Faculty of Health Sciences

Introduction to repeated measurements

Analysis of repeated measurements 2018 (Ph.D. + FSV)

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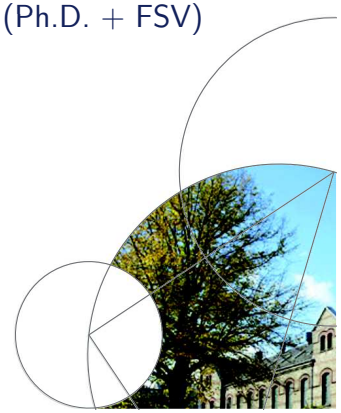

Day 1 contents

- Course aims and practicalities.
- Basic concepts for correlated and clusted data
- Descriptive statistics
- The multivariate normal distribution
- Analysis of baseline-follow up studies
- SAS/R: data handling, descriptive statistics, analysis.

Supplementary reading: FLW chapters 1, 2, 3, and 5.
R-/SAS-demos from course webpages.

Outline

About the course

What are repeated measurements?

Basics of longitudinal data (FLW chapters 1 & 2)

The multivariate normal distribution

Analysis of baseline follow-up studies (FLW chapters 3 & 5)

Baseline adjustment (FLW section 5.6)

Data management and computation

Course material and practical information

http://staff.pubhealth.ku.dk/~jufo/RepeatedMeasures2018

- Course description and updates
- Lecture notes, exercises, supplementary material.

As supplementary reading we recommend:

- G.M. Fitzmaurice, N.M. Laird & J.H. Ware :
  Applied Longitudinal Analysis (2nd edition),
  John Wiley & sons, 2011
- Available as e-book at KB (free download for KU-students).
- www.biostat.harvard.edu/~fitzmaur/ala2e

ATT: Exercise classes

ROOM ALLOCATIONS ARE PRELIMINARY. ONCE YOU HAVE SIGNED UP I MIGHT CHANGE THEM TO ENSURE A MORE EVEN DISTRIBUTION ON ROOMS / TEACHERS...

Ph.D. students please sign up:

- **R-classes:** Tuesdays in 2-2-02, fridays in 7-0-08.
- **SAS-classes:** Both days in 2-1-02.

Master students don't need to sign up:

- **SAS-classes:** Both days in 2-0-42.

Aims of the course

We aim to teach you to:

- understand and interpret advanced statistical analyses
- perform your own analyses using SAS or R.
- understand the output from a statistical program package - in general, i.e. other than SAS and R.
- judge the assumptions behind the different analyses and the statistical consequences of your study design.
- make suitable presentations of the results from your analyses.

To create a better platform for communication between 'users' of statistics and statisticians to benefit subsequent collaboration.

- **I look forward to seeing you at my consultation :)**

Topics for the course

Models for **dependent data**.

Quatitative outcomes (course days 1-4 & 6):

- Linear mixed models
- Variance component models (multi-level models)

Binary outcomes (course day 5):

- Generalized linear mixed models aka subject specific models
- Population average models aka generalized estimating equations

Not covered:

- Censored data (survival analysis, recurrent events)
- Multivariate data (several different outcomes at once)

Prerequisites

You are motivated (from your own research project)

You have an **open mind** towards mathematical model descriptions.

You have a **basic knowledge** of statistics including:

- the normal distribution, mean and standard deviation/variance
- estimates, standard errors, confidence intervals
- correlation, regression, ANOVA, linear models.
- t-tests, χ^2-tests, F-tests
- generalized linear models (logistic and possion regression)

You are **familiar with SAS or R programming**.

ATT Ph.D. students: To pass the course

SIGN THE ATTENDANTS LIST which are passed around

- twice a day - one in the morning, one in the afternoon,
- at otherwise randomized times.

80% ATTENDANCE IS REQUIRED TO PASS

- Note: 80% of 12 lists is at least 10 signatures in total.

PLEASE NOTE THAT:

- You cannot sign in advance, for last week, or for your friends!

Master students: One week take home assignment after lectures are over.

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What are repeated measurents?

Repeated measurements refer to data where the *same outcome* has been measured *several times*, in *several situations* or at *several spots*, on the same subjects.

- Special case: longitudinal means repeatedly over time.

Examples of repeated measurents

Subjects should be understood in a **wide sense**:

- Repeated measuremenst on a patient or person.
- **or** on a mouse, dog, blood sample, or cell line.

Replicates can be made:

- Over time.
- Under different cirkumstances/treatments.
- With different measurement device.
- On different limbs or locations of the body.

What is clustered data?

Repeated measurements are termed clustered data when the same outcome is measured on groups of subjects that are somehow related. They share a heritage, an environment, or such.

Examples of clustered data

Clusters could be:

- Siblings, families, or school classes.
- Clinics, hospitals, or GPs.

But also:

- Litters or cages.
- Plates (in a laboratory experiment).

Or any kind of clustering due to multiple:

- Operators or sessions.

Your own data

Repeated measurements, clustered data or both?

- What kind of subjects/clusters?
- Longitudinal data, spatial correlation, technical replicates?

Outcome type?

- Quantitative (normal), binary, or other?

Specific study design?

- E.g. baseline-follow up study, cross-over study, cluster-randomized trial, reproducibility of a measurement method?
- Prospective or retrospective study?
- Randomized or non-randomized groups/treatments?

Statistical analysis must account for repetitions!

The **usual assumption** is that observations are **independent**.

If you have repeated or clustered measurements ...

- the assumption of independence is violated.

Ignoring the repetitions/clustering most often leads to:

- p-values that are too small or too large.
- confidence intervals that are too wide or too narrow.

It is wrong to analyse repeated measurements data with an ordinary GLM or ANOVA model!!!

- But a lot of people do it anyway and get it published ...

Warm up example: A pre-post study

Average daily dietary intake for 11 women over 11 pre-menstrual **and** 11 post-menstrual days.

Subject	Pre-menstrual	Post-menstrual	Difference
1	5260	3910	1350
2	5470	4220	1250
3	5640	3885	1755
4	6180	5160	1020
5	6390	5645	745
6	6515	4680	1835
7	6805	5265	1540
8	7515	5975	1540
9	7515	6790	725
10	8230	6900	1330
11	8770	7335	1435
Mean	6753.6	5433.2	1320.5
SD	1142.1	1216.8	366.7

D.G. Altman: *Practical Statistics for Medical Research*, Section 9.5

Paired data

The most simple example of clustered or repeated measurements.

- Two replicates per subject or two subjects per cluster

Examples of paired data:

- Same person with treatment and placebo.
- A baseline and a follow-up measurement.
- Twin study.
- Comparison of two measurement methods or reliability of a measurement method.

Quantiative outcomes are analysed with the paired t-test (assuming pairs are complete, lecture 6: missing data).

Example: Paired vs unpaired comparison

To compare pre-menstrual and post-menstrual dietary intake.

- Test $H_0:\ \mu_1 = \mu_2$ (i.e. pre-mean = post-mean).
- Find a confidence interval for $\mu_1 - \mu_2$.

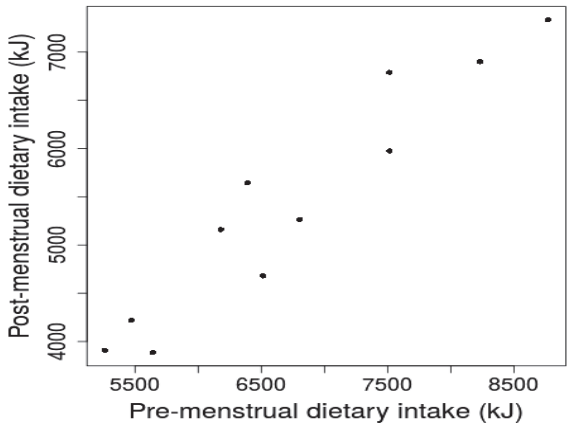
Note the very different results:

Analysis	Estimate (95% CI)	P-value
Right: paired t-test	1320 (1074;1567)	0.0000003
Wrong: two-sample t-test	1320 (271; 2370)	P=0.01625

The paired test is much more powerful.

Explanation: it's all about the correlation

There is a strong dependence between pre- and post-intake for the same woman (correlation 0.95, 95%CI: 0.83-0.99).



To get the analysis right we need to account for the correlation.

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Case: A baseline follow-up study

A randomized clinical trial was conducted to compare *Eplerenone* with standard treatment of patients with chronic kidney disease.

Outcome: Augmentation index (aix), smaller is better.

Repeated measurements at:

- baseline,
- after 12 weeks (safety),
- after 24 weeks (end point).

Note: The study was planned with 37 subjects in each group, but only 25 and 26, resp. could be treated within the time limit.

Boesby et al: *Eplerenone Attenuates Pulse Wave Reflection in Chronic Kidney Disease Stage 3–4 - A Randomized Controlled Study*, PLOS ONE 2013.

Typical set-up for longitudinal measurements

Longitudinal measurements are typically taken as a function of either **age** or **duration of treatment/disease** in a . . .

Single group study (easy case)

- One population followed over time.
- Does the outcome change systematically with time?

Parallel group study (a bit harder)

- Two or more populations, e.g. different gender or diagnosis.
- Do the time courses differ between the groups?

Randomized group study (a bit more tricky)

- Two or more different treatments.
- Do the time courses differ between the groups?

Merits of longitudinal studies

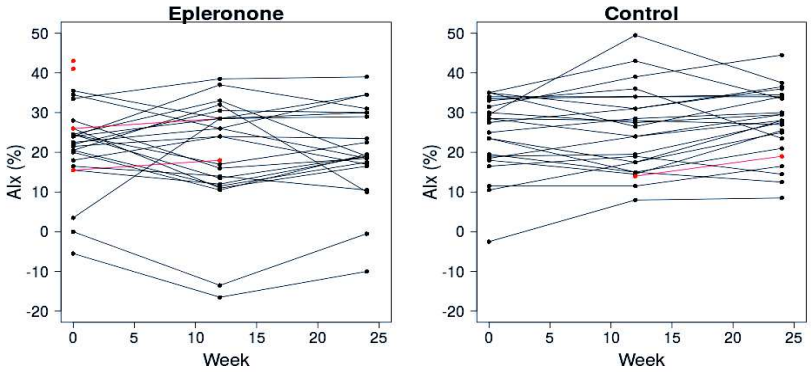
In longitudinal studies measurements are taken repeatedly on the same subjects over time.

- This allows us to study changes over time **within subjects** and factors that influence these changes, e.g. treatment.
- By comparing each subjects responses at two or more occations we eliminate extraneuous but unavoidable sources of variabitlity among subjects. Thus we obtain more accurate estimates and more certain conclusions about changes over time than in cross-sectional studies.

Drawbacks: Statistics becomes more complicated.

Visualizing data: Spaghettiplots

Good for visual inspection because replicates are connected!



Note: Missing data due to failed measurements, side effects, relapse or other illness (missing data discussed further in lecture 6).

Why visualization is so important

Graphical description of the data is useful for:

- **Exploratory data analysis** and **hypothesis generation**.
- **Aiding interpretation** of planned analyses.
- **Presentation** or **saying it in figures** rather than in numbers.
- **Spotting outliers** that could otherwise spoil your analysis.
- Rough **assessment of model assumptions** such as normal distribution or linear trend over time.

Note: Having a large dataset is no excuse for omitting graphical description. You can divide your data into subgroups or at least look at random subsamples.

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The distribution of repeated outcomes

Repeated measurements are characterized by being

- mutually dependent or **correlated**.

We need to model their **joint distribution**.

Model for quantiative data: the multivariate normal distribution

- Location-parameters: **mean-vector**

  We have a list of means, one for each occation.

- Variability-parameters: **covariance-matrix**

  We have a list of variances, one for each occation ...

  and a table of cross-correlations.

Eplerenone: Summary statistics

Trends in means, SDs or cross-correlations over time?

Eplerenone group

Week	N	Mean	SD
0	26	22.3	11.1
12	24	19.9	13.7
24	22	20.4	11.4

Corr	0	12	24
0	1.00	0.68	0.73
12	0.68	1.00	0.82
24	0.73	0.82	1.00

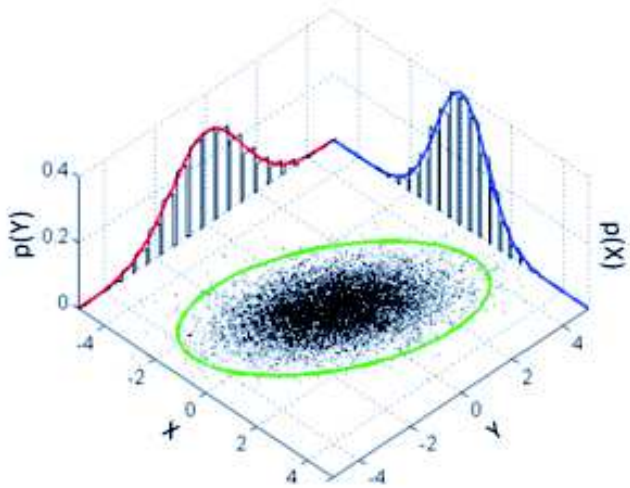
Control group

Week	N	Mean	SD
0	24	24.7	9.4
12	24	25.3	10.6
24	24	27.3	8.7

Corr	0	12	24
0	1.00	0.79	0.76
12	0.79	1.00	0.80
24	0.76	0.80	1.00

Note: May be misleading if data is not normal.

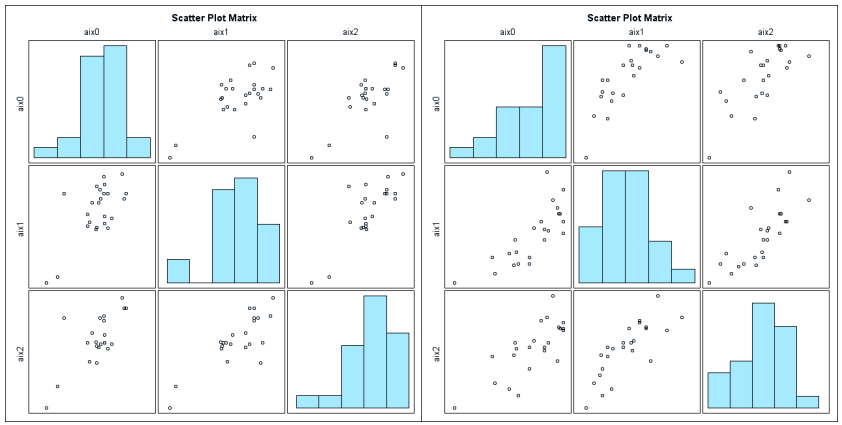
Multivariate normal data as we see it



Source: Wikipedia.

Eplerenone: Scatter plots

Left: Eplerenone. **Right:** Controls.



Better check of normal distribution: use residual diagnostics (later).

What if data is not normally distributed?

The **usual assumption** is that outcomes from the same subject follow a **multivariate normal distribution**.

But linear mixed models for repeated outcomes are **robust**.

- If sample size is not too small.
- If the distribution of the data is not too skewed.
- If outliers are not too frequent or too extreme.

So your data doesn't have to be perfectly normal.

Highly **skewed data** should be **transformed**.

Models for binary data are treated in lecture 5.

Basic concepts: covariance and correlation

Warning: Statistical software often display the covariances, **not** the correlations, as default output.

Both are used to describe the linear association between two variables assumed to have a joint (i.e. 2D) normal distribution.

- **The covariance** between two measurements is:

$$\mathrm{Cov}(Y_1, Y_2) = E\{(Y_1 - \mu_1)(Y_2 - \mu_2)\}$$

  ... in squared units of the original measurements.

- **The correlation** between two measurements

$$\mathrm{Cor}(Y_1, Y_2) = \frac{\mathrm{Cov}(Y_1, Y_2)}{\mathrm{SD}(Y_1)\mathrm{SD}(Y_2)}$$

  ... it has no units - interpretation is free of scale.

Technical model description (books, output)

The **mean-vector** of the 3D normal distribution is denoted by:

$$(\mu_1, \mu_2, \mu_3)$$

The **covariance** and **correlation matrices** by:

$$\mathrm{Cov} = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 \end{pmatrix}, \quad \mathrm{Cor} = \begin{pmatrix} 1 & \rho_{12} & \rho_{13} \\ \rho_{21} & 1 & \rho_{23} \\ \rho_{31} & \rho_{32} & 1 \end{pmatrix}$$

NOTE:

- Variances $\sigma_1^2, \sigma_2^2, \sigma_3^2$ along the diagonal in Cov.
- 1's along the diagonal in Cor.
- Both are symmetric $\sigma_{ij} = \sigma_{ji}$ and $\rho_{ij} = \rho_{ji}$.
- Note the relation $\rho_{ij} = \sigma_{ij} / \sqrt{\sigma_i^2 \cdot \sigma_j^2}$.

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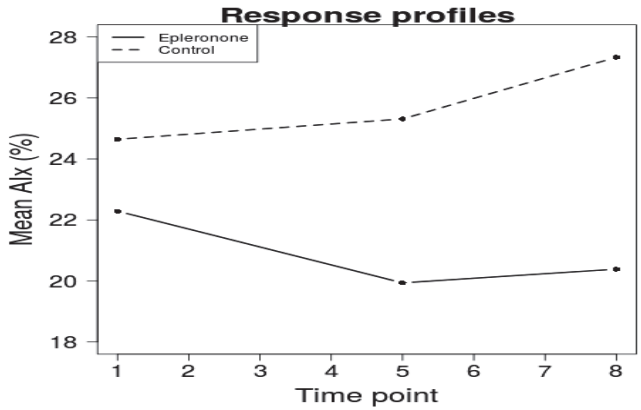
Eplerenone: group-averages over time



- Seeming improvement over time with Eplerenone.
- Seeming worsening with standard treatment.
- But what about statistical uncertainty?

1. Analysis of single group studies

Estimation of change over n time points within a population.

- Similar to one-way ANOVA only with correlated data.
- **Covariate:** time (categorical)
- **Balanced design**, but possibly incomplete data.
- Does a change occur over time?

Interest is in the mean parameters (systematic effects)

	group = Control alone
time=0	μ_1
time=12	μ_2
time=24	μ_3

One-way ANOVA type analysis

Example: The scientific interest was to investigate whether a change had occured within the control group at final follow-up.

Describe means for the three time points as:

	Mean in population with standard treatment
time=0	$\mu_1 = \beta_1$
time=12	$\mu_2 = \beta_1 + \beta_2$
time=24	$\mu_3 = \beta_1 + \beta_3$

- Mean at baseline is reference (intercept parameter)
- Change over time (time effect parameters)
- **The nullhypothesis is** $H_0: \ \beta_3 = 0.$

Output from demo program (ckd-demo #1)

Estimates, standard errors, (confidence intervals), p-values:

```
Effect      week   Estimate    StdError      DF   t Value   Pr > |t|
Intercept           24.2936      1.8975    23.7     12.80     <.0001
week        12       1.1356      1.3738    22.8      0.83     0.4170
week        24       3.1326      1.3060    23.4      2.40     0.0248
week         0            0           .       .         .          .
```

```
(Confidence intervals omitted due to lack of space)
```

Note:

- Data from control group only.
- Baseline (`week=0`) is the intercept.
- SAS and R output is similar.

Eplerenone: results

Expected change in AIX (%) with standard treatment

Week	Mean change (95% CI)	P-value
12	+1.14 (-1.71;+3.98)	P=0.42
24	+3.13 (+0.43;+5.83)	P=0.02

A significant change in mean AIX at final follow-up was found for the patients on standard treatment corresponding to an estimated worsening of 3.13% (95% CI 0.43% to 5.83%, P=0.02).

ATT:

- This is our first example of a linear mixed model analysis.
- Baseline characteristics are usually reported separately (e.g. table 1 with descriptive statistics).
- But how does standard treatment compare to Eplerenone?

Linear mixed models (LMMs)

We use linear mixed models to analyze quantitative repeated measurements and clustered data (many different designs . . .).

Systematic effects (means) are modeled **similar to ordinary linear models, (g)lms,** including relevant explanatory variables such as time, treatment, diagnosis, age, gender, etc.

Additional specification of the covariance is needed due to the repeated measurements, but with a **balanced design** and only few time points we **don't have to make specific assumptions** -

An unstructured covariance pattern can be applied, i.e.:

- One variance parameter for each time point
- One correlation parameter for each pair of time points
- $n + \frac{n(n-1)}{2}$ parameters in total with n time points.

Merits of the linear mixed model

We can use the linear mixed model to describe differences between groups at any time point or changes between any two time points.

E.g. using PROC MIXED in SAS or `lme`, `lmer` or `gls` in `R`.

Computationally this is an advantage compared to making many t-tests. Everything is computed at one go.

Linear mixed models handles data that are missing at random optimally whereas t-tests may be biased (more on this lecture 6).

There is a gain in statistical power when doing baseline adjustment in the analysis of randomized studies (more on this later today).

2. Analysis of parallel group studies

Comparison of change over n time points within g groups of subjects (e.g. different diagnoses or non-randomized treatments).

- Similar to two-way ANOVA only with correlated data.
- **Covariates:** group and time (both categorical) + interacton.
- **Balanced design**, but possibly incomplete data.
- Do the groups evolve differently with time?

Interest is in the mean parameters (systematic effects)

	group = Control	group = Eplerenone
time=0	μ_{11}	μ_{21}
time=12	μ_{12}	μ_{22}
time=24	μ_{13}	μ_{23}

What is the main hypothesis?

The linear mixed model allows for testing a **large** number of different hypothesis about the mean parameters.

Which hypotheses are *relevant* depend on the subject matter.

Example: The scientific hypothesis was that there would be a positive effect of Eplerenone compared to the standard treatment at final follow up.

The relevant statistical nullhypothesis is:

$$H_0\text{: } \mu_{13} - \mu_{11} = \mu_{23} - \mu_{21},$$

I.e. same change in means in the two groups at last follow-up.

Two-way ANOVA type model for the means

Describe means for the six time-treatment combinations as:

	group = Control	group = Eplerenone
time=0	β_1	$\beta_1 + \beta_4$
time=12	$\beta_1 + \beta_2$	$\beta_1 + \beta_2 + \beta_4 + \beta_5$
time=24	$\beta_1 + \beta_3$	$\beta_1 + \beta_3 + \beta_4 + \beta_6$

- Mean of standard treatment at baseline is reference (intercept)
- Change over time with standard treatment (time estimates)
- Difference between groups at baseline (group estimate)
- Differences in time effects between the groups (interaction or time⋆group estimates)

  The nullhypothesis is $H_0 : \beta_6 = 0$.

Output from demo-program (ckd-demo #2)

Note: Here baseline (`week=0`) and the control group (`group=0`) is the reference point (intercept). Additional estimates of changes over time for the Eplerenone group can be obtained by resetting the reference point (to `group=1`).

Effect	week	treat	Estimate	StdError	DF	t Value	Pr > |t|
Intercept			24.3431	2.0793	49.4	11.71	<.0001
week	12		1.0887	1.7694	46.2	0.62	0.5414
week	24		3.0895	1.4995	44.5	2.06	0.0452
week	0		0	.	.	.	.
group		1	-2.0547	2.8999	48.9	-0.71	0.4820
group		0	0	.	.	.	.
week*group	12	1	-1.9493	2.4871	45.8	-0.78	0.4372
week*group	12	0	0	.	.	.	.
week*group	24	1	-3.6078	2.1298	45.3	-1.69	0.0971
week*group	24	0	0	.	.	.	.
week*group	0	1	0	.	.	.	.
week*group	0	0	0	.	.	.	.

(Confidence intervals omitted due to lack of space)

Eplerenone: results

Changes in mean AIX (%) since baseline estimated by the two-way ANOVA type linear mixed model

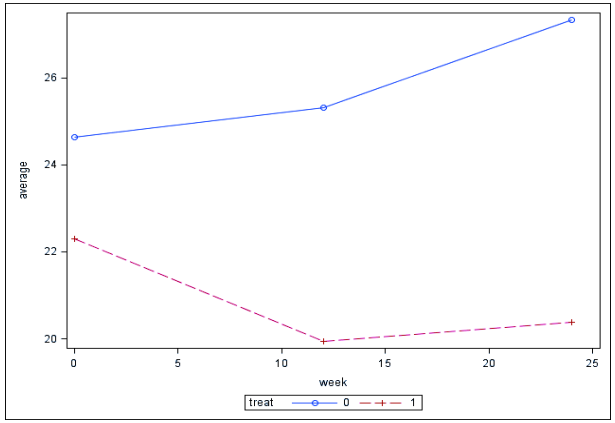
Week	Control	Eplerenone	Difference	P-value
12	1.09 (-2.47;4.65)	-0.86 (-4.38;2.66)	-1.95 (-6.96;3.06)	P=0.44
24	3.09 (0.07;6.11)	-0.51 (-3.56;2.53)	-3.61 (-7.90;0.68)	P=0.10

There is a seeming improvement at last follow-up with Eplerenone compared to standard treatment with a mean difference in change in AIX of -3.61 (95% CI: -7.90 to 0.68, $P = 0.10$) .

But: The difference between the treatments is not significant . . .

(**and** the analysis is suboptimal for a randomized study →).

Estimated response profiles (ckd-demo #2)



Note: Model predictions of the population means over time. Not identical to averages over time (due to implicit imputation of missing data, see lecture 6).

Alternative test of difference i time-trends

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
week	2	44.5	0.99	0.3794
group	1	47	1.84	0.1817
week*group	2	44.5	1.43	0.2490

By testing H_0: No `group*time`-interaction we test that:

- mean change over time is identical in all groups ...
- ... **at all follow-up times**.

But: If we aim to confirm a treatment effect we will get more power by testing the **effect at final follow-up** (and even more power when doing baseline adjustment →).

Post hoc testing

That the group∗time interaction is significant indicate that there is a difference in changes over time between the groups, but ...

- **not** between *which time points*.
- **not** between *which groups*, if there are more than two.

To find out where differences occur we have to look at estimated differences between specific groups at specific time points.

- The total number of comparisons may become large in particular if there are many time points (or several groups).
- **We ought to adjust for multiple testing!**

Read about this in P.H.Wesfall, R.D.Tobias & R.D.Wolfinger: *Multiple comparisons and multiple testing in SAS (2nd edition)*, SAS Press, 2011.

LSMEANS (SAS only, see ckd-demo)

Estimate the means for all time-group-combinations and **all possible differences** between them.

Differences of Least Squares Means

Effect	week	group	_week	_group	Estimate	Error	DF	t Value	Pr > |t|
week*group	12	1	12	0	-4.0040	3.5909	45.5	-1.12	0.2707
week*group	12	1	24	1	-0.3423	1.5282	46.8	-0.22	0.8237
week*group	12	1	24	0	-6.0048	3.2739	54.8	-1.83	0.0721
week*group	12	1	0	1	-0.8606	1.7478	45.4	-0.49	0.6248
week*group	12	1	0	0	-2.9153	3.2720	62	-0.89	0.3764
week*group	12	0	24	1	3.6617	3.2988	55.4	1.11	0.2718
week*group	12	0	24	0	-2.0008	1.4868	44.9	-1.35	0.1852
week*group	12	0	0	1	3.1434	3.2554	60.1	0.97	0.3381
week*group	12	0	0	0	1.0887	1.7694	46.2	0.62	0.5414
week*group	24	1	24	0	-5.6625	2.9505	46	-1.92	0.0612
week*group	24	1	0	1	-0.5183	1.5125	46	-0.34	0.7334
week*group	24	1	0	0	-2.5730	2.9485	63.7	-0.87	0.3861
week*group	24	0	0	1	5.1442	2.9019	60.7	1.77	0.0813
week*group	24	0	0	0	3.0895	1.4995	44.5	2.06	0.0452
week*group	0	1	0	0	-2.0547	2.8999	48.9	-0.71	0.4820

Not all comparisons are interesting, though.

Outline

About the course

What are repeated measurements?

Basics of longitudinal data (FLW chapters 1 & 2)

The multivariate normal distribution

Analysis of baseline follow-up studies (FLW chapters 3 & 5)

Baseline adjustment (FLW section 5.6)

Data management and computation

3. Analysis of randomized studies

Example: CKD patients were randomized to Eplerenone or standard treatment.

- We know that **the two treatment groups cannot differ systematically at baseline** since they represent two random samples from the **same** population.
- We are **wasting statistical power** when estimating the difference between the baseline means.

So should we *leave out* the baseline measurement?

- No, then we loose information about changes over time and again the power of the test of treatment effect is reduced.

Constrained LMM for randomized studies

	group = Control	group = Eplerenone
time=0	β_1	$\beta_1 + 0$
time=12	$\beta_1 + \beta_2$	$\beta_1 + \beta_2 + 0 + \beta_4$
time=24	$\beta_1 + \beta_3$	$\beta_1 + \beta_3 + 0 + \beta_5$

- Intercept.
- Time effect with standard treatment
- Difference between groups at baseline = **0!**
- Differences in time-effects (interaction)

Computational trick: Define a treatment variable containing the *de facto treatment* each patient received at each separate time, so that all belong to the same treatment-group at baseline.

Eplerenone: final results (ckd-demo #3)

Changes in mean AIX (%) since baseline (with adjustment).

Week	Control	Eplerenone	Difference	P-value
12	1.20 (-2.38;4.78)	-0.95 (-4.50;2.59)	-2.16 (-7.24;2.92)	P=0.40
24	3.36 (0.42;6.30)	-0.76 (-3.75;2.22)	-4.12 (-8.24;-0.01)	P=0.049

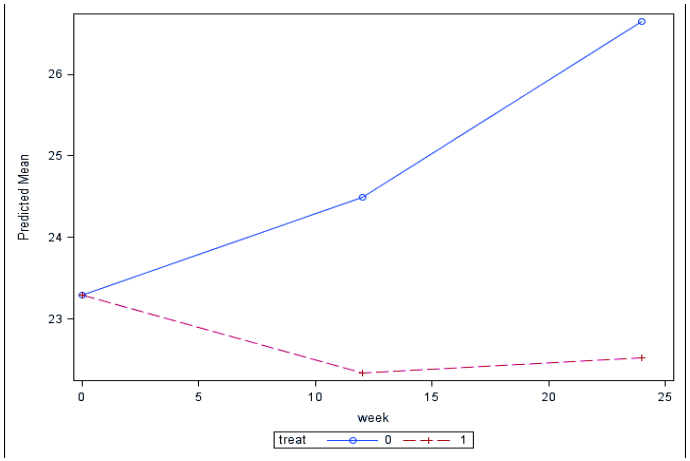
Significant difference at last follow-up in favour of Eplerenone.

Output from SAS (output from R is highly similar):

Effect	week	treat	Estimate	StdError	DF	t Value	Pr > |t|	Alpha
Intercept			23.2879	1.4430	50	16.14	<.0001	0.05
week	12		1.2017	1.7816	46.8	0.67	0.5033	0.05
week	24		3.3608	1.4643	48.3	2.30	0.0261	0.05
week	0		0	.	.	.	.	.
week*treat	12	1	-2.1552	2.5240	46	-0.85	0.3976	0.05
week*treat	12	0	0	.	.	.	.	.
week*treat	24	1	-4.1247	2.0436	45.9	-2.02	0.0494	0.05
week*treat	24	0	0	.	.	.	.	.
week*treat	0	0	0	.	.	.	.	.

(confidence intervals omitted)

cLMM: predicted response profiles



Note: Model predictions of the population means over time.

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How do you analyze **your** baseline follow-up study?

All code used to analyze the CKD-study can be found in the ckd-demo files at the course webpage.

- The program file allows you to run the analyses.
- The pdf file explains the program and the output.

Choose either the SAS or the R version for your convenience.

Exercise classes:

- Teachers will give a brief demonstration in SAS/R.
- Try out the demo if you like.
- Proceed to exercise 1 to make similar analyses.

Preparing data for analysis

Most often raw data is stored in the wide format (e.g. in Excell).

- one record per subject (i.e. one row or data line).
- several columns with outcomes from different occations

Example:

id	sex	age	group	aix0	aix1	aix2
1	1	57	0	10.5	17.5	25.0
2	1	48	0	-2.5	8.0	8.5
3	2	54	1	18.0	24.0	23.5
...						

BUT: To fit a linear mixed model with **any statistical software** data must be *transformed* to the so-called long format ...

(Check out the ckd-demo program to see how to do it).

The long format

- Multiple records for each subject (one for each occation)
- Each row contains only one observation of the outcome.
- A `time`-variable identifies the time of measurement.
- An `id`-variable identifies measurements from same subject.

Obs	id	sex	age	group	week	aix
1	1	1	57	0	0	10.5
2	1	1	57	0	12	17.5
3	1	1	57	0	24	25.0
4	2	1	48	0	0	-2.5
5	2	1	48	0	12	8.0
6	2	1	48	0	24	8.5
7	3	2	54	1	0	18.0
8	3	2	54	1	12	24.0
9	3	2	54	1	24	23.5
10	4	2	46	1	0	26.0
...