Pre/post measurements

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Analysis of longitudinal data

Advantages

- More power than cross sectional studies
- Each subject is its own control person
- Information about individual changes

Challenges

- Missing values
- Predictors can change over time
- In cross over designs: carry over effects

Data schema

Person	Time	Observation	Covariates		
1	1	y_{11}	x_{111}	$\ldots$	x_{11p}
1	2	y_{12}	x_{121}	$\ldots$	x_{12p}
.	.	.	.	$\ldots$	.
1	n_1	y_{1n_1}	x_{1n_11}	$\ldots$	x_{1n_1p}
.	.	.	.	$\ldots$	.
.	.	.	.	$\ldots$	.
N	1	y_{N1}	x_{N11}	$\ldots$	x_{N1p}
N	2	y_{N2}	x_{N21}	$\ldots$	x_{N2p}
.	.	.	.	$\ldots$	.
N	n_N	y_{Nn_N}	x_{Nn_N1}	$\ldots$	x_{Nn_Np}

Data schema

Person	Time	Observation	Covariates		
1	1	y_{11}	x_{111}	$\dots$	x_{11p}
1	2	y_{12}	x_{121}	$\dots$	x_{12p}
.	.	.	.	$\dots$	.
1	n_1	y_{1n_1}	x_{1n_11}	$\dots$	x_{1n_1p}
.	.	.	.	$\dots$	.
.	.	.	.	$\dots$	.
N	1	y_{N1}	x_{N11}	$\dots$	x_{N1p}
N	2	y_{N2}	x_{N21}	$\dots$	x_{N2p}
.	.	.	.	$\dots$	.
N	n_N	y_{Nn_N}	x_{Nn_N1}	$\dots$	x_{Nn_Np}

Today we will consider the simplest case with only two time points: pre and post score

Outline

1. t test
2. Change score analysis
3. Analysis of Covariance
4. Example: Acupuncture for shoulder pain

1 t test

t test for dependent samples (comparing two time points)

- Straightforward analysis for two time points $n = 2$
- Consider for each person the change score $d_i = y_{i2} - y_{i1}$ and the linear model

$$d_i = \beta_0 + \varepsilon_i$$
$$y_{i2} = \beta_0 + y_{i1} + \varepsilon_i$$

  with $\varepsilon_i \sim N(0, \sigma^2)$ i.i.d.
- Interpretation:

  β_0 average change score
- Hypothesis:
  Is there change between the first and second time point ($H_0 \colon \beta_0 = 0$)?
- Which effects are not considered by this?

t test for dependent samples (comparing two time points)

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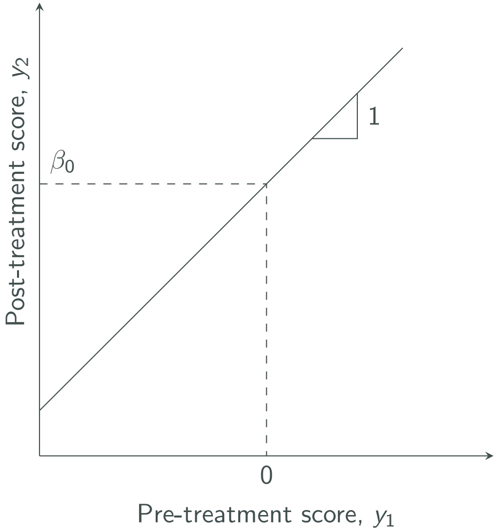
- Interpretation:

$$\beta_0 \quad \text{average change score}$$

- Hypothesis:
  Is there change between the first and second time point ($H_0 : \beta_0 = 0$)?
- Which effects are not considered by this?
- It is unclear if change is due to the treatment or just appeared over time

t test for comparing two time points



t test for comparing two time points

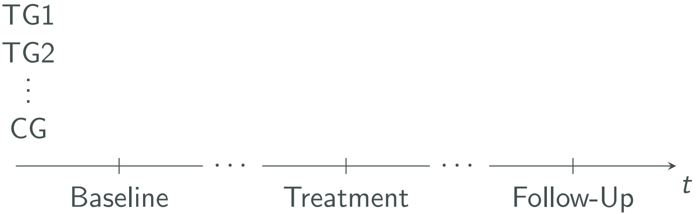
```
# simulate two dependent time points
cg <- MASS::mvrnorm(n = 50, mu = c(10,10),
                    Sigma = matrix(c(1,.9,.9,1), 2))
tg <- MASS::mvrnorm(n = 50, mu = c(10,15),
                    Sigma = matrix(c(1,.9,.9,1), 2))

sim <- as.data.frame(rbind(cg, tg))
names(sim) <- c("t1", "t2")

# add group variable
sim$group <- factor(rep(c("CG", "TG"), each = 50))

# group means
aggregate(cbind(t1, t2) ~ group, data = sim, FUN = mean)
```

t test for comparing two time points

```r
# t test
t.test(sim$t2, sim$t1, paired = TRUE)

# add change score
sim$d <- sim$t2 - sim$t1

# linear model
lm1 <- lm(d ~ 1, data = sim)
lm2 <- lm(t2 ~ offset(t1), data = sim)

# visualization
plot(t2 ~ t1, data = sim)
abline(coef(lm2), 1)
```

Better design

- At least two groups are observed before (y_{i1}) and after (y_{i2}) a treatment



- Research question:
  Do groups differ in the strength of their change?

t test of follow-up score of two groups

- In regression notation with $x_i = 1$, if ith person is part of the treatment group, and else 0:

$$y_{i2} = \beta_0 + \beta_1 x_i + \varepsilon_i$$

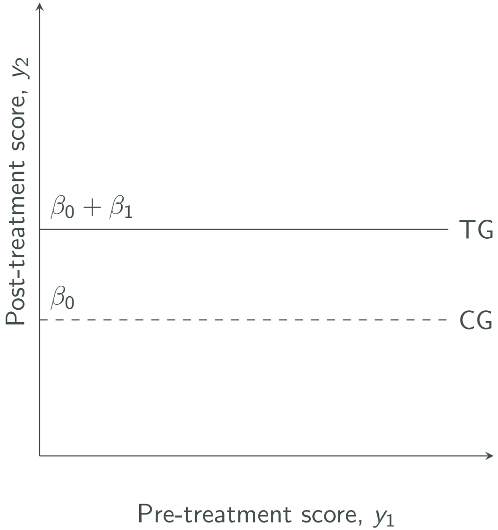
  with $\varepsilon_i \sim N(0, \sigma^2)$ i.i.d.

- Interpretation:

β_0	average follow-up score of reference group
β_1	effect of treatment group

- Hypothesis:
  Do groups differ at the second time point $(H_0 : \beta_1 = 0)$?
- Since the baseline score is not considered, estimate of the change is biased

t test of follow-up score of two groups



t test of follow-up score of two groups

```
# t test
t.test(t2 ~ group, data = sim, var.equal = TRUE)

# linear model
lm3 <- lm(t2 ~ group, data = sim)

# visualization
plot(t2 ~ t1, sim)
abline(h = cumsum(coef(lm3)))
```

2 Change score analysis

Change score analysis

- Regression model

$$
\begin{aligned}
d_i &= \beta_0 + \beta_1 x_i + \varepsilon_i \\
y_{i2} - y_{i1} &= \beta_0 + \beta_1 x_i + \varepsilon_i \\
y_{i2} &= \beta_0 + y_{i1} + \beta_1 x_i + \varepsilon_i
\end{aligned}
$$

  with $\varepsilon_i \sim N(0, \sigma^2)$ i.i.d.

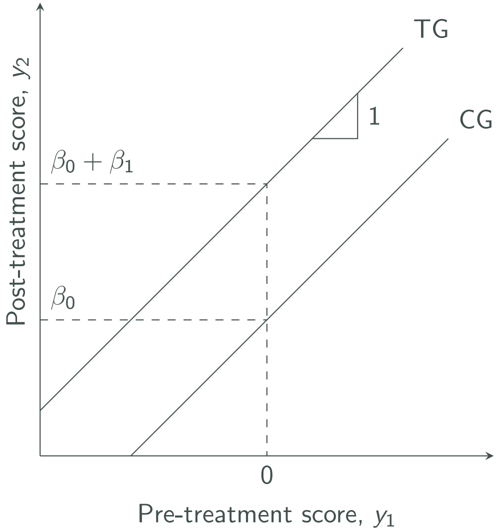
- Interpretation:

  β_0 average change score for reference group

  β_1 difference to β_0 in treatment group

- Hypotheses:
  - Is there change in the reference group ($H_0: \beta_0 = 0$)?
  - Does the change differ between groups ($H_0: \beta_1 = 0$)?

Change score analysis



Change score analysis

```r
# regression model
lm4 <- lm(t2 ~ offset(t1) + group, data = sim)

# visualization
plot(t2 ~ t1, data = sim)
abline(coef(lm4)[1], 1)
abline(coef(lm4)[1] + coef(lm4)[2], 1)
```

Regression to the mean

- Change score analysis is based on the often too restrictive assumption that the follow-up score depends on the baseline score with a slope of 1
- Often baseline scores are negatively correlated with the change scores: Persons with low (bad) scores improve more than persons with high scores
- This regression to the mean lets us expect a slope of < 1 which has to be estimated from the data

3 Analysis of Covariance

Analysis of Covariance (ANCOVA)

- Regression model

$$y_{i2} = \beta_0 + \beta_1\, y_{i1} + \beta_2\, x_i + \varepsilon_i$$

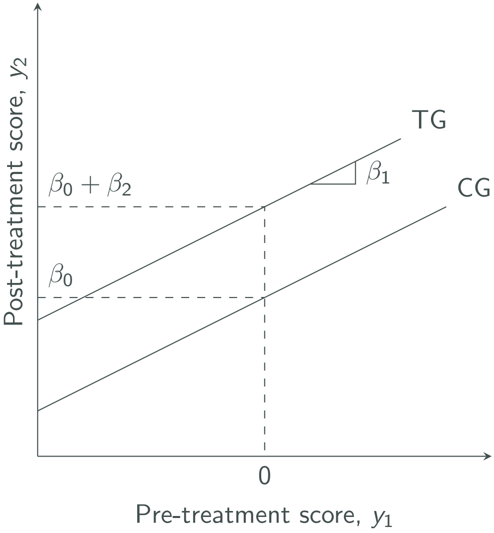
  with $\varepsilon_i \sim N(0, \sigma^2)$ i.i.d.
- Interpretation:

  β_0 average follow-up score in the reference group for $y_{i1} = 0$

  β_1 effect of baseline score

  β_2 difference to follow-up score in the treatment group
- Hypotheses:
  - Is there a relationship between baseline and follow-up score ($H_0: \beta_1 = 0$)?
  - Do the follow-up scores in the groups differ for persons with identical baseline scores ($H_0: \beta_2 = 0$)?

Analysis of Covariance (ANCOVA)



Adjusted means

- With an ANCOVA model we can predict average follow-up scores for persons with the same baseline score
- For example, we get
$$\hat{y}_{i2} = \hat{\beta}_0 + \hat{\beta}_1 \, \bar{y}_1 + \hat{\beta}_2 \, x_i$$
for an average baseline score $\bar{y}_1$
- These conditional means are sometimes called (baseline) adjusted means

Analysis of Covariance (ANCOVA)

```
# ancova
lm5 <- lm(t2 ~ t1 + group, data = sim)

# adjusted means
predict(lm5, newdata = data.frame(t1 = mean(sim$t1),
                                  group = c("CG", "TG")))

# ancova with change score
lm5a <- lm(d ~ t1 + group, data = sim)

# visualization
plot(t2 ~ t1, data = sim)
abline(coef(lm5)[1], coef(lm5)[2])
abline(coef(lm5)[1] + coef(lm5)[3], coef(lm5)[2])
```

Analysis of Covariance with change score

- Regression model

$$
\begin{aligned}
d_i &= \beta_0 + \beta_1\, y_{i1} + \beta_2\, x_i + \varepsilon_i \\
y_{i2} - y_{i1} &= \beta_0 + \beta_1\, y_{i1} + \beta_2\, x_i + \varepsilon_i \\
y_{i2} &= \beta_0 + (1 + \beta_1)\, y_{i1} + \beta_2\, x_i + \varepsilon_i
\end{aligned}
$$

- For testing the difference of change in the groups (β_2) it is irrelevant if the dependent variable is the follow-up score or the change score

Different slopes for groups

- Regression model

$$y_{i2} = \beta_0 + \beta_1\, y_{i1} + \beta_2\, x_i + \beta_3\, (y_{i1} \cdot x_i) + \varepsilon_i$$

  with $\varepsilon_i \sim N(0, \sigma^2)$ i.i.d.

- Interpretation:

  β_0 average follow-up score in reference group for $y_{i1} = 0$

  β_1 effect of baseline score

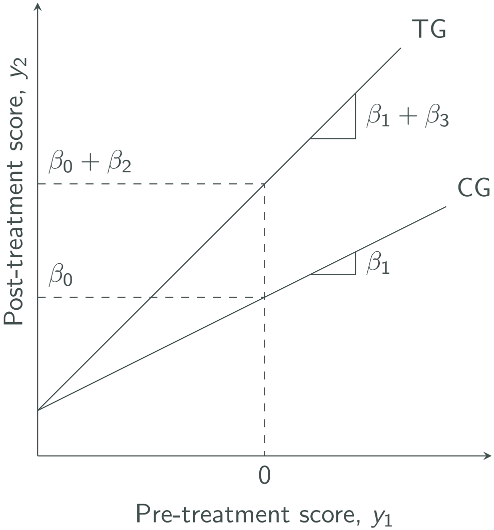
  β_2 difference to follow-up score in treatment group

  β_3 difference between slopes in reference and treatment groups

- Hypothesis:
  Does effect of baseline score depend on group $(H_0: \beta_3 = 0)$?

- Interpretation of adjusted means independently of baseline score implies $\beta_3 = 0$

Interaction between baseline score and group



Interaction between baseline score and group

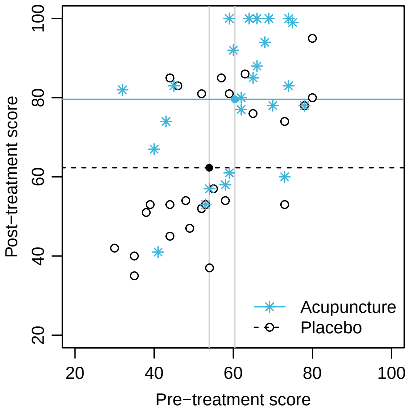
```
# regression model with interaction
lm6 <- lm(t2 ~ t1 * group, data = sim)

# visualization
plot(t2 ~ t1, data = sim)
abline(coef(lm6)[1], coef(lm6)[2])
abline(coef(lm6)[1] + coef(lm6)[3], coef(lm6)[2] + coef(lm6)[4])

# models are nested
anova(lm4, lm5, lm6)
```

4 Example: Acupuncture for shoulder pain

Example: Acupuncture for shoulder pain

- Kleinhenz et al. (1999) investigate the effect of acupuncture on the improvement of mobility for 52 patients with shoulder pain
- Patients are randomly assigned to two groups (placebo vs. acupuncture)
- Before and after the treatment a mobility score is measured
- Vickers and Altman (2001) show advantages of an analysis of covariance compared to other methods based on these data

Acupuncture: Follow-up analysis

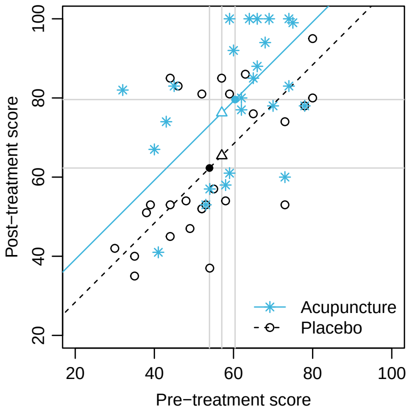


	Pla	Acu	Diff
Baseline	53.9	60.4	6.5
Follow-up	62.3	79.6	17.3
Change sc.	8.4	19.2	10.8
ANCOVA			12.7

$$y_{i2} = \beta_0 + \beta_1 x_i + \varepsilon_i$$

$$\hat{\beta}_1 = 17.3, 0.95\text{-CI: } (7.5, 27.1)$$

Acupuncture: Change score analysis

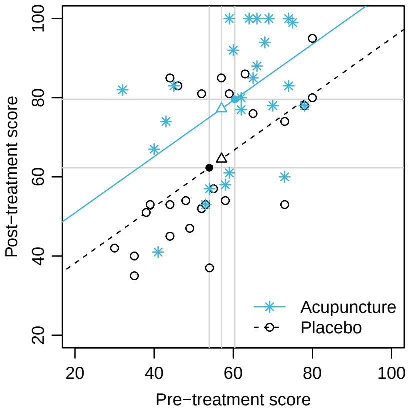


	Pla	Acu	Diff
Baseline	53.9	60.4	6.5
Follow-up	62.3	79.6	17.3
Change sc.	8.4	19.2	10.8
ANCOVA			12.7

$$y_{i2} = \beta_0 + y_{i1} + \beta_1 x_i + \varepsilon_i$$

$$\hat{\beta}_1 = 10.8\ (2.3, 19.4)$$

Acupuncture: ANCOVA



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Baseline	53.9	60.4	6.5
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Change sc.	8.4	19.2	10.8
ANCOVA			12.7

$$y_{i2} = \beta_0 + \beta_1\, y_{i1} + \beta_2\, x_i + \varepsilon_i$$

$$\hat{\beta}_2 = 12.7\ (4.1, 21.3)$$

Example: Acupuncture for shoulder pain

```r
# read data
dat <- read.table("kleinhenz.txt", header = TRUE)
dat$grp <- factor(dat$grp, levels = c("plac", "acu"))

# follow-up analysis
m1 <- lm(post ~ grp, data = dat)
summary(m1)
confint(m1)

# change score analysis
m2 <- lm(post ~ offset(pre) + grp, data = dat)

# ancova
m3 <- lm(post ~ pre + grp, data = dat)
```

Example: Acupuncture for shoulder pain

```
# testing if slopes differ
m4 <- lm(post ~ pre * grp, data = dat)
anova(m3, m4)

# adjusted means
predict(m3, newdata = data.frame(pre = mean(dat$pre),
                                 grp = c("plac", "acu")))

# visualization
plot(post ~ pre, data = dat, xlim = c(20,100), ylim = c(20,100))
abline(coef(m3)[1], coef(m3)[2])
abline(coef(m3)[1] + coef(m3)[3], coef(m3)[2])
```

Summary

- We considered the basic case when several groups are observed at two time points (baseline and follow-up)
- Analysis of these kind of data considers the difference

$$d_i = y_{i2} - y_{i1}$$

  or the adjusted follow-up scores which are considered to be independent
- Analysis of Covariance
  - has the highest power to detect differences for average change compared to the other methods
  - must be cautiously interpreted when groups are not randomly assigned

5 Linear mixed-effects model

Linear mixed-effects model

- Regression notation with indicator variable for time $(t_{i1} = 0,\ t_{i2} = 1)$ and group (x_i)

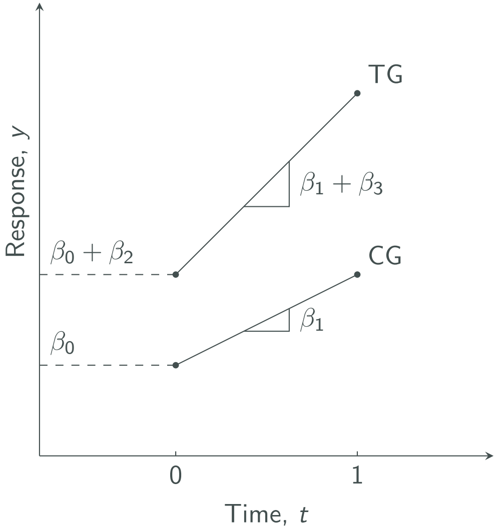
$$y_{ij} = \beta_0 + \beta_1\, t_{ij} + \beta_2\, x_i + \beta_3\, (t_{ij} \cdot x_i) + \upsilon_i + \varepsilon_{ij}$$

  with $\upsilon_i \sim N(0, \sigma_\upsilon^2)$ and $\varepsilon_{ij} \sim N(0, \sigma^2)$

- Interpretation:

β_0	mean baseline value in reference group
β_1	time effect (slope) in reference group
β_2	effect of treatment group
β_3	effect on the slope of treatment group

Linear mixed-effects model



Linear mixed-effects model

- For the two groups with $j = 1, 2$, we get

$$y_{i1} = \beta_0 + \beta_2\, x_i + \upsilon_i + \varepsilon_{i1}$$
$$y_{i2} = \beta_0 + \beta_1 + \beta_2\, x_i + \beta_3\, x_i + \upsilon_i + \varepsilon_{i2}$$

- For the change score, we then get

$$y_{i2} - y_{i1} = \beta_1 + \beta_3\, x_i + (\varepsilon_{i2} - \varepsilon_{i1})$$

- Since ε_{ij} are independent, this results in the equation for the change score analysis

$$y_{i2} - y_{i1} = \beta_1 + \beta_3\, x_i + \varepsilon_i$$

  with

$$\varepsilon_i = \varepsilon_{i2} - \varepsilon_{i1} \sim N(0, \sigma_d^2 = 2\sigma^2)$$

$\rightarrow$ LMM for two time points is equivalent to change score analysis!

Example: Acupuncture for shoulder pain

```
# read data
dat <- read.table("kleinhenz.txt", header = TRUE)
dat$grp <- factor(dat$grp, levels = c("plac", "acu"))

# change score analysis
m1 <- lm(post ~ offset(pre) + grp, data = dat)
# LMM
datl <- reshape(dat, direction = "long",
                varying = list(1:2), v.names = "score")
datl$time <- factor(datl$time, levels = 1:2, labels = c("pre", "post"))
m2 <- lmer(score ~ grp * time + (1 | id), data = datl)
# compare residual variances
sigma(m1)^2
2 * sigma(m2)^2
```

References

Kleinhenz, J., Streitberger, K., Windeler, J., Güßbacher, A., Mavridis, G., & Martin, E. (1999).Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain*, *83*(2), 235–241.

Vickers, A. J., & Altman, D. G. (2001).Analysing controlled trials with baseline and follow up measurements. *BMJ*, *323*(7321), 1123–1124.