Repeated Measures Data

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Clustered/Repeated

- Data is sampled in some unit
- Within that unit multiple measures
  - clinic: people
  - household: family member
  - patients: measured values
- Clinic/Households: clustered data
- Repeated measures: longitudinal data

Data is Different

- Used to assumption of independence -- comes from an idea of sampling units
- Multiple measures per unit, likely correlated
- Need to keep account of this correlation
- May even need to model this correlation *simpler for clustered than longitudinal*

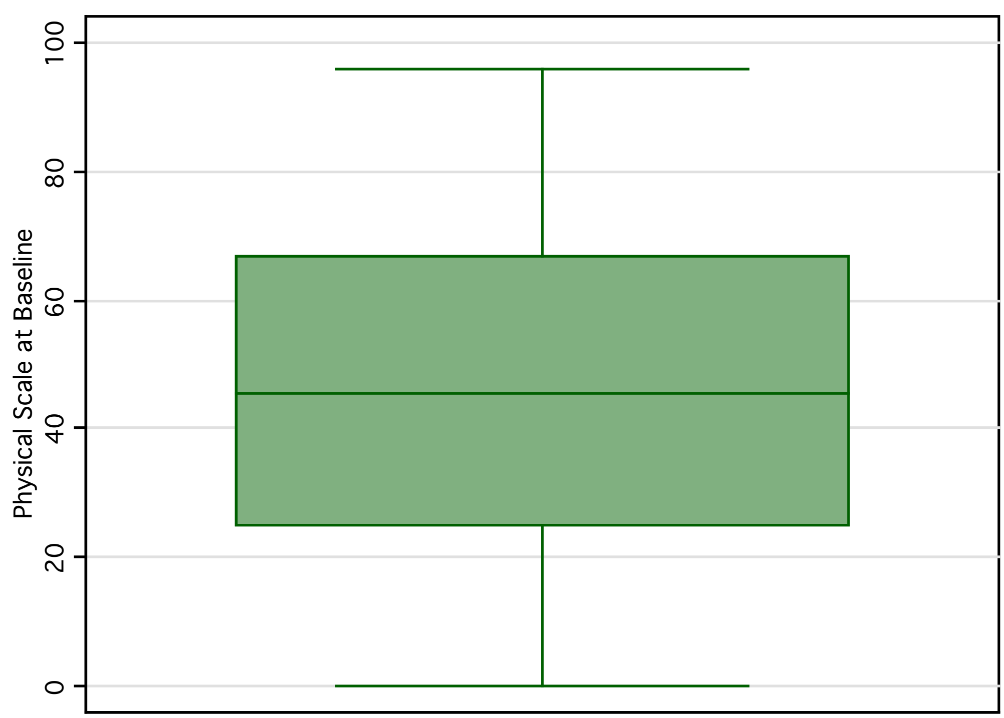
Longitudinal Data

- Measure a series of factors in a group of subjects over a defined follow-up period
- Example: AIDS Care Study in Uganda
- HIV+ ppts followed after initiation of anti-retroviral therapy (ARV)
- Outcomes: CD4, viral load, scales of function and well-being

Sample Question

- Outcome: scale of physical well-being ranging from 0-100
- How does it change after ARV initiation?
- Is the change affected by baseline CD4 count? Is it affected by baseline depression?

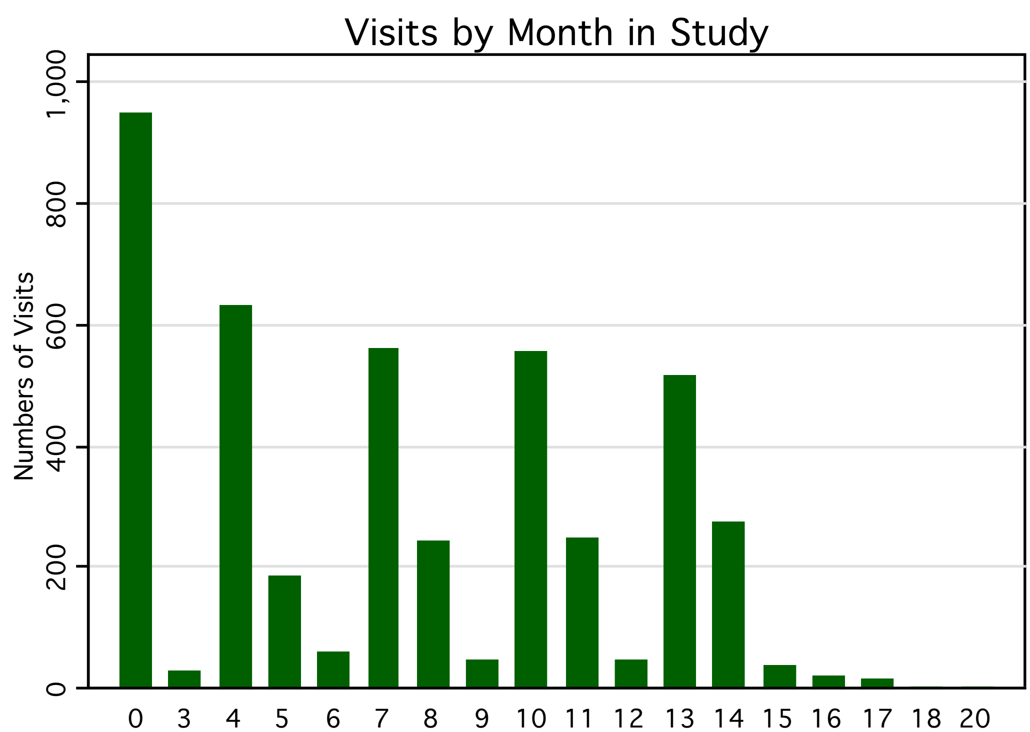
Boxplot of Baseline Physical Scale



Features of Longitudinal Data

- Varying follow-up periods
- Measures not always precisely timed
- Correlation within subject over time

I will focus primarily on continuous outcomes most issues are largely similar for binary or count responses



Correlated Measures Across Time*

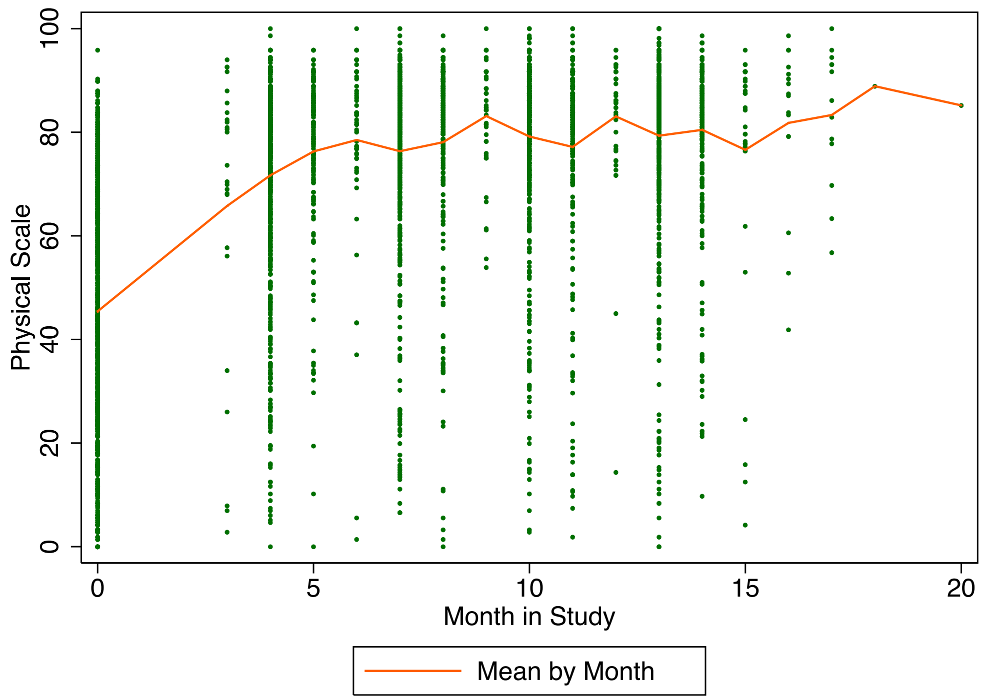
	physic~0	physic~1	physic~2	physic~3	physic~4
physical0	1.0000				
physical1	0.3776	1.0000			
physical2	0.3063	0.5167	1.0000		
physical3	0.2283	0.4159	0.5757	1.0000	
physical4	0.2257	0.3218	0.3573	0.4851	1.0000

* Grouped by quarter in the study

Modeling Longitudinal Data

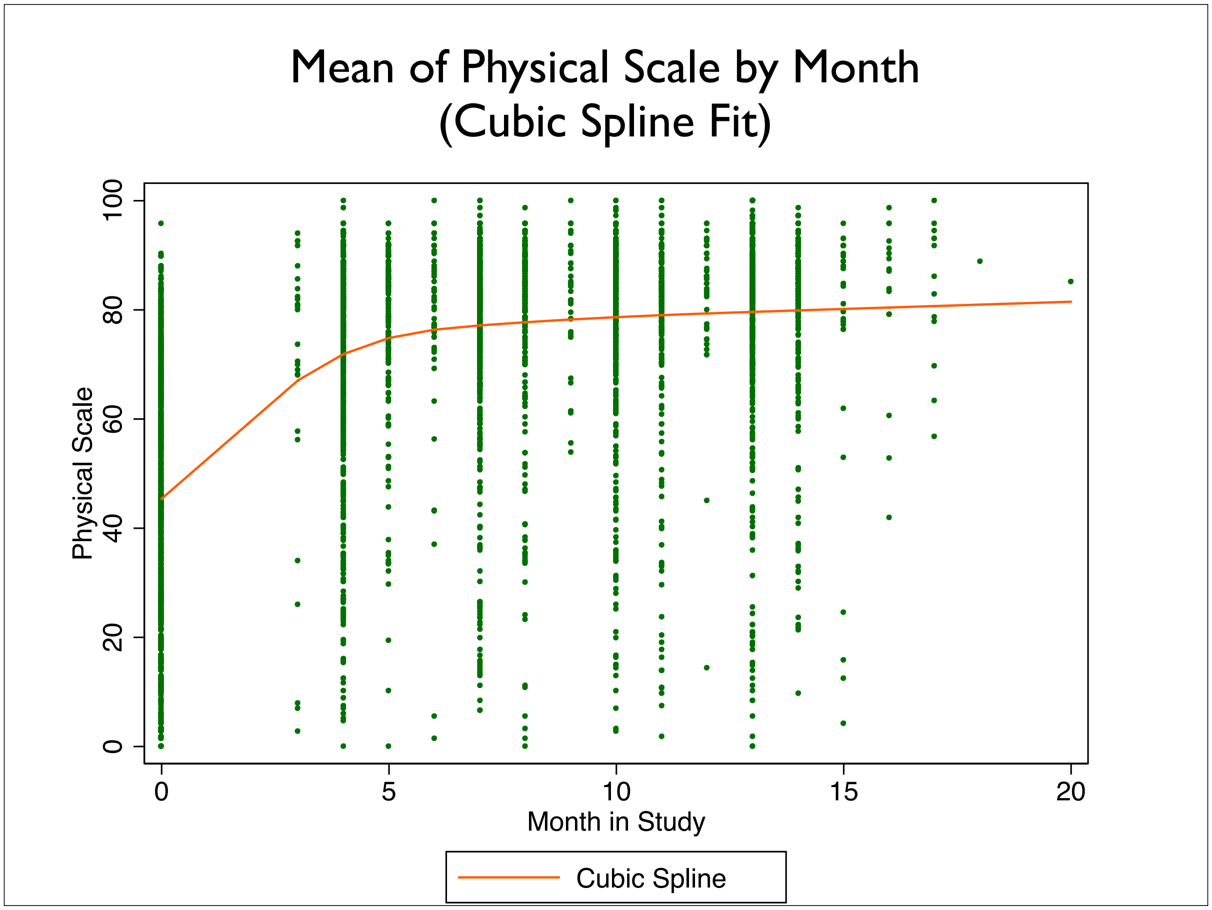
- Two parts
- Mean Structure: What factors affect the average value (time? predictors? both?)
- Correlation structure: How does correlation change over time?
- First step.... explore the data to inform modeling

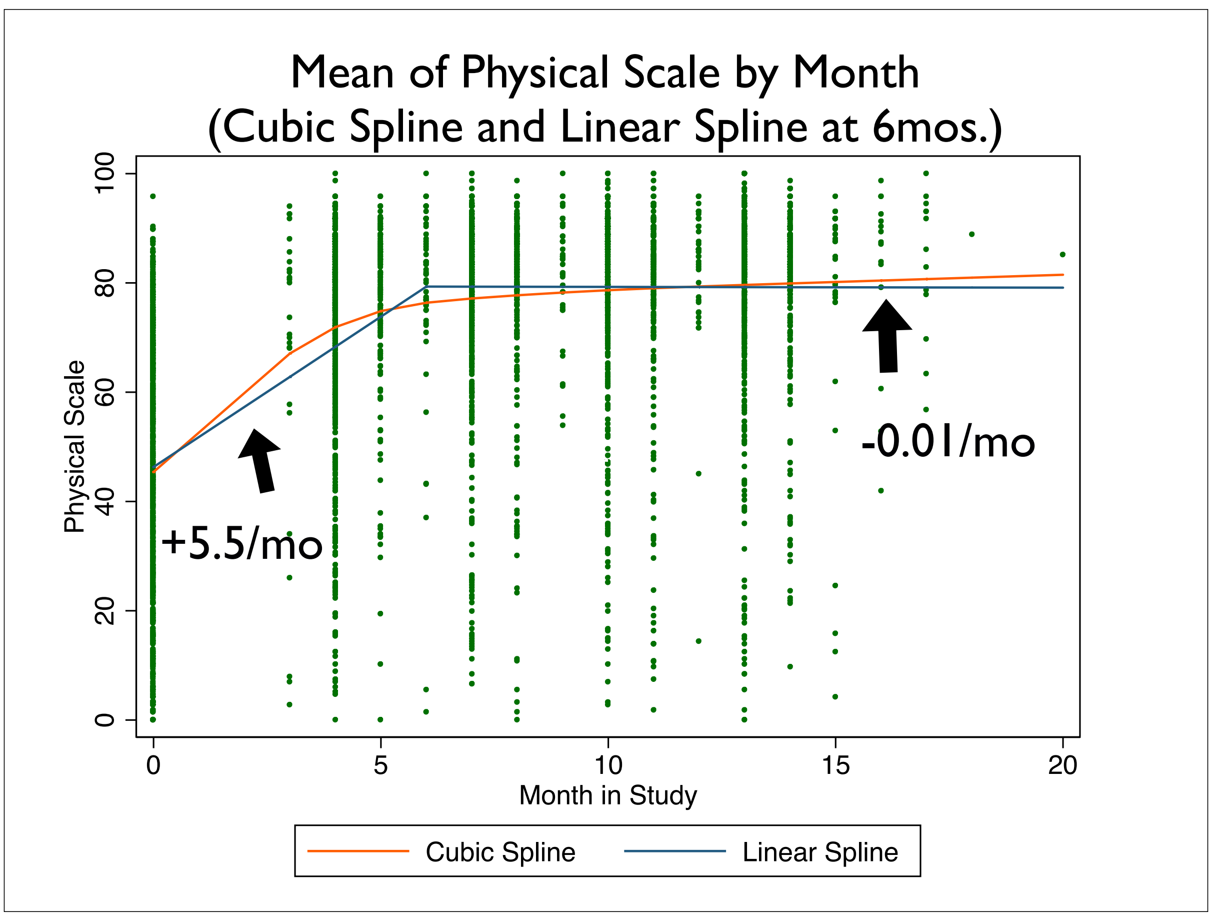
Mean of Physical Scale by Month



Cubic Splines

- Exploratory technique
- Fits a smooth curve through a cloud of points
- Flexible: doesn't have to make a straight line

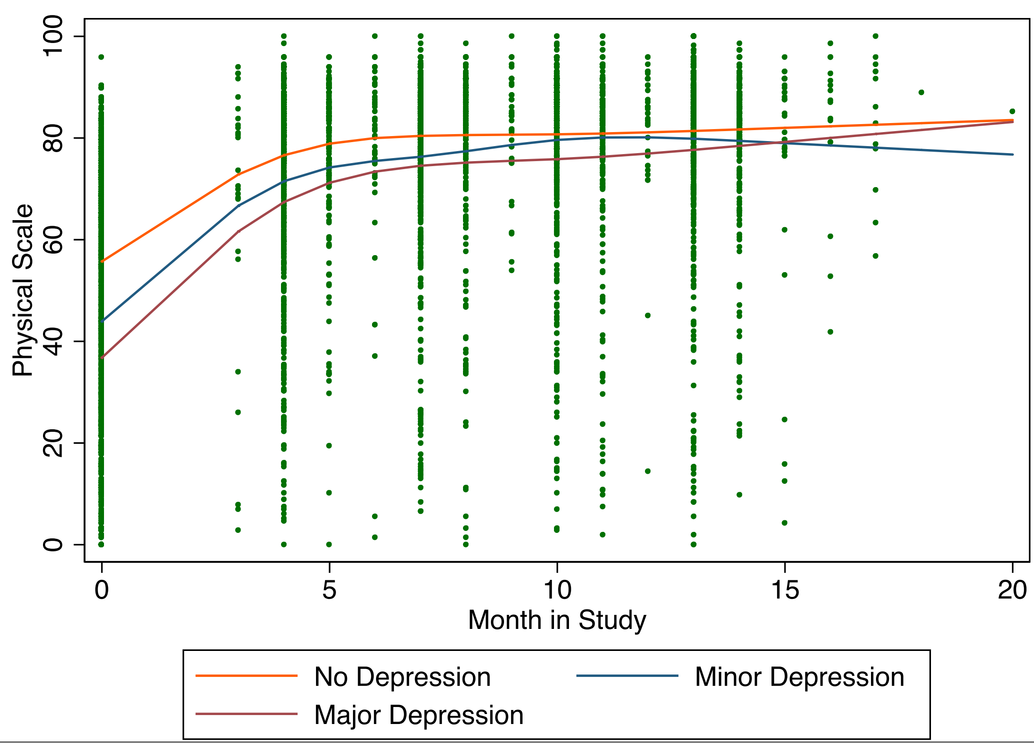

Mean of Physical Scale by Month
(Cubic Spline Fit)
Physical Scale
0
20
40
60
80
100
0
5
10
15
20
Month in Study
Cubic Spline


Mean of Physical Scale by Month
(Cubic Spline and Linear Spline at 6mos.)
Physical Scale
0
20
40
60
80
100
+5.5/mo
-0.01/mo
0
5
10
15
20
Month in Study
Cubic Spline
Linear Spline

Depression and Physical Functioning

- Used baseline CESD instrument
  > 27, 16 to 26, <16
- Depression: major, minor, none
- How does baseline depression affect physical function after ARV treatment?
- Explore this question before heavy modeling

Mean of Physical Scale by Month by Baseline Depression (Cubic Spline)



Information for Modeling the Mean*

- The effect of depression varies with time (the effect of time varies by depression)
  interaction between time and depression
- The trajectories are non-linear
  ouch!
  need to treat time as a factor (grouping) or use a flexible method (e.g., splines)

*no matter what technique you use

Very Simple Analysis

before treatment

```
reg phys i.depress if month==0

      Source |       SS       df       MS              Number of obs =     913
-------------+------------------------------           F(  2,   910) =   58.06
       Model |  59947.1204     2  29973.5602           Prob > F      =  0.0000
    Residual |  469754.145   910  516.213346           R-squared     =  0.1132
-------------+------------------------------           Adj R-squared =  0.1112
       Total |  529701.265   912  580.812791           Root MSE      =   22.72

------------------------------------------------------------------------------
    physical |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   depressed |
          1  |  -11.87678    1.90932    -6.22   0.000    -15.62396     -8.1296
          2  |   -18.9506   1.770853   -10.70   0.000    -22.42603   -15.47516
             |
       _cons |   55.75984   1.270105    43.90   0.000     53.26716    58.25251
------------------------------------------------------------------------------
```

Very Simple Analysis

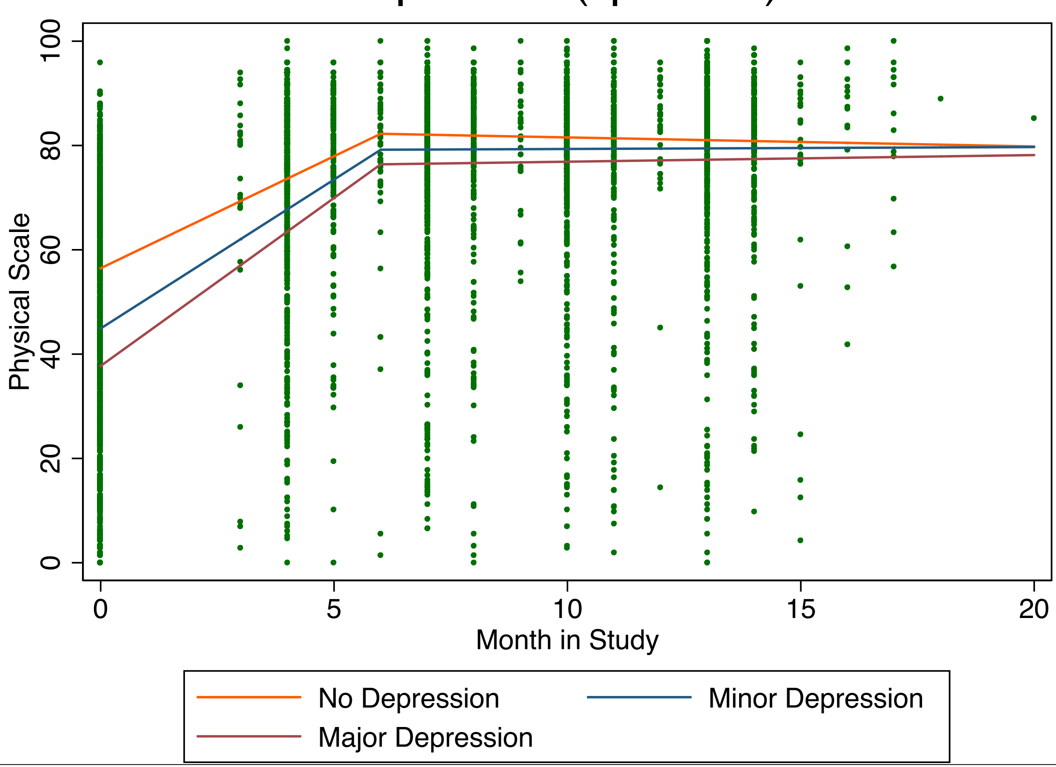
4 months after treatment

```
. reg phys i.depress if month==4

      Source |       SS       df       MS              Number of obs =     826
-------------+------------------------------           F(  2,   823) =    2.10
       Model |  1266.98873     2  633.494367           Prob > F      =  0.1228
    Residual |  247973.601   823  301.304497           R-squared     =  0.0051
-------------+------------------------------           Adj R-squared =  0.0027
       Total |   249240.59   825  302.109806           Root MSE      =  17.358

------------------------------------------------------------------------------
    physical |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   depressed |
          1  |  -.7459929   1.523518    -0.49   0.625    -3.736432    2.244446
          2  |  -2.829356   1.422033    -1.99   0.047    -5.620594   -.0381176
             |
       _cons |   81.12603   1.005529    80.68   0.000     79.15232    83.09973
------------------------------------------------------------------------------
```


Mean of Physical Scale by Month by Baseline Depression (Spline Fit)



Spline Output

Not Depressed

physical	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
before 6mos.	4.296064	.2365165	18.16	0.000	3.832137	4.759991
after 6mos.	-.1736788	.1886747	-0.92	0.357	-.5437642	.1964066
baseline	56.46386	.9602246	58.80	0.000	54.58038	58.34734

Mean Score at Baseline = 56.5

First 6 months, average change of +4.3 per month

After 6 months, average change of -0.17 per month

Spline Output

Mildly Depressed

physical	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
before 6mos.	5.711129	.2902105	19.68	0.000	5.141758	6.2805
after 6mos.	.037069	.2326473	0.16	0.873	-.4193671	.4935052
baseline	44.91511	1.175242	38.22	0.000	42.60937	47.22084

Mean Score at Baseline = 44.9

First 6 months, average change of +5.7 per month

After 6 months, average change of +0.04 per month

Spline Output

Major Depression

physical	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
before 6mos.	6.442615	.2775006	23.22	0.000	5.898299	6.986931
after 6mos.	.1269116	.2258695	0.56	0.574	-.3161302	.5699534
baseline	37.72776	1.113948	33.87	0.000	35.54276	39.91277

Mean Score at Baseline = 37.7

First 6 months, average change of +6.4 per month

After 6 months, average change of +0.13 per month

One Problem

- That analysis didn't take into account the correlation

	physic~0	physic~1	physic~2	physic~3	physic~4
physical0	1.0000				
physical1	0.3776	1.0000			
physical2	0.3063	0.5167	1.0000		
physical3	0.2283	0.4159	0.5757	1.0000	
physical4	0.2257	0.3218	0.3573	0.4851	1.0000

Modeling Correlation

- Correlation=0:independence
- Correlations all equal: exchangeable
- Correlations diminish steady as farther apart in time: AR(1)
- Need some sense of correlation in one's data

Next Step

- A bonefide longitudinal model
- Two major options:
  - Mixed effects models
  - Generalized estimating equations

Two major modeling strategies

- Random effects: requires explicit model for correlation, needs to be correct for full validity
- GEE: required to nominate model for correlation, doesn't need to be right to be valid if close, standard errors will be smaller

Other differences arise if data is binary or counts

For a GEE model

- Need: "link". This describes how predictors related to outcome. If data continuous, link is almost always "identity". If binary, almost always "logit"
- Need distribution family: if cts, usually "Normal"; if binary, should be binomial

For a GEE model, cont.

- Select correlation structure: independence, exchangeable, AR(1)
- Pick one closest to data or independence is fine
- Request "robust" standard errors ensures validity if your guess was wrong

For this data

- Link: identity, Family: normal
- Use the mean structure given before interaction between depression & time
- Nominated correlation: independence
- Spline with a "knot" at 6 months

Stata Command & Output: Depressed Pts.

xtgee phys *predictors* if dep==1, family(normal) link(identity) i(idno) t(mo) corr(indep) robust

Note coefficients have not changed, only the std. errs., Z's & CIs

(Std. Err. adjusted for clustering on idno)

physical	Coef.	Semirobust Std. Err.	z	P>|z|	[95% Conf.	Interval]
before 6mos.	6.442615	.242425	26.58	0.000	5.967471	6.917759
after 6mos.	.1269116	.1827468	0.69	0.487	-.2312656	.4850889
baseline	37.72776	1.301259	28.99	0.000	35.17734	40.27819

Better Model

xtgee phys c.mosp1##dep c.mosp2##dep, family(normal) link(identity) i(idno) t(mo) corr(indep) robust

(Std. Err. adjusted for clustering on idno)

physical	Coef.	Semirobust Std. Err.	z	P>|z|	[95% Conf.	Interval]
mosp1	4.296064	.2354781	18.24	0.000	3.834535	4.757593
depressed						
1	-11.54875	1.80214	-6.41	0.000	-15.08088	-8.01662
2	-18.73609	1.730903	-10.82	0.000	-22.1286	-15.34358
depressed# c.mosp1						
1	1.415065	.3813247	3.71	0.000	.6676825	2.162448
2	2.146551	.3378082	6.35	0.000	1.484459	2.808643
mosp2	-.1736788	.1563033	-1.11	0.266	-.4800277	.1326701
depressed# c.mosp2						
1	.2107479	.2547885	0.83	0.408	-.2886284	.7101242
2	.3005905	.2403482	1.25	0.211	-.1704833	.7716642
_cons	56.46386	1.142711	49.41	0.000	54.22418	58.70353

Some Thoughts

- Two levels of modeling for longitudinal data: means and correlations
- Means can be hard to model and require careful exploration
- GEE is a useful technique and allows you to avoid needing to model correlation
- That is all is does for you...but that’s good

Mixed Modeling

- More parametric approach
- Explicitly models the correlation
- Modeling correlation requires knowledge of type of models

Correlation

Exchangeable Correlation

	physic~0	physic~1	physic~2	physic~3	physic~4
physical0	1.0000				
physical1	0.4000	1.0000			
physical2	0.4000	0.4000	1.0000		
physical3	0.4000	0.4000	0.4000	1.0000	
physical4	0.4000	0.4000	0.4000	0.4000	1.0000

Correlation is same across any 2 timepoints

Single correlation parameter -- rho = 0.40

Not usually plausible for longitudinal data

Random effect is a way to induce this

Correlation

Autoregressive 1 - (AR1) Correlation

	physic~0	physic~1	physic~2	physic~3	physic~4
physical0	1.0000				
physical1	0.5000	1.0000			
physical2	0.2500	0.5000	1.0000		
physical3	0.1250	0.2500	0.5000	1.0000	
physical4	0.0625	0.1250	0.2500	0.5000	1.0000

Correlation for timepoints adjacent = 0.50

timepoints 1 measure apart = 0.50*0.50

timepoints 2 measure apart = 0.50*0.50

More plausible for longitudinal data -- if measures at equally spaced timepoints

Correlation

Unstructured Correlation

	physic~0	physic~1	physic~2	physic~3	physic~4
physical0	1.0000				
physical1	0.3776	1.0000			
physical2	0.3063	0.5167	1.0000		
physical3	0.2283	0.4159	0.5757	1.0000	
physical4	0.2257	0.3218	0.3573	0.4851	1.0000

No model for the correlation -- totally free

Can take long time to converge in Stata

Or fail to converge -- requires lots of parameters

Mixed Model -- AR(1)

xtmixed phys c.mosp1##dep c.mosp2##dep || idno:, residual(ar 1, t(mo))

physical	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
mosp1	4.336866	.225644	19.22	0.000	3.894612	4.77912
depressed						
1	-11.51941	1.639709	-7.03	0.000	-14.73318	-8.305645
2	-18.62879	1.52096	-12.25	0.000	-21.60982	-15.64776
depressed# c.mosp1						
1	1.314409	.3404492	3.86	0.000	.6471413	1.981678
2	1.969806	.3181863	6.19	0.000	1.346172	2.593439
mosp2	-.1822822	.1858448	-0.98	0.327	-.5465314	.181967
depressed# c.mosp2						
1	.2369709	.2808057	0.84	0.399	-.3133982	.7873399
2	.413691	.2635603	1.57	0.117	-.1028776	.9302596
_cons	56.16341	1.090842	51.49	0.000	54.0254	58.30142

Mixed Model -- AR(1)

xtmixed phys c.mosp1##dep c.mosp2##dep || idno:, residual(ar 1, t(mo))

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
idno: Identity				
sd(_cons)	9.622091	.6090749	8.499408	10.89307
Residual: AR(1)				
rho	.7073725	.0188279	.6685106	.7423818
sd(e)	17.21154	.3314007	16.57411	17.87348

LR test vs. linear regression: chi2(2) = 816.77 Prob > chi2 = 0.0000

Correlation 1 month apart = 0.71

Correlation 2 months apart = 0.71* 0.71 = 0.50

Correlation 3 months apart = 0.71^3 = 0.35

Mixed Model -- Exch

xtmixed phys c.mosp1##dep c.mosp2##dep || idno:,

physical	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
mosp1	4.296664	.2105279	20.41	0.000	3.884037	4.709291
depressed						
1	-11.56244	1.60663	-7.20	0.000	-14.71137	-8.413502
2	-18.55899	1.490839	-12.45	0.000	-21.48098	-15.637
depressed# c.mosp1						
1	1.351961	.3176372	4.26	0.000	.7294035	1.974518
2	1.964092	.2966764	6.62	0.000	1.382617	2.545567
mosp2	-.2061081	.1689812	-1.22	0.223	-.5373052	.125089
depressed# c.mosp2						
1	.2122151	.2552857	0.83	0.406	-.2881356	.7125658
2	.3355955	.2396816	1.40	0.161	-.1341719	.8053629
_cons	56.41977	1.068939	52.78	0.000	54.32469	58.51485

Mixed Model -- Exch

xtmixed phys c.mosp1##dep c.mosp2##dep || idno:,

```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
idno: Identity               |
                   sd(_cons) |   11.73131   .3963987      10.97955    12.53454
-----------------------------+------------------------------------------------
                sd(Residual) |   15.65877   .1920512      15.28685    16.03975
------------------------------------------------------------------------------
```

Correlation = $11.7^2/(11.7^2 + 15.7^2) = 0.36$

Random Effects

- Easy way to specify a correlation model
- Like a unknown shared predictor
  - for a person -- person level covariate
  - for a clinic -- clinic level covariate
- Induces a covariance structure

Example of Random Effects

- Suppose people selected within clinics and clinic is treated as random effect
- xtmixed phys *predictors* || clinic: || idno:, residual(ar 1, t(mo))
- Random effects for clinic and AR1 for time

GEE v. Mixed Models

- Longitudinal data models have two levels
  - model for mean structure
  - model for correlation structure
- GEE and Mixed models differ in the second part
- GEE allows you to pay little attention to the correlation structure

GEE

- With GEE you nominate a correlation structure
- GEE valid if correlation is wrong
  you can even assume independence
- Recovers validity from "robust" standard error
- If # clusters < 10, robust SE is not great -- need to be cautious

Mixed Models

- Normal based model -- more parametric
- Has a formal model for dependence -- should be approximately correct
- Can handle multiple layers of clustering
  very complicated structures
- Can answer questions about clustering
- Behaves better in certain missing data situations (discussed in coming weeks)

Bottom Line

- If you have >1 level of clustering
- Have questions which involve clustering pretty rare
- Desire subject specific interpretation not common
- Then, you should seek about mixed models
- Modeling correlation and specifying it is not easy

Remember

- Pay careful attention to modeling means interactions with time are not uncommon
- Effects often depend on time in a complex way
- Choose those interactions judiciously
- GEE doesn't really mitigate these issues *still have to model mean carefully*