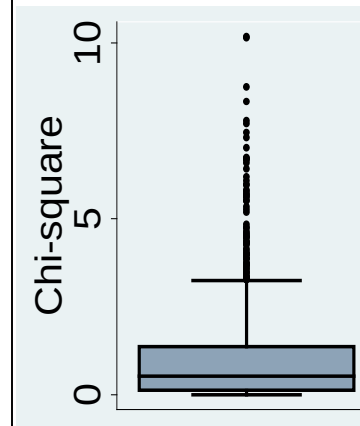


Repeated Measures, Part I

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

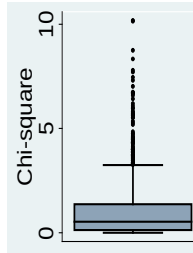


May, 2017

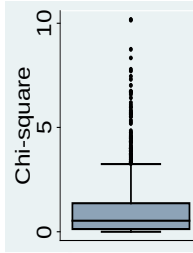


Outline

1. Motivating examples and introduction
2. Analysis of the fecal fat data
3. Accommodating correlated data
4. Correlation structures
5. Long and wide data formats
6. Descriptive methods for longitudinal data
7. Summary



Example: Fecal fat

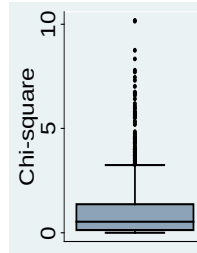


Lack of digestive enzymes in the intestine can cause bowel absorption problems. This will be indicated by excess fat in the feces. Pancreatic enzyme supplements can be given to ameliorate the problem. Does the supplement form make a difference? (Graham, Enzyme replacement therapy of exocrine pancreatic insufficiency in man. *NEJM*, **296**: 1314-17, 1977 – But note: sex information made up for illustration.)



Example: Fecal fat

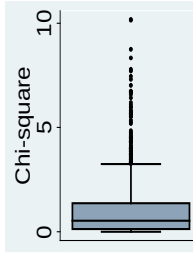
Considerable person to person variability



PatID / Sex	Fecal Fat (g/day)				Avg
	Pill type				
	None	Tablet	Capsule	Coated Capsule	
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



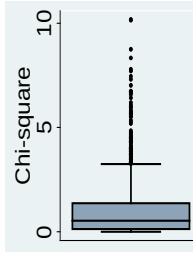
Example: Practice style and back pain (Korff, Barlow, Cherkin, and Deyo, 1994)



Forty-four primary care physicians in a large HMO were classified according to their practice style in treating back pain management (low, moderate or high frequency of prescription of pain medication and bed rest). An average of 24 patients per physician was followed for 2 years (1 month, 1 year and 2 year followups) after the indexed visit. Outcome measures included functional measures (pain intensity, activity limitation days, etc.), patient satisfaction (e.g., “After your visit with the doctor, you fully understood how to take care of your back problem”), and cost.

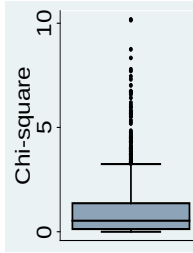


Example: Osteoarthritis Initiative (OAI): www.oai.ucsf.edu



The OAI is a multi-center, longitudinal, prospective observational study of knee osteoarthritis (OA). 4,796 men and women ages 45-79 were enrolled between 2004 and 2006. Image (X-ray and MRI), demographic, and clinical data are being collected yearly. Some of the variables measured over time are: pain scores (one for each knee), presence of OA as judged from X-ray (one for each knee), functional limitation scores (one per person).

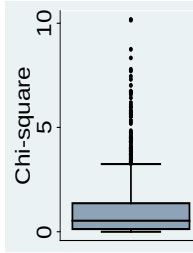
Example: Study of Osteoporotic Fractures (SOF): sof.ucsf.edu



The Study of Osteoporotic Fractures (SOF) is a longitudinal, prospective study of osteoporosis, breast cancer, stroke, and total and cause-specific mortality. In 1986, SOF enrolled 9,704 women and continues to track these women with clinical visits every 2 years. Data from the first seven visits are now available to the public. The data include measures of bone mineral density (BMD), sex and calcitropic hormones, tests of strength and function, cognitive exams, use of medication, health habits and much more.



Introduction: Hierarchical data



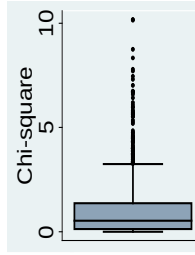
Hierarchical data (responses and/or predictors) are data collected from different levels within a study.

May be repeated measures data (e.g., fecal fat), clustered or multilevel data (e.g., back pain) or longitudinal data (over time, e.g., OAI or SOF).

A characteristic of hierarchical data is that predictors can be measured at any level in the hierarchy.



Some prototypical questions: Fecal fat example

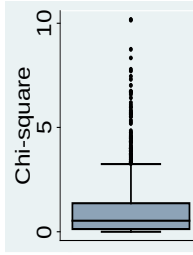


Question 1: Does fecal fat depend on the repeated measures factor, pill type?

Question 2: Does fecal fat depend on the non-repeated measures factor, sex?

Some prototypical questions:

Back pain example



Question 1: Does log cost depend on the
between physician factor, practice style?

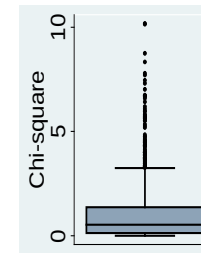
Question 2: Does understanding of physician
recommendation depend on practice style?

Question 3: Does log cost depend on the within
physician, between patient factor, sex of the
patient?

Question 4: Is there between physician
variability in treatment of similar patients?

Some prototypical questions:

SOF



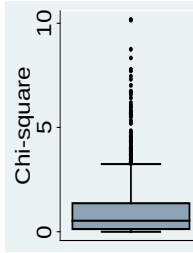
Question 1: Is change in BMD related to age at menopause? (time invariant predictor of change)

Question 2: Is change in BMD related to change in BMI? (time varying predictor of change)

Question 3: Which participants are maintaining cognitive function into their 9th and 10th decades of life? (subject specific prediction)



Introduction

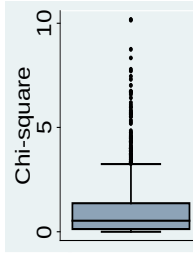


- Analysis technique depends on nature of the *outcome* variable and research question.
 - Binary: logistic regression (e.g., BMI>30)
 - Odds ratios, area under ROC curve
 - Numeric: linear regression (e.g., BMI, BMD)
 - Also – time to event (Cox model or pooled logistic regression), count outcomes (Poisson regression)
- Methods need to be modified for hierarchical data.



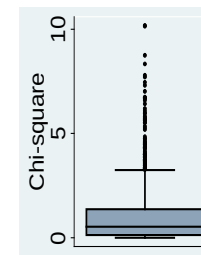
Accommodating hierarchical data

- Repeated measures/clustering in the *outcome* requires new methods of analysis. But not in the predictor.
- SOF: Is visit 8 cognitive status (outcome) related to previous (repeatedly measured across multiple visits) physical activity? Does not have repeated measures on the outcome.
- This situation can be accommodated by including multiple values of physical activity as predictors or by calculating summary measure(s) (e.g., average physical activity).





Fecal fat data analysis



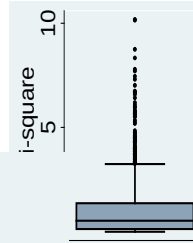
```
. tabstat fecfat, by(pilltype) stats(n mean sd min max)
```

Summary for variables: fecfat
by categories of: pilltype (Type of pill)

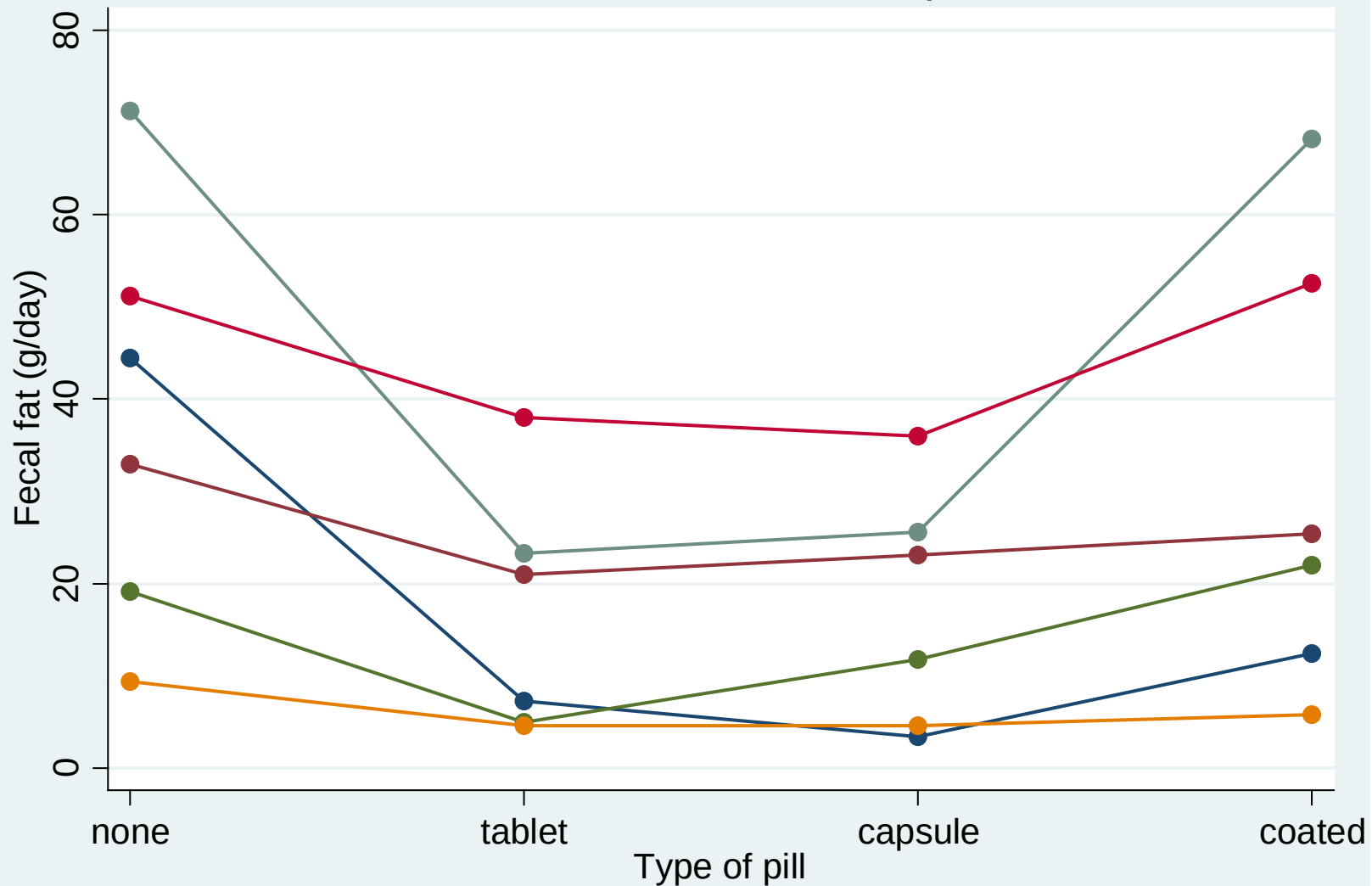
pilltype	N	mean	sd	min	max
none	6	38.08333	22.47447	9.4	71.3
tablet	6	16.53333	13.32091	4.6	38
capsule	6	17.41667	12.93745	3.4	36
coated	6	31.06667	24.2641	5.8	68.2
Total	24	25.775	20.00214	3.4	71.3



Fecal fat data analysis

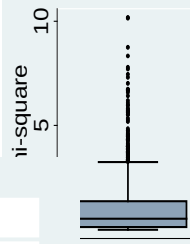
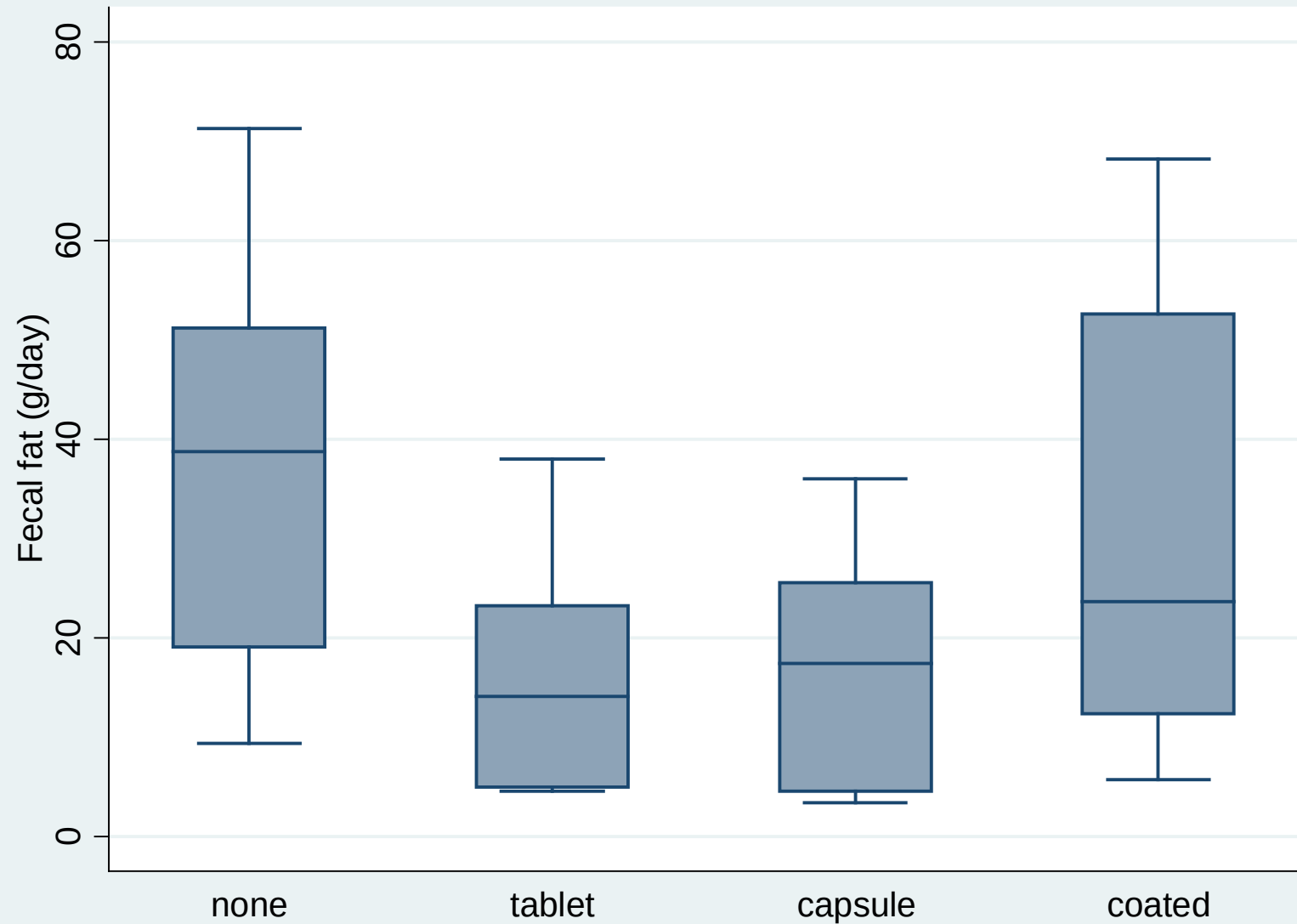


Fecal fat values for each patient





Fecal fat data analysis





Regression/ANOVA ignoring sex effects (a wrong analysis)



```
. regress fecfat i.pilltype
```

Source	SS	df	MS	Number of obs	=	24
Model	2008.6017	3	669.533901	F(3, 20)	=	1.86
Residual	7193.36328	20	359.668164	Prob > F	=	0.1687
				R-squared	=	0.2183
				Adj R-squared	=	0.1010
Total	9201.96498	23	400.085434	Root MSE	=	18.965

fecfat	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
pilltype						
tablet	-21.55	10.9494	-1.97	0.063	-44.39005	1.29005
capsule	-20.66667	10.9494	-1.89	0.074	-43.50672	2.173384
coated	-7.016668	10.9494	-0.64	0.529	-29.85672	15.82338
_cons	38.08333	7.742396	4.92	0.000	21.93298	54.23369

```
. testparm i.pilltype
```

```
( 1)  2.pilltype = 0
```

```
( 2)  3.pilltype = 0
```

```
( 3)  4.pilltype = 0
```

```
F( 3, 20) = 1.86
```

```
Prob > F = 0.1687
```

Difference between average for Tablet – None

(16.53 – 38.08 = -21.55)

Overall test, p=0.17



A hierarchical analysis

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

GEE population-averaged model

Group variable: patid

Link: identity

Family: Gaussian

Correlation: exchangeable

Number of obs =

Number of groups =

Obs per group:

min = 4

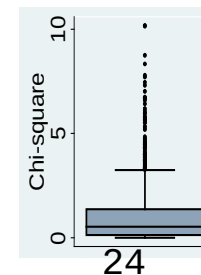
avg = 4.0

max = 4

Wald chi2(3) = 22.53

Scale parameter: 299.7235

Prob > chi2 = 0.0001



fecfat	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
pilltype						
tablet	-21.55	5.451781	-3.95	0.000	-32.23529	-10.86471
capsule	-20.66667	5.451781	-3.79	0.000	-31.35196	-9.981373
coated	-7.016668	5.451781	-1.29	0.198	-17.70196	3.668626
_cons	38.08333	7.067808	5.39	0.000	24.23068	51.93598

```
. testparm i.pilltype
```

```
( 1)  2.pilltype = 0
```

```
( 2)  3.pilltype = 0
```

```
( 3)  4.pilltype = 0
```

chi2(3) = 22.53

Prob > chi2 = 0.0001



A hierarchical analysis



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

```
GEE population-averaged model
```

```
Group variable:                patid
```

```
Link:                          identity
```

```
Family:                        Gaussian
```

```
Correlation:                   exchangeable
```

```
Number of obs      =          24
```

```
Number of groups   =           6
```

```
Obs per group:
```

```
    min =           4
```

```
    avg =          4.0
```

```
    max =           4
```

```
Wald chi2(3)      =          22.53
```

```
Prob > chi2       =          0.0001
```

```
Scale parameter:                299.7235
```

fecfat	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
pilltype						
tablet	-21.55	5.451781	-3.95	0.000	-32.23529	-10.86471
capsule	-20.66667	5.451781	-3.79	0.000	-31.35196	-9.981373
coated	-7.016668	5.451781	-1.29	0.198	-17.70196	3.668626
_cons	38.08333	7.067808	5.39	0.000	24.23068	51.93598

```
. xtcorr
```

```
Estimated within-patid correlation matrix R:
```

```

      c1      c2      c3      c4
r1  1.0000
r2  0.7025  1.0000
r3  0.7025  0.7025  1.0000
r4  0.7025  0.7025  0.7025  1.0000

```



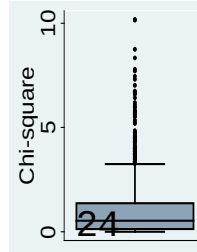
A hierarchical analysis (variation)

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

```
GEE population-averaged model
Group variable:                patid
Link:                          identity
Family:                        Gaussian
Correlation:                   exchangeable

Number of obs      =      24
Number of groups   =       6
Obs per group: min =       4
                  avg =     4.0
                  max =       4

Wald chi2(3)       =     11.71
Prob > chi2        =     0.0084
(Std. Err. adjusted for clustering on patid)
```



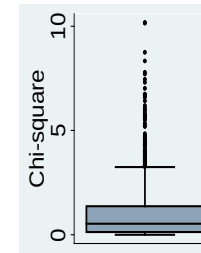
		Robust				
fecfat		Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
pilltype						
	tablet	-21.55	6.931847	-3.11	0.002	-35.13617 -7.96383
	capsule	-20.66667	7.349407	-2.81	0.005	-35.07124 -6.262094
	coated	-7.016668	5.246295	-1.34	0.181	-17.29922 3.265881
	_cons	38.08333	9.175163	4.15	0.000	20.10034 56.06632

```
. testparm i.pilltype
( 1) 2.pilltype = 0
( 2) 3.pilltype = 0
( 3) 4.pilltype = 0
```

```
      chi2( 3) =    11.71
Prob > chi2 =    0.0084
```

Coefficient unchanged, but SE is slightly different (6.93 versus 5.45 without robust)

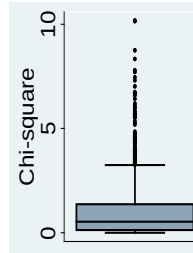
Accommodating hierarchical data



- The usual statistical methods (multiple regression, basic ANOVA, logistic regression, and many others) assume observations are independent.
- *Important idea:* observations taken within the same subgroup in a hierarchy are often more similar to one another than to observations in different subgroups, other things being equal. [correlated]
- Failure to accommodate the hierarchical nature of the data can lead to incorrect SEs, p-values and confidence intervals, sometimes grossly incorrect.



Regr/ANOVA with sex effects (incorrect analysis)



```
. regress fecfat i.pilltype i.sex
```

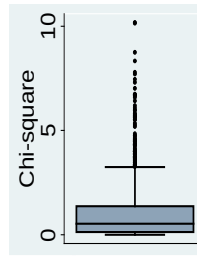
Source	SS	df	MS	Number of obs	=	24
Model	3110.21668	4	777.554169	F(4, 19)	=	2.43
Residual	6091.7483	19	320.618332	Prob > F	=	0.0837
				R-squared	=	0.3380
				Adj R-squared	=	0.1986
Total	9201.96498	23	400.085434	Root MSE	=	17.906

fecfat	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
pilltype						
tablet	-21.55	10.33793	-2.08	0.051	-43.18753	.0875334
capsule	-20.66667	10.33793	-2.00	0.060	-42.3042	.9708671
coated	-7.016668	10.33793	-0.68	0.505	-28.6542	14.62087
1.sex	13.55	7.31002	1.85	0.079	-1.750047	28.85005
_cons	31.30833	8.172851	3.83	0.001	14.20236	48.41431

Sex effects are borderline
statistically significant



A hierarchical analysis



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

Iteration 1: tolerance = 9.971e-16

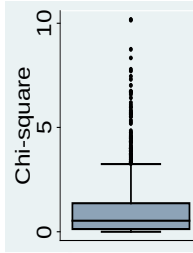
GEE population-averaged model		Number of obs	=	24
Group variable:	patid	Number of groups	=	6
Link:	identity	Obs per group: min	=	4
Family:	Gaussian	avg	=	4.0
Correlation:	exchangeable	max	=	4
		Wald chi2(4)	=	24.00
Scale parameter:	253.8228	Prob > chi2	=	0.0001

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

Fecal fat data analysis - summary

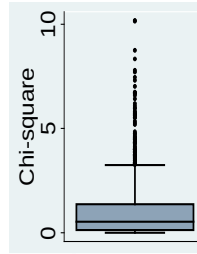


- Failing to accommodate the hierarchical nature of the data led to grossly incorrect statistical inferences.
- Estimates were unchanged, but SEs were affected. (In general estimates tend to be little affected, but do change slightly).
- The proper hierarchical analysis can lead to smaller or larger SEs compared to a naïve analysis.

Not just an academic concern ...

J Assist Reprod Genet
DOI 10.1007/s10815-010-9518-0

EMBRYO BIOLOGY



A prospective randomized sibling-oocyte study of two media systems for culturing cleavage-stage embryos—impact on fertilization rate

Received: 30 July 2010 / Accepted: 19 November 2010
© Springer Science+Business Media, LLC 2010

Not just an academic concern ...

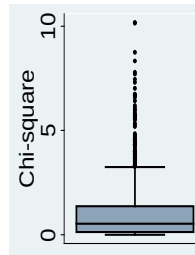
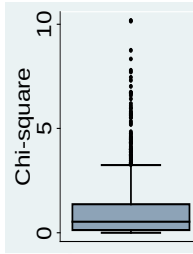


Table 2 Demographic data of patients included in the study is shown

Patients included (<i>n</i>)	110
Female age, mean $\pm$ SD (years)	33.9 $\pm$ 3.8
Infertility diagnosis, <i>n</i> (%)	
Tubal factor	8 (7.3)
Endometriosis	8 (7.3)
Unexplained	30 (27.3)
Anovulation	12 (10.9)
Male factor	37 (33.6)
Other	15 (13.6)
No. of oocytes retrieved per patient, mean $\pm$ SD	10.9 $\pm$ 4.8

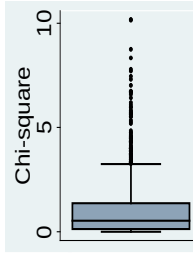
Not just an academic concern ...



Statistical analysis

at least 269 oocytes in each group. Comparison of normal fertilisation rates, polyploid rates, embryo quality and embryo utilization rates was performed using the Chi-square test. Positive hCG rates, clinical pregnancy rates, implantation rates and delivery rates were compared by using the Fisher's exact test (two-tailed). A value of $p < 0.05$ was considered statistically significant.

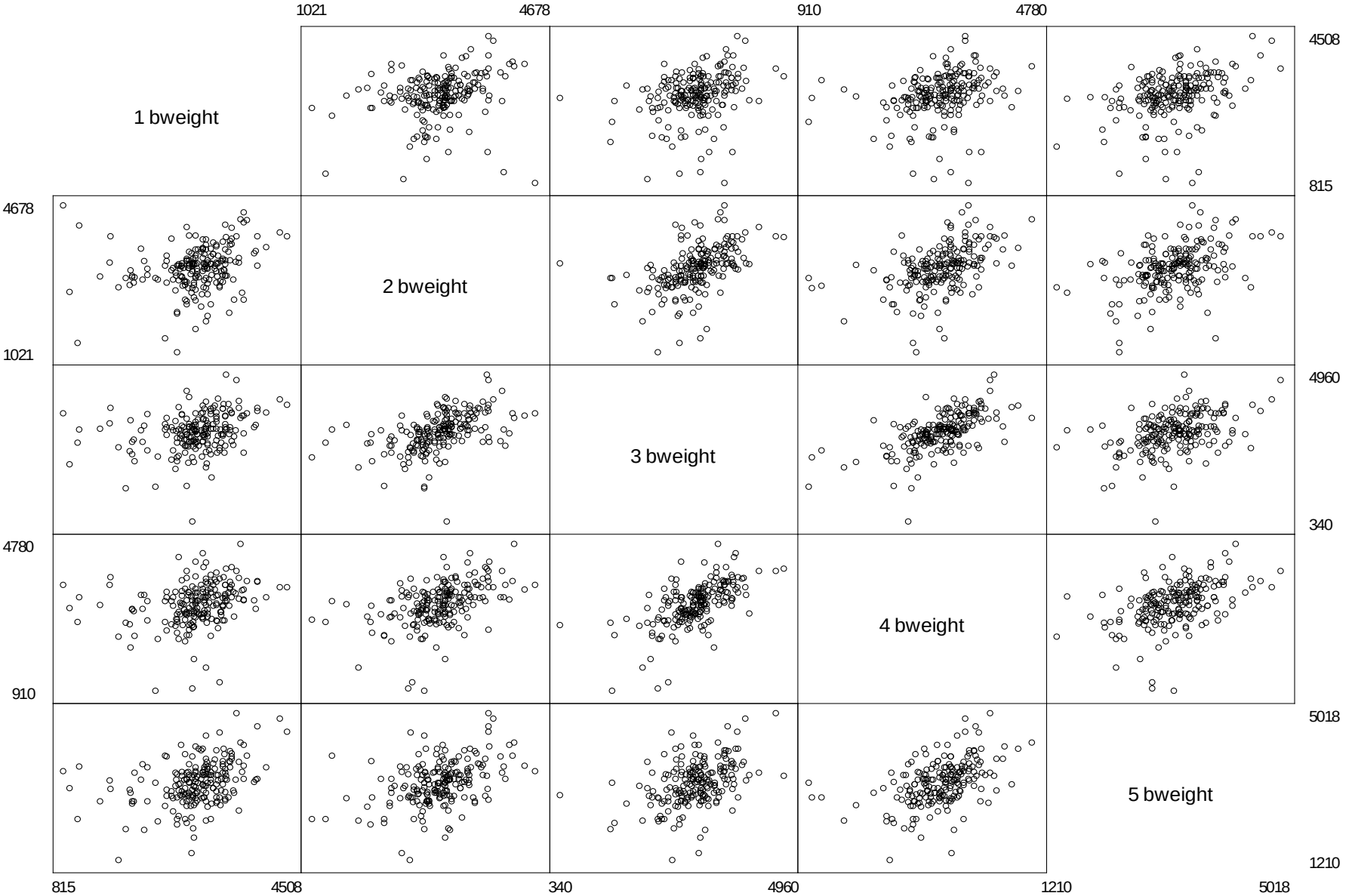
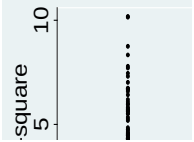
Correlation structures



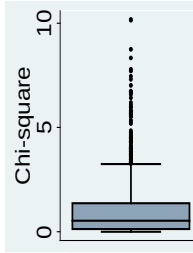
With continuous, balanced data we can plot the measurements that occur at different time points (or are repeated measurements of different types). The “Georgia babies” dataset follows successive birthweights of infants to mothers (each of whom had five children) from vital statistics in Georgia. We are interested in whether birthweight increases with birth order and mothers’ age. In lab we will generate the following plots.



Georgia Babies



Georgia Babies



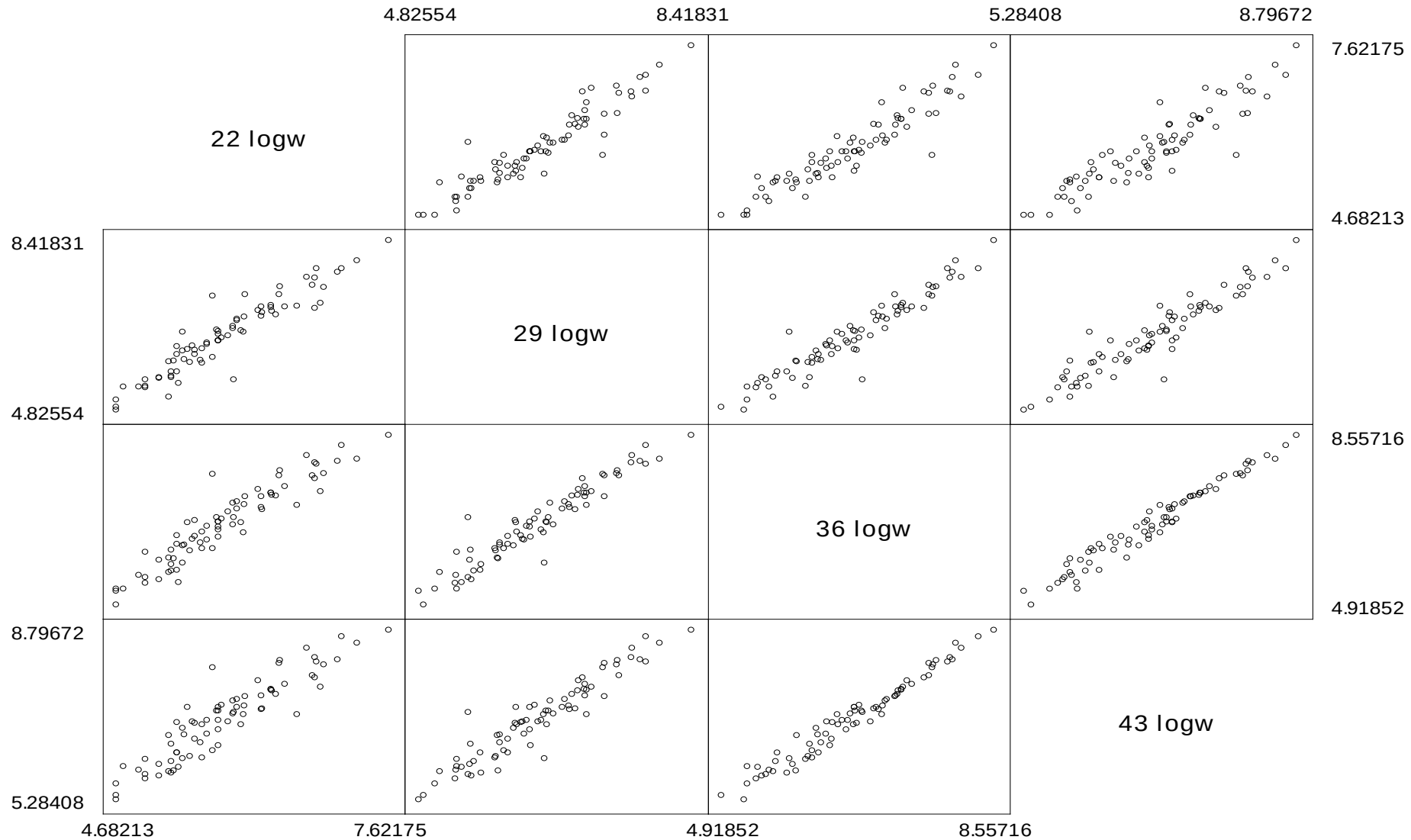
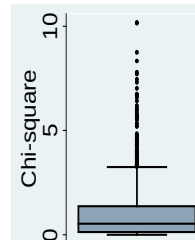
- Another common summary is the correlation matrix. Here is the correlation matrix for the Georgia babies data set:

```
. pwcorr  bweight1 bweight2 bweight3 bweight4 bweight5
          | bweight1 bweight2 bweight3 bweight4 bweight5
-----+-----
bweight1 |    1.0000
bweight2 |    0.2282    1.0000
bweight3 |    0.2950    0.4833    1.0000
bweight4 |    0.2578    0.4676    0.6185    1.0000
bweight5 |    0.3810    0.4261    0.4233    0.4642    1.0000
```

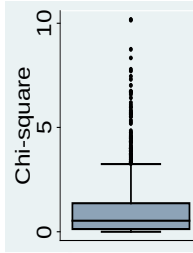
- How do we read this? Why isn't there anything in the top right hand corner?



Here is another example, giving the log weights (why log?) of mice for several weeks of measurement, mostly reflecting gain in tumor weight



Tumor/weight



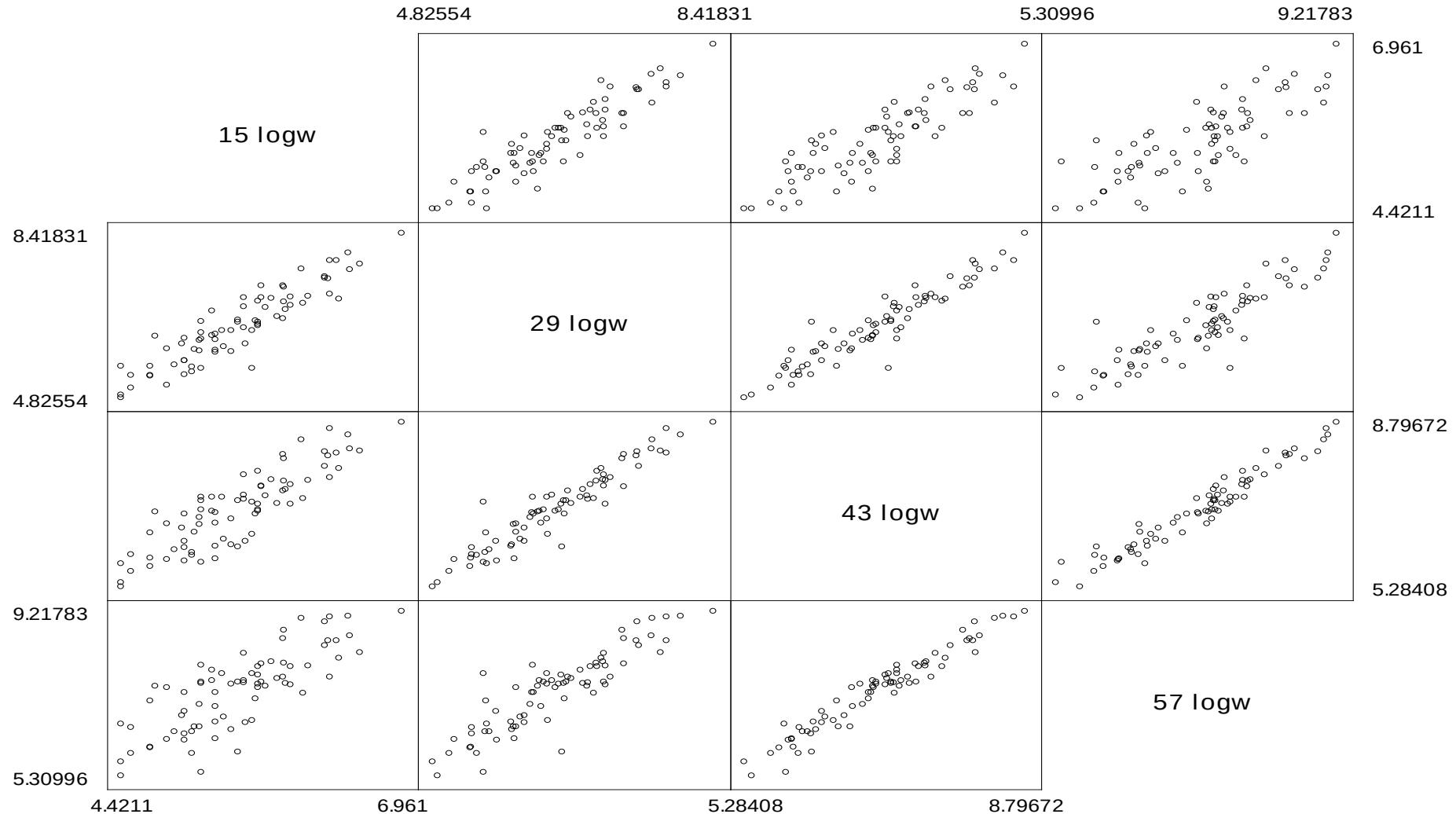
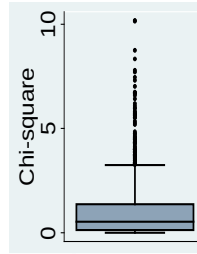
- And here is the corresponding correlation matrix:

```
pwcorr  logw22 logw29 logw36 logw43
          |  logw22  logw29  logw36  logw43
-----+-----
      logw22 |    1.0000
      logw29 |    0.9414    1.0000
      logw36 |    0.9400    0.9568    1.0000
      logw43 |    0.9190    0.9466    0.9803    1.0000
```

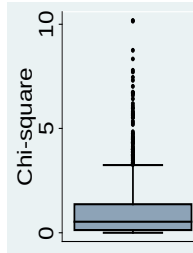



Tumor/weight

Here is a different collection of weeks for the same dataset. What does this suggest?



Tumor/weight



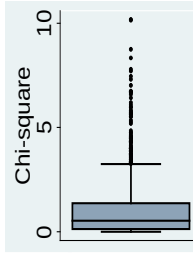
Here is the correlation matrix for that set of weeks:

```
pwcorr  logw15 logw29 logw43 logw57
```

```
-----+-----
      |  logw15  logw29  logw43  logw57
logw15 |  1.0000
logw29 |  0.9145  1.0000
logw43 |  0.8713  0.9466  1.0000
logw57 |  0.7937  0.8952  0.9692  1.0000
```

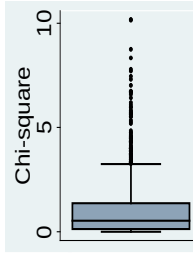


Correlation structures



- The Georgia babies and tumor data sets are tidy because each “subject” has the same collection of observations (five observations for each mom and a tumor weight for each week). This is called “balanced” data.
- The Korff et al, back pain example is an example of unbalanced data, both because the sample sizes are unequal and because the “case-mix” is unequal. Because we don’t have a variable on which to reasonably order the observations (like parity for the Georgia babies data or time for the tumor data), there is not a reasonable plot we can make. But why are the data correlated in the back pain example?

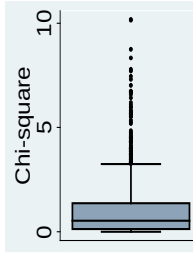
Correlation structures



- Back to the tumor data: With 10 weeks of tumor data, there is the correlation of week 1 with week 2, week 1 with week 3, ..., week 9 with week 10 for 45 unique correlations in all.
- Rather than having to estimate a separate correlation between each pair of times, we often use a simpler correlation “structure,” both for ease of model specification and for statistical efficiency.



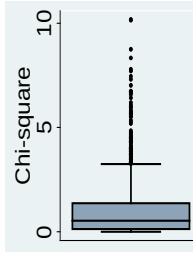
Correlation structures



- Common correlation structures used in STATA are:
 1. Exchangeable (all correlations equal).
 2. Autoregressive (correlations closer in time are more highly correlated, but drop off to zero as the difference in time increases).
 3. Unstructured (no assumptions made – estimate a separate correlation for each pair of time points).
 4. Independent (all correlations zero).
- In an AR(1) structure, if the correlation of adjacent time points is, say, 0.8, then the correlation of observations two time points apart is $0.8^2 = 0.64$.



Correlation structures



Which correlation structures do you feel best describe the examples we've considered?

Georgia babies

Tumor weights weeks 22 through 43

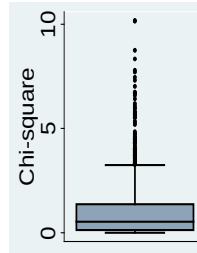
Tumor weights weeks 15 through 57

Back pain



Data layouts for longitudinal/clustered data

For longitudinal analyses: “long format”

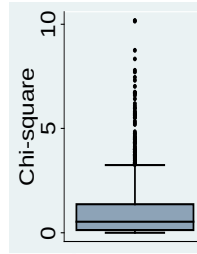


id	visit	gender	bmi	totbmd
9000296	2	M	29.8	0.82
9000296	4	M	29.8	0.8
9000296	6	M	29.4	0.8
9000296	8	M	29.4	0.79
...				
9000798	2	F	32.4	0.4
9000798	4	F	32.3	0.41
9000798	6	F	32.3	0.39
9000798	8	F	32.5	0.39



Data layouts for longitudinal/clustered data

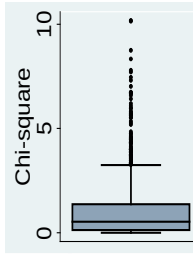
For change score analyses: “wide format”



id	v02bmi	v04bmi	v06bmi
9000296	29.8	29.4	29.1
9000798	32.4	32.3	32.5

In lab: how to convert data back and forth between the two data formats.

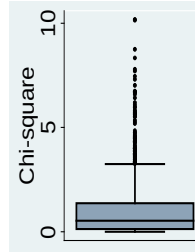
Example: HERS



Heart and Estrogen/Progestin Study (HERS - Hulley, *et al*, 1998, *JAMA*), was a randomized trial with long-term, yearly followup. `pptid` is the participant ID and `nvisit` is the visit number, with 0 being baseline:

```
. xtset pptid nvisit
      panel variable:  pptid (unbalanced)
      time variable:  nvisit, 0 to 5, but with gaps
                   delta:  1 unit
```

Descriptive methods: pattern of data



```
. xtdescribe
  pptid:  1, 2, ..., 2763          n =      2763
  nvisit: 0, 1, ..., 5            T =        6
      Delta(nvisit) = 1 unit
      Span(nvisit)  = 6 periods
      (pptid*nvisit uniquely identifies each observation)
```

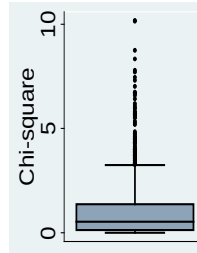
Distribution of T_i: min 5% 25% 50% 75% 95% max

 1 2 4 5 5 6 6

Freq.	Percent	Cum.	Pattern
-----+-----			
1469	53.17	53.17	11111.
531	19.22	72.39	1111..
327	11.83	84.22	111111
119	4.31	88.53	111...
106	3.84	92.36	1.....
87	3.15	95.51	11....
40	1.45	96.96	111.1.
22	0.80	97.76	1111.1
11	0.40	98.15	11.11.
51	1.85	100.00	(other patterns)
-----+-----			
2763	100.00		XXXXXX



Descriptive methods: variation between vs within individuals

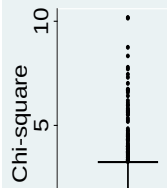


```
. xtsum bmi glucose white htnmeds
```

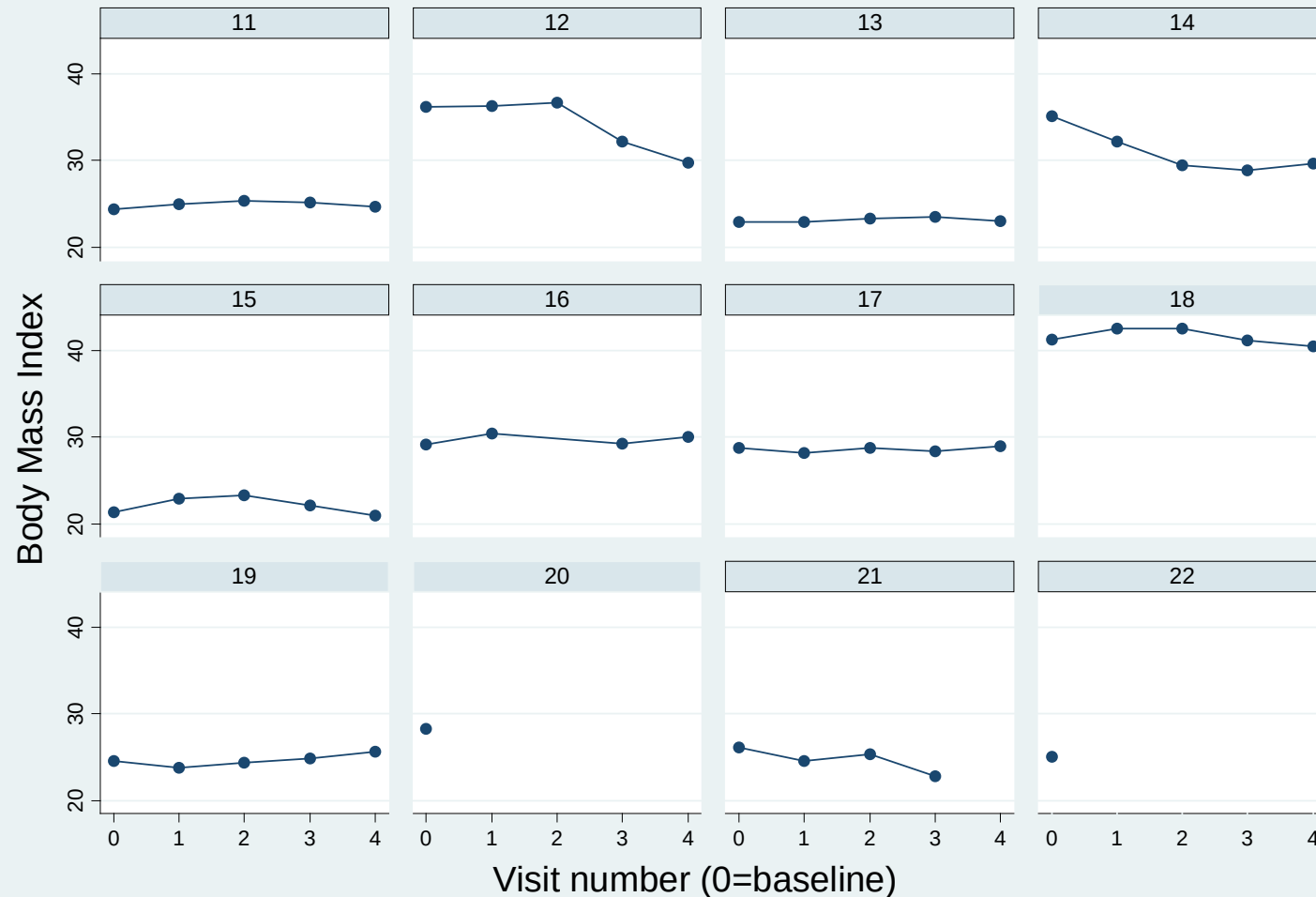
Variable		Mean	Std. Dev.	Min	Max	Observations
-----+-----						
bmi	overall	28.52184	5.565558	14.73	57.56	N = 12258
	between		5.506242	15.21	54.89667	n = 2761
	within		1.174147	20.50784	38.41184	T-bar = 4.4397
-----+-----						
glucose	overall	113.4589	41.18884	4	478	N = 7608
	between		36.56199	53	311	n = 2763
	within		20.33938	-59.20781	322.7922	T-bar = 2.75353
-----+-----						
white	overall	.8936408	.3083091	0	1	N = 12533
	between		.3153701	0	1	n = 2760
	within		0	.8936408	.8936408	T-bar = 4.54094
-----+-----						
htnmeds	overall	.8341568	.3719546	0	1	N = 12548
	between		.324773	0	1	n = 2763
	within		.1811389	.0008235	1.66749	T-bar = 4.54144



Descriptive methods: graphing variation over time



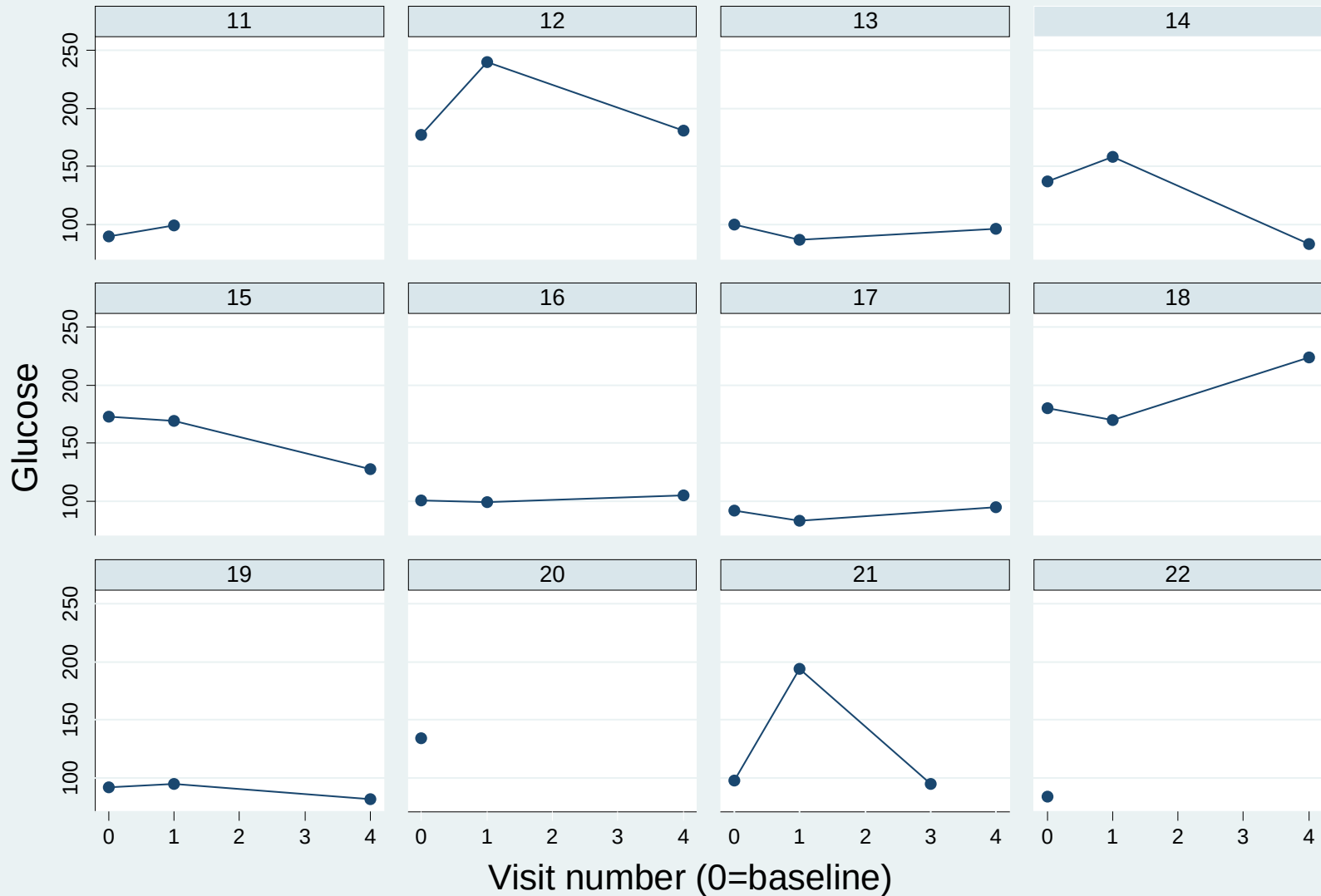
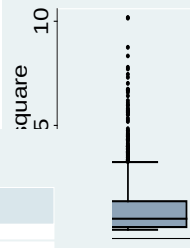
`twoway (connected bmi nvisit) if pptid>10 & pptid<23, by(pptid)`



Graphs by subject id



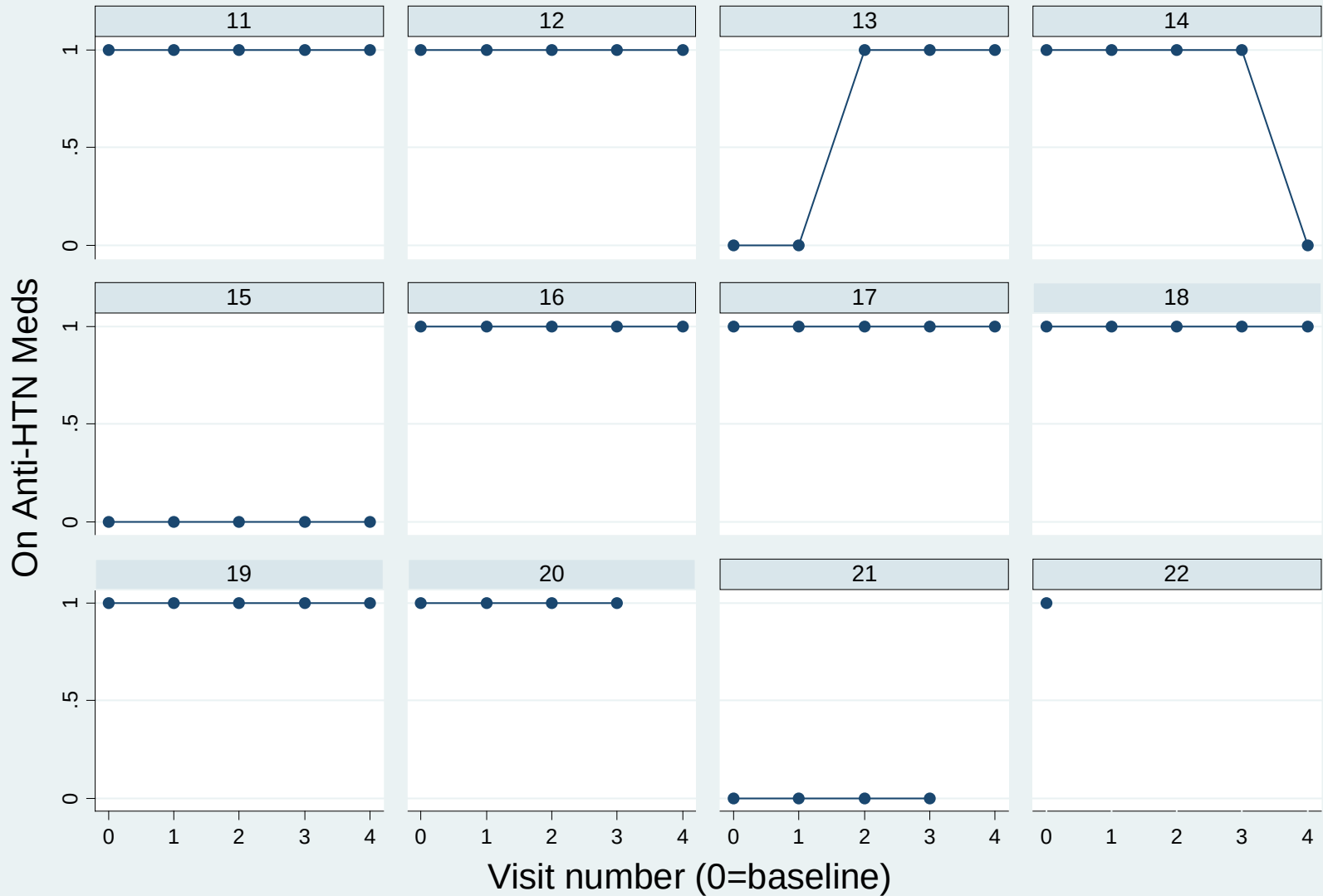
Descriptive methods: graphing



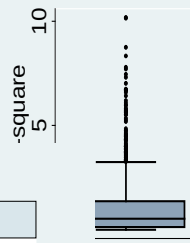
Graphs by subject id



Descriptive methods: graphing

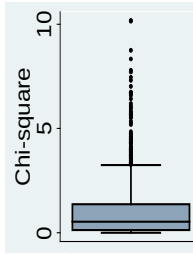


Graphs by subject id



Summary – Part 1

- Hierarchical data structures are common.
- They lead to correlated data.
- Ignoring the correlation can be a serious error.
- Not easy to predict whether a proper, correlated data analysis will yield larger or smaller standard errors compared to an incorrect analysis that assumes all the data are independent.



Summary – Part 2

- We will often need to specify a correlation “structure” when using correlated data methods.
- Repeated measures analyses need data in “long” format, but “wide” format is more convenient for certain calculations.
- Stata has convenient, built-in functions that generate descriptive statistics to better understand hierarchical data. Use them before embarking on formal statistical analyses.

