This afternoon: Summarizing homework and exercises

- Exercise 3: Weight and height
- Exercise 5, 6, and 8: CRP
- Exercise 9: Smoke

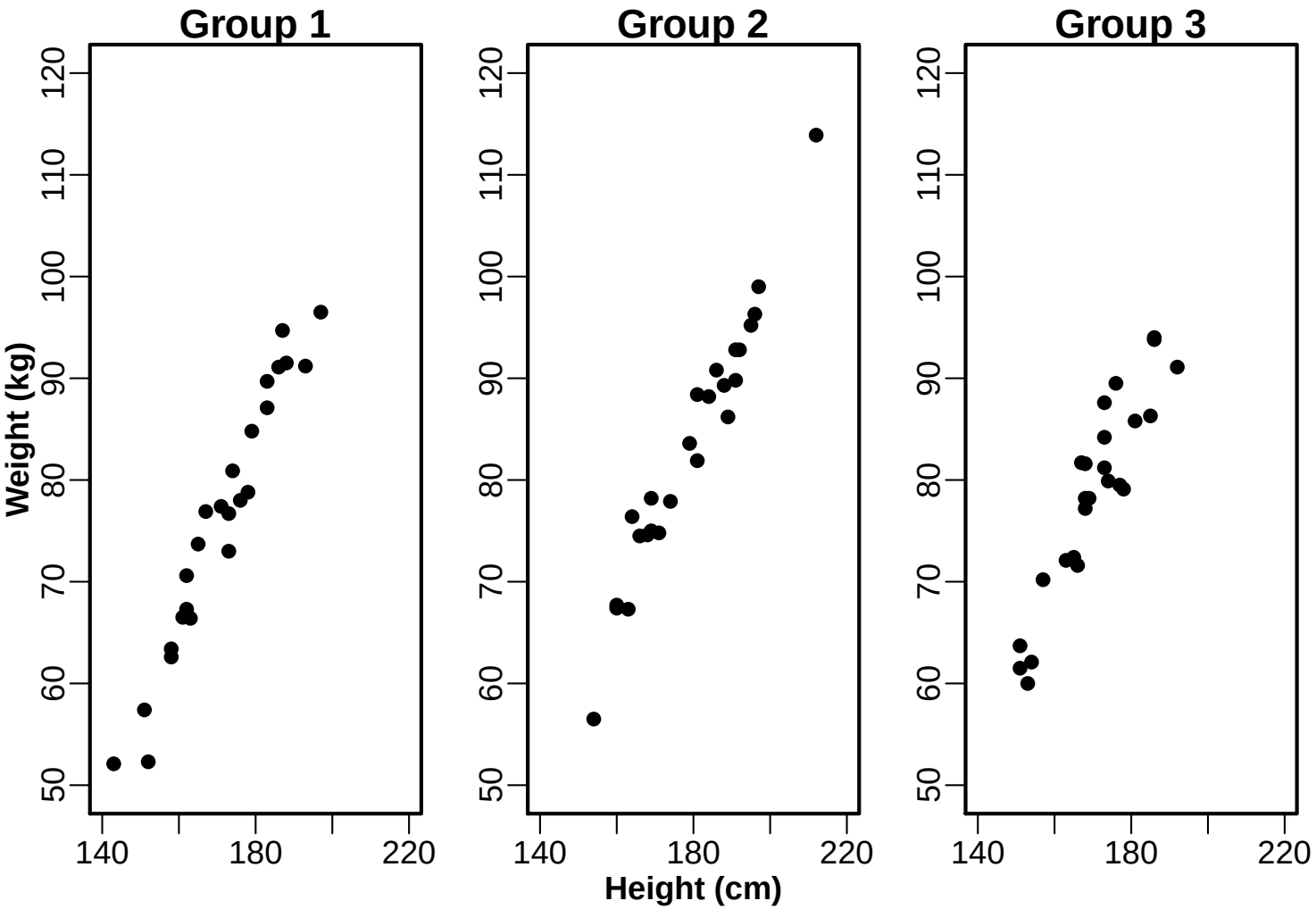
Weight and height

Data: Weight and height for each subject in three groups.

Group	n	Weight mean	Weight sd	Height mean	Height sd	Correlation
1	25	76.024	12.935	171.32	13.892	0.9745
2	25	83.140	12.476	179.20	14.555	0.9763
3	25	78.500	9.853	170.16	11.331	0.9266

We will focus on comparing group 1 and 3.

Scatter plots of weight and height



Comparison of group 1 and 3 based on weight and height

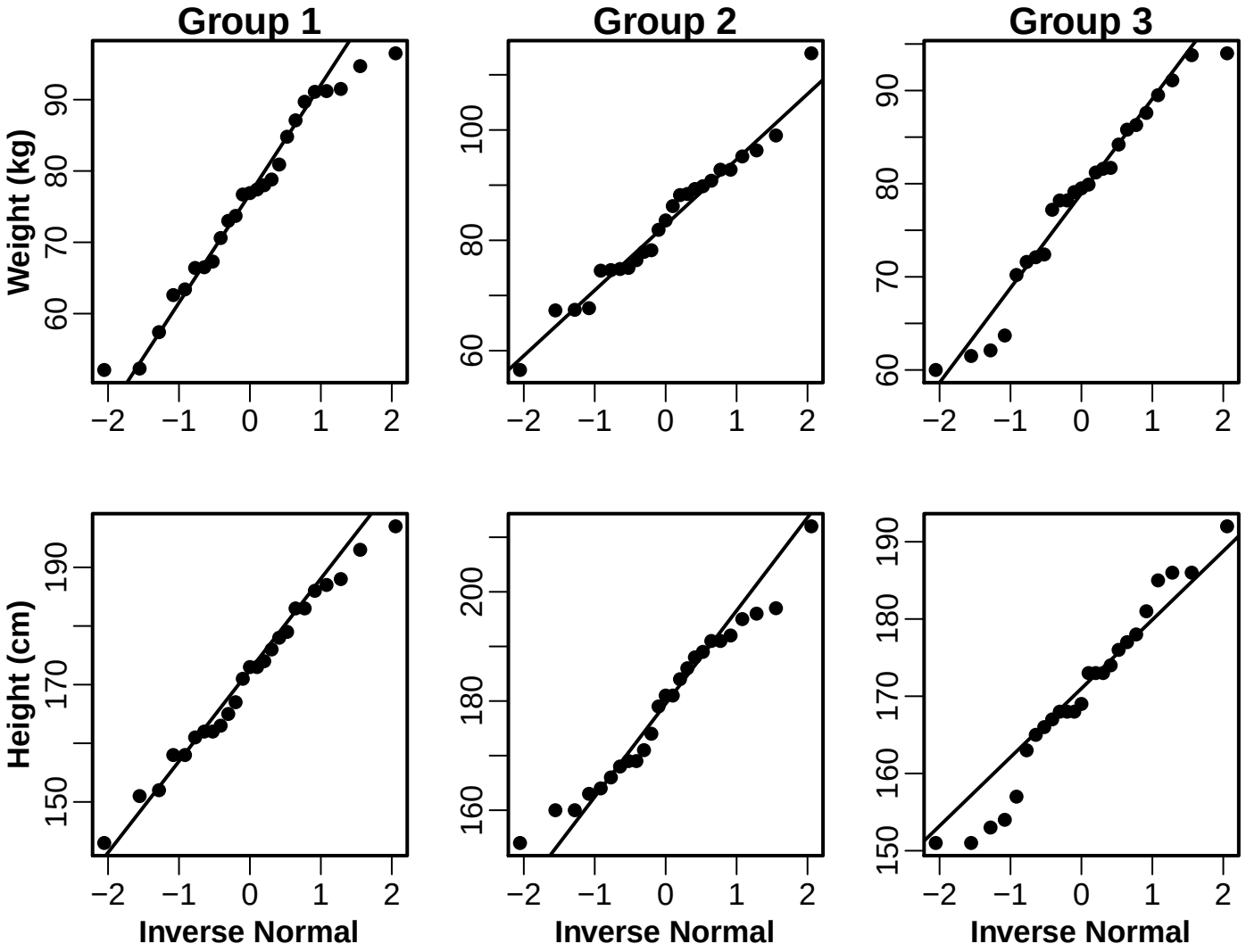
If we compare group 1 and 3 we get:

Individual t-test:

Characteristic	Group	Mean	sd	p
Weight	1	76.0	12.9	
	3	78.5	9.9	0.45
Height	1	171.3	13.9	
	3	170.2	11.3	0.75

So apparently no difference between group 1 and 3, but what about the **correlation** between weight and height?

QQ-plots for weight and height



Multivariate analysis of weight and height

Multivariate analysis using Hotelling's test:

The standard deviations for weight and height and their correlation are not significantly different in the two groups, p=0.27 (`mvtest cov`).

Hotelling's test for equal means (weight and height) in the two groups:

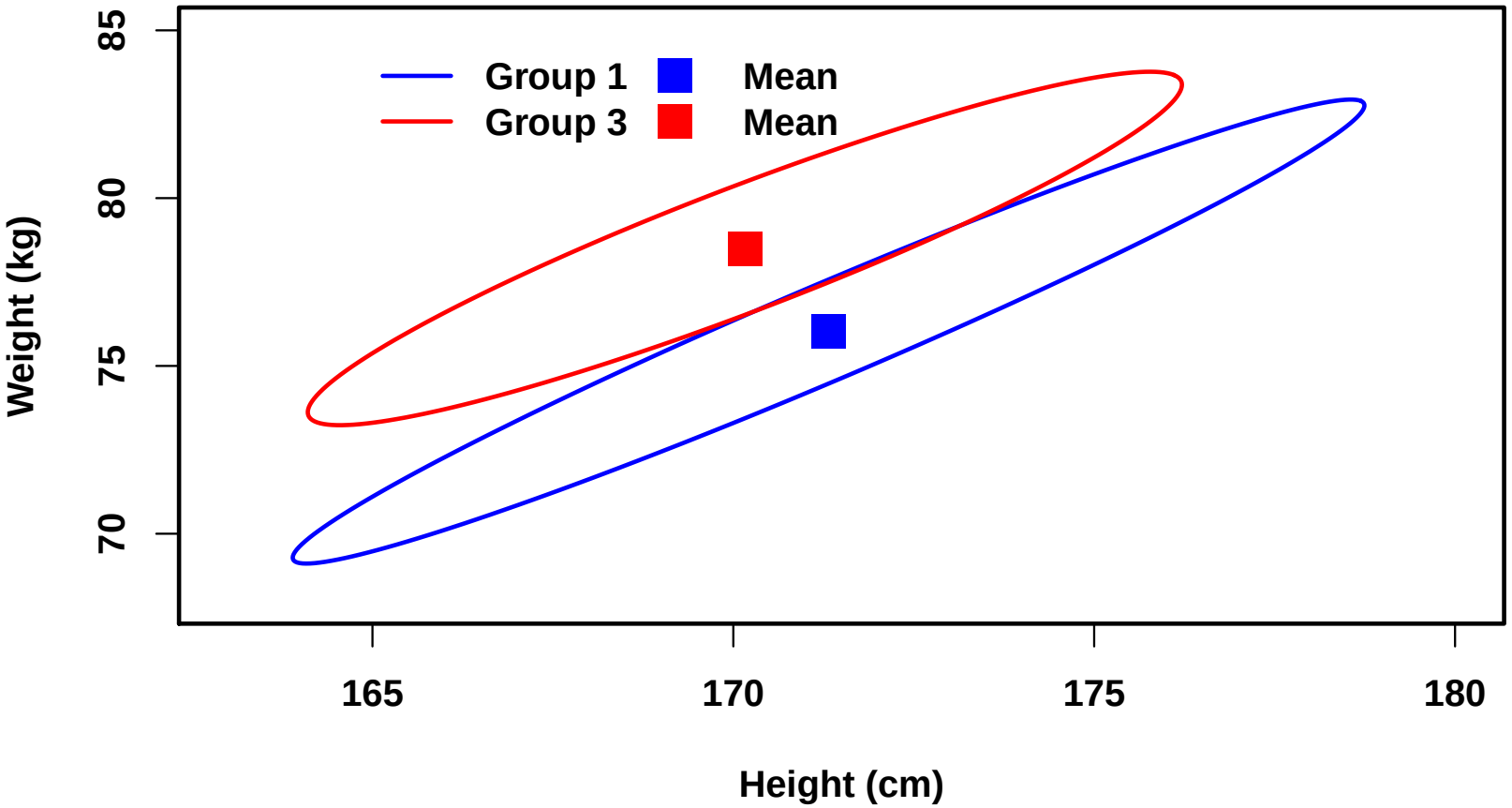
$$p = 0.0032$$

This does not agree with the univariate analysis?

Group 1-3	Difference (95%-CI)	p-value (t-test)
Weight (kg)	-2.48 (-9.01 - 4.06)	0.45
Height (cm)	1.16 (-6.05 - 8.27)	0.75

Confidence ellipses for weight and height

Simultaneous confidence limits for weight and height in each group.



CRP in neonatal pigs

Data: 22 neonatal pigs randomized to two groups

1. Sternotomy and Cardio Pulmonary Bypass (CPB, n=12)
2. Sternotomy (sham, n=10)

CRP measured at 4 time points:

1. Baseline, immediately after anaesthesia
2. 5 minutes after weaning off CPB
3. 2 hours after CPB
4. 4 hours after CPB

The development in CRP over time

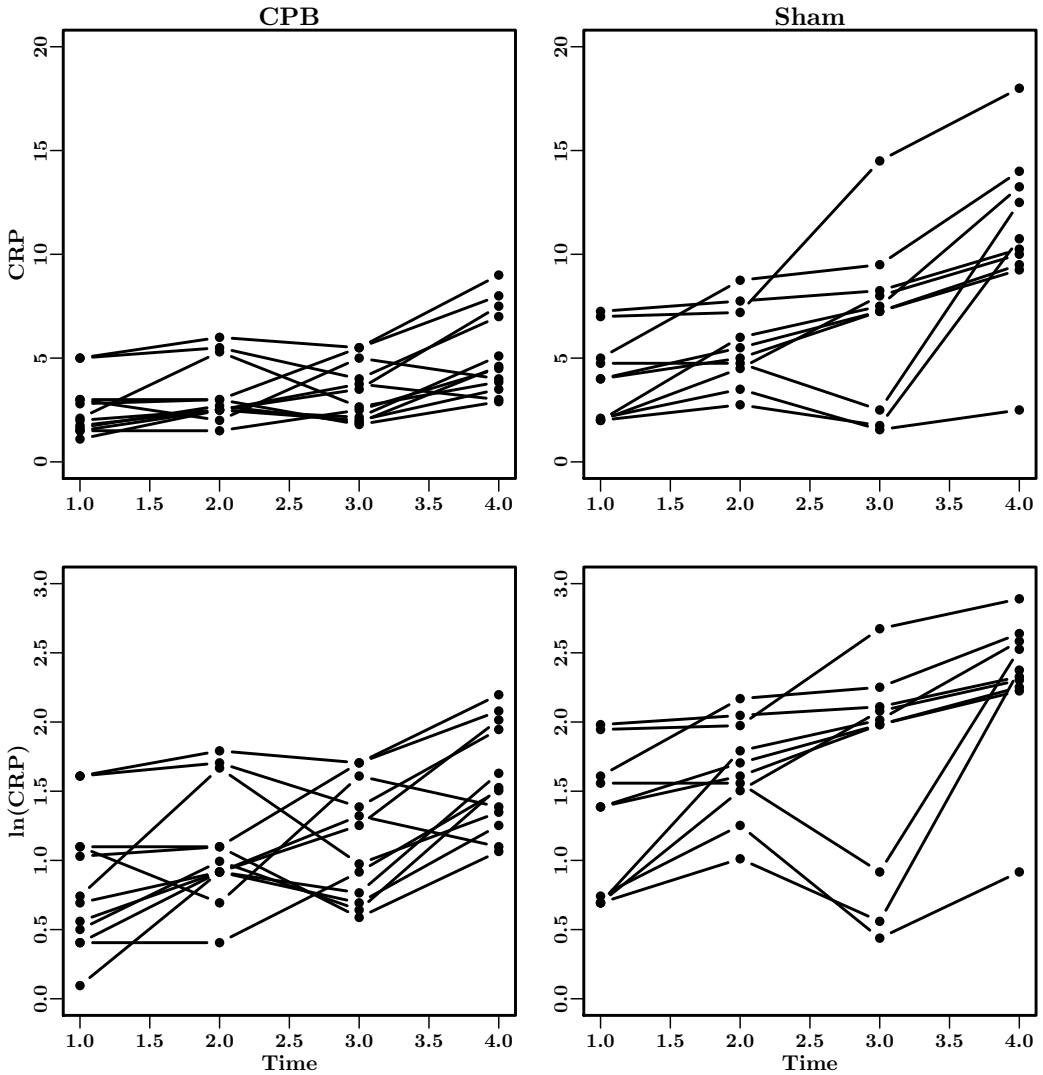
We want to compare the two groups regarding the development over time:

- **Test 1**: Test for parallel curves (compute successive differences and test for equal differences in the two groups)
- **Test 2**: Test for equal levels in the two groups (if we accept that the curves are parallel)
- **Test 3**: Test for constant curves (if there is no treatment effect)

We will consider:

- Scale for analyzing the data (original or log)
- Choice of repeated measurement model
- Model validation
- How to present the results

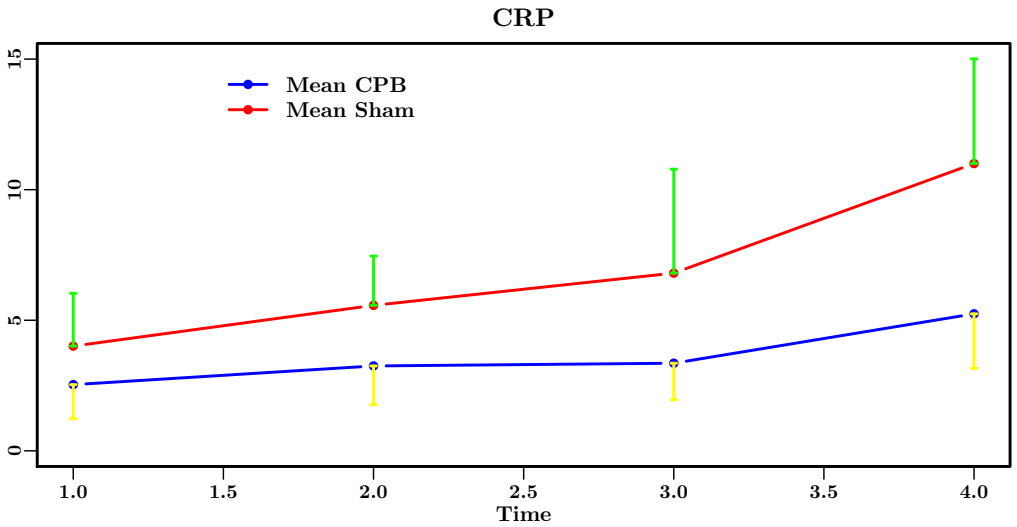
CRP over time: Grouped individual curves

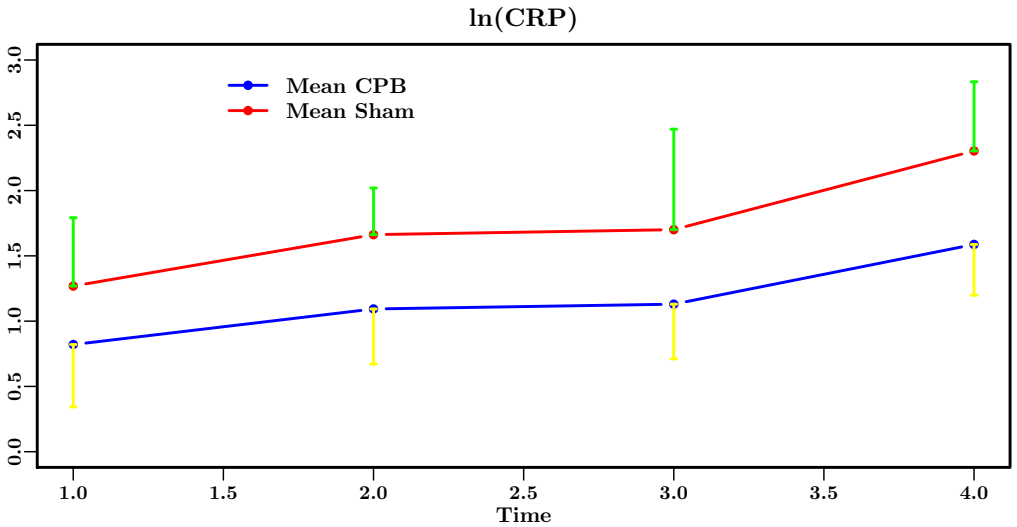


CRP: The variability increases with time?

log(CRP): The variability is more homogeneous?

CRP over time: Mean curves



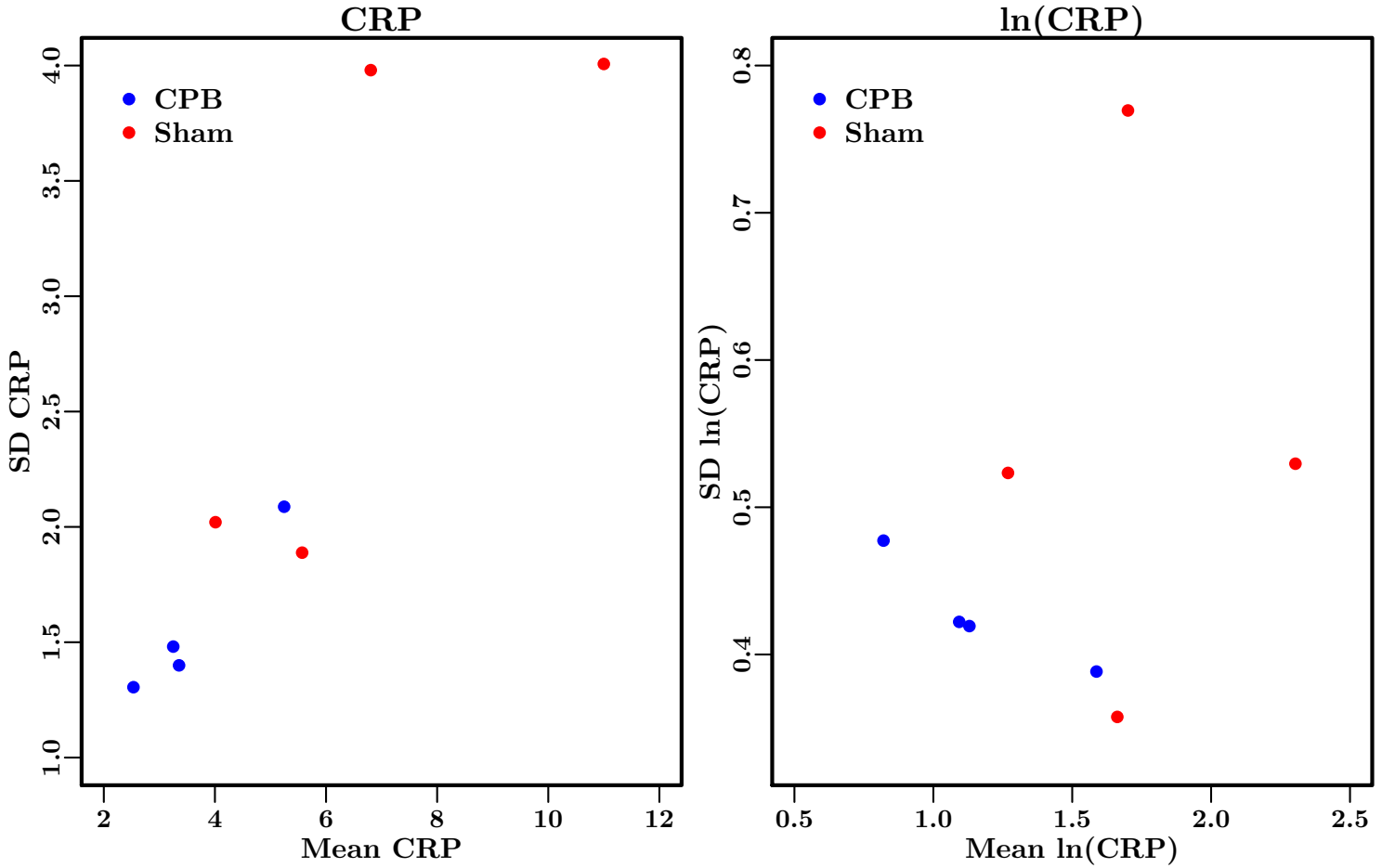


CRP: The distance between the two curves increases with time?

log(CRP): Constant distance, that is parallel curves?

CRP over time: SD plotted against the mean

One mean and sd for each group and time point.

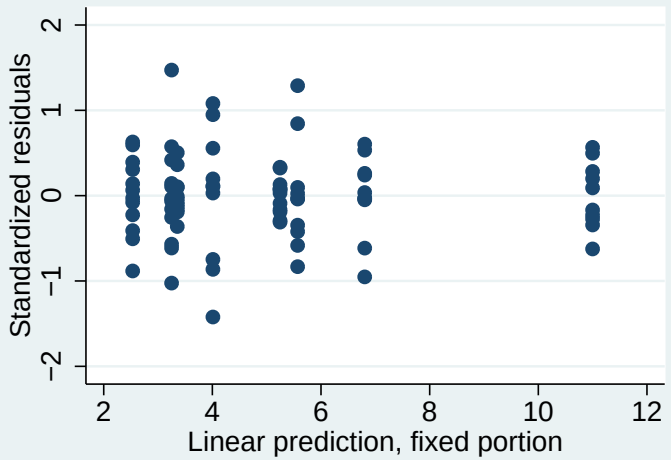


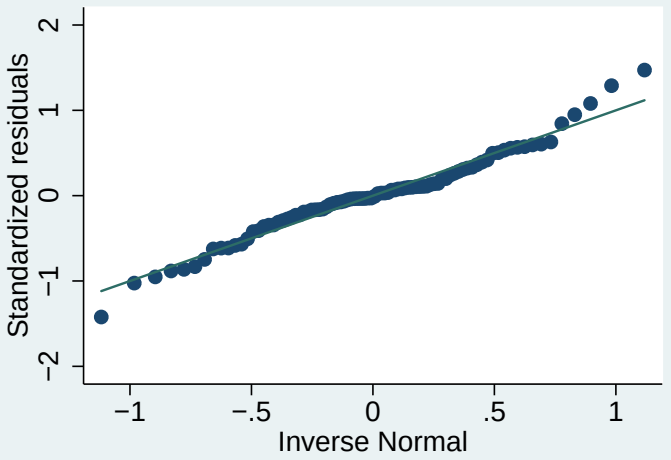
CRP over time: The pairwise differences

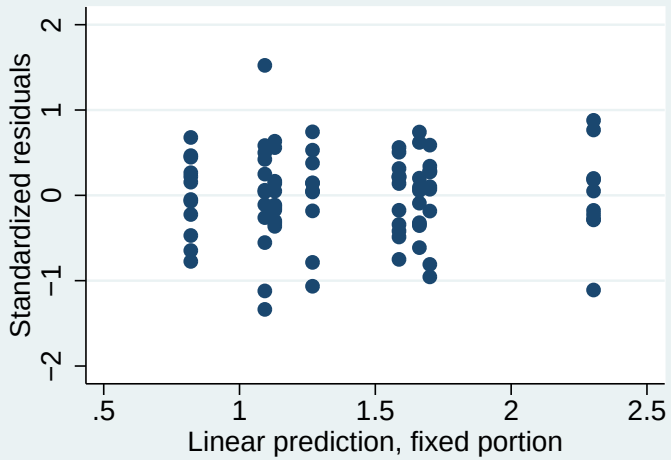
Note:

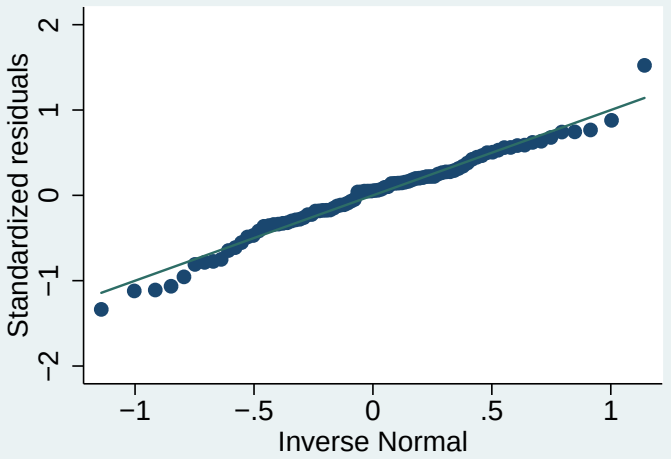
- The pairwise differences (over time) could in principle exhibit a more constant variability than the raw data.
- Let us first examine whether the raw data can be described by a multivariate normal distribution in each group.
- If this is accepted, we test whether the standard deviations and correlations are the same in the two groups.

CRP: Residual plots for the CRP and log(CRP) data









CRP or log(CRP)?

Based on **raw data** and **differences over time**:

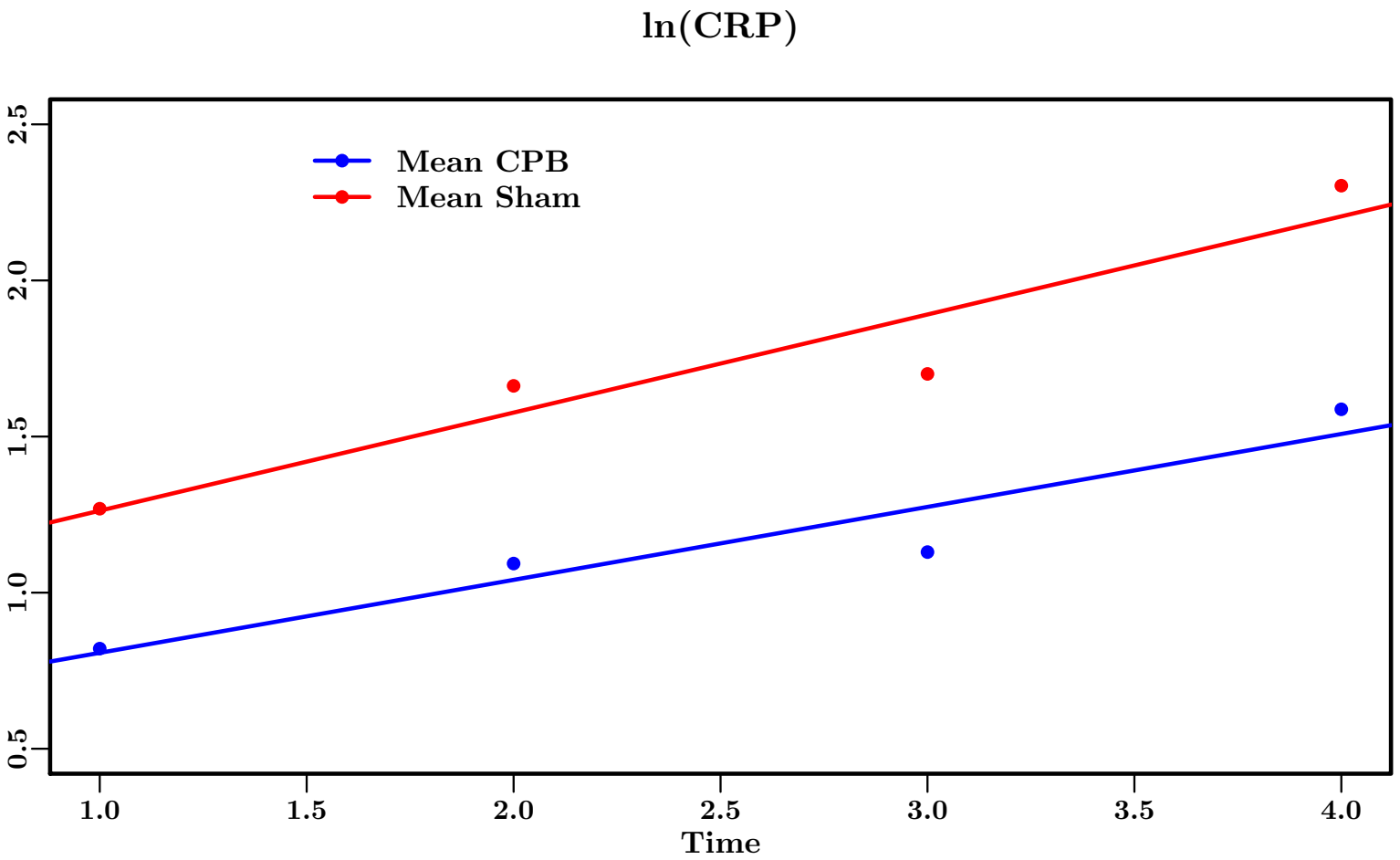
	CRP	**ln(CRP)**
QQ-plots	OK	OK
Same sd's and correlations in the two groups	p=0.035	p=0.31
Parallel curves	p=0.019	p=0.72

We would probably choose to analyze the data on the **log-scale**.

Summary

- The statistical analysis was performed on a logarithmic scale.
- On log-scale the hypothesis of equal standard deviations and correlations in the two groups was accepted (p=0.31).
- A test for parallel curves was accepted (p=0.72).
- A test for equal curves in the two groups was rejected (p=0.003).
- In each group a test for no development over time was rejected (CPB: p=0.006, Sham: p=0.007).
- The estimated effect of CPB (Sham-CPB on log-scale) was 0.58 (0.22; 0.93).
  The median CRP-level in the Sham-group was 78% (25%; 153%) higher than that in the CPB-group **at all time points also time=0!**

CRP: Random Coefficient Model on log-scale



CRP: Stata-output from the Random Coefficient Model

Note: We use `time1 = time - 1` so that the intercept corresponds to the baseline level.
Part of the output from:

```
mixed lncrp bn.group c.time1 bn.group#c.time1 || id: time1, cov(un)
```

lncrp	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
group CPB	-.4552144	.1930813	-2.36	0.018	-.8336469	-.0767819
Sham	0	(omitted)				
time1	.3142581	.0534478	5.88	0.000	.2095023	.4190139
group#c.time1						
CPB	-.0805914	.0723687	-1.11	0.265	-.2224314	.0612486
Sham	0	(omitted)				
_cons	1.262466	.1426	8.85	0.000	.9829748	1.541957

No significant difference between the slopes of the two lines (p=0.265).

CRP: The Random Coefficient Model with common slope

Part of the output from:

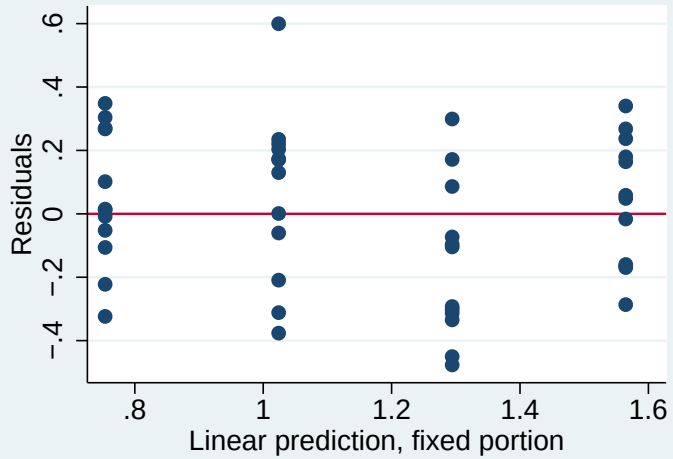
```
mixed lncrp bn.group c.time1 || id: time1, cov(un)
```

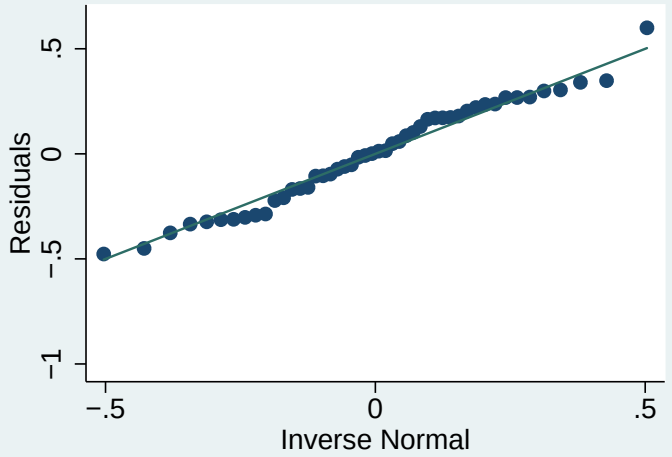
```
------------------------------------------------------------------------------
       lncrp |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 group  CPB  |  -.5727464   .1616838    -3.54   0.000    -.8896409   -.2558519
       Sham  |           0  (omitted)
       time1 |   .2702991   .0370362     7.30   0.000     .1977094    .3428888
       _cons |   1.326574   .1310589    10.12   0.000     1.069703    1.583445
------------------------------------------------------------------------------
```

Significant difference between the two lines (significant difference between the two intercepts, $p<0.001$).

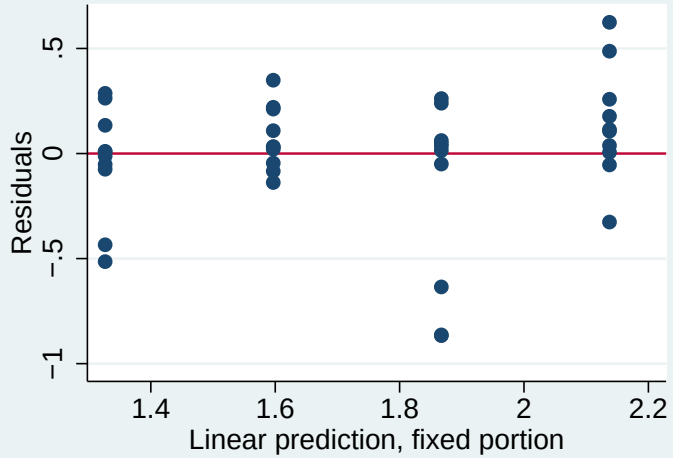
Note: The estimated difference is similar to that in the previous analysis (-0.58).

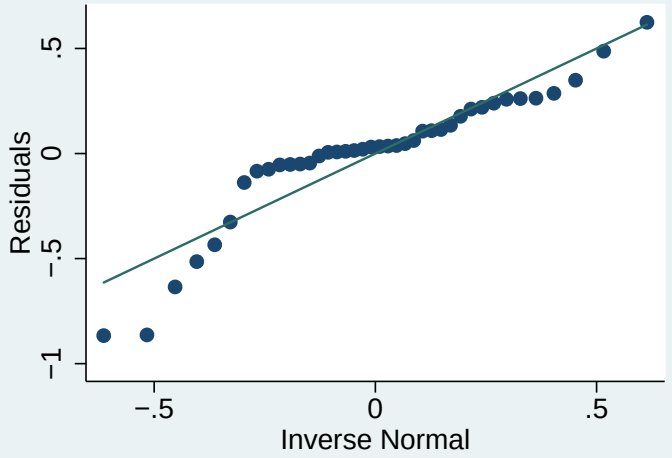
CRP: Model validation for the RCM





CPB:
OK





Sham:
OK?

FEV_1 and smoke

Design: Cross-over study with 3 treatments and 12 subjects.

5 factors to consider:

Conc: The 3 treatments (doses: 0, 200, and 400 ug/m3)

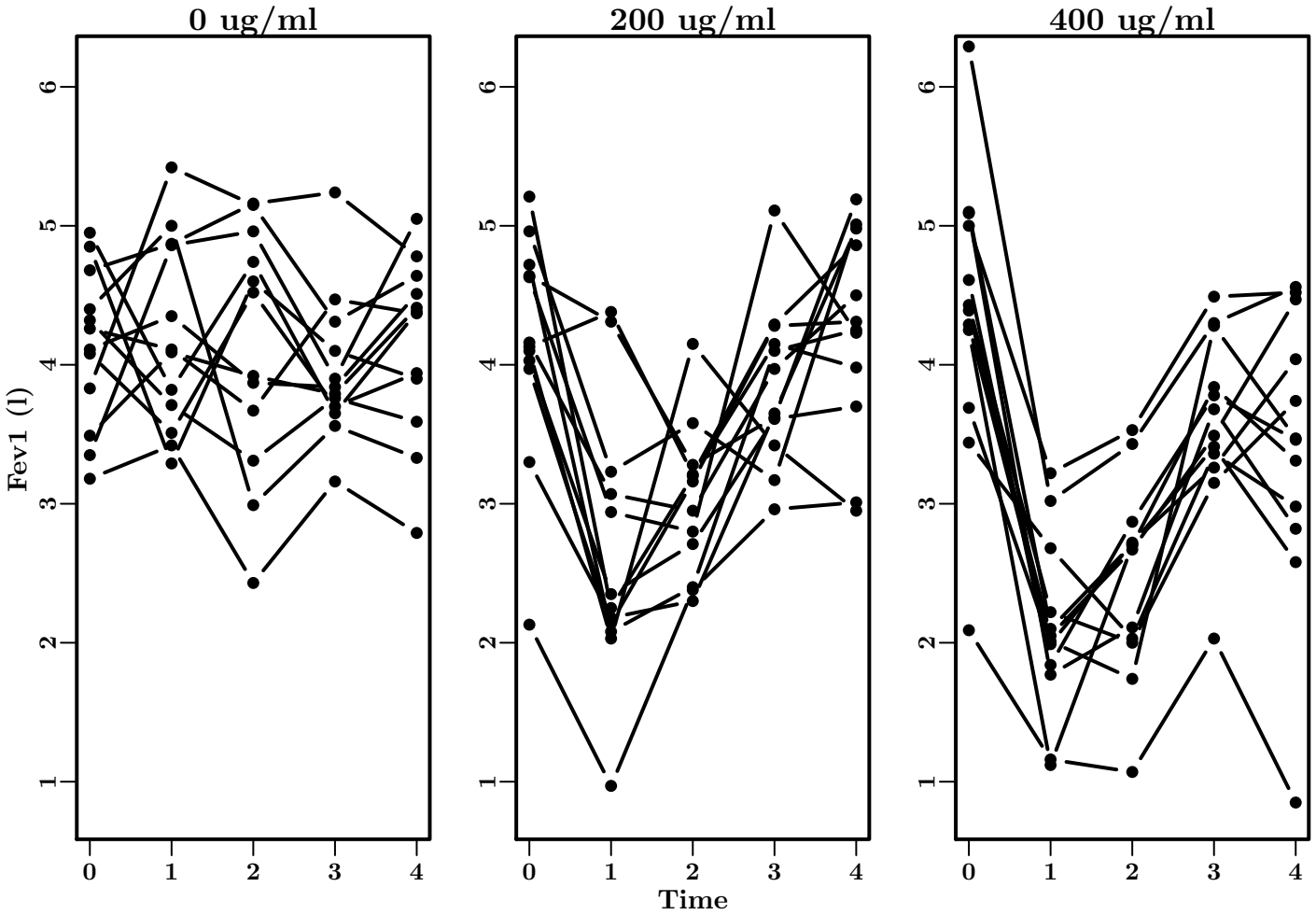
Time: The 5 measurement time points (baseline, 30 min, 2 h, 4 h, and 6

Day: The 3 experimental days (14 days in between)

Order: 3 treatments can be given in 6 different orders (carry-over effect?)

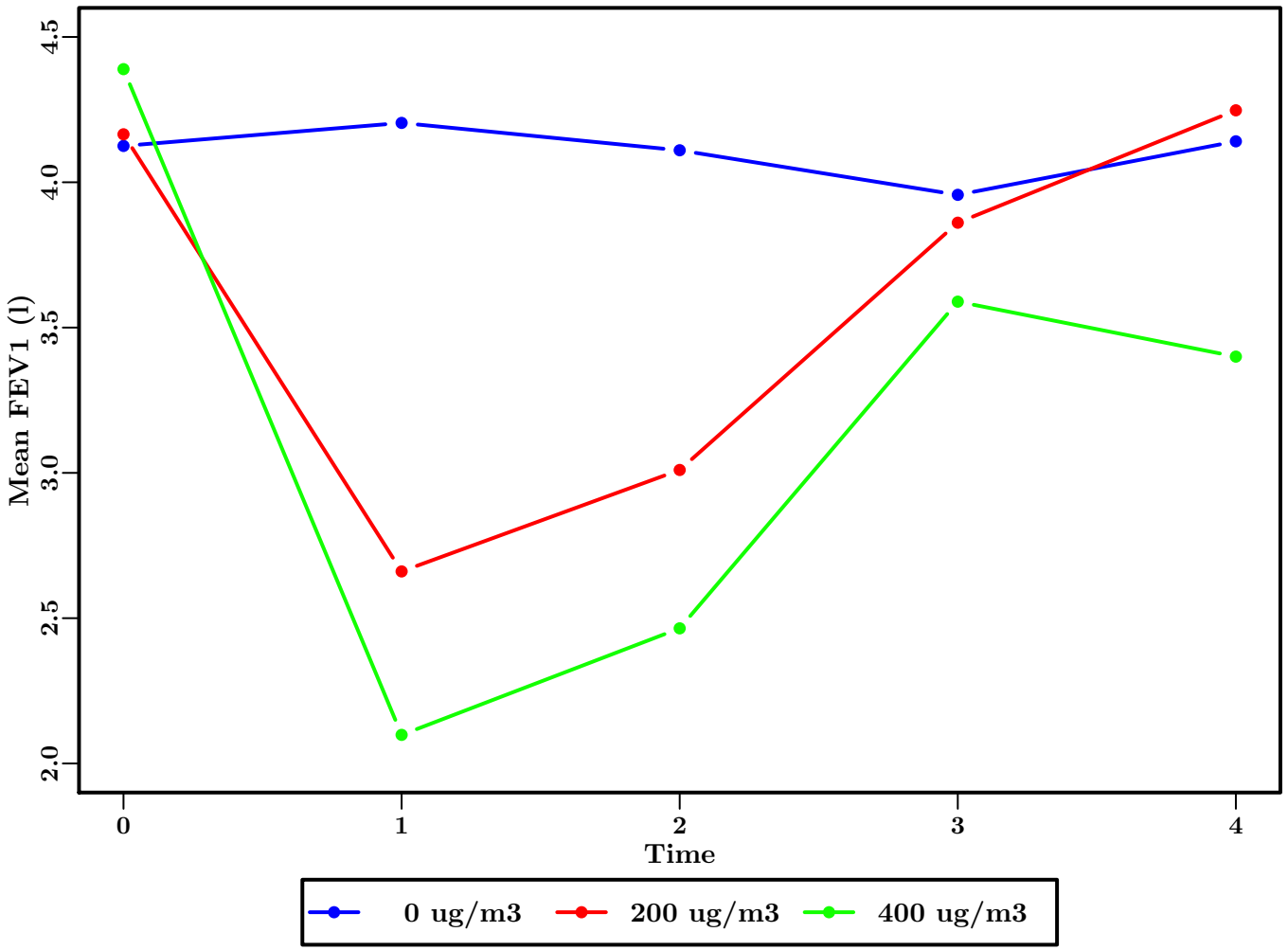
Sub: The 12 subjects (2 randomized to each ordering)

FEV_1 and smoke: Grouped individual curves



Similar within and between subject variation in the three treatment groups.

FEV_1 and smoke: Mean curves



FEV_1 and smoke: The analysis in Stata

In **Stata** the smoke data are analyzed using the univariate repeated measurement model in the following way:

```
anova fev1 order/sub day conc/sub#day time conc#time, ///
      bse(sub#day) repeated(time)
```

Note that the order of the terms in the `anova`-command is important:

1. `order/sub` — `sub` is the highest level
2. `day conc/sub#day` — `sub#day` is the next level
3. `time conc#time` — the residual variation is the lowest level

The analysis of all the data can also be done using `mixed` in **Stata**:

```
mixed fev1 bn.order bn.day bn.conc##bn.time || sub: || day:
```

FEV_1 and smoke: Output from anova in Stata

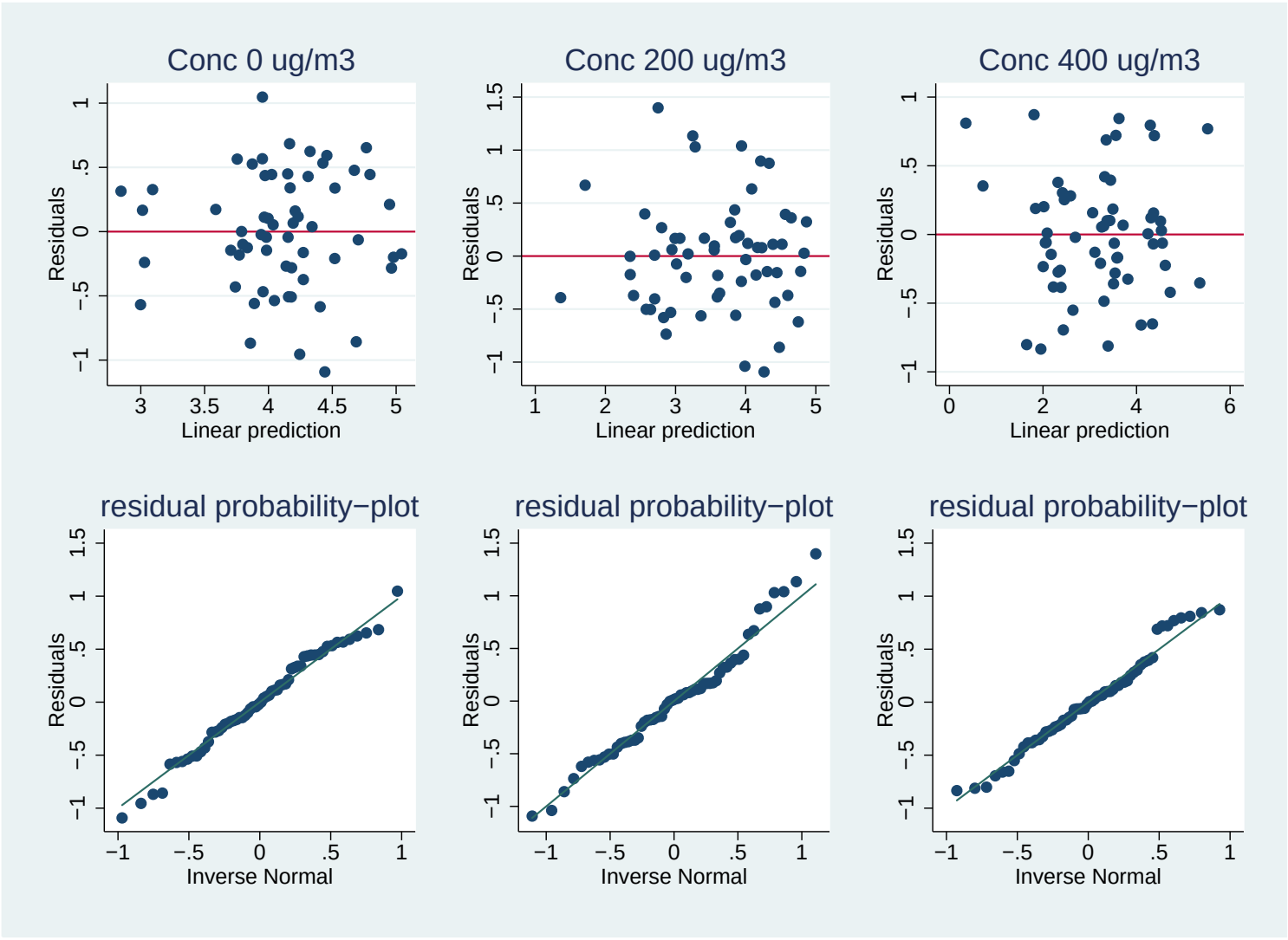
```
                  Number of obs =     180     R-squared     =  0.7883
                  Root MSE      = .545361     Adj R-squared =  0.7130
    Source |  Partial SS    df       MS           F     Prob > F
-----------+----------------------------------------------------
     Model |   146.22137    47  3.11109298      10.46     0.0000
     order |  11.2357365     5  2.24714731       0.44     0.8054
       sub |  30.4588088     6  5.07646813
-----------+----------------------------------------------------
       day |  2.10456305     2  1.05228152       2.15     0.1428
      conc |  6.31116623     2  3.15558312       6.44     0.0069
   sub#day |  9.79468626    20  .489734313
-----------+----------------------------------------------------
      time |  38.7599307     4  9.68998269      32.58     0.0000
 conc#time |  26.3799861     8  3.29749827      11.09     0.0000
  Residual |  39.2593241   132  .297419122
-----------+----------------------------------------------------
     Total |  185.480694   179   1.036205
```

FEV_1 and smoke: Results from the statistical tests

We conclude the following from the **Stata**-output regarding the hypotheses:

1. The order in which the different doses are given is not significant (p=0.81 and p=0.39 using `mixed`).
2. There is no systematic differences between days (periodic effect, training effect, hay fever season and so on, p=0.14, and p=0.08 using `mixed`).
3. The interaction between dose and time is highly significant ($p < 0.0001$ also with `mixed`) implying that the curves are not parallel.

FEV_1 and smoke: Checking the assumptions



FEV_1 and smoke: Is the FEV_1 back to normal after 6 hours?

We look at each dose separately as the curves are not parallel.

```
mixed fev1 bn.order bn.day bn.conc##bn.time || sub: || day:

contrast r(0 4).time@conc, eff
```

	Contrast	Std. Err.	z	P>|z|	[95% Conf.	Interval]
fev1						
time@conc						
(4 vs 0) 0 ug/m3	.0158334	.2131643	0.07	0.941	-.401961	.4336278
(4 vs 0) 200 ug/m3	.0825	.2131643	0.39	0.699	-.3352944	.5002944
(4 vs 0) 400 ug/m3	-.9891667	.2131643	-4.64	0.000	-1.406961	-.5713723