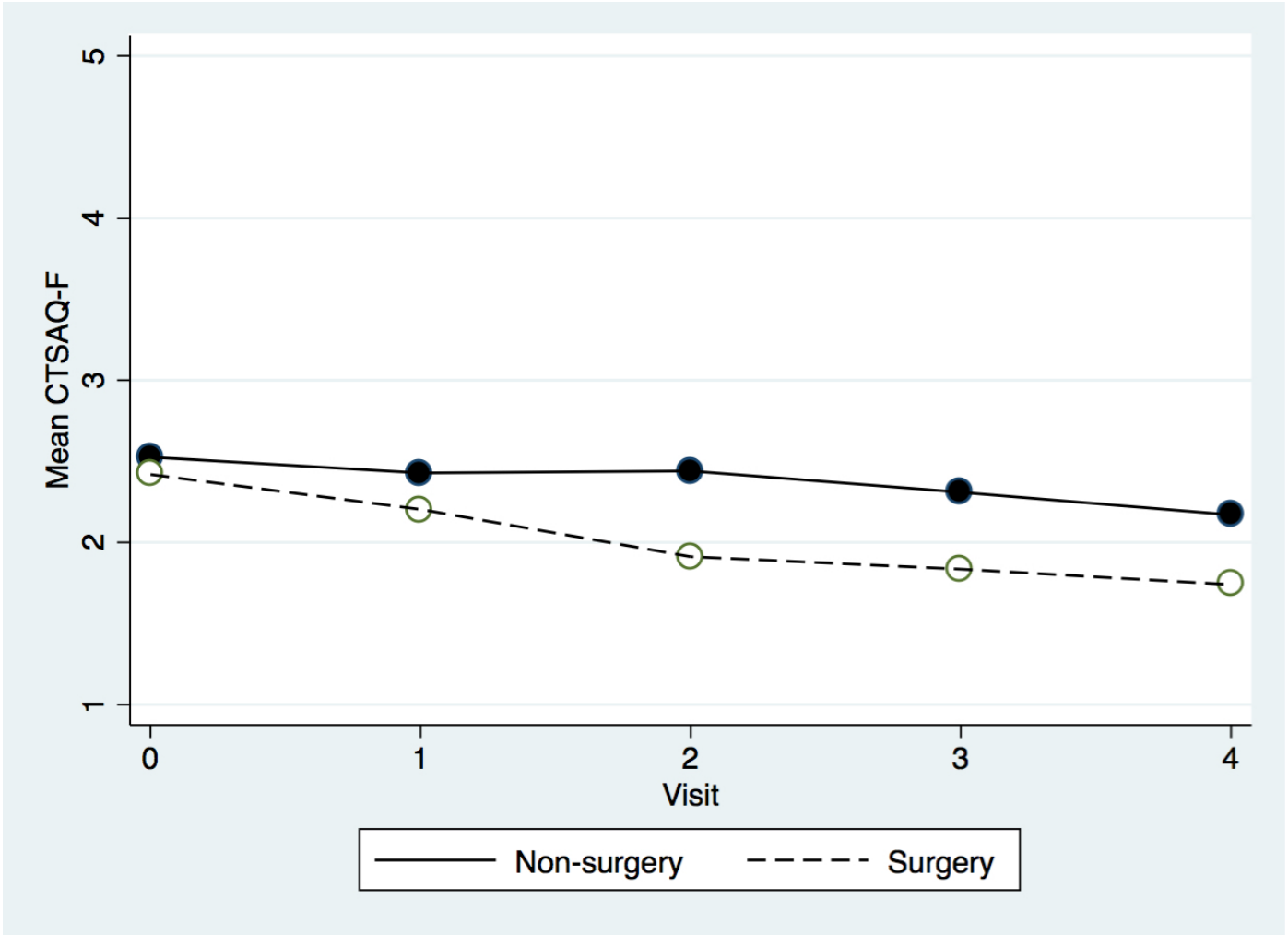

```
graph twoway (lfit ctsaqf visit) (scatter ctsaqf visit)
    if(ID<=13062 & ID!=13009 & treatassign==0), by(ID, legend(off))
    xtitle("Visit") ytitle("CTSAQ-F")
```

Linear trajectories, surgery arm




```
graph twoway (lfit ctsaqf visit) (scatter ctsaqf visit)
    if (ID<=13101 & ID!=13009 & treatassign==1), by(ID, legend(off))
    xtitle("Visit") ytitle("CTSAQ-F")
```

Mean CTSAQF




```
collapse (mean) ctsaqf, by(visit treatassign)
graph twoway (scatter ctsaqf visit if treatassign==0) (line ctsaqf visit if treatassign==0)
    (scatter ctsaqf visit if treatassign==1) (line ctsaqf visit if treatassign==1)
```

Means and variances

```
. use "cts.dta", clear
. bysort treatassign: summarize ctsaqf0 ctsaqf1 ctsaqf2 ctsaqf3 ctsaqf4

-------------------------------------------------------------------------------
-> treatassign = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
     ctsaqf0 |        59    2.526164    .8197035          1          4
     ctsaqf1 |        56    2.428075    .9304938   1.111111   4.444445
     ctsaqf2 |        54    2.440586    .8689515   1.111111   4.555555
     ctsaqf3 |        46    2.309136    .9266844          1          4
     ctsaqf4 |        52    2.169948    .9620186          1   4.222222

-------------------------------------------------------------------------------
-> treatassign = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
     ctsaqf0 |        57    2.418616      .81565          1   4.555555
     ctsaqf1 |        51     2.20347    .8369104          1          4
     ctsaqf2 |        50    1.911667    .8834815          1   4.111111
     ctsaqf3 |        48    1.835069    .7985738          1   3.777778
     ctsaqf4 |        49    1.740079     .789603          1   4.111111
```

- Both treatment groups improve, but surgery group improves more
- Variance is larger in non-surgery group after baseline
- Missing data exist in both treatment groups

Correlation

```
. bysort treatassign: cor ctsaqf0 ctsaqf1 ctsaqf2 ctsaqf3 ctsaqf4

-------------------------------------------------------------------------------------------------------------------
-> treatassign = 0
(obs=41)
             |  ctsaqf0  ctsaqf1  ctsaqf2  ctsaqf3  ctsaqf4
-------------+---------------------------------------------
     ctsaqf0 |   1.0000
     ctsaqf1 |   0.7378   1.0000
     ctsaqf2 |   0.7772   0.8564   1.0000
     ctsaqf3 |   0.7209   0.6886   0.6161   1.0000
     ctsaqf4 |   0.5524   0.2956   0.3895   0.6302   1.0000

-------------------------------------------------------------------------------------------------------------------
-> treatassign = 1
(obs=44)
             |  ctsaqf0  ctsaqf1  ctsaqf2  ctsaqf3  ctsaqf4
-------------+---------------------------------------------
     ctsaqf0 |   1.0000
     ctsaqf1 |   0.4972   1.0000
     ctsaqf2 |   0.4816   0.5598   1.0000
     ctsaqf3 |   0.6316   0.5810   0.7144   1.0000
     ctsaqf4 |   0.4689   0.4148   0.6653   0.7948   1.0000
```

- Strong positive correlations across most measurement pairs
- **Note**: Only a subset of participants has measurements at all times

Generate change variables

```
. use "cts.dta", clear

. gen change1 = ctsaqf1 - ctsaqf0
(9 missing values generated)

. gen change2 = ctsaqf2 - ctsaqf0
(12 missing values generated)

. gen change3 = ctsaqf3 - ctsaqf0
(22 missing values generated)

. gen change4 = ctsaqf4 - ctsaqf0
(15 missing values generated)
```

POST results

```
. ttest ctsaqf1, by(treatassign) unequal
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    diff |            .2246051    .1708647               -.1141886    .5633989
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9042         Pr(|T| > |t|) = 0.1915          Pr(T > t) = 0.0958

. ttest ctsaqf2, by(treatassign) unequal
------------------------------------------------------------------------------
    diff |            .5289197    .1720282                .1876663    .8701732
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9986         Pr(|T| > |t|) = 0.0027          Pr(T > t) = 0.0014

. ttest ctsaqf3, by(treatassign) unequal
------------------------------------------------------------------------------
    diff |            .4740662    .1787573                .1188674    .8292649
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9953         Pr(|T| > |t|) = 0.0095          Pr(T > t) = 0.0047

. ttest ctsaqf4, by(treatassign) unequal
------------------------------------------------------------------------------
    diff |            .4298687    .1747044                .083138    .7765995
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9922         Pr(|T| > |t|) = 0.0156          Pr(T > t) = 0.0078
```

CHANGE results

```
. ttest change1, by(treatassign) unequal
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    diff |            .1737167    .1352344               -.0944641    .4418975
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.8991         Pr(|T| > |t|) = 0.2018          Pr(T > t) = 0.1009

. ttest change2, by(treatassign) unequal
---------+--------------------------------------------------------------------
    diff |            .4199838    .1323821                .1571383    .6828293
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9990         Pr(|T| > |t|) = 0.0020          Pr(T > t) = 0.0010

. ttest change3, by(treatassign) unequal
---------+--------------------------------------------------------------------
    diff |            .4085163    .1300207                .1502486    .6667839
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9989         Pr(|T| > |t|) = 0.0023          Pr(T > t) = 0.0011

. ttest change4, by(treatassign) unequal
---------+--------------------------------------------------------------------
    diff |            .3499259    .1583154                .0357083    .6641434
------------------------------------------------------------------------------
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9853         Pr(|T| > |t|) = 0.0294          Pr(T > t) = 0.0147
```

ANCOVA results

```
. reg ctsaqf1 treatassign ctsaqf0
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 treatassign |  -.1880334   .1280921    -1.47   0.145    -.4420449    .0659782
     ctsaqf0 |   .7186659   .0780039     9.21   0.000     .5639812    .8733505
       _cons |   .6208691   .2151494     2.89   0.005     .1942197    1.047519
------------------------------------------------------------------------------

. reg ctsaqf2 treatassign ctsaqf0
------------------------------------------------------------------------------
 treatassign |  -.4477759   .1257977    -3.56   0.001    -.6973248    -.198227
     ctsaqf0 |    .744877   .0783514     9.51   0.000     .5894489    .9003051
       _cons |   .5655304   .2155771     2.62   0.010     .1378835    .9931773
------------------------------------------------------------------------------

. reg ctsaqf3 treatassign ctsaqf0
------------------------------------------------------------------------------
 treatassign |  -.4234999   .1250043    -3.39   0.001    -.6718056   -.1751942
     ctsaqf0 |   .7714167    .078626     9.81   0.000     .6152359    .9275975
       _cons |   .4320349   .2111155     2.05   0.044     .0126799    .8513899
------------------------------------------------------------------------------

. reg ctsaqf4 treatassign ctsaqf0
------------------------------------------------------------------------------
 treatassign |  -.3807795   .1485411    -2.56   0.012    -.6755546   -.0860045
     ctsaqf0 |   .6140536    .095983     6.40   0.000     .4235784    .8045289
       _cons |   .6657885    .256818     2.59   0.011     .1561415    1.175435
------------------------------------------------------------------------------
```

Results for each timepoint

Method	3 months Mean (SE)	6 months Mean (SE)	9 months Mean (SE)	12 months Mean (SE)
POST	0.22 (0.17)	0.53 (0.17)	0.47 (0.18)	0.43 (0.17)
CHANGE	0.17 (0.14)	0.42 (0.13)	0.41 (0.13)	0.35 (0.16)
ANCOVA	0.19 (0.13)	0.45 (0.13)	0.42 (0.13)	0.38 (0.15)

- Standard errors are lower when baseline information is incorporated into the model (CHANGE and ANCOVA)
- Estimated difference (control group minus surgical group) also varies across methods due to difference in baseline values

CTSQAF at 12 months

```
. reg ctsaqf4 i.treatassign ctsaqf0 i.idgroup

      Source |       SS           df       MS      Number of obs   =       101
-------------+----------------------------------   F(5, 95)        =     10.42
       Model |  28.9616934         5  5.79233869   Prob > F        =    0.0000
    Residual |    52.82623        95  .556065579   R-squared       =    0.3541
-------------+----------------------------------   Adj R-squared   =    0.3201
       Total |  81.7879234       100  .817879234   Root MSE        =     .7457

------------------------------------------------------------------------------
      ctsaqf4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
1.treatassign |  -.4044936   .1494477    -2.71   0.008    -.7011847   -.1078025
      ctsaqf0 |   .5731743   .0999908     5.73   0.000     .3746674    .7716811
              |
      idgroup |
           2  |   .3308508   .2287227     1.45   0.151    -.1232212    .7849228
           3  |   .2787628   .1904006     1.46   0.146    -.0992302    .6567559
           4  |    .348587   .3311843     1.05   0.295     -.308897    1.006071
              |
        _cons |   .5481683   .2692172     2.04   0.045     .0137046    1.082632
------------------------------------------------------------------------------
```

- Significant difference in adjusted mean CTSQAF at 12 months, indicating superiority of surgery
- Symptoms in both groups improved, but surgical treatment led to better outcome than did non-surgical treatment
- Clinical relevance of this difference was modest

GEE-independence

```
. xtset ID visit
. xtgee ctsaqf i.treatassign ctsaqfbase visit i.idgroup if visit!=0, corr(ind) robust

GEE population-averaged model                   Number of obs     =        406
Group variable:                         ID      Number of groups  =        113
Link:                             identity      Obs per group:
Family:                           Gaussian                    min =          1
Correlation:                   independent                    avg =        3.6
                                                              max =          4
                                                Wald chi2(6)      =     279.51
Scale parameter:                  .4272453      Prob > chi2       =     0.0000

Pearson chi2(406):                  173.46      Deviance          =     173.46
Dispersion (Pearson):             .4272453      Dispersion        =   .4272453

                                    (Std. Err. adjusted for clustering on ID)
------------------------------------------------------------------------------
             |               Robust
      ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
1.treatassign |  -.3751375   .0918769    -4.08   0.000    -.5552128   -.1950621
   ctsaqfbase |   .6863645    .051109    13.43   0.000     .5861927    .7865362
        visit |  -.0986751   .0294508    -3.35   0.001    -.1563977   -.0409526
              |
      idgroup |
           2  |   .1686268   .1410721     1.20   0.232    -.1078695    .4451231
           3  |   .1920815   .0985599     1.95   0.051    -.0010923    .3852554
           4  |   .2965143    .301465     0.98   0.325    -.2943464    .8873749
              |
        _cons |   .7439989   .1631982     4.56   0.000     .4241363    1.063861
------------------------------------------------------------------------------
```

GEE-exchangeable

```
. xtgee ctsaqf i.treatassign ctsaqfbase visit i.idgroup if visit!=0, corr(exc) robust

GEE population-averaged model                   Number of obs     =        406
Group variable:                           ID    Number of groups  =        113
Link:                               identity    Obs per group:
Family:                             Gaussian                  min =          1
Correlation:                   exchangeable                   avg =        3.6
                                                              max =          4
                                                Wald chi2(6)      =     288.18
Scale parameter:                    .4278235    Prob > chi2       =     0.0000

                                    (Std. Err. adjusted for clustering on ID)
------------------------------------------------------------------------------
             |               Robust
      ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
1.treatassign |  -.3822556   .0940684    -4.06   0.000    -.5666262    -.197885
   ctsaqfbase |   .6973972    .051547    13.53   0.000     .5963669    .7984275
        visit |   -.099509   .0294018    -3.38   0.001    -.1571355   -.0418825
              |
      idgroup |
           2  |   .2219611   .1469105     1.51   0.131    -.0659783    .5099004
           3  |   .1999074   .0996394     2.01   0.045     .0046177    .3951971
           4  |   .3226388   .2931943     1.10   0.271    -.2520116    .8972891
              |
        _cons |   .7186626   .1665791     4.31   0.000     .3921736    1.045152
------------------------------------------------------------------------------
```

Estimated correlation for exchangeable structure: 0.33

Random intercepts model

```
. xtmixed ctsaqf i.treatassign ctsaqfbase visit i.idgroup if visit!=0 || ID:

Mixed-effects ML regression                     Number of obs     =        406
Group variable: ID                              Number of groups  =        113

------------------------------------------------------------------------------
       ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
1.treatassign |  -.3827374   .0935113    -4.09   0.000    -.5660162   -.1994586
   ctsaqfbase |     .69779   .0597652    11.68   0.000     .5806523    .8149277
        visit |  -.0996199   .0231201    -4.31   0.000    -.1449344   -.0543054
              |
      idgroup |
           2  |   .2249026   .1438888     1.56   0.118    -.0571142    .5069194
           3  |   .2000988    .114091     1.75   0.079    -.0235154    .4237131
           4  |   .3236464   .2071348     1.56   0.118    -.0823304    .7296231
              |
        _cons |   .7179688   .1768892     4.06   0.000     .3712722    1.064665
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
ID: Identity                 |
                   sd(_cons) |   .4043584   .0413511      .3309174    .4940982
-----------------------------+------------------------------------------------
                sd(Residual) |   .5181374    .021511      .4776464    .5620609
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 59.46         Prob >= chibar2 = 0.0000
```

Random intercepts and slopes model

```
. xtmixed ctsaqf i.treatassign ctsaqfbase visit i.idgroup if visit!=0 || ID: visit

Mixed-effects ML regression                     Number of obs     =        406
Group variable: ID                              Number of groups  =        113

------------------------------------------------------------------------------
       ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
1.treatassign |  -.3634586   .0952163    -3.82   0.000    -.5500792    -.176838
   ctsaqfbase |    .708189   .0605365    11.70   0.000     .5895396    .8268385
        visit |   -.097303   .0241826    -4.02   0.000       -.1447    -.049906
              |
      idgroup |
            2 |   .2035679   .1470293     1.38   0.166    -.0846042      .49174
            3 |   .1738886   .1157013     1.50   0.133    -.0528818     .400659
            4 |   .3416728   .2102585     1.63   0.104    -.0704262    .7537718
              |
        _cons |   .6938094   .1765334     3.93   0.000     .3478102    1.039809
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
ID: Independent              |
                  sd(visit) |    .103634   .0218799      .0685158    .1567522
                  sd(_cons) |   .3541862   .0506153       .267664    .4686767
-----------------------------+------------------------------------------------
               sd(Residual) |   .4912322   .0229461      .4482561    .5383287
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 66.87                 Prob > chi2 = 0.0000
```

Treatment

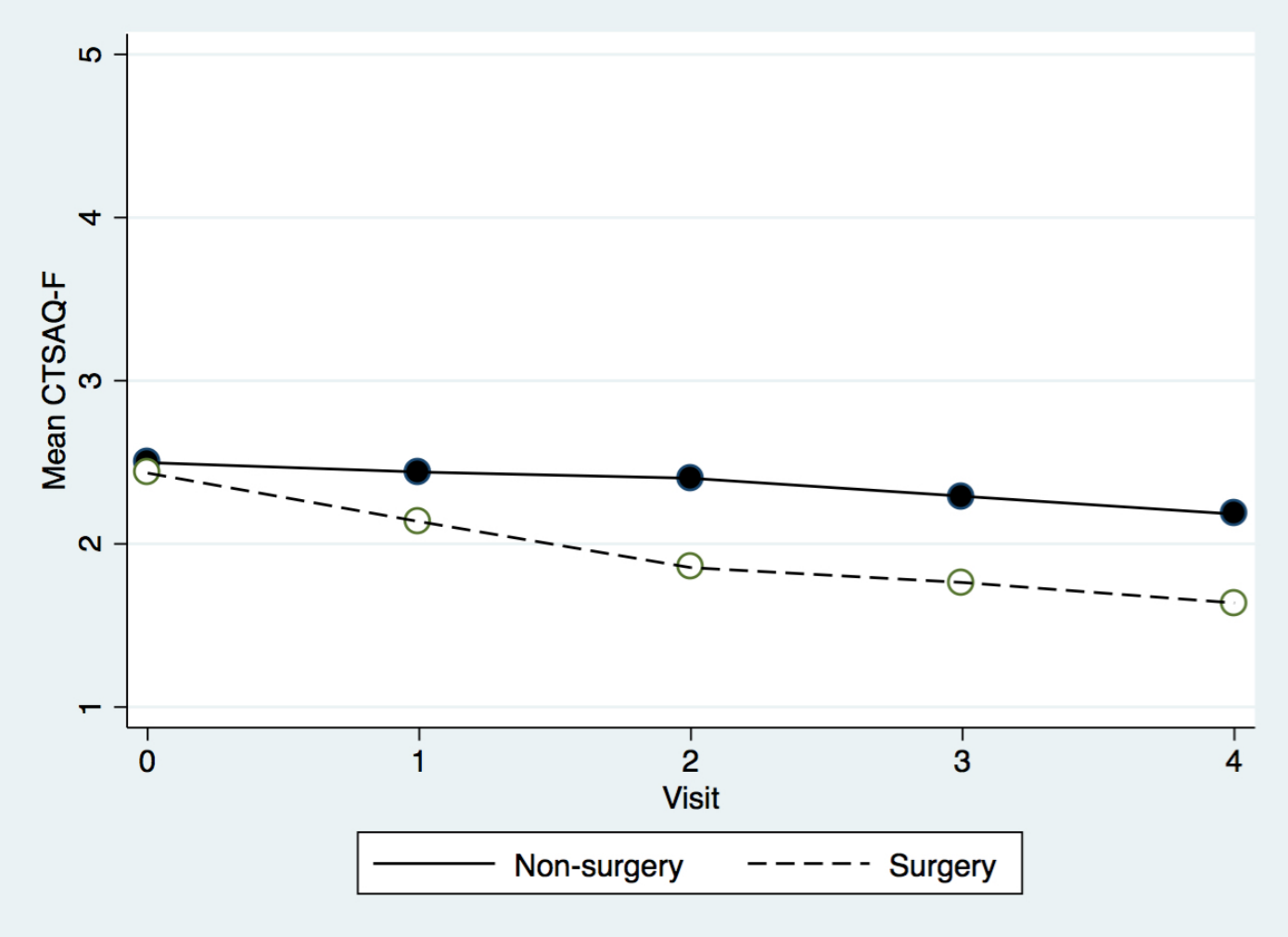
```
. tab treatassign

treatassign |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |         59       50.86       50.86
          1 |         57       49.14      100.00
------------+-----------------------------------
      Total |        116      100.00

. tab treatassign surgical

treatassig |                    surgical
         n |         0          1          2          3          4 |     Total
-----------+-------------------------------------------------------+----------
         0 |        36          3          5         10          5 |        59
         1 |        13         42          0          2          0 |        57
-----------+-------------------------------------------------------+----------
     Total |        49         45          5         12          5 |       116
```

- Of 57 assigned to surgery, 42 had it by 3 months and 13 never had it
- Of 59 assigned to no surgery, 23 actually had surgery during the study

Treatment

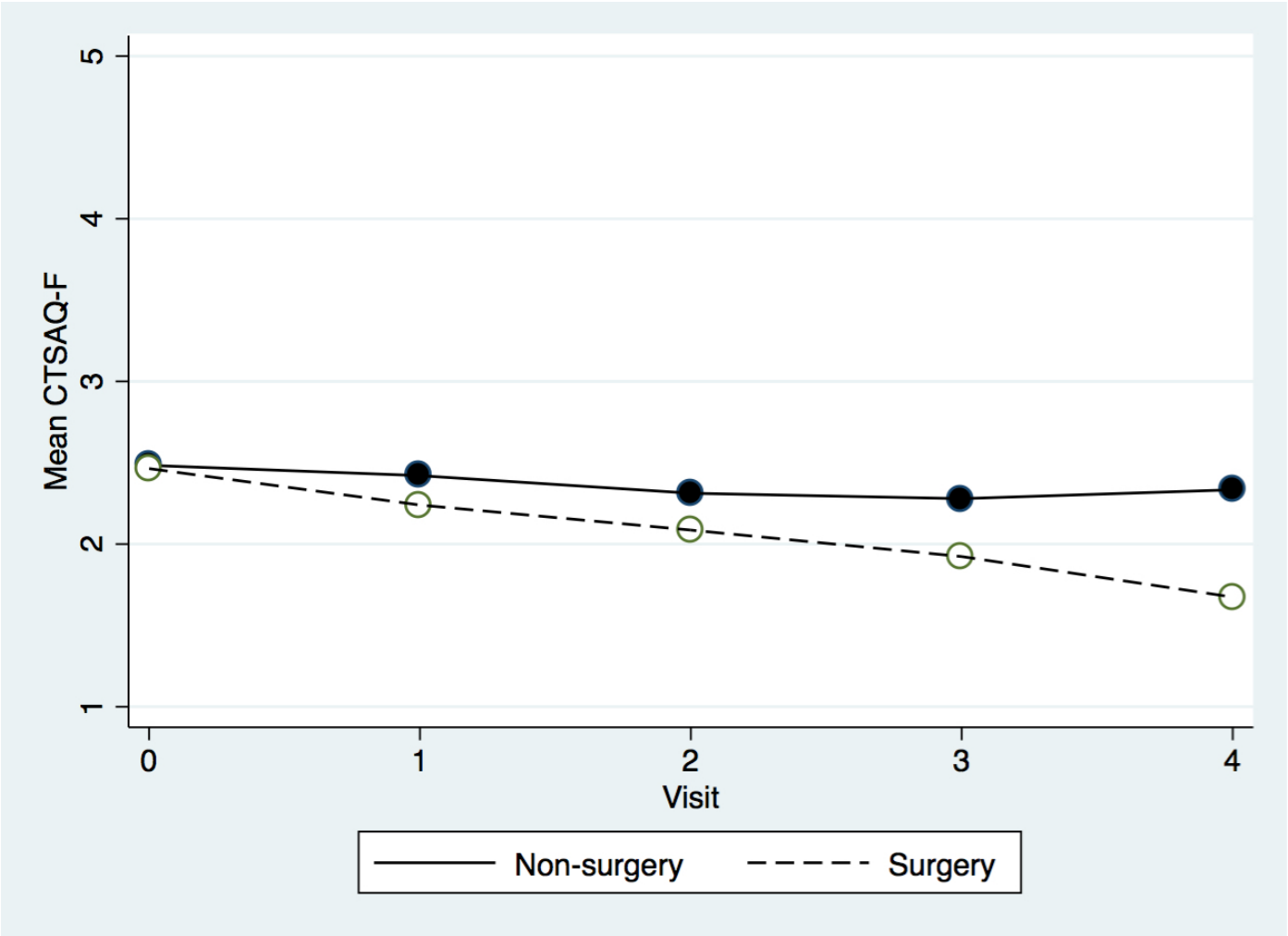
```
. gen surgby3 = (surgical==1)
. gen surgby9 = (surgical==1 | surgical==2 | surgical==3)
. collapse (mean) surgby3 surgby9 treatassign, by(ID)
. tab treatassign surgby3, row

    (mean) |
treatassig |    (mean) surgby3
         n |         0          1 |     Total
-----------+----------------------+----------
         0 |        56          3 |        59
           |     94.92       5.08 |    100.00
-----------+----------------------+----------
         1 |        15         42 |        57
           |     26.32      73.68 |    100.00
-----------+----------------------+----------
     Total |        71         45 |       116
           |     61.21      38.79 |    100.00

. tab treatassign surgby9, row

    (mean) |
treatassig |    (mean) surgby9
         n |         0          1 |     Total
-----------+----------------------+----------
         0 |        41         18 |        59
           |     69.49      30.51 |    100.00
-----------+----------------------+----------
         1 |        13         44 |        57
           |     22.81      77.19 |    100.00
-----------+----------------------+----------
     Total |        54         62 |       116
           |     46.55      53.45 |    100.00
```

Mean CTSQAF, 3-month exposure




```
collapse (mean) ctsaqf, by(visit surgby3)
graph twoway (scatter ctsaqf visit if surgby3==0) (line ctsaqf visit if surgby3==0)
    (scatter ctsaqf visit if surgby3==1) (line ctsaqf visit if surgby3==1)
```

Mean CTSQAF, 9-month exposure




```
collapse (mean) ctsaqf, by(visit surgby9)
graph twoway (scatter ctsaqf visit if treatassign==0) (line ctsaqf visit if treatassign==0)
    (scatter ctsaqf visit if treatassign==1) (line ctsaqf visit if treatassign==1)
```

Random intercepts model, 3-month exposure

```
. xtmixed ctsaqf i.surgby3 ctsaqfbase visit i.idgroup if visit!=0 || ID:

Mixed-effects ML regression                     Number of obs     =        406
Group variable: ID                              Number of groups  =        113

------------------------------------------------------------------------------
      ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   1.surgby3 |  -.4247889   .0942773    -4.51   0.000    -.6095689   -.2400088
  ctsaqfbase |   .6942694   .0589891    11.77   0.000     .5786528     .809886
       visit |  -.0987913    .023115    -4.27   0.000    -.1440959   -.0534867
             |
     idgroup |
           2 |   .1692243    .141553     1.20   0.232    -.1082145    .4466631
           3 |   .1562546   .1123475     1.39   0.164    -.0639425    .3764518
           4 |   .3212111   .2041408     1.57   0.116    -.0788975    .7213196
             |
       _cons |   .7414371   .1751162     4.23   0.000     .3982156    1.084659
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
ID: Identity                 |
                   sd(_cons) |    .396328   .0410477      .3235161    .4855274
-----------------------------+------------------------------------------------
                sd(Residual) |   .5181171   .0215015      .4776432    .5620205
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 56.89         Prob >= chibar2 = 0.0000
```

Random intercepts model, 9-month exposure

```
. xtmixed ctsaqf i.surgby9 ctsaqfbase visit i.idgroup if visit!=0 || ID:

Mixed-effects ML regression                     Number of obs     =        406
Group variable: ID                              Number of groups  =        113

------------------------------------------------------------------------------
      ctsaqf |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   1.surgby9 |  -.3506798   .0956318    -3.67   0.000    -.5381146    -.163245
  ctsaqfbase |   .7059564    .060592    11.65   0.000     .5871983    .8247144
       visit |  -.0991131   .0231051    -4.29   0.000    -.1443983    -.053828
             |
     idgroup |
           2 |   .1844937   .1456744     1.27   0.205    -.1010229    .4700103
           3 |    .142673   .1159134     1.23   0.218    -.0845131     .369859
           4 |   .2888596   .2096172     1.38   0.168    -.1219826    .6997018
             |
       _cons |   .7451643    .183143     4.07   0.000     .3862106    1.104118
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
ID: Identity                 |
                   sd(_cons) |    .413744    .041421      .3400289    .5034399
-----------------------------+------------------------------------------------
                sd(Residual) |   .5176204   .0214542      .4772335    .5614251
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 64.22         Prob >= chibar2 = 0.0000
```

Summary

- Small but statistically significant difference between groups, showing an improvement due to surgical treatment
- Analyses focused on average "cross-sectional" differences; could also explore differences in trends between groups
- Consistent results across analyses, even though different methods require different assumptions, particularly regarding missing data
- Reasonable people disagree about how to include baseline measurements in repeated measures regression models. . .
  - As a covariate (as was done here)
  - As an outcome
- Intention-to-treat estimate possibly understated due to crossovers; as-treated analyses are subject to possible selection biases

Overview

Big picture: GEE

- Marginal mean regression model
- Model for longitudinal correlation
- Semi-parametric model: mean + correlation
- Form an unbiased estimating function
- Estimates obtained as solution to estimating equation
- Model-based or empirical variance estimator
- Robust to correlation model mis-specification
- Large sample: $n \geq 40$
- Testing with Wald tests
- Marginal or population-averaged inference
- Efficiency of non-independence correlation structures
- Missing completely at random (MCAR)
- Time-dependent covariates and endogeneity
- Only one source of positive or negative correlation
- R package `geepack`; Stata command `xtgee`

Big picture: GLMM

- Conditional mean regression model
- Model for population heterogeneity
- Subject-specific random effects induce a correlation structure
- Fully parametric model based on exponential family density
- Estimates obtained from likelihood function
- Conditional (fixed effects) and maximum (random effects) likelihood
- Approximation or numerical integration to integrate out γ
- Requires correct parametric model specification
- Testing with likelihood ratio and Wald tests
- Conditional or subject-specific inference
- Induced marginal mean structure and 'attenuation'
- Missing at random (MAR)
- Time-dependent covariates and endogeneity
- Multiple sources of positive correlation
- R package `lme4`; Stata commands `mixed`, `melogit`

Final summary

Generalized estimating equations

- Provide valid estimates and standard errors for regression parameters of interest even if the correlation model is incorrectly specified $(+)$
- Empirical variance estimator requires sufficiently large sample size $(-)$
- Always provide population-averaged inference regardless of the outcome distribution; ignores subject-level heterogeneity $(+/-)$
- Accommodate only one source of correlation $(-/+)$
- Require that any missing data are missing completely at random $(-)$

Final summary

Generalized linear mixed-effects models

- Provide valid estimates and standard errors for regression parameters only under stringent model assumptions that must be verified $(-)$
- Provide population-averaged or subject-specific inference depending on the outcome distribution and specified random effects $(+/-)$
- Accommodate multiple sources of correlation $(+/-)$
- Require that any missing data are missing at random $(-/+)$

Advice

- Analysis of longitudinal data is often complex and difficult
- You now have versatile methods of analysis at your disposal
- Each of the methods you have learned has strengths and weaknesses
- Do not be afraid to apply different methods as appropriate
- Statistical modeling should be informed by exploratory analyses
- Always be mindful of the scientific question(s) of interest

Resources

Introductory

- Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. Wiley, 2004.
- Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/ Hierarchical Models*. Cambridge University Press, 2007.
- Hedeker D, Gibbons RD. *Longitudinal Data Analysis*. Wiley, 2006.

Advanced

- Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*, 2nd Edition. Oxford University Press, 2002.
- Molenbergs G, Verbeke G. *Models for Discrete Longitudinal Data*. Springer Series in Statistics, 2006.
- Verbeke G, Molenbergs G. *Linear Mixed Models for Longitudinal Data*. Springer Series in Statistics, 2000.

Thank you!