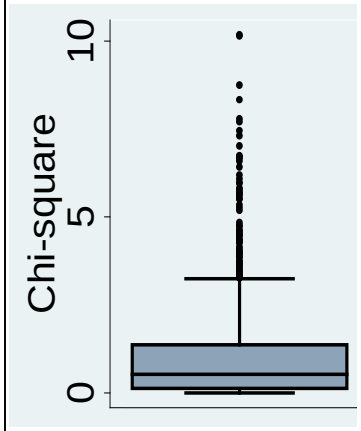
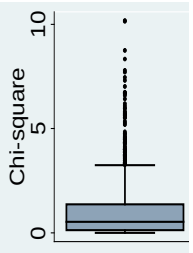
Repeated Measures, Lecture 2, Part 2

Charles E. McCulloch,
Division of Biostatistics,
Dept of Epidemiology and Biostatistics,
UCSF

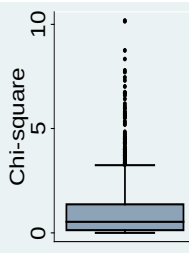




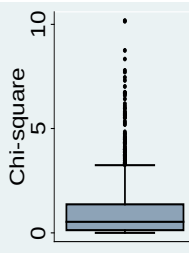
Last time

1. Two overarching analysis approaches to accommodating correlation
2. Longitudinal designs
3. GEE (`xtgee`) methods for numerical outcomes

Today



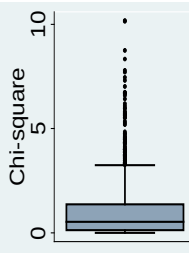
1. Mixed models for numerical outcomes (`mixed`)
2. Model checking
3. Summary



Mixed effects models

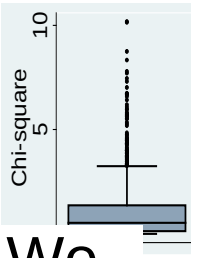
- Models for correlated data are often specified by declaring one or more of the categorical predictors in the model to be *random factors*. (Otherwise they are called *fixed factors*.) Models with both fixed and random factors are called *mixed effects models.*
- Random factors allow for factor-level-specific terms in the model. For example, if subject were specified as a random factor then each subject would be allowed their own intercept. *However*, random factors are different than including subject as a categorical predictor.

Fixed versus Random Factors

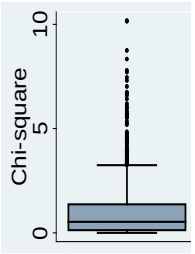


- With a random factor we assume that the *effects* associated with the levels of a factor can be regarded as a random sample from some reasonable population of effects. (If yes then random, if no then fixed).
- This is what we ordinarily do for any sample – we ask if we can regard it as a random sample from a larger population. For hierarchical data structures we ask the question over again for each level.

Notes on fixed vs random Factors

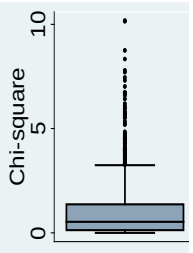


1. Continuous variables are virtually never random effects. We typically treat a variable as continuous because knowing the outcome for one value of the variable tells us something about the nearby values (hence the effects are not random). Do not confuse this with the fact that, if we have a random sample of subjects, their ages are a random sample of ages.
2. Scope of inference: Inferences can be made on a statistical basis to the *population* from which the levels of the random factor have been selected.
3. Incorporation of correlation in the model: Observations that share the same level of the random effect are being modeled as correlated.
4. Accuracy of estimates: Using random factors involves making extra assumptions but gives more accurate estimates.
5. Estimation method: Different estimation methods must be used. (Mixed effects regression methods).



Fixed versus Random Practice

- Fecal fat example. Factors? Fixed? Random?
  - Factors: sex, pilltype, participant
  - Random: participant (rest fixed).
- Back pain example. Factors? Fixed? Random?
  - Factors: Physician, time (1m, 1y, 2y), sex of the patient, patient, age of the patient, pain was thoracic (yes/no).
  - Random: Physician, patient (rest fixed).



MIXED for continuous outcomes

`mixed` is for approximately normally distributed outcomes and is an analog of multiple linear regression. Here is the command syntax:

```
mixed depvar fix_effects || rand_
effects: , cov(corr structure) reml
```

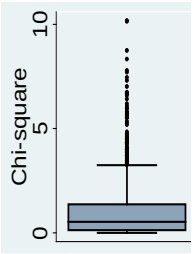
Punctuation important!

I like to use the REML option

Example: Georgia babies

```
mixed bweight birthord initage ||
  momid:, reml
```

Recall: Fecal fat example



	Fecal Fat (g/day)				
	Pill type				
PatID / Sex	**None**	**Tablet**	**Capsule**	**Coated Capsule**	**Avg**
1 – M	44.5	7.3	3.4	12.4	16.900
2 – M	33.0	21.0	23.1	25.4	25.625
3 – M	19.1	5.0	11.8	22.0	14.475
4 – F	9.4	4.6	4.6	5.8	6.100
5 – F	71.3	23.3	25.6	68.2	47.100
6 – F	51.2	38.0	36.0	52.6	44.450
Avg	38.08	16.53	17.42	31.07	25.775

mixed for the fecal fat example

Summary information about hierarchy

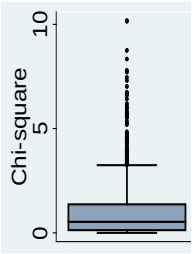
The usual coef and SE

Summary of variation in random intercepts (sd(_cons)) and residuals (sd(Residual))

Test of H0: no clustering

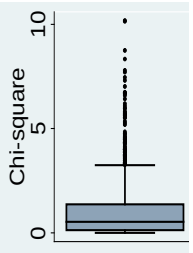
```
. mix... fecfat i.pilltype || patid:, reml stddev
Mixed                                            Number of obs      =        24
Group variable: patid                            Number of groups   =         6
                                                 Obs per group:
                                                              min =         4
                                                              avg =       4.0
                                                              max =         4
                                                 Wald chi2(3)       =     18.77
Log restricted-like...                           Prob > chi2        =    0.0003
--------------------                            ---------------------------------
      fecfat |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    pilltype |
     tablet  |     -21.55   5.972126    -3.61   0.000    -33.25515   -9.844849
    capsule  |  -20.66667   5.972126    -3.46   0.001    -32.37182   -8.961516
     coated  |  -7.016668   5.972126    -1.17   0.240    -18.72182    4.688483
             |
                                                          22.90851    53.25816
-                                                     ----------------------
-                                                     ----------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
patid: Identity              |
                   sd(_cons) |   15.89558   5.567271      8.001132    31.57922
-----------------------------+------------------------------------------------
                sd(Residual) |   10.34403   1.888552      7.232396    14.79439
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 12.52         Prob >= chibar2 = 0.0002
```

Mixed model analyses



- You get estimates of the regression coefficients (with the same interpretation as in regular linear regression), but accounting for the correlated data.
- Also get an understanding of how the variability in the data is attributable to various levels in the hierarchy.
- sd(_cons) is the standard deviation of the person-specific *true* intercepts. So 15.89558 is the standard deviation, across people, of their true baseline values.

Mixed model analyses



- Total variance = sum of all estimated variances.

Total variance = (patient SD)^2+(residual SD)^2

= (15.89558)^2 + (10.34403)^2

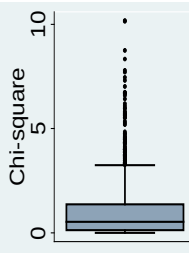
= 252.6695+ 106.9990 = 359.6685

- Intraclass correlation (ICC)

ICC = (patient SD)^2/(total variance)

= 252.6695/359.6685 = 0.703

xtgee: Fecal fat example

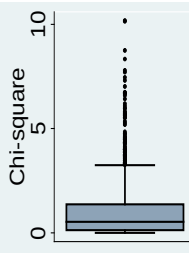



```
. xtgee fecfat i.pilltype i.sex, i(patid)

GEE population-averaged model                   Number of obs      =         24
Group variable:                      patid      Number of groups   =          6
Link:                              identity     Obs per group: min =          4
Family:                            Gaussian                    avg =        4.0
Correlation:                   exchangeable                    max =          4
                                                Wald chi2(4)       =      24.00
Scale parameter:                   253.8228     Prob > chi2        =     0.0001

------------------------------------------------------------------------------
      fecfat |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    pilltype |
           2 |     -21.55   5.451781    -3.95   0.000    -32.23529   -10.86471
           3 |  -20.66667   5.451781    -3.79   0.000    -31.35196   -9.981373
           4 |  -7.016668   5.451781    -1.29   0.198    -17.70196    3.668626
             |
       1.sex |       13.55   11.16389     1.21   0.225    -8.330816    35.43082
       _cons |   31.30833   8.570992     3.65   0.000      14.5095    48.10717
------------------------------------------------------------------------------
```

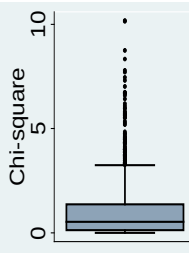
Study of cognitive decline



Outcome is the mini-mental state exam, a numerical score from 0 to 30 (original version of the 3MS).

Question: Do participants with better physical functioning at baseline (measured in quartiles of a physical function exam) show lower rates of cognitive decline?

Study of cognitive decline



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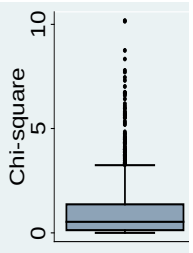
Question: Do participants with better physical functioning at baseline (measured in quartiles of a physical function exam) show lower rates of cognitive decline?

MIXED model syntax:

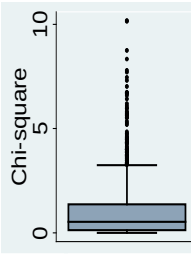
Model diagnostics: predictors



Nothing new in these models on the predictor side of the equation. For checking linearity do the usual:

Plot residuals versus predictors (RVP), transform predictors (e.g., try quadratic), try splines, categorize predictors. Not as many built-in diagnostics as for `regress` so have to do it "manually."

Model diagnostics: normality/outliers

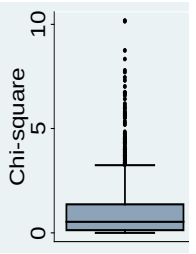


Calculate residuals

```
mixed:  predict resids, residuals
xtgee:  predict preds
        gen resids=outcome-preds
```

Plot residuals versus predicted values and look for outliers, unequal variances (but some mixed models allow unequal variances as does the robust option in `xtgee`), histogram of residuals.

Model diagnostics: normality/outliers



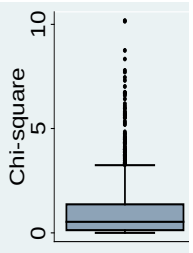
If you find issues – do the “usual”:

1. Try removing outliers to assess their influence.
2. Try transformations to alleviate non-normality, unequal variances.
3. Use bootstrap. But - only works for one level of hierarchical data, you need to use the `cluster()` option, and requires a fair number of clusters.

or

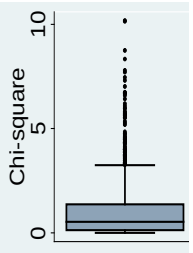
4. Use `xtgee` but specify a different distribution.

Terminology



GEE type models are sometimes called “population averaged” or “marginal” models because they hypothesize a relationship (e.g., logistic regression) that holds averaged over all subjects in a population. Random effects models (like those fit by MIXED) are sometimes called “subject specific” or “conditional” because they are built using random effects that are specific to a subject (e.g., a doctor or patient effect).

Summary



- Approximately normally distributed outcomes can be handled with mixed models (`mixed`) or generalized estimating equations (`xtgee`).
- Mixed models have the advantage of handling multiple levels of clustering and more explicit modeling of sources of variability and correlation. Better with missing data.
- Generalized estimating equations (when using the robust option) makes fewer assumptions.
- Model checking is similar to regression models for non-hierarchical data with some exceptions:
  - With a bootstrap need to cluster resample.
  - `mixed` can model certain forms of unequal variance.
  - `xtgee` can directly model non-normally distributed outcomes
  - `xtgee` can accommodate unequal variances with the robust option. More on these latter two next lecture.