Interpreting Coefficients in Marginal vs. Mixed Models

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Interpreting βs in Correlated Data Models

Model Type	Outcome is…	Interpret βs as…
Marginal	Continuous (MLM)	Population-average change
Marginal	Categorical/Count (GEE)	Population-average change
Mixed	Continuous (LMM)	Population-average change OR **subject-specific change** (identical)
Mixed	Categorical/Count (GLMM)	**Subject-specific change**

Population-Average vs. Subject-Specific Interpretations

- In marginal (any outcome) or linear mixed models (continuous outcomes), these are the same thing

- In GLMMs for categorical or count outcomes, they are not

- Why?
  - Let's consider a simple example

Population-Average vs. Subject-Specific Interpretations

- A study of 3 people (A, B, and C) that we treat with, say, aspirin to prevent, say, heart attacks
  - Have different baseline risks that we account for with a random intercept

Individual	Baseline Risk	Post-Treatment Risk	RD (Linear Model)
A	0.80	0.67	-0.13
B	0.50	0.33	-0.17
C	0.20	0.11	-0.09
Population Average	0.50	0.37	-0.13

Unknown in reality, assuming we know for our example

Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

Population-Average vs. Subject-Specific Interpretations

Individual	Baseline Risk of D	Post-Treatment Risk of D	RD (Linear Model)
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B	0.50	0.33	-0.17
C	0.20	0.11	-0.09
Population Average	0.50	0.37	-0.13

- Say we model risk using a linear mixed model (questionable, but bear with me):
  - $Risk_{ij} = \beta_0 + b_{0i} + \beta_1 \, Post_{ij}$ where Post = 1 if post-treatment, 0 if baseline
  - Average of individual risk differences: $\frac{-0.13+(-0.17)+(-0.09)}{3} = \mathbf{-0.13}$
  - Difference in population-average risks: $0.37 - 0.50 = \mathbf{-0.13}$
  - $\beta_1 = 0.13$ and can be interpreted in two ways:
    - After treating everyone with aspirin, the average risk of a heart attack in the population dropped by 0.13.
    - After treatment with aspirin, the typical subject exhibited a drop in the risk of heart attack of 0.13.

Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

Population-Average vs. Subject-Specific Interpretations

Individual	Baseline Ln-Odds of D	Post-Treatment Ln-Odds of D	Difference in Ln-Odds
A	1.39	0.71	-0.68
B	0.00	-0.71	-0.71
C	-1.39	-2.09	-0.70
Population Average	$\ln\left(\frac{0.50}{0.50}\right) = 0.00$	$\ln\left(\frac{0.37}{0.63}\right) = -0.53$	**???**

- Say we model risk using logistic regression:
  - $logit(Risk_{ij}) = \beta_0 + b_{0i} + \beta_1\, Post_{ij}$ where Post = 1 if post-treatment, 0 if baseline
  - **Marginal Model:** Difference in population-average log-odds: $-0.53 - 0.00 = \mathbf{-0.53}$
  - **Mixed Model:** Average of individual log-odds differences: $\frac{-0.68+(-0.71)+(-0.70)}{3} = \mathbf{-0.69}$
  - Which one is "right"???

Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

Population-Average vs. Subject-Specific Interpretations

Individual	Baseline Ln-Odds of D	Post-Baseline Ln-Odds of D	Difference in Ln-Odds
A	1.39	0.71	-0.68
B	0.00	-0.71	-0.71
C	-1.39	-2.09	-0.70
Population Average	$\ln\left(\frac{0.50}{0.50}\right) = 0.00$	$\ln\left(\frac{0.37}{0.63}\right) = -0.53$	$\mathbf{-0.53}$ **or** $\mathbf{-0.69}$

- Which one is "right?"
  - Would you believe…both? It depends on your question!
- **Marginal model** → $\beta_1 = -0.53$ → OR = 0.59
  - Interpretation: After treating everyone with aspirin, the odds of a heart attack were 41% lower, on average, across our *study population*.
- **Mixed model** → $\beta_1 = -0.69$ → OR = 0.50
  - Interpretation: After treatment with aspirin, the *typical subject* exhibited a 50% reduction in their odds of a heart attack.

Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

Population-Average vs. Subject-Specific Interpretations

- Marginal Interpretation: After treating everyone with aspirin, the odds of a heart attack were 41% lower, on average, across our *study population*.
- Mixed Interpretation: After treatment with aspirin, the *typical subject* exhibited a 50% reduction in their odds of a heart attack.

- How can both of these be true?
  - Dig way way way way WAY back to median vs. mean…

Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

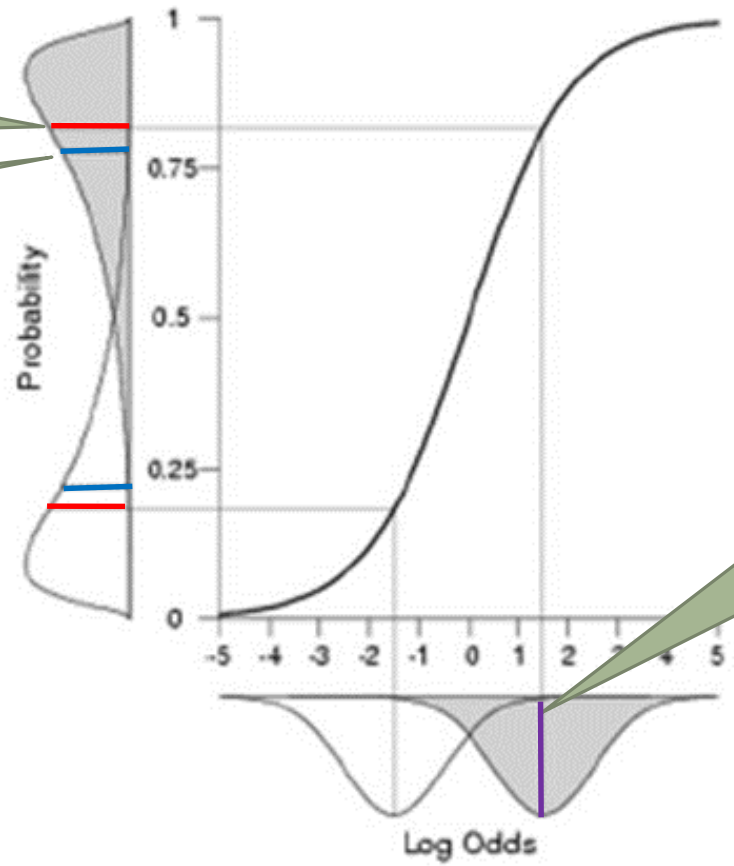
Population-Average vs. Subject-Specific Interpretations

"Median" = probability of D (at baseline) for a "typical" individual

"Mean" = prevalence of disease (at baseline) in the population

"Median"≠ "Mean"

Marginal Model contrasts population means.
Mixed model contrasts population medians (i.e. "typical" subject at baseline vs. post-baseline)



"Median" = log-odds of D (at baseline) for a "typical" individual
"Mean" = average log-odds of D (at baseline) in the population
Median = Mean

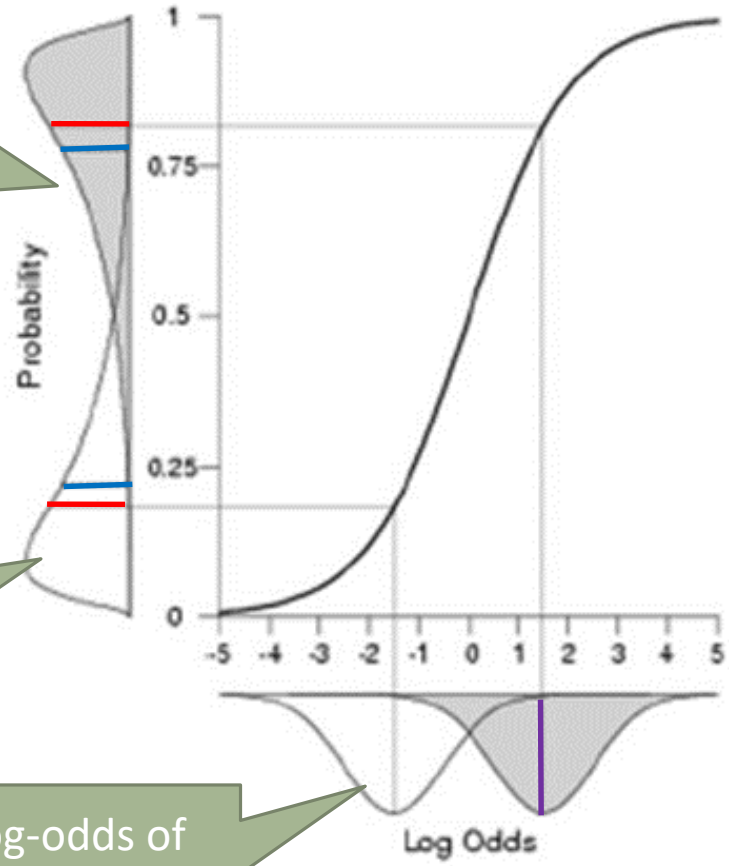
Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

Population-Average vs. Subject-Specific Interpretations

A linear model *assumes* these distributions are **normal** (conditional on all predictors) – not skewed as shown here. So linear model *assumes* mean = median!

...but after treatment, we're left with a bunch of low-risk people, with a few remaining high-risk

After treatment, the log-odds of disease for everyone shift uniformly lower...



Source: Adapted from Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.*.

GLMM Coefficient Interpretations

- In GLMMs, the βs have **subject-specific interpretations**
  - Makes sense with time-dependent covariates (e.g. smoking)
    - What will happen to an individual in our study if they stop smoking?
  - Makes less sense with time-independent covariates (e.g. race)?
    - What will happen to an individual in our study if they change from African-American to white?
    - Could assume we are really comparing two different individuals with the same set of random effects?

Source: https://cdn.shopify.com/s/files/1/0535/6917/products/YouAreSpecial.jpg?v=1501475226;
http://www.neighborhoodarchive.com/images/mrn/episodes/1686/snapshot20110830050514.jpg

Example: Onychomycosis Study

Onychomycosis Trial Example

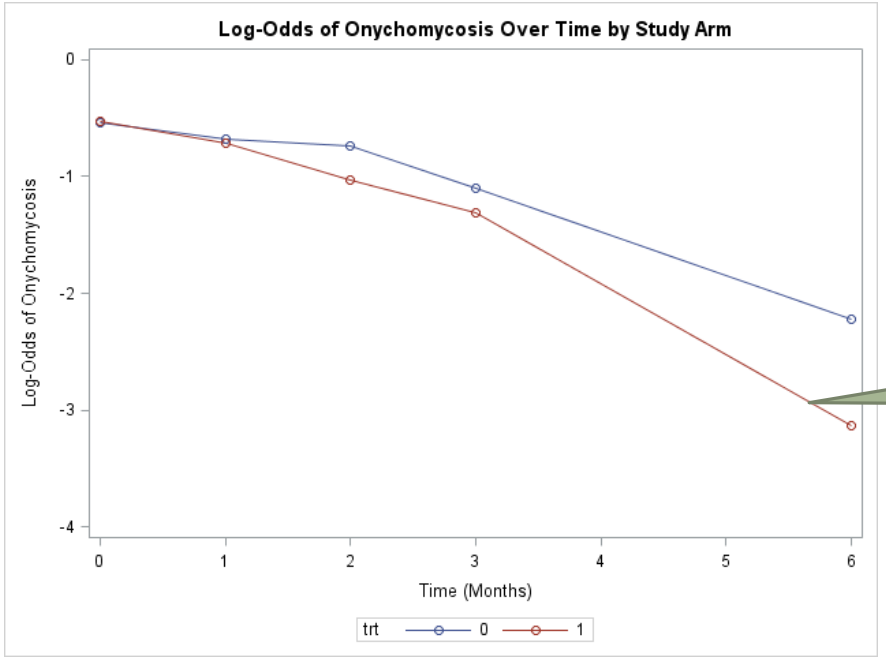
- Randomized trial of two oral antifungal treatments K = 294 subjects
  - N = 1,908 measures of onycholysis (separation of nail from nail bed)
  - n_i = 1 to 7, unbalanced
- Outcome: Y = none/mild or moderate/severe onycholysis (0/1), measured at time = 0 (baseline) and approximately 4, 8, 12, 24, 36, and 48 weeks
  - For this example, we are limiting to just the first 24 weeks
- Exposure: oral antifungal treatment (Itraconazole = 0, Terbinafine = 1)
  - No controls
- Covariates: None
- **Research Question**: How does terbinafine impact the risk of moderate/severe onycholysis over time?

Source: Fitzmaurice, Laird, and Ware. *Applied Longitudinal Data Analysis.* https://content.sph.harvard.edu/fitzmaur/ala2e/. De Backer, M., et al (1998). Journal of the American Academy of Dermatology, 38, 57-63.

Marginal Model for Onychomycosis Data

GEE Model, CS working correlation structure:

$$logit(E(Y_{ij})) = \beta_0 + \beta_1 Time_{ij}$$

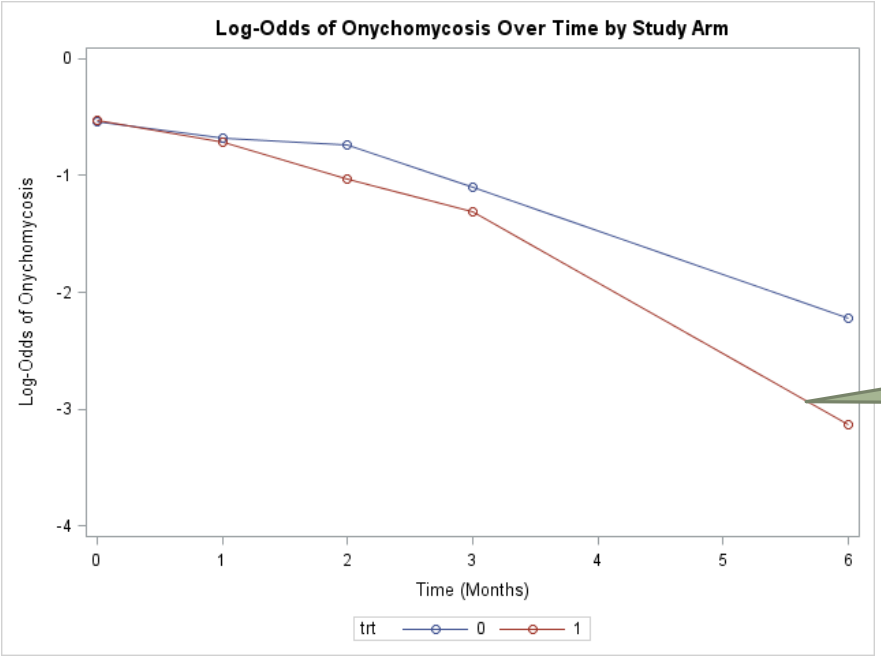


Just looking at terbafine to simplify example

Random Intercept Model for Onychomycosis Data

Model with Random Intercept for Subject:

$$logit(E(Y_{ij}|b_i)) = \beta_0 + b_{0i} + \beta_1 Time_{ij} \text{ where } b_{0i} \sim N(0, \sigma_0^2)\ iid$$



Just looking at terbafine to simplify example

Comparing Results of Two Models

GLMM with Random Intercept

Solutions for Fixed Effects								
Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept	-0.6158	0.2576	293	-2.39	0.0175	0.05	-1.1228	-0.1087
time	-0.8879	0.05109	1036	-17.38	<.0001	0.05	-0.9882	-0.7877

- $e^{-0.8879} = 0.41$. Interpretation?
  - 59% lower odds of moderate/severe onycholysis each month for <u>a patient</u> treated with terbinafine

GEE with CS Correlation Structure

Analysis Of GEE Parameter Estimates						
Empirical Standard Error Estimates						
Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	-0.4007	0.1253	-0.6463	-0.1552	-3.20	0.0014
time	-0.2809	0.0317	-0.3430	-0.2188	-8.86	<.0001

- $e^{-0.2809} = 0.76$. Interpretation?
  - 24% lower odds of moderate/severe onycholysis each month in the <u>population of patients</u> given terbinafine

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GLMM with Random Intercept

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- 24% lower odds of moderate/severe onycholysis each month in the <u>population of patients</u> given terbinafine

- Which of these is right?
  - Both!
    - …Zach, that's not helpful. I have a study to do, which model should I use?
    - It depends! On your research question!
      - Do you want to know what happens to your study population, or to a typical individual in it?
        - **Research Question**: How does terbafine impact the risk of moderate/severe onycholysis over time? Could ask it either way; it's up to you

Summary

Key Points

- βs in marginal models have a population-average interpretation
  - e.g. 24% lower odds of moderate/severe onycholysis each month in the population of patients treated with terbafine

- βs in mixed models have a subject-specific interpretation
  - e.g. 59% lower odds of moderate/severe onycholysis each month for a patient treated with terbafine