Faculty of Health Sciences

Correlated data

Longitudinal measurements

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Longitudinal data

Outline

- Designs
- Models for the mean
- Covariance patterns
- Random regression
- Baseline considerations.

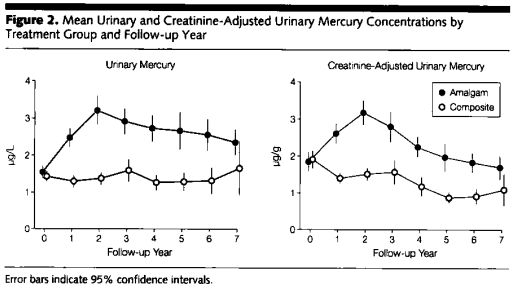
Typical set-up for repeated measurements

- Two or more groups of subjects
  (typically receiving different treatments)
- Possible randomization at baseline
- Longitudinal measurements of the same quantity over time for each subject, typically as a function of
  - time (duration of treatment)
  - age
  - cumulative dose of some drug

Level 1: Single observations
Level 2: Patients/Subjects

Examples from literature, I

Example: Safety of dental amalgam restorations in children.



Reference: T.A DeRouen et.al: Neurobehavioral Effects of Dental Amalgam in Children. A Randomized Clinical Trial.
JAMA 2006, p. 1784

Examples from literature, II

Example: Effect of low-dose methylprednisolone on lung function in patients with ARDS.

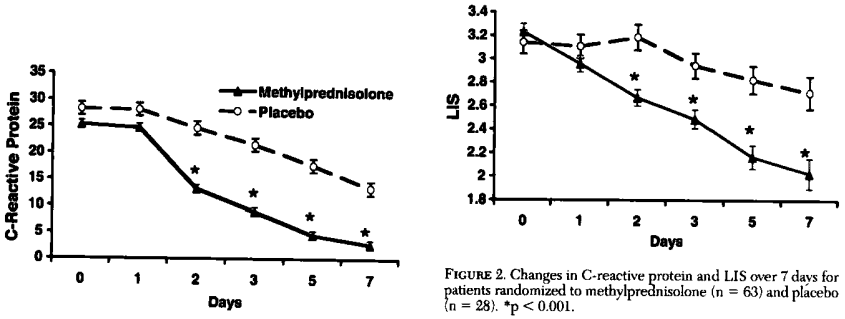


FIGURE 2. Changes in C-reactive protein and LIS over 7 days for patients randomized to methylprednisolone (n = 63) and placebo (n = 28). *p < 0.001.

Reference: G.U. Meduri et.al: Methylprednisolone Infusion in Early Severe ARDS*. Results of a Randomized Controlled Trial. *CHEST 2007, p. 954*

Problems with the traditional presentation of data

- Comparison of groups for each time point separately
  - is *inefficient*
  - has a high risk of leading to chance significance
  - Tests are not independent, since they are carried out on the same subjects
  - Interpretation may be difficult
- Changes over time
  - cannot be evaluated 'by eye' because we cannot see the pairing

Take care with average curves

- They may hide important structures
- They give no indication of the variation in the time profiles
- Always make a spaghetti-plot (a picture of individual time profiles)
- **Do not** average over individual profiles, unless these have identical shapes, i.e. only shifts in level are seen between individuals.
- **and not** in case of drop-outs or missing observations that are not missing completely at random (more on this in lecture 4)

Average curves are of course not possible for unbalanced designs...

Design issues - data structure and data types

- Type of study: Randomized or Observational
- Observation schedule: Fixed times of observation vs. ad hoc observations
- Data structure: Variables and observations, wide and long formats
- Data type: Quantitative vs. categorical

Type of study

Randomized: One homogeneous population is studied:

- Measurement at baseline - before (or at) randomization
- Randomization to two (or more) treatment groups
- A couple of measurements after initiation of treatment

Observational: Two (or more) populations are studied:

- Men and women, two different diseases, or two genotypes
- Some well defined time zero

Observation schedule

Fixed time points: = Balanced: All individuals are seen/measured at regular/fixed intervals, e.g.

- Equidistant: every 5 minutes, or every month
- Every month for the first half a year, then every 6 months

Ad hoc sampling: not very attractive....

- The doctor decides when to see the patient next time
- The patient comes to visit when he/she feels the need

Even designs planned to be balanced turn out to be more or less unbalanced....

Data structure

Variables: The columns of the data set:

- Patient id: Used for identification of measurements belonging to the same individual
- Group: Disease group or Randomization group
- Time

Observation: One for each visit, i.e. several for each individual

Baseline: When did the treatment start?

- Right from the first visit? No baseline issue
- After the first visit? We have a baseline issue

Data types

Quantitative: Data with a meaningful zero and meaningful intervals between possible values:

- Numerical: All values possible in a certain range, e.g. birth weight, blood pressure, ...
- Counts: Non-negative integers, e.g. Number of children, Number of seizures per month, ...

Categorical: Data labels

- Binary: Complications, yes or no (0 or 1)
- Nominal: with no ordering, e.g. type of illness
- Ordinal: with a natural ordering, e.g. degree of pain: 0,1,2 or 3

Example: Calcium supplements

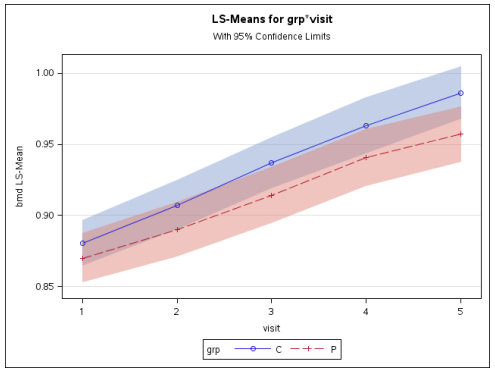
A total of 112 11-year old girls were randomized to receive either calcium or placebo.

Outcome:
BMD=bone mineral density, in $\frac{g}{cm^2}$,
measured every 6 months (5 visits)

Scientific question:
Does calcium improve the rate of bone gain for adolescent women?

Average time profiles

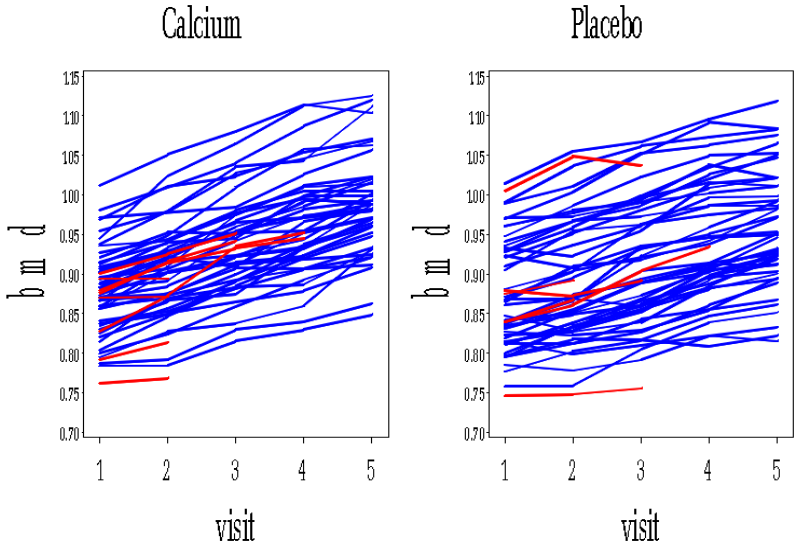
with confidence limits
(constructed from `proc glimmix`, see p. 88)



but are such averages reasonable in this situation?

Individual profiles

Spaghetti plots



Model for Bone Mineral Density

Mean value: Describe the overall pattern of time changes in the two groups:

- Effects of group (calcium vs. placebo) and time
- An interaction between group and time
  since our question is: Do the two groups evolve differently over time?

Covariance: Describe a reasonable correlation structure, along with variance for the different time points

- Observations on the same individual should be correlated
- Maybe the variation increases over time?
- Maybe observations close in time are more correlated than some which are more separated in time?

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Assuming no independence

will allways be wrong, and will lead to errors

- Type 2 errors for level 1=within covariates (time), i.e. too big standard errors
  We may fail to see potentially important effects
- Type 1 errors for level 2=between covariates (group), i.e. too small standard errors
  We get too many significances, and "find" effects that are not there

The precise choice of covariance structure is often not *that* crucial, although it may still change the results quite a bit, depending on.....

Simple analyses strategies

will not be optimal, but sometimes feasible – and easy

Analyze carefully chosen characteristics for each individual (i.e. reduce to simple analyses, with no correlation issue):

- The endpoint
- The change from baseline to endpoint
- The slopes for the time effect (see p. 19)
- AUC: the area under the curve
- etc

Individual comparisons for each time point is *not* recommended

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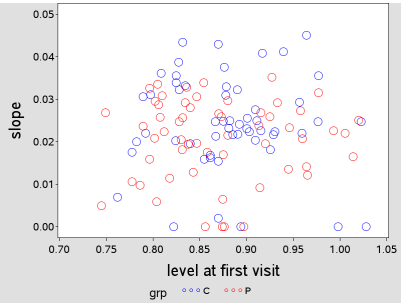
Individual regression lines for each girl

Scatterplot of slopes vs level at first visit:



The slopes seem to be bigger in the Calcium group

Results from individual regression

Estimates with standard errors in brackets:

Group	Level at visit 1	Slope
P	0.8697 (0.0086)	0.0206 (0.0014)
C	0.8815 (0.0088)	0.0244 (0.0014)
Difference	0.0118 (0.0123)	0.0039 (0.0019)
P	0.34	0.050

Slopes are at the edge of being significantly different, but information is not used in an optimal fashion

Response profiles

as seen last time

- Unstructured mean value:
  Separate mean value for each time, for each group
- Unstructured covariance:
  Any (positive definite) 5×5 covariance matrix

Very flexible, but
can only be used for balanced data

Unstructured covariance in PROC MIXED

We specify unstructures mean in the `model` statement,
and unstructures covariance in the `repeated` statement:

```
proc mixed data=calcium;
  class grp girl visit;
  model bmd=grp visit grp*visit /
            ddfm=kr outpredm=fit_un;
repeated visit / type=UN subject=girl r rcorr;
run;
```

We also create an output data set `fit_un`

Output from TYPE=UN model

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	0.003951	0.004195	0.004172	0.004247	0.003955
2	0.004195	0.004734	0.004718	0.004817	0.004528
3	0.004172	0.004718	0.004971	0.005052	0.004735
4	0.004247	0.004817	0.005052	0.005336	0.004989
5	0.003955	0.004528	0.004735	0.004989	0.004903

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9699	0.9414	0.9250	0.8987
2	0.9699	1.0000	0.9727	0.9585	0.9399
3	0.9414	0.9727	1.0000	0.9809	0.9592
4	0.9250	0.9585	0.9809	1.0000	0.9755
5	0.8987	0.9399	0.9592	0.9755	1.0000

Output from TYPE=UN model, II

Fit Statistics

-2 Res Log Likelihood	-2346.3
AIC (smaller is better)	-2316.3

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
grp	1	109	2.55	0.1129
visit	4	93.9	248.70	<.0001
grp*visit	4	93.9	2.70	0.0355

We detect a difference in the patterns of the two groups.

Unstructured covariance

Advantages with unstructured covariance

- We do not force a wrong covariance structure upon our observations.
- We gain some insight in the actual structure of the covariance.

Drawbacks of the unstructured covariance

- We use quite a lot of parameters to describe the covariance structure. The result may therefore be unstable.
- It cannot be used for small data sets
- It can only be used in case of balanced data (all subjects have to be measured at identical times)

Can we do something *simpler*?

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The simplest covariance structure

...except for independence, of course....

- Random intercept (lecture 3)
- Compound symmetry
  - Possible for all sampling designs
  - Often a reasonable approximation, but not allways....

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Compound symmetry

also called exchangeability:

- The variances are the same for all observations
- All pairs of observations on the same subject are equally correlated
  $\text{Corr}(y_{r1}, y_{r2}) = \rho$
- The correlation matrix for 6 observations is

$$\begin{pmatrix} 1 & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho \\ \rho & \rho & 1 & \rho & \rho \\ \rho & \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & \rho & 1 \end{pmatrix}$$

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Compound symmetry in SAS

with additional options for printing covariance (`r`) and correlation (`rcorr`):

```
proc mixed data=calcium;
class grp girl visit;
model bmd=grp visit grp*visit /
            ddfm=kr outpredm=fit_cs s cl;
repeated visit / type=CS subject=girl r rcorr;
run;
```

The options `ddfm=satterth` (- or `kr`):

- When the distributions are exact, they have no effect
  - in balanced situations
- When approximations are necessary, these two are considered best
  - in unbalanced situations, i.e for almost all observational designs
  - in case of missing observations
- It may give rise to fractional degrees of freedom
- The computations may require a little more time, but in most cases this will not be noticable
- When in doubt, use it!

Output for Compound Symmetry

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	0.004674	0.004439	0.004439	0.004439	0.004439
2	0.004439	0.004674	0.004439	0.004439	0.004439
3	0.004439	0.004439	0.004674	0.004439	0.004439
4	0.004439	0.004439	0.004439	0.004674	0.004439
5	0.004439	0.004439	0.004439	0.004439	0.004674

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9498	0.9498	0.9498	0.9498
2	0.9498	1.0000	0.9498	0.9498	0.9498
3	0.9498	0.9498	1.0000	0.9498	0.9498
4	0.9498	0.9498	0.9498	1.0000	0.9498
5	0.9498	0.9498	0.9498	0.9498	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
CS	girl	0.004439
Residual		0.000235

Output for Compound Symmetry, II

Fit Statistics

-2 Res Log Likelihood	-2188.8
AIC (smaller is better)	-2184.8

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
grp	1	110	2.63	0.1078
visit	4	382	619.36	<.0001
grp*visit	4	382	5.30	0.0004

No doubt, we see an interaction `grp*visit`
...but is the model OK? Later.....

Random girl level, output, III

Solution for Fixed Effects

Effect	grp	visit	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha
Intercept			0.9576	0.009131	122	104.87	<.0001	0.05
grp	C		0.02951	0.01304	122	2.26	0.0254	0.05
grp	P		0	.	.	.	.	.
visit		1	-0.08750	0.003100	382	-28.22	<.0001	0.05
visit		2	-0.06748	0.003103	381	-21.75	<.0001	0.05
visit		3	-0.04342	0.003117	381	-13.93	<.0001	0.05
visit		4	-0.01619	0.003148	381	-5.14	<.0001	0.05
visit		5	0	.	.	.	.	.
grp*visit	C	1	-0.01912	0.004445	382	-4.30	<.0001	0.05
grp*visit	C	2	-0.01255	0.004448	381	-2.82	0.0050	0.05
grp*visit	C	3	-0.00622	0.004480	381	-1.39	0.1661	0.05
grp*visit	C	4	-0.00679	0.004517	381	-1.50	0.1337	0.05
grp*visit	C	5	0	.	.	.	.	.
grp*visit	P	1	0	.	.	.	.	.
grp*visit	P	2	0	.	.	.	.	.
grp*visit	P	3	0	.	.	.	.	.
grp*visit	P	4	0	.	.	.	.	.
grp*visit	P	5	0	.	.	.	.	.

- Difference between groups at visit 5
- Difference increases over time

Automatic Model checks

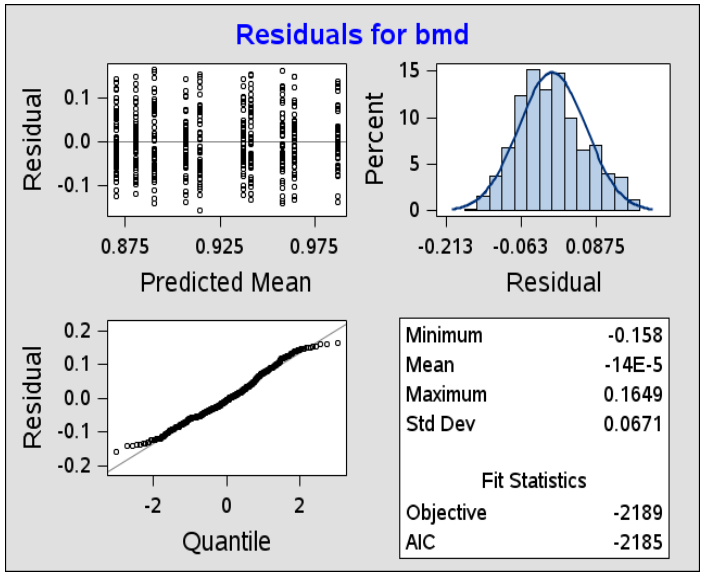
from the ods-system:

Two types of residuals:

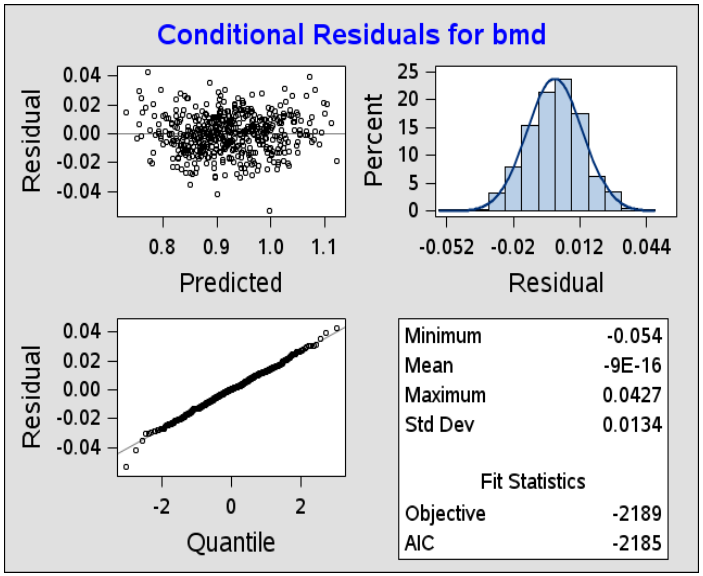
Ordinary	Observed minus predicted group mean (only systematic effects)
Conditional	Observed minus predicted individual mean value (systematic and random effects)

More to follow in lecture 4

Model check, ordinary residuals



Model check, conditional residuals



Correlated observations

Remember:
If we fail to take the correlation into account,
we will experience:

- Type 2 errors for level 1=within covariates (time), i.e. too big standard errors
  We may fail to see potentially important effects
- Type 1 errors for level 2=between covariates (group), i.e. too small standard errors
  We get too many significances, and "find" effects that are not there

The precise choice of covariance structure is often not *that* crucial,
although it may still change the results quite a bit,
as we have already noticed.....

Level 1 (within) covariates (unit: single observations)

- Time itself
- Covariates varying with time:
  blood pressure, heart rate, age
- Interaction between group and time

If correlation is not taken into account, we ignore the paired situation, leading to low efficiency, i.e. too large P-values
Type 2 error

Effects may go undetected!

Incorrect analysis

Correlation ignored

```
proc glm data=calcium;
  class grp visit;
  model bmd=grp visit grp*visit / solution;
run;
```

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	0.05063714	0.05063714	11.05	0.0010
visit	4	0.64369784	0.16092446	35.10	<.0001
grp*visit	4	0.00649557	0.00162389	0.35	0.8411

The interaction is not detected
since we "forgot" the pairing

Level 2 (between) covariates (unit: individuals)

- Treatment
- Gender, age

If correlation is ignored, we act as if we have more information than we actually have, leading to **too small P-values**
Type 1 error

'Noise' may be taken to be real effects!

Covariance structure for random intercept

$$\begin{pmatrix} \omega_B^2+\sigma_W^2 & \omega_B^2 & \omega_B^2 & \omega_B^2 & \omega_B^2 \\ \omega_B^2 & \omega_B^2+\sigma_W^2 & \omega_B^2 & \omega_B^2 & \omega_B^2 \\ \omega_B^2 & \omega_B^2 & \omega_B^2+\sigma_W^2 & \omega_B^2 & \omega_B^2 \\ \omega_B^2 & \omega_B^2 & \omega_B^2 & \omega_B^2+\sigma_W^2 & \omega_B^2 \\ \omega_B^2 & \omega_B^2 & \omega_B^2 & \omega_B^2 & \omega_B^2+\sigma_W^2 \end{pmatrix}$$

$$= (\omega_B^2+\sigma_W^2) \begin{pmatrix} 1 & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho \\ \rho & \rho & 1 & \rho & \rho \\ \rho & \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & \rho & 1 \end{pmatrix}$$

This means that *the distance in time is not taken into account!!*

But:
Observations taken close to each other in time will often be more closely correlated than observations taken further apart!

Alternative specifications

Note, that the specification `'TYPE=CS'` in the `repeated` statement can be written in two other ways:

```
random girl;
```

```
random intercept / subject=girl;
```

This will be the topic of lecture 3,

but we shall also use something similar a little later on today (random regression, p. 58ff)

Comparison of covariance structures

Use the **likelihood**:

- Good models have large values of likelihood L and therefore small values of *deviance*: $-2\log L$
- Use differences in deviances ($\Delta = -2\log Q$) and compare to χ^2 with degrees of freedom equal to the difference in parameters

Comparison of CS and UN:

$$\begin{aligned} -2\log Q &= 2346.3 - 2188.8 \\ &= 157.5 \sim \chi^2(15-2) = \chi^2(13) \Rightarrow P < 0.0001 \end{aligned}$$

Compound symmetry is not suitable

*Different forms of the likelihood

- Default likelihood is the **REML**-likelihood, where the mean value structure has been 'eliminated'
- The *traditional* likelihood may be obtained using an extra option:
  `proc mixed method=ml;`
- Comparison of covariance structures:
  Use either of the two likelihoods
- Comparison of mean value structures:
  Use only the *traditional* likelihood (**ML**) only!

Covariance/correlation structures

- Unstructured covariance
  - uses up a lot of parameters, i.e. demands a large dataset
    $\frac{T(T+1)}{2} = 15$ covariance parameters ($T = 5$)
  - and not too many time points
- Compound symmetry does not seem to fit

Other possibilities:

- 'Patterned', e.g. an autoregressive structure
- Random regression
- many others....

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Autoregressive structure - of first order

In case of **equidistant times**, this specifies the following covariance structure

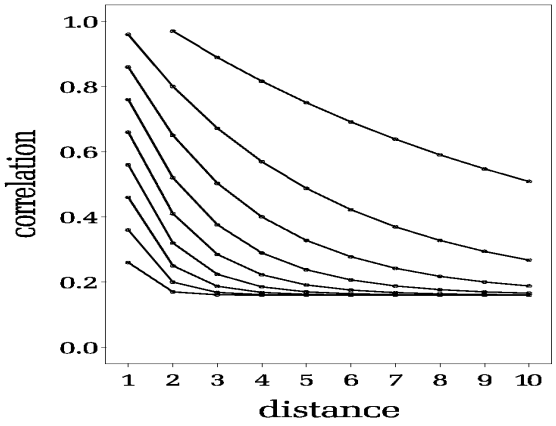
$$\sigma^2 \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 & \rho^4 \\ \rho & 1 & \rho & \rho^2 & \rho^3 \\ \rho^2 & \rho & 1 & \rho & \rho^2 \\ \rho^3 & \rho^2 & \rho & 1 & \rho \\ \rho^4 & \rho^3 & \rho^2 & \rho & 1 \end{pmatrix}$$

i.e. the correlation decreases (in powers) with the distance between observations.

The non-equidistant analogue is $\text{Corr}(Y_{git_1}, Y_{git_2}) = \rho^{|t_1 - t_2|}$

Autoregressive correlation

– as a function of distance between the measurements for $\rho = 0.1, \ldots, 0.9$



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Autoregressiove covariance structure in SAS

```
proc mixed data=calcium;
class grp girl visit;
model bmd=grp visit grp*visit /
            ddfm=kr outpredm=fit_ar1 s cl;
repeated visit / type=AR(1) subject=girl r rcorr;
run;
```

Output from TYPE=AR(1) structure

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9708	0.9425	0.9150	0.8883
2	0.9708	1.0000	0.9708	0.9425	0.9150
3	0.9425	0.9708	1.0000	0.9708	0.9425
4	0.9150	0.9425	0.9708	1.0000	0.9708
5	0.8883	0.9150	0.9425	0.9708	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
AR(1)	girl	0.9708
Residual		0.004412

Fit Statistics

-2 Res Log Likelihood	-2318.6	<-----used later
AIC (smaller is better)	-2314.6	

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
grp	1	113	2.74	0.1003
visit	4	383	230.12	<.0001
grp*visit	4	383	2.82	0.0251

Note:
Comparison of models with different covariance structures requires, that the models are *nested*

This is **not** the case for `CS` and `AR(1)`!

Therefore, we have to compare both of them with the model which combines the two covariance structures:

```
proc mixed data=calcium;
  class grp girl visit;
  model bmd=grp visit grp*visit /
            ddfm=satterth outpredm=fit_ar1;
random intercept / subject=girl g;
repeated visit / type=AR(1)
                 subject=girl rcorr;
run;
```

Combination of CS and AR(1)

In case of **equidistant times**, this combined model specifies the following covariance structure

$$\begin{pmatrix} \omega^2+\sigma^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2\rho^2 & \omega^2+\sigma^2\rho^3 & \omega^2+\sigma^2\rho^4 \\ \omega^2+\sigma^2\rho & \omega^2+\sigma^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2\rho^2 & \omega^2+\sigma^2\rho^3 \\ \omega^2+\sigma^2\rho^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2\rho^2 \\ \omega^2+\sigma^2\rho^3 & \omega^2+\sigma^2\rho^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2 & \omega^2+\sigma^2\rho \\ \omega^2+\sigma^2\rho^4 & \omega^2+\sigma^2\rho^3 & \omega^2+\sigma^2\rho^2 & \omega^2+\sigma^2\rho & \omega^2+\sigma^2 \end{pmatrix}$$

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9708	0.9425	0.9150	0.8883
2	0.9708	1.0000	0.9708	0.9425	0.9150
3	0.9425	0.9708	1.0000	0.9708	0.9425
4	0.9150	0.9425	0.9708	1.0000	0.9708
5	0.8883	0.9150	0.9425	0.9708	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
Intercept	girl	0
AR(1)	girl	0.9708
Residual		0.004413

Fit Statistics

-2 Res Log Likelihood	-2318.6	<-----used later
AIC (smaller is better)	-2314.6	

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
grp	1	113	2.74	0.1003
visit	4	383	230.12	<.0001
grp*visit	4	383	2.82	0.0251

More covariance structures

Toeplitz, `type=TOEP`,
A banded structure:

$$\begin{pmatrix} \sigma^2 & \sigma_1 & \sigma_2 & \sigma_3 & \sigma_4 \\ \sigma_1 & \sigma^2 & \sigma_1 & \sigma_2 & \sigma_3 \\ \sigma_2 & \sigma_1 & \sigma^2 & \sigma_1 & \sigma_2 \\ \sigma_3 & \sigma_2 & \sigma_1 & \sigma^2 & \sigma_1 \\ \sigma_4 & \sigma_3 & \sigma_2 & \sigma_1 & \sigma^2 \end{pmatrix}$$

More covariance structures, II

Heterogeneous Autoregressive, `type=ARH(1)`,
An autoregressive structure, with time-dependent variance:

$$\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho & \sigma_1\sigma_3\rho^2 & \sigma_1\sigma_4\rho^3 & \sigma 1\sigma_5\rho^4 \\ \sigma_2\sigma_1\rho & \sigma_2^2 & \sigma_2\sigma_3\rho & \sigma_2\sigma_4\rho^2 & \sigma_2\sigma_5\rho^3 \\ \sigma_3\sigma_1\rho^2 & \sigma_3\sigma_2\rho & \sigma_3^2 & \sigma_3\sigma_4\rho & \sigma_3\sigma_5\rho^2 \\ \sigma_4\sigma_1\rho^3 & \sigma_4\sigma_2\rho^2 & \sigma_4\sigma_3\rho & \sigma_4^2 & \sigma_4\sigma_5\rho \\ \sigma_5\sigma_1\rho^4 & \sigma_5\sigma_2\rho^3 & \sigma_5\sigma_3\rho^2 & \sigma_5\sigma_4\rho & \sigma_5^2 \end{pmatrix}$$

See also SAS documentation, with many more suggestions
Try e.g. to google "`sas mixed repeated type=`"

Comparison of covariance structures

Model	-2 log L	cov. par.	$\Delta = -2\log Q$	*df*	P
UN	2346.3	15			
			27.7	12	0.006
AR(1) + CS	2318.6	3			
			0	1	1
AR(1)	2318.6	2			
			129.8	1	< 0.0001
CS	2188.8	2			

Conclusions?

- The autoregressive structure is definitely better than CS, but not good quite enough...

Test of no interaction GRP*VISIT

– for various choices of covariance structure

Covariance structure	Test statistic $\sim$ distribution	P value
Independence	0.35 $\sim$ F(4,491)	0.84
Compound symmetry	5.30 $\sim$ F(4,382)	0.0004
Autoregressive	2.86 $\sim$ F(4,382)	0.023
Unstructured	2.72 $\sim$ F(4,107)	0.034

Not quite identical conclusions!

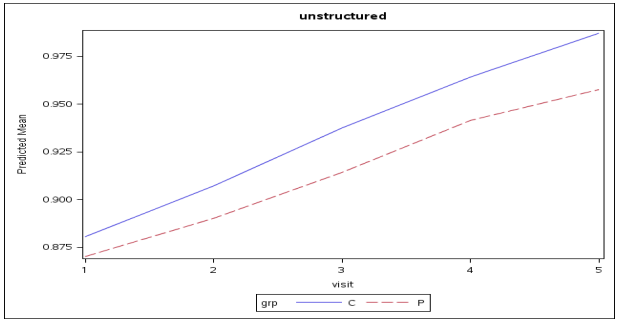
Predicted mean time profiles

In SAS: Use the outpredm=-option
or the ODS-system

Profiles are *almost* identical for all choices of covariance structures

- For balanced designs, they agree completely and equal simple averages
- They agree for time points with no missing values (here the first visit)

Predicted profiles for the **unstructured** covariance



- The evolution over time looks pretty linear
- Include `time=visit` as a quantitative covariate?
- What about the baseline difference? Later....

Individual growth rates?

The time course is *reasonably* linear, but maybe the girls have **different growth rates (slopes)**?

If we let Y_{git} denote BMD for the i'th girl (in the g'th group) at time t (t=1,$\cdots$,5), we could look at the model:

$$y_{git} = a_{gi} + b_{gi}t + \varepsilon_{git}, \quad \varepsilon_{git} \sim N(0, \sigma^2_W)$$

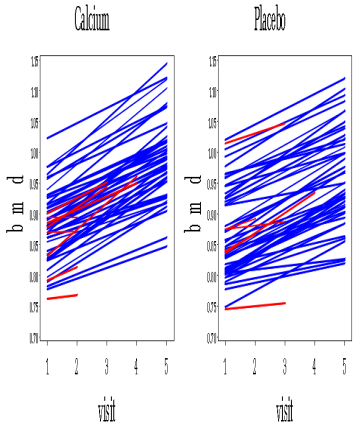
i.e., with different intercepts and different slopes for each girl

Random regression

We let each individual (girl) have

- her own level a_{gi}
- her own slope b_{gi}

but...



Population variation of lines

... we *bind* these individual 'parameters' (a_{gi} and b_{gi}) together by bivariate normal distributions (much like the picture on p. 19)

$$\begin{pmatrix} a_{gi} \\ b_{gi} \end{pmatrix} \sim N_2\left(\begin{pmatrix} \alpha_g \\ \beta_g \end{pmatrix}, G\right)$$

$$G = \begin{pmatrix} \tau_a^2 & \omega \\ \omega & \tau_b^2 \end{pmatrix} = \begin{pmatrix} \tau_a^2 & \rho\tau_a\tau_b \\ \rho\tau_a\tau_b & \tau_b^2 \end{pmatrix}$$

G describes the **population variation** of the lines, i.e. the inter-individual (between) variation.

Estimation in random regression

We define `time` as a replicate of `visit`, but now we do not include it in the `class`-statement, so we are doing regression on quantitative time, i.e. a linear trend in time, instead of an unstructured profile.
The interaction `grp*time` allows the slopes to differ in the two groups:

```
proc mixed covtest data=calcium;
class grp girl;
model bmd=grp time grp*time / ddfm=kr s cl;
random intercept time /
       type=un subject=girl g v vcorr;
run;
```

Output from random regression

Estimated G Matrix

Row	Effect	girl	Col1	Col2
1	Intercept	101	0.004105	3.733E-6
2	time	101	3.733E-6	0.000048

Estimated V Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	0.004285	0.004211	0.004263	0.004314	0.004366
2	0.004211	0.004435	0.004410	0.004509	0.004608
3	0.004263	0.004410	0.004681	0.004703	0.004850
4	0.004314	0.004509	0.004703	0.005022	0.005092
5	0.004366	0.004608	0.004850	0.005092	0.005459

Estimated V Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9660	0.9518	0.9300	0.9027
2	0.9660	1.0000	0.9677	0.9553	0.9364
3	0.9518	0.9677	1.0000	0.9700	0.9594
4	0.9300	0.9553	0.9700	1.0000	0.9725
5	0.9027	0.9364	0.9594	0.9725	1.0000

Output from random regression, II

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	-2341.6
AIC (smaller is better)	-2333.6

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
grp	1	110	0.33	0.5685
time	1	96.4	982.57	<.0001
time*grp	1	96.4	8.16	0.0053

Output from random regression, III

Solution for Fixed Effects

Effect	grp	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha
Intercept		0.8471	0.008646	110	97.98	<.0001	0.05
grp	C	0.007058	0.01234	110	0.57	0.5685	0.05
grp	P	0	.	.	.	.	.
time		0.02242	0.001099	95.8	20.39	<.0001	0.05
time*grp	C	0.004494	0.001574	96.4	2.86	0.0053	0.05
time*grp	P	0	.	.	.	.	.

Solution for Fixed Effects

Effect	grp	Lower	Upper
Intercept		0.8300	0.8643
grp	C	-0.01740	0.03151
grp	P	.	.
time		0.02023	0.02460
time*grp	C	0.001371	0.007618
time*grp	P	.	.

Thus, we find an extra increase in BMD of 0.0045(0.0016) g per cm^3 per **half year**, when giving calcium supplement.

Note concerning MIXED-notation

- It is necessary to use `TYPE=UN` in the RANDOM-statement in order to allow intercept and slope to be arbitrarily correlated
- Default option in RANDOM is `TYPE=VC`, which only specifies variance components with different variances
- If `TYPE=UN` is omitted, we may experience convergence problems and sometimes totally incomprehensible results.

In this particular case, the correlation between intercept and slope is not that impressive - actually only 0.0084 - (intercept is not completely out of range in this example, since it refers to `visit=0`).

Individual regressions approach

Merits:

- Easy to understand and interpret

Drawbacks:

- Suboptimal in case of unequal sample sizes
- Only simple models feasible
- Difficult to include covariates

Random regression approach

Merits:

- Uses all available information
- Optimal procedure if the model holds
- Easy to include covariates

Drawbacks:

- Biased in case of informative missing values or informative sample sizes

What to choose in this example?

- Random regression gives
  - steeper slope
  - almost identical levels at age 11
- The girls with flat low profiles tend to be shorter:

  Why??

Actually – as it always happens –

- The girls are only seen **approximately** twice a year
- The actual dates are available and are translated into `ctime`, the internal date representation in SAS, denoting days since ....
- We can no longer use the construction `type=UN`, but still the `random`-statement and the `CS` in the `repeated`-statement.
- A lot of other covariance structures will still be possible, e.g. The non-equidistant analogue to the autoregressive structure is Corr$(Y_{git_1}, Y_{git_2}) = \rho^{|t_1 - t_2|}$ which is written as `TYPE=SP(POW)(ctime)`

Furthermore,

- the girls were not precisely 11 years at the first visit

  As a covariate, we ought to have the specific age of the girl, but unfortunately, these are not available.

Note, that this will mostly affect the intercept estimates!

Using the newly constructed *ctime* as covariate

```
proc mixed covtest data=calcium;
class grp girl;
model bmd=grp ctime ctime*grp / ddfm=satterth s;
random intercept ctime / type=un subject=girl g;
run;
```

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-1221.35800531	
1	2	-2316.64715219	0.02023229
2	1	-2316.64847895	0.02011117
3	1	-2316.64847962	0.02010938
48	1	-2317.30142030	0.01737561
49	1	-2317.30142036	0.01737561
50	1	-2317.30142043	0.01737561

WARNING: Did not converge.

No convergence, why?

The variable `ctime` has much too large values, with a very small range, and we get **numerical instability**.

We normalize, to approximate age or `age11`:

```
age=(ctime-11475)/365.25+12;
age11=age-11;      /* intercept at age 11 */
```

Variable	N	Mean	Minimum	Maximum
ctime	501	11475.08	11078.00	11931.00
bmd	501	0.9219202	0.7460000	1.1260000
visit	560	3.0000000	1.0000000	5.0000000
age	501	12.0002186	10.9130732	13.2484600
age11	501	1.0002186	-0.0869268	2.2484600

Reading in and defining age

```
data tbbmd;
   infile cards missover;
   input dummy $ @10 visit1 date7. bmd1 @24 visit2 date7. bmd2
         @38 visit3 date7. bmd3 @52 visit4 date7. bmd4 @66 visit5 date7. bmd5;

   girl=substr(dummy,1,3);
   grp=substr(dummy,4,1);

   drop dummy;

cards;
    101C 01MAY90 0.815 05NOV90 0.875 24APR91 0.911 30OCT91 0.952 29APR92 0.970
    102P 01MAY90 0.813 05NOV90 0.833 15APR91 0.855 21OCT91 0.881 13APR92 0.901
    103P 02MAY90 0.812 05NOV90 0.812 17APR91 0.843 23OCT91 0.855 15APR92 0.895
    104C 09MAY90 0.804 12NOV90 0.847 29APR91 0.885 11NOV91 0.920 19JUN92 0.948
.....etc......etc
;
run;
```

Reading in and defining age, II

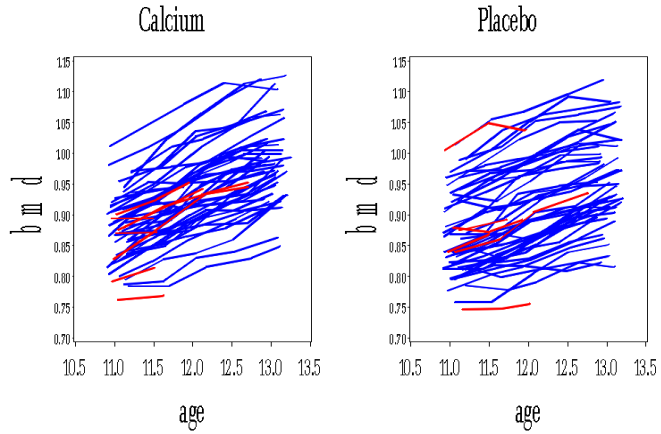
```
data tbbm; set tbbmd;
ctime=visit1; bmd=bmd1; visit=1; output;
ctime=visit2; bmd=bmd2; visit=2; output;
ctime=visit3; bmd=bmd3; visit=3; output;
ctime=visit4; bmd=bmd4; visit=4; output;
ctime=visit5; bmd=bmd5; visit=5; output;
run;

data calcium; set tbbm;

time=visit;
sctid=(ctime-11475)/278;
age=(ctime-11475)/365.25+12;

age11=age-11;
age13=age-13;
person=1*girl;
run;
```

New spaghetti plots



Random regression, covariate age11:

$$y_{git} = a_{gi} + b_{gi}(\text{age-11}) + \varepsilon_{git}$$

Random regression, using actual age (age11=age−11):

```
proc mixed covtest data=calcium;
class grp girl;
model bmd=grp age11 grp*age11 / ddfm=kr s cl;
random intercept age11 /
       type=un subject=girl g v vcorr;
run;
```

Estimated G Matrix

Row	Effect	grp	girl	Col1	Col2
1	Intercept	C	101	0.004215	0.000095
2	age11	C	101	0.000095	0.000180

Estimated V Correlation Matrix for girl(grp) 101 C

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9664	0.9537	0.9321	0.9056
2	0.9664	1.0000	0.9687	0.9566	0.9385
3	0.9537	0.9687	1.0000	0.9697	0.9590
4	0.9321	0.9566	0.9697	1.0000	0.9723
5	0.9056	0.9385	0.9590	0.9723	1.0000

Fit Statistics

-2 Res Log Likelihood	-2350.1
AIC (smaller is better)	-2342.1

Output, continued

Solution for Fixed Effects

Effect	grp	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha
Intercept		0.8667	0.008689	110	99.75	<.0001	0.05
grp	C	0.01113	0.01240	110	0.90	0.3715	0.05
grp	P	0	.	.	.	.	.
age11		0.04529	0.002155	96	21.02	<.0001	0.05
age11*grp	C	0.008891	0.003081	96.6	2.89	0.0048	0.05
age11*grp	P	0	.	.	.	.	.

Solution for Fixed Effects

Effect	grp	Lower	Upper
Intercept		0.8495	0.8839
grp	C	-0.01345	0.03570
grp	P	.	.
age11		0.04102	0.04957
age11*grp	C	0.002776	0.01501
age11*grp	P	.	.

In this model, we quantify the effect of a calcium supplement to 0.0089 (0.0031) g per cm^3 per **year**.

Results from random regression

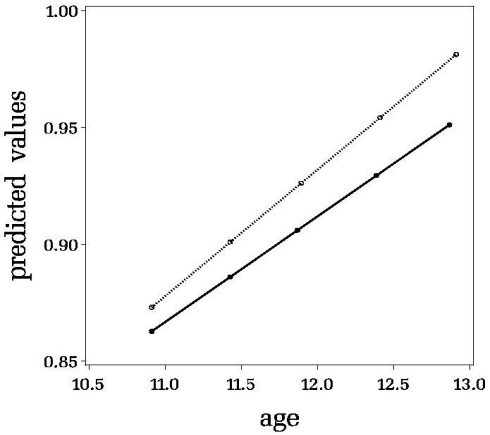
Group	Level at age 11	Slope
P	0.8667 (0.0087)	0.0453 (0.0022)
C	0.8778 (0.0088)	0.0542 (0.0022)
Difference	0.0111 (0.0124)	0.0089 (0.0031)
P	0.37	0.0048

Compare to results from individual regressions (p. 20):

Comparison of slopes for different covariance structures

Covariance structure	$-2 \log L$	Cov.par.	Difference in slopes	P
Independence	-1245.0	1	0.0094 (0.0086)	0.27
Compound Symmetry	-2251.7	2	0.0089 (0.0020)	< 0.0001
Exponential (Autoregressive)	-2372.0	2	0.0094 (0.0032)	0.0038
Random Regression	-2350.1	4	0.0089 (0.0031)	0.0048

Predicted values from random regression



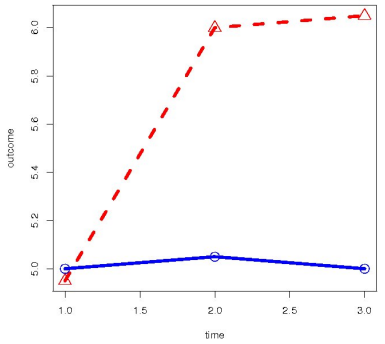
It looks as if there is a difference right from the start (although we have previously seen this to be *insignificant*, P=0.37).

Baseline adjustment?

Assume visit 1 is a baseline measurement

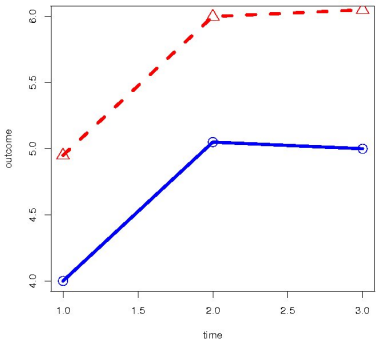
- The two groups are *known* to be equal at baseline
- To include this measurement in the comparison between groups
  - may weaken a possible difference between these (type 2 error)
  - may convert a treatment effect to an interaction
- Dissimilarities *may* be present in small studies
- For 'slowly varying' outcomes, even a small difference may produce non-treatment related differences, i.e. **bias**

Hypothetical comparison of two treatment groups, A



- Truth: Constant difference between the treatments
- Finding: Interaction between time and treatment

Hypothetical comparison of two treatment groups, B



- Truth: No effect of treatment
- Finding: Constant difference between treatments

Baseline difference?

- Randomized studies,
  typical comparison of treatments.
- Take care with interpretations:
  Any effect may be due to *either* group or baseline
  Take baseline into account in the analysis.
- Observational studies,
  typical comparison of groups, different kinds of illnesses, men and women,....
  Here, baseline differences may be natural

The scientific question answered depends upon the model

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No systematic baseline difference

Approaches for handling individual baseline differences:

- Use follow-up data only (exclude baseline from analysis)
  - most reasonable if correlation between repeated measurements is very low
- Subtract baseline from successive measurements
  - most reasonable if correlation between repeated measurements is very high
- Build a constrainted model, forcing groups to have equal means at baseline
- Use baseline measurement as a covariate (ANCOVA)
  - may be used for any degree of correlation
  - but is somewhat involved for more than two observations over time

Excluding baseline (4 follow-up visits only)

```
proc mixed covtest noclprint data=calcium; where visit>1;
class grp girl;
model bmd=grp age11 grp*age11 / ddfm=kr s;
random intercept age11 / type=un subject=girl g;
estimate "difference at age 13" grp 1 -1 grp*age11 2 -2;
run;
```

Effect	grp	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		0.8647	0.009749	103	88.70	<.0001
grp	C	0.009832	0.01386	103	0.71	0.4796
grp	P	0	.	.	.	.
age11		0.04634	0.002291	92.3	20.23	<.0001
age11*grp	C	0.007456	0.003282	92.5	2.27	0.0254
age11*grp	P	0	.	.	.	.

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
difference at age 13	0.02474	0.01383	102	1.79	0.0765

Estimated gain at the age 13: 0.0247 (0.0138) g per cm^3

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cLMM: Constrainted model

Equal baseline means in the two groups
obtained by *leaving out* `grp` in the `model`-statement:

```
proc mixed data=calcium noclprint;
class grp girl;
model bmd=age11 grp*age11 / ddfm=satterth s;
random intercept age11 / type=un subject=girl g;
estimate "difference at age 13" grp*age11 2 -2;
run;
```

Effect	grp	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		0.8721	0.006193	111	140.84	<.0001
age11		0.04534	0.002151	96.2	21.08	<.0001
age11*grp	C	0.008803	0.003074	96.8	2.86	0.0051
age11*grp	P	0	.	.	.	.

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
difference at age 13	0.01761	0.006149	96.8	2.86	0.0051

Estimated gain at the age 13: 0.0176 (0.0061) g per cm^3

Appendix: Code for the figure on p. 14

```
ODS graphics on;
proc glimmix PLOTS=ALL data=calcium;
class grp girl visit;
model bmd=grp visit grp*visit / ddfm=kr s;
random _residual_ / type=un subject=girl group=grp;
lsmeans visit*grp
        / plots=(meanplot(join clband sliceby=grp));
run;
ODS graphics off;
```