JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

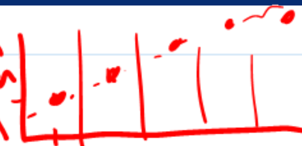
Lecture 9

Review of logistic regression model assumptions
Models for longitudinal / clustered binary responses

→ marginal
Conditional

Review of logistic regression assumptions

observed proportion of $Y_i=1$



% Predicted/estimated $Pr(Y_i=1)$

- And solutions to violations

1)
- Mean model is "correctly" specified
  - Violation impact estimation of association parameters
  - Plot average predicted vs. observed proportions within quintiles or deciles of predicted values
  - Plot average predicted vs. observed proportions as a function continuous exposure
  - Summary tables of average predicted vs. observed proportions by level of categorical exposure
  - SOLUTION: change your mean model

2)
- Observations are independent

inference

  - Violation impacts estimation of standard errors, confidence intervals, hypothesis tests
  - SOLUTIONS:
    - Marginal logistic regression model fit using generalized estimating equations
    - Conditional logistic regression model

random effects models

conditional logistic regression

matched case control study

Review of logistic regression assumptions

$Y_i \sim \text{Bernoulli}(\mu_i)$ $E(Y_i) = \mu_i$

$\boxed{Var(Y_i) = \mu_i(1-\mu_i)}$ $= Pr(Y_i = 1)$

- Variance is correctly specified
  - Logistic model assumes: Var(Y) = p(1-p)
  - Under or over-dispersion
  - Compute Var(Y) and compare with ~~predicted~~ Model based variance, overall or by select variables
  - SOLUTION: → standard variance formula
    - Bootstrap
    - GLM: family = "quasibinomial" assumes Var(Y) = ϕ x p x (1-p) where ϕ = 1/(n-k) sum of squared Pearson residuals

      k ↳ # of predictors

$\phi < 1$ underdispersion

$\phi > 1$ overdispersion

- There are no "influencial" observations
  - DFFITS or DFBETAS

Two example studies

longitudinal study

$Y_{ij} = \begin{cases} 0 & \text{poor resp function} \\ 1 & \text{good resp function} \end{cases}$

i = individual j = assessment time

- Placebo-controlled trial to improve respiratory function
  - 111 patients
  - Baseline + 4 follow-ups
  - Compare the change in odds from baseline to follow-up across the active treatment vs. placebo groups.

clustered design

- Matched case-control study looking at effect of exogenous estrogens on the risk of endometrial cancer
  - 63 matched sets: one case + 4 controls
  - Alive in same community at the time of diagnosis for the case, age within 1 year, same marital status and entered community at roughly the same time
  - Do women who use estrogens, have a history of gall-bladder disease or hypertension at increased risk of endometrial cancer?

Two approaches to modeling

- Marginal models

$Y_{ij} = \begin{cases} 0 \\ 1 \end{cases}$

i = cluster j = sub unit

$X_{ij} = \begin{cases} 0 \\ 1 \end{cases}$

The goal is to compare odds of an outcome across subsets of the population
→ correlation in the data is nuisance

$$\log\left[\frac{Pr(Y_{ij}=1 \mid X_{ij}=1)}{Pr(Y_{ij}=0 \mid X_{ij}=1)}\right] - \log\left[\frac{Pr(Y_{ij}=1 \mid X_{ij}=0)}{Pr(Y_{ij}=0 \mid X_{ij}=0)}\right]$$

Y_{ij} \ X_{ij}	0	1
0		
1		

- Conditional models

Compare the odds of an outcome across exposure groups among persons in the cluster

$$\log\left[\frac{Pr(Y_{ij}=1 \mid X_{ij}=1, b_i)}{Pr(Y_{ij}=0 \mid X_{ij}=1, b_i)}\right] - \log\left[\frac{Pr(Y_{ij}=1 \mid X_{ij}=0, b_i)}{Pr(Y_{ij}=0 \mid X_{ij}=0, b_i)}\right]$$

Marginal model: GLM Review

- Requires specification of 3 components

$Y_i = \begin{cases} 0 \\ 1 \end{cases}$ $\quad X_i$: p covariates

$i = 1, \ldots, n$ # of observations

1) distribution of Y_i

$Y_i \sim \text{Bernoulli}(\mu_i)$, $\mu_i = Pr(Y_i = 1)$

$Var(Y_i) = \mu_i(1-\mu_i)$

$g(\mu_i) = X_i'\beta$ $\quad g(\mu_i) =$ logit link

$\hookrightarrow g^{-1}(X_i'\beta) = \mu_i$

Marginal model: GLM review

- For a logistic regression model, we derived the likelihood function, log likelihood function and score equations.

Y_i = independent

- Recall the score equation:

$$\operatorname{Var}(\underset{\substack{n\times 1 \\ \text{vector}}}{Y}) = \begin{bmatrix} \mu_1(1-\mu_1) & & 0 \\ & \ddots & \\ 0 & & \mu_n(1-\mu_n) \end{bmatrix}_{n\times n}$$

$$
\begin{aligned}
U(\beta) &= X'(Y - \mu(\beta)) \\
&= \left(\frac{\partial \mu}{\partial \beta}\right)' V^{-1}(Y - \mu(\beta)) \\
&= \sum_{i=1}^{n} \left(\frac{\partial \mu_i}{\partial \beta}\right)' V_i^{-1}(Y_i - \mu_i(\beta)) = 0
\end{aligned}
$$

solve for β

where $\frac{\partial \mu}{\partial \beta} = VX$, $V = diag\,[\mu(\beta)(1-\mu(\beta))]$, $V_i = \mu_i(\beta)(1-\mu_i(\beta))$.

Marginal Model: Longitudinal GLM

- You need to include one additional element in the model specification

$$Y_{ij} = \begin{cases} 0 \\ 1 \end{cases}$$

$i = 1, \dots, m$ # of individuals

$j = 1, \dots, n_i$ # of assessments for individual i

X_{ij}

$$Y_{ij} \sim \text{Bernoulli}(\mu_{ij}) \Rightarrow Var(Y_{ij}) = \mu_{ij}(1-\mu_{ij})$$

$$\text{logit} \Rightarrow g(\mu_{ij}) = X_{ij}'\beta$$

$$* \; Corr(Y_{ij}, Y_{ik}) = f(\alpha, j, k)$$

$$Var(Y) = \begin{bmatrix} Var(Y_1) & & 0 \\ & \ddots & \\ 0 & & Var(Y_m) \end{bmatrix}$$

$$\underbrace{Var(Y_i)}_{n_i \times 1 \text{ vector}} = \underbrace{\begin{bmatrix} \mu_{i1}(1-\mu_{i1}) & & ? \\ & \ddots & \\ ? & & \mu_{in_i}(1-\mu_{in_i}) \end{bmatrix}}_{n_i \times n_i}$$

$$Cov(Y_{ij}, Y_{ik}) \neq 0$$

Marginal Model: Longitudinal GLM

- In linear models, we could easily write out the joint distribution for Y_i , the vector of responses for cluster i

$$Y_i \sim MVN(\mu_i, V_i)$$

- In general, it is hard to write out the joint distribution of a Bernoulli random variable, Poisson random variable, etc.
- We don't use maximum likelihood estimation here
- Derive estimates of β using multivariate version of the score equation (estimating equation)

no likelihood fnctn ⇒ no LRTs

Wald tests

Marginal Model: Generalized Estimating Equations

- Estimation procedure is called generalized estimating equations (GEE)

Zeger
Liang

- Weighted least squares when Y_i is multivariate normal is a special case.
- GEE:

$$\sum_{i=1}^{m} \left[\frac{\partial \mu_i}{\partial \beta}\right]' V_i^{-1}(Y_i - \mu_i(\beta)) = 0$$

$Y_i, \mu_i(\beta) \Rightarrow$ vectors
V_i = matrix

- GLM:

$$\sum_{i=1}^{n} \left(\frac{\partial \mu_i}{\partial \beta}\right)' V_i^{-1}(Y_i - \mu_i(\beta))$$

$V_i, Y_i, \mu_i(\beta) \Rightarrow$ scalars

Example: Exploratory data analysis, mean model

- Placebo-controlled trial of respiratory function

Outcome = good resp function

Pre randomization

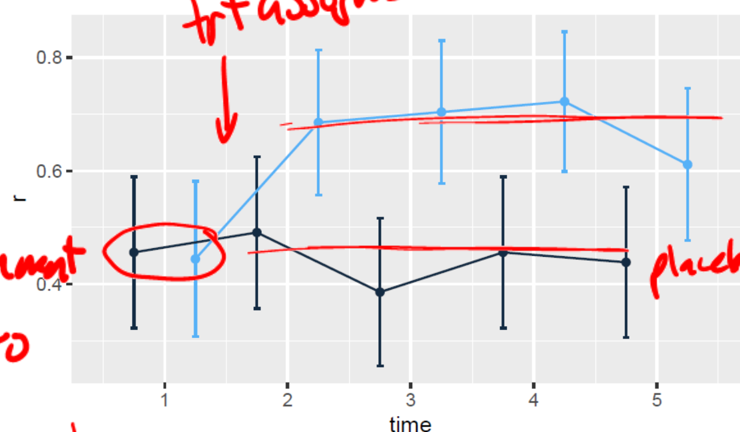
- Baseline (time 1) and 4 follow-ups (times 2 through 5)
- Treatment is assigned after baseline respiratory function is recorded

		1	2	3	4	5
placebo	0	0.4561404	0.4912281	0.3859649	0.4561404	0.4385965
Trt	1	0.4444444	0.6851852	0.7037037	0.7222222	0.6111111

$$Pr(Y_{ij} = 1 \mid time = j)$$

* at baseline, no trt assignment
* just compare baseline to post

trt assigns



placebo

Example: Mean model specification and interpretation

- Model specification:

$$logit[Pr(Y_{ij} = 1 | post_{ij}, trtmnt01_i)] = \beta_0 + \beta_1 post_{ij} + \beta_2 post_{ij} \times trtmnt01_i$$

- β_0: log odds of a good respiratory response at baseline → applies to both trt groups
- β_1: log odds ratio of a good respiratory response comparing follow-up to baseline among patients receiving the placebo
- $\beta_1 + \beta_2$: log odds ratio of a good respiratory response comparing follow-up to baseline among patients receiving the active treatment
- β_2: treatment effect! Does the relative improvement in the odds of a good response comparing follow-up to baseline differ for the patients receiving active treatment vs. placebo

Example: Exploratory data analysis, correlation structure

- How do we assess the degree of correlation in the data?

- Linear models:
  - Pairwise correlation coefficients between each follow-up time
  - Autocorrelation function, $Corr(Y_{ij}, Y_{ik}) = f(\alpha, j, k)$ → banded by -1, 1
  - Use the above to propose a model for the correlation structure → exchangable → AR1

- Logistic models:
  - $Corr(Y_{ij}, Y_{ik}) = f(\alpha, \mu_{ij}, \mu_{ik})$ and is constrained by $\boxed{\mu_{ij}, \mu_{ik}}$ $\boxed{.05}$ $\mu_{ij} = .10$, $\mu_{ik} = .07$
  - Alternative to the correlation, we can measure association over time using odds ratios

$$OR(Y_{ij}, Y_{ik}) = \frac{Pr(Y_{ij} = 1, Y_{ik} = 1)Pr(Y_{ij} = 0, Y_{ik} = 0))}{Pr(Y_{ij} = 1, Y_{ik} = 0)Pr(Y_{ij} = 0, Y_{ik} = 1))}$$

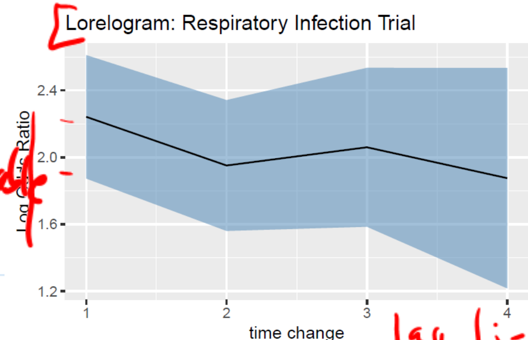
Y_{ik} 0 1

Y_{ij} 0 1

m

exchangeable

ar1



lag |j-k|

Example: Fitting the model in R using gee

gee ⇒ model based se

→ assumes var, corr models hold

⇒ robust variance estimate

```
data$post = ifelse(data$time>1,1,0)
data$postXtrt = data$post * data$trtmnt01
fit.exch = gee(r~post+post:trtmnt01,data=data,
        family="binomial",corstr="exchangeable",id=id)
##
## Coefficients:
##                    Estimate Naive S.E.    Naive z Robust S.E.   Robust z
## (Intercept)     -0.19885086  0.1915041 -1.0383635   0.1907707 -1.0423556
## post            -0.04097561  0.1943549 -0.2108288   0.2103911 -0.1947592
## post:trtmnt01    1.00825259  0.2457427  4.1028787   0.2624356  3.8419053
##
## Estimated Scale Parameter:  1.007704
## Number of Iterations:  2
##
## Working Correlation
##           [,1]      [,2]      [,3]      [,4]      [,5]
## [1,] 1.0000000 0.4673692 0.4673692 0.4673692 0.4673692
## [2,] 0.4673692 1.0000000 0.4673692 0.4673692 0.4673692
## [3,] 0.4673692 0.4673692 1.0000000 0.4673692 0.4673692
## [4,] 0.4673692 0.4673692 0.4673692 1.0000000 0.4673692
## [5,] 0.4673692 0.4673692 0.4673692 0.4673692 1.0000000
```

βs

model

model

geeglm

exchangeable

$Corr(Y_{ij}, Y_{ik})$ ⇒ Pearson residuals

Example: Interpretation of results

```
## Coefficients:
##                  Estimate Naive S.E.    Naive z Robust S.E.   Robust z
## (Intercept)   -0.19885086  0.1915041 -1.0383635   0.1907707 -1.0423556
## post          -0.04097561  0.1943549 -0.2108288   0.2103911 -0.1947592
## post:trtmnt01  1.00825259  0.2457427  4.1028787   0.2624356  3.8419053
```

$\exp(\hat{\beta}_s)$ model/naive robust

```
##               Marg Marg LL Marg UL MargR LL MargR UL
## (Intercept)   0.820  0.559   1.202    0.560    1.200
## post          0.960  0.651   1.416    0.630    1.462
## post:trtmnt01 2.741  1.677   4.481    1.622    4.633
```

- Interpretation of parameters:

$\exp(\hat{\beta}_0) = .82$ odds of a good respiratory outcome at baseline

$\exp(\hat{\beta}_1) = .96$ Among placebo group, the odds of a good respiratory outcome decreased by 4% following randomization.

$\exp(\hat{\beta}_1) \times \exp(\hat{\beta}_2) = .96 \times 2.7 \approx 2.6$

Example: Comparison across working correlation models

- Compare the results to the model fit assuming independence

model | naive

```
##                Marg Marg LL Marg UL MargR LL MargR UL   Ind Ind LL Ind UL
## (Intercept)   0.820   0.559   1.202    0.560    1.200 0.820  0.559  1.202
## post          0.960   0.651   1.416    0.630    1.462 0.970  0.608  1.547
## post:trtmnt01 2.741   1.677   4.481    1.622    4.633 2.679  1.802  3.982
##               IndR LL IndR UL
## (Intercept)     0.560   1.200
## post            0.620   1.519
## post:trtmnt01   1.437   4.994
```

Conditional Models

- Random effects logistic regression model:

Conditional Models

$$
\begin{aligned}
logit[Pr(Y_{ij} = 1 | post_{ij}, trtmnt01_i, b_i)] &= \beta_{0i}^c + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0) trtmnt01_i \\
&= \beta_0^c + b_i + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0) trtmnt01_i
\end{aligned}
$$

where $b_i \sim N(0, \sigma^2)$ and the covariates are independent of b_i.

Interpretation:

- β_{0i}^c: defines a patient specific log-odds of a good respiratory response at baseline
- $\beta_{0i}^c = \beta_0^c + b_i$, where $b_i \sim N(0, \sigma^2)$: β_0^c is the log-odds of a good respiratory response for the average patient (i.e. $b_i = 0$)
- $\beta_{0i}^c = \beta_0^c + b_i$, where $b_i \sim N(0, \sigma^2)$: b_i represents the deviation from this average log-odds of a good respiratory response for patient i

Example: Logistic regression with random intercept

$$
\begin{aligned}
logit[Pr(Y_{ij} = 1|post_{ij}, trtmnt01_i, b_i)] &= \beta_{0i}^c + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0)trtmnt01_i \\
&= \beta_0^c + b_i + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0)trtmnt01_i
\end{aligned}
$$

where $b_i \sim N(0, \sigma^2)$ and the covariates are independent of b_i.

$$
\mu_{ij}^c = \frac{exp(\beta_0^c + b_i + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0)trtmnt01_i)}{1 + exp(\beta_0^c + b_i + \beta_1^c I(post_{ij} > 0) + \beta_2^c I(post_{ij} > 0)trtmnt01_i)}
$$

- Slopes are log [ratio of individual odds]!

Example: Random intercept logistic model in R using glmer

```
ri.fit = glmer(r~post + postXtrt+(1|id),data=data,family="binomial",nAGQ=7)
summary(ri.fit)
```

```
## Random effects:
##  Groups Name        Variance Std.Dev.
##  id     (Intercept) 6.49     2.55
## Number of obs: 555, groups:  id, 111
##
## Fixed effects:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -0.4212     0.3667   -1.15     0.25
## post         -0.0834     0.3683   -0.23     0.82
## postXtrt      1.9452     0.4850    4.01  6.1e-05 ***
```

- Intercept: For the average or typical patient (i.e. $b_i = 0$), the probability of a good response is $\frac{\exp(-0.42)}{1+\exp(-0.42)} = 0.40$
- You can compute baseline probability of a good response for any patient by: $\frac{\exp(-0.42+b_i)}{1+\exp(-0.42+b_i)}$

Example: Interpretation

```
ri.fit = glmer(r~post + postXtrt+(1|id),data=data,family="binomial",nAGQ=7)
summary(ri.fit)
```

```
## Random effects:
##  Groups Name        Variance Std.Dev.
##  id     (Intercept) 6.49     2.55
## Number of obs: 555, groups:  id, 111
##
## Fixed effects:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -0.4212     0.3667   -1.15     0.25
## post         -0.0834     0.3683   -0.23     0.82
## postXtrt      1.9452     0.4850    4.01  6.1e-05 ***
```

Comparison of marginal and conditional slope terms

Compare the marginal (β) and conditional (β^c) parameter estimates.

```
cbind(summary(fit.exch)$coeff[,1],summary(ri.fit)$coeff[,1])
```

```
##                  [,1]      [,2]
## (Intercept) -0.1989 -0.42120
## post        -0.0410 -0.08343
## postXtrt     1.0083  1.94525
```

- Recall our discussion of confounding: Assume b_i is independent of covariates (as we do in random effects models)

$$\text{Marginal model:} \quad logit[Pr(Y_{ij}|X_{ij})] = \beta_0 + \beta_1 X_{ij}$$

$$\text{Conditional model:} \quad logit[(Pr(Y_ij|X_{ij}, b_i))] = \beta_0^c + \beta_1^c X_{ij} + b_i$$

In general:

- β = change in log population odds per unit change in X
- β^c = change in cluster-specific log odds per unit change in X

Next time...

- Quick comments on estimation
  - Conditional logistic regression where we don't assume a distribution for b_i
  - Application to matched case control study

- Motivation and regression models for Poisson random variables