

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

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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+ pts followed after initiation of anti-retroviral therapy (ARV)
- Outcomes: CD4, viral load, scales of function and well-being

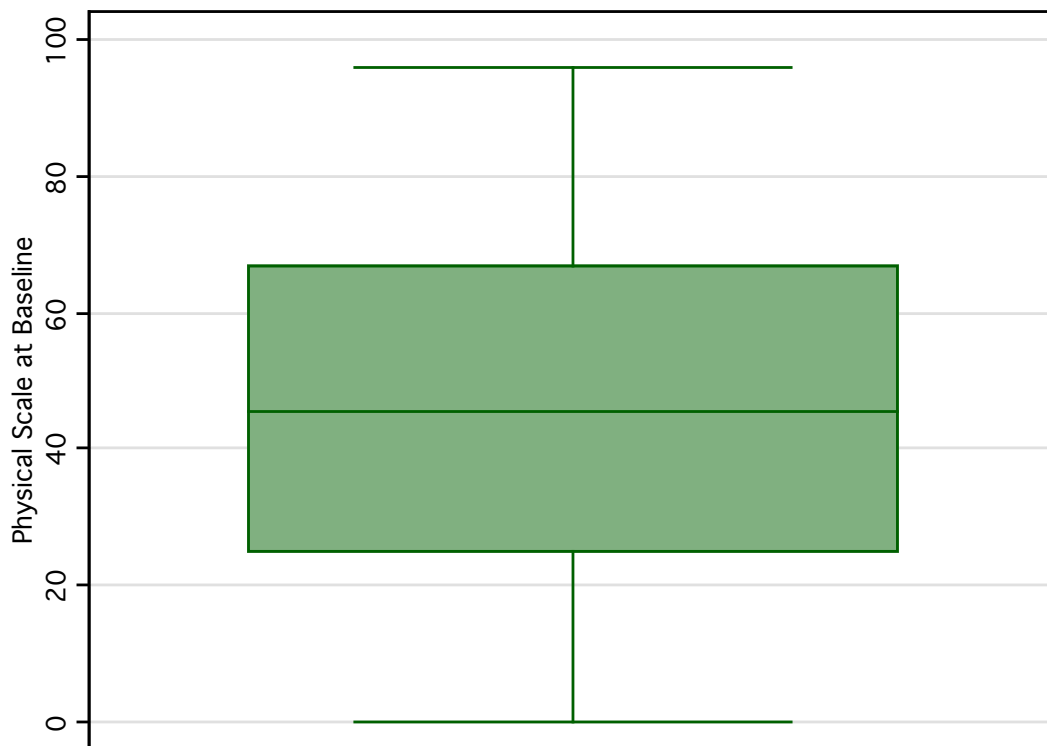
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Sample Question

- 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?

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Boxplot of Baseline Physical Scale



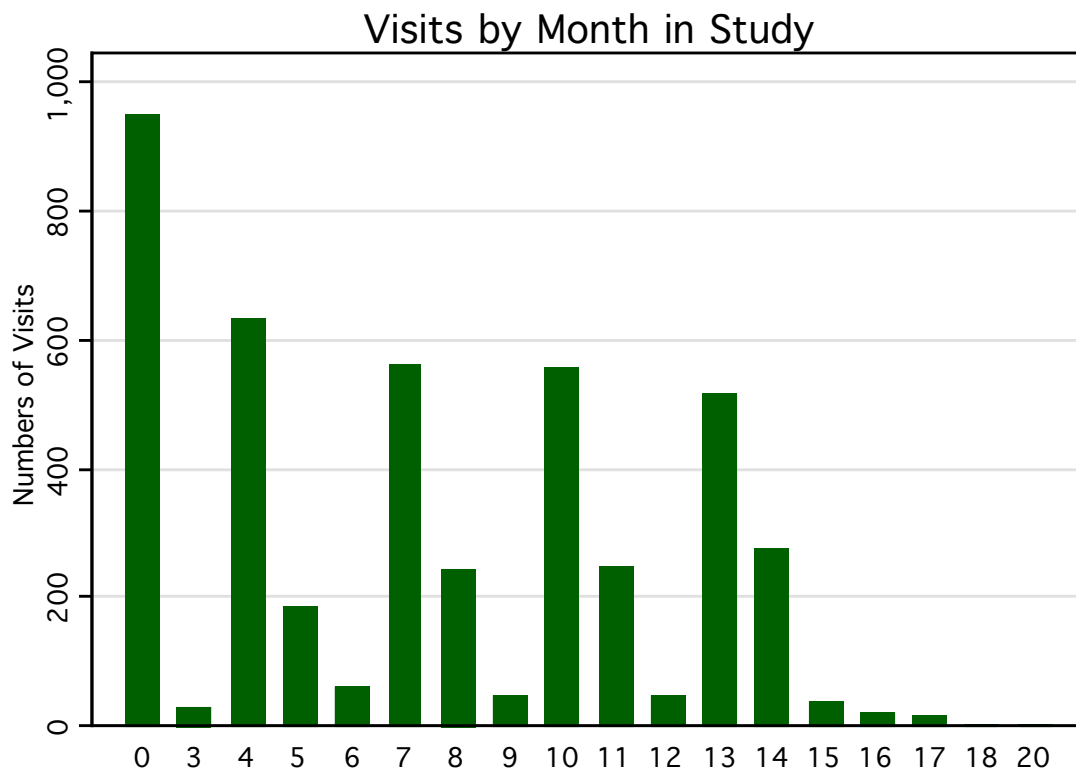
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Features of Longitudinal Data

- 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

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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

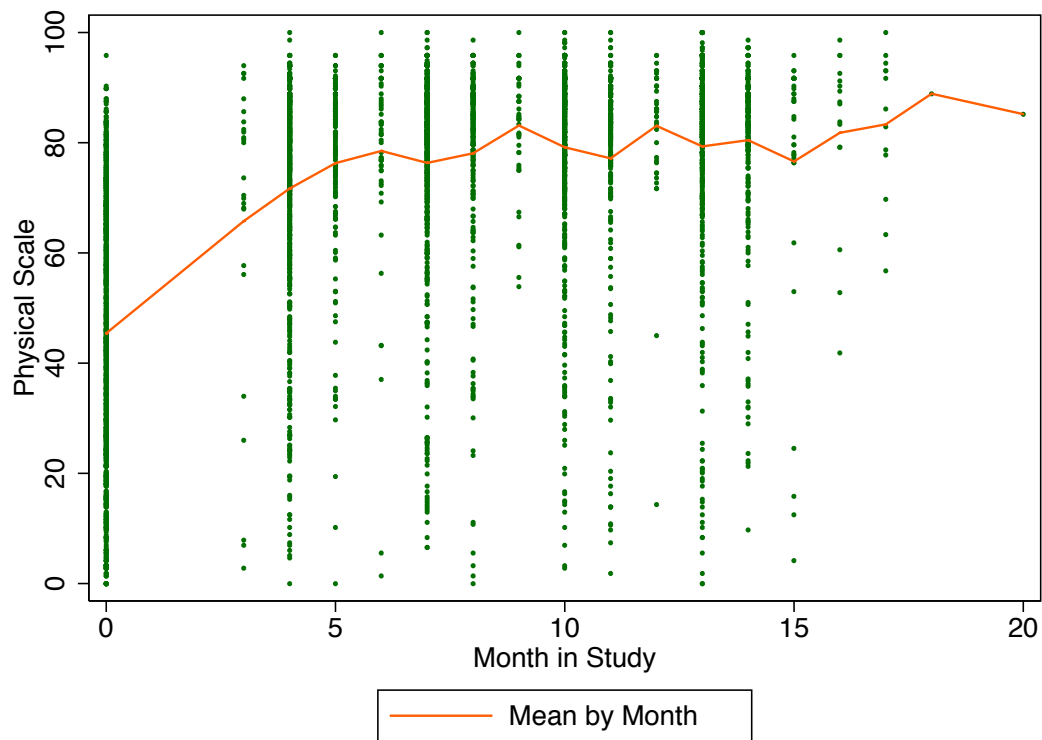
* Grouped by quarter in the study

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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



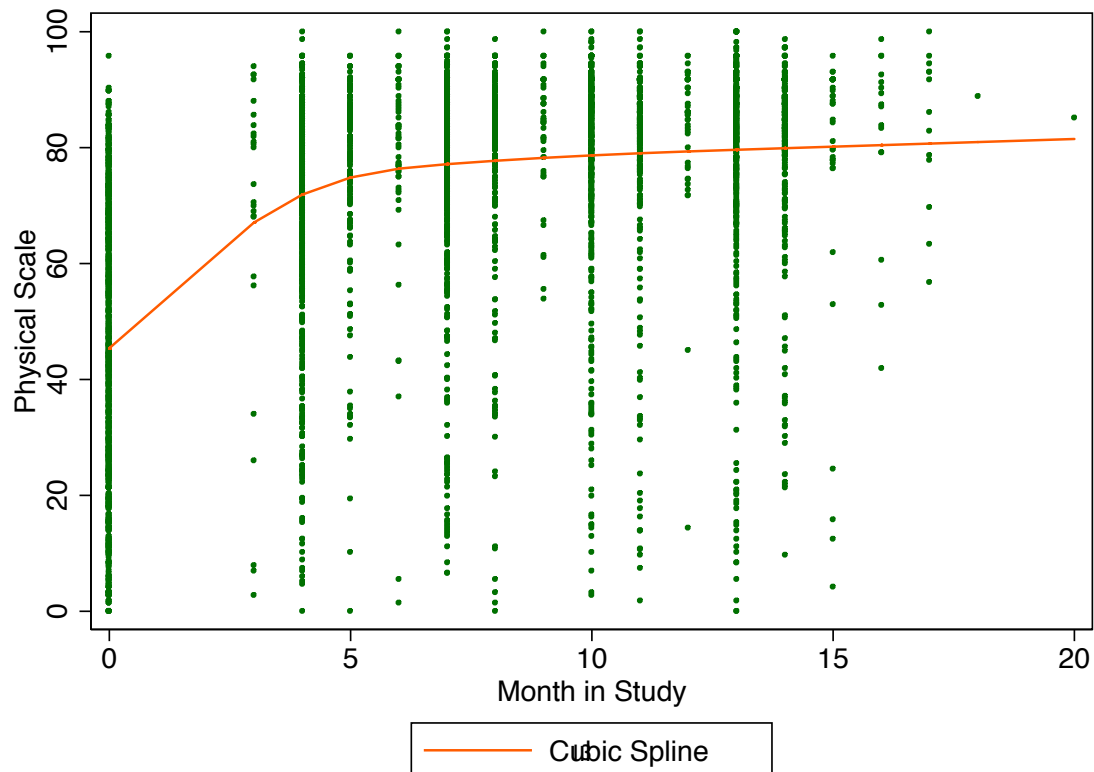
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Cubic Splines

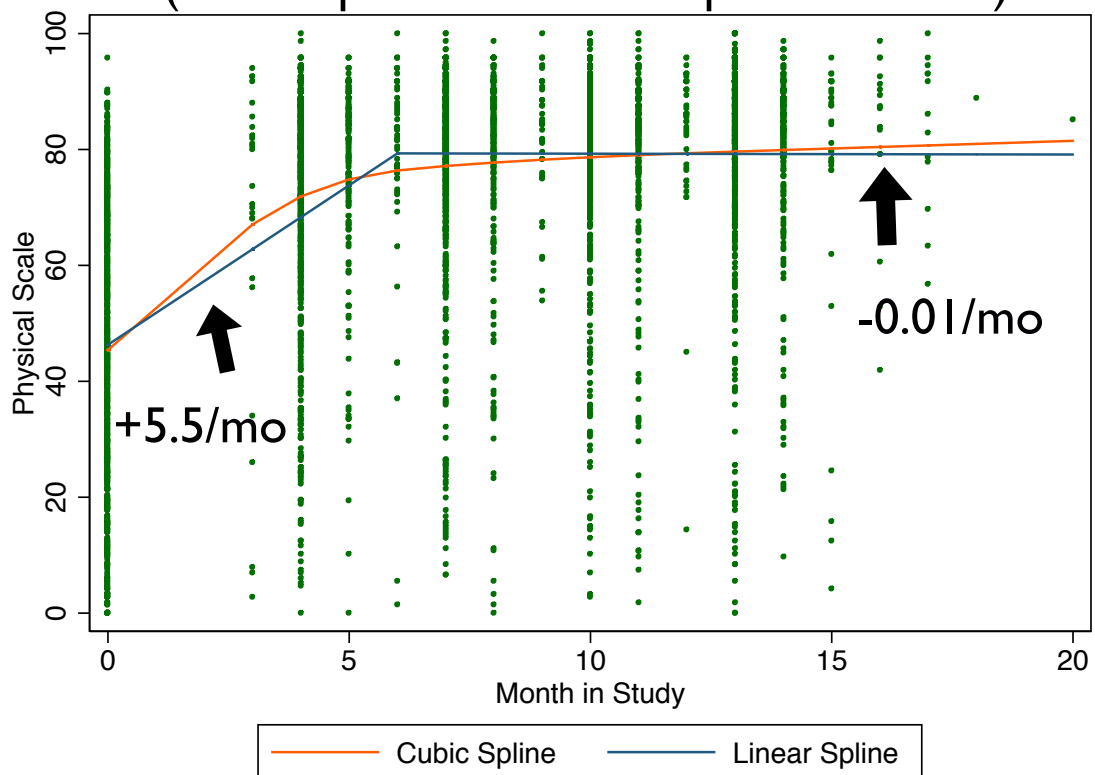
- Exploratory technique
- Fits a smooth curve through a cloud of points
- Flexible: doesn't have to make a straight line

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Mean of Physical Scale by Month
(Cubic Spline Fit)



Mean of Physical Scale by Month
(Cubic Spline and Linear Spline at 6mos.)

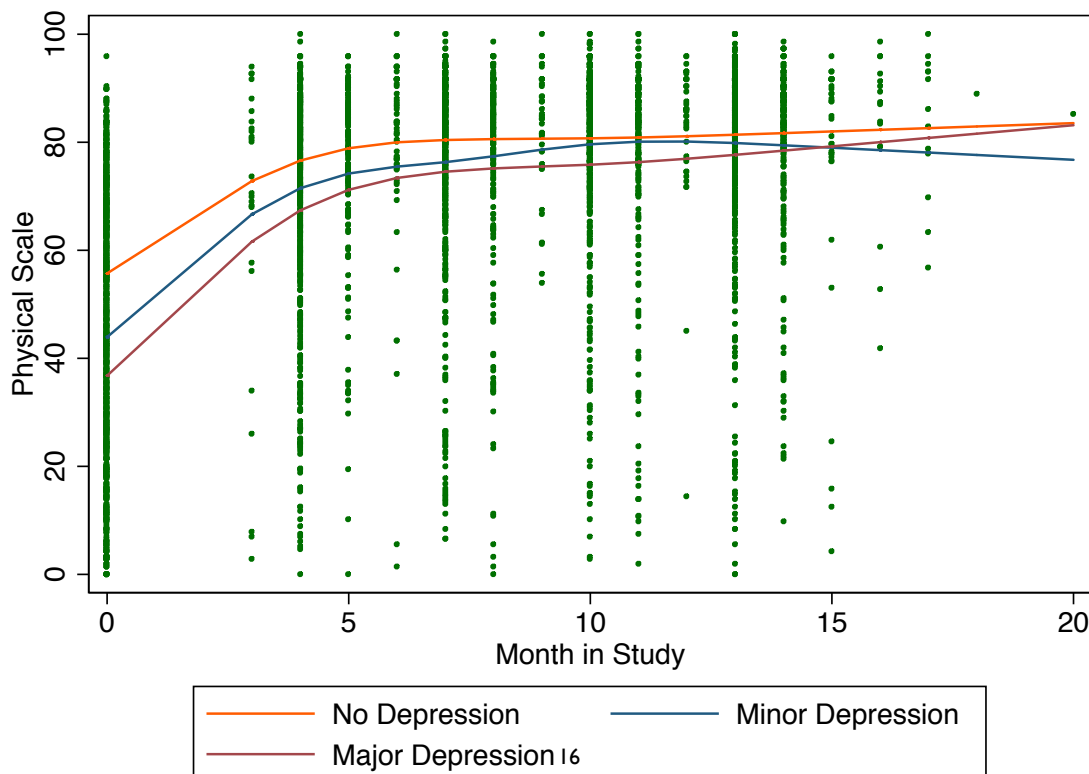


Depression and Physical Functioning

- 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

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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

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Very Simple Analysis before treatment

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

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

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Very Simple Analysis

4 months after treatment

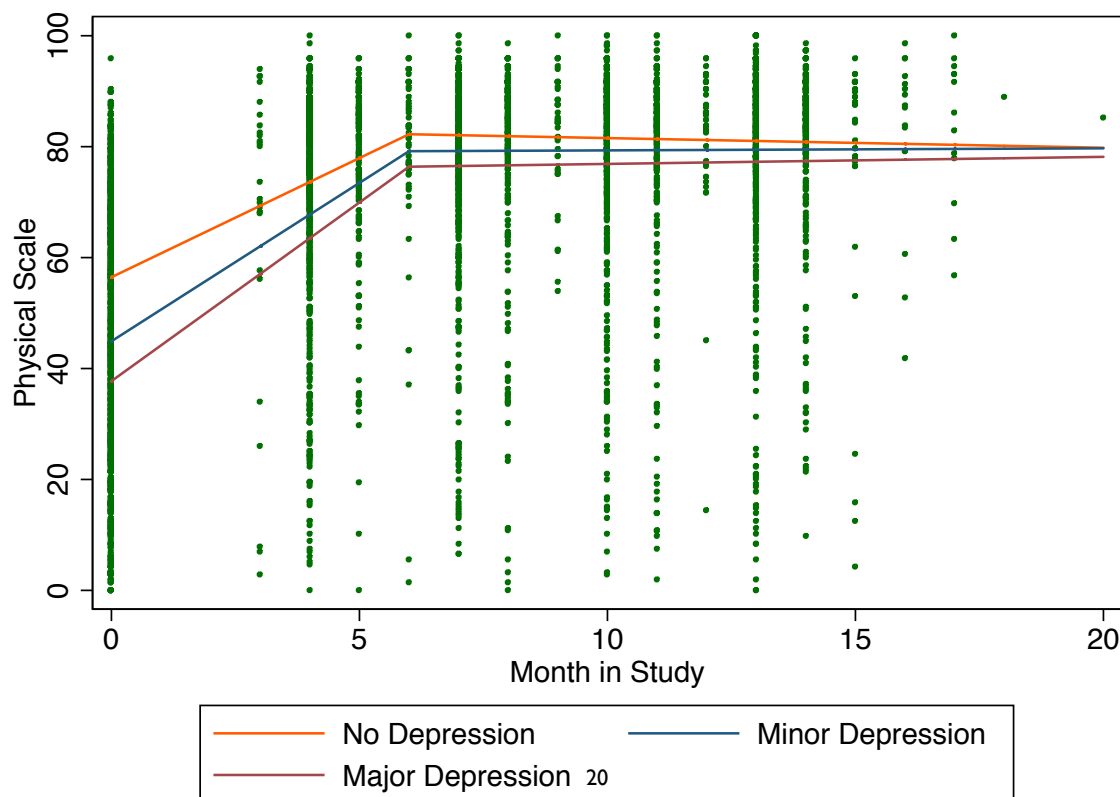
```
. reg phys i.depress if month==4
```

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

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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

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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

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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

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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

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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

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Next Step

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

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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

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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

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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

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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

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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	Semirobust		z	P> z	[95% Conf. Interval]	
	Coef.	Std. Err.				
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

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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	Semirobust		z	P> z	[95% Conf. Interval]	
	Coef.	Std. Err.				
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

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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 it does for you...but that's good

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Mixed Modeling

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

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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

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Correlation

Autoregressive I - (AR I) 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 apart = 0.50×0.50

timepoints 2 apart = $0.50 \times 0.50 \times 0.50$

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

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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

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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

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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 = $0.71^3 = 0.35$

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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

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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

$$\text{Correlation} = 11.7^2 / (11.7^2 + 15.7^2) = 0.36$$

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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

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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

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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

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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

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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)

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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

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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*

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