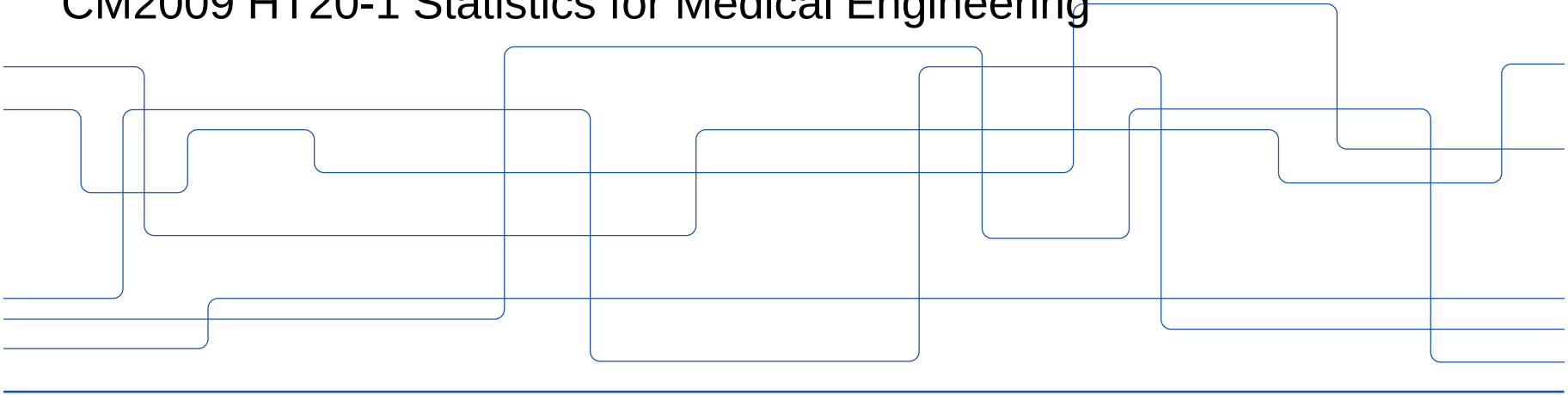
KTH ROYAL INSTITUTE OF TECHNOLOGY

Fixed effects, random effects, mixed effects

Adam S. Darwich

darwich@kth.se

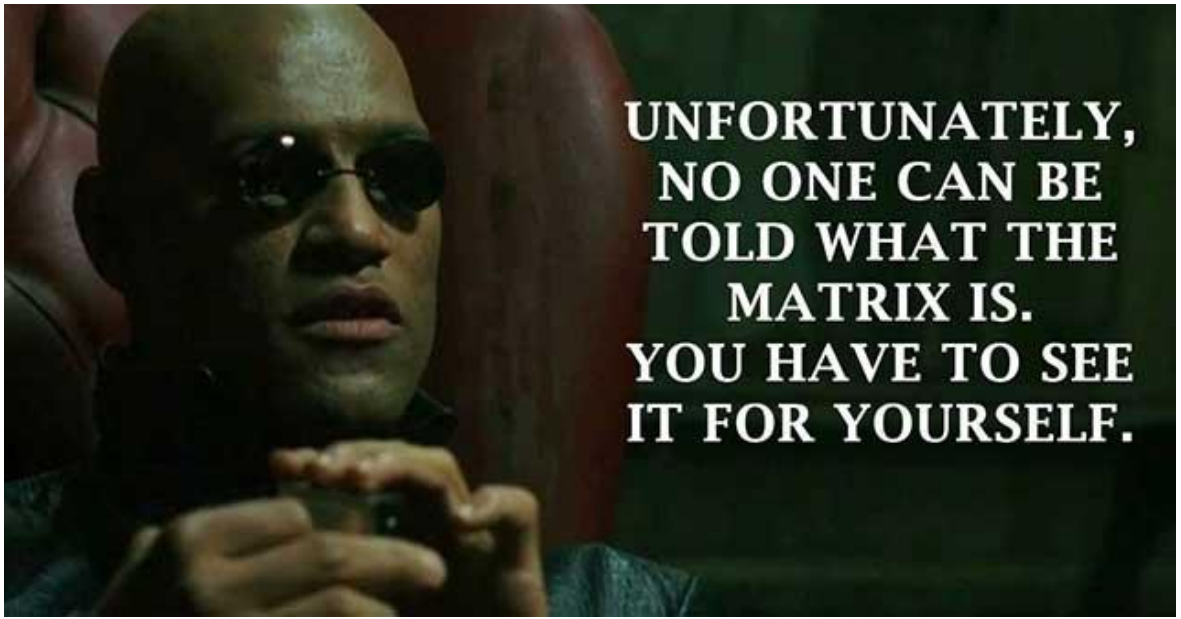
CM2009 HT20-1 Statistics for Medical Engineering



Mixed effects modelling combines fixed and random effects.

But what are fixed effects?

semantics versus mathematics



classical regression model

$$y = \alpha + x \cdot \beta + \varepsilon$$

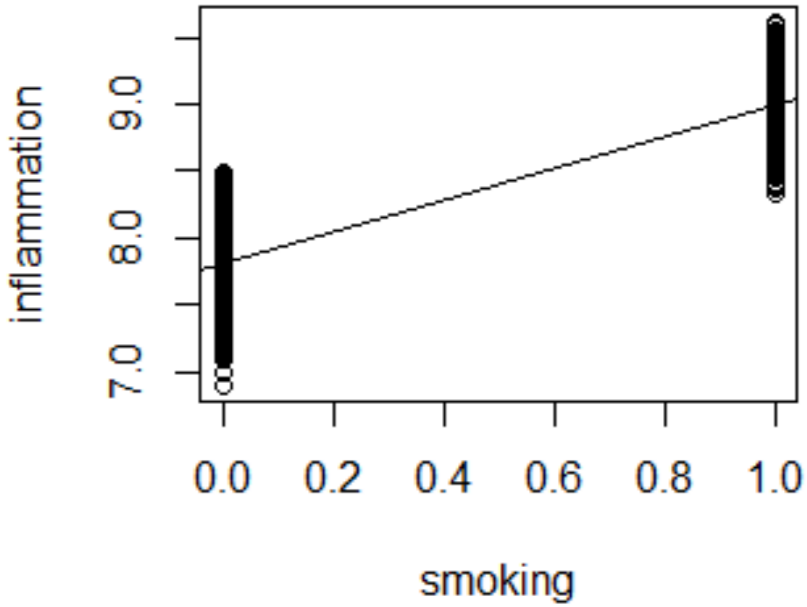
classical regression model

$$y = \alpha + x \cdot \beta + \epsilon$$

Let us consider the deterministic formula:

$$\hat{y} = \alpha + x \cdot \beta$$

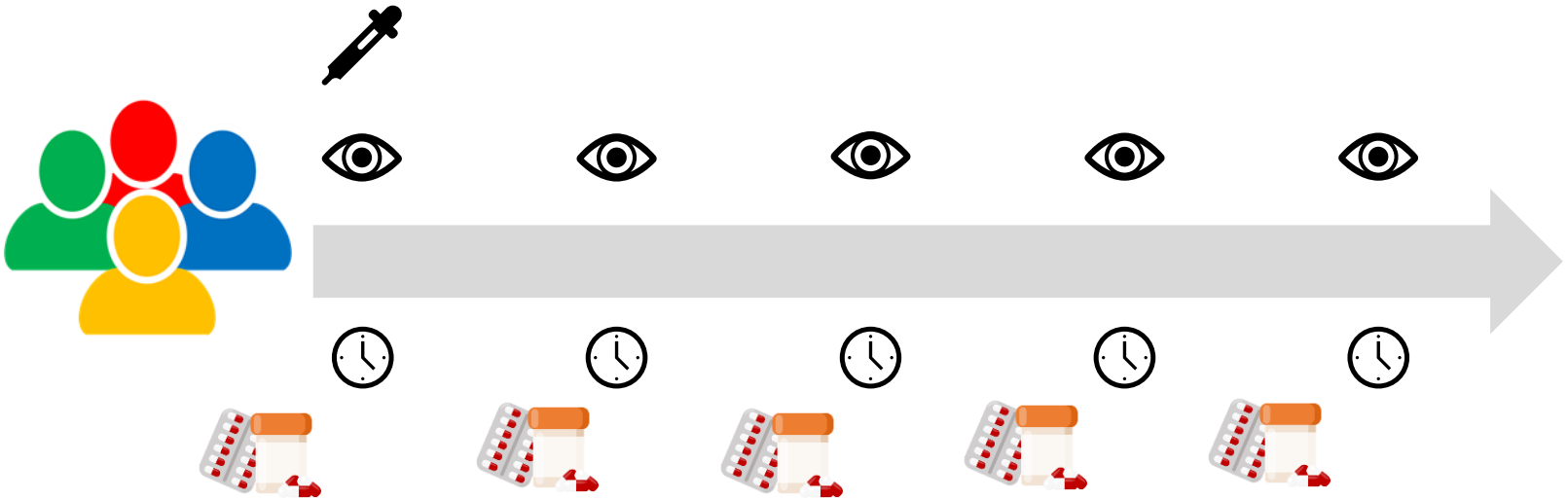
where yhat is the predicted, or expected, dependent variable given the predictor, or indicator, β and an intercept of α.



$$\mathbf{inflam} = \mathbf{7.8} + \mathbf{1.2} \cdot \boldsymbol{smoking} + \boldsymbol{error}$$

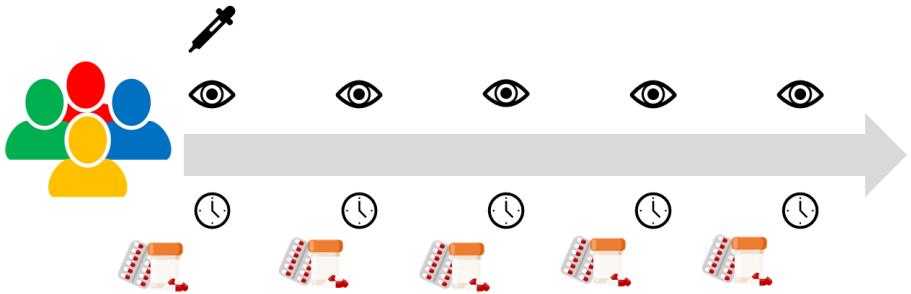
```
fit1 <- lm(inflammation ~ smoking)
summary(fit1)
plot(inflammation ~ smoking)
abline(fit1)
```

Repeated measures data



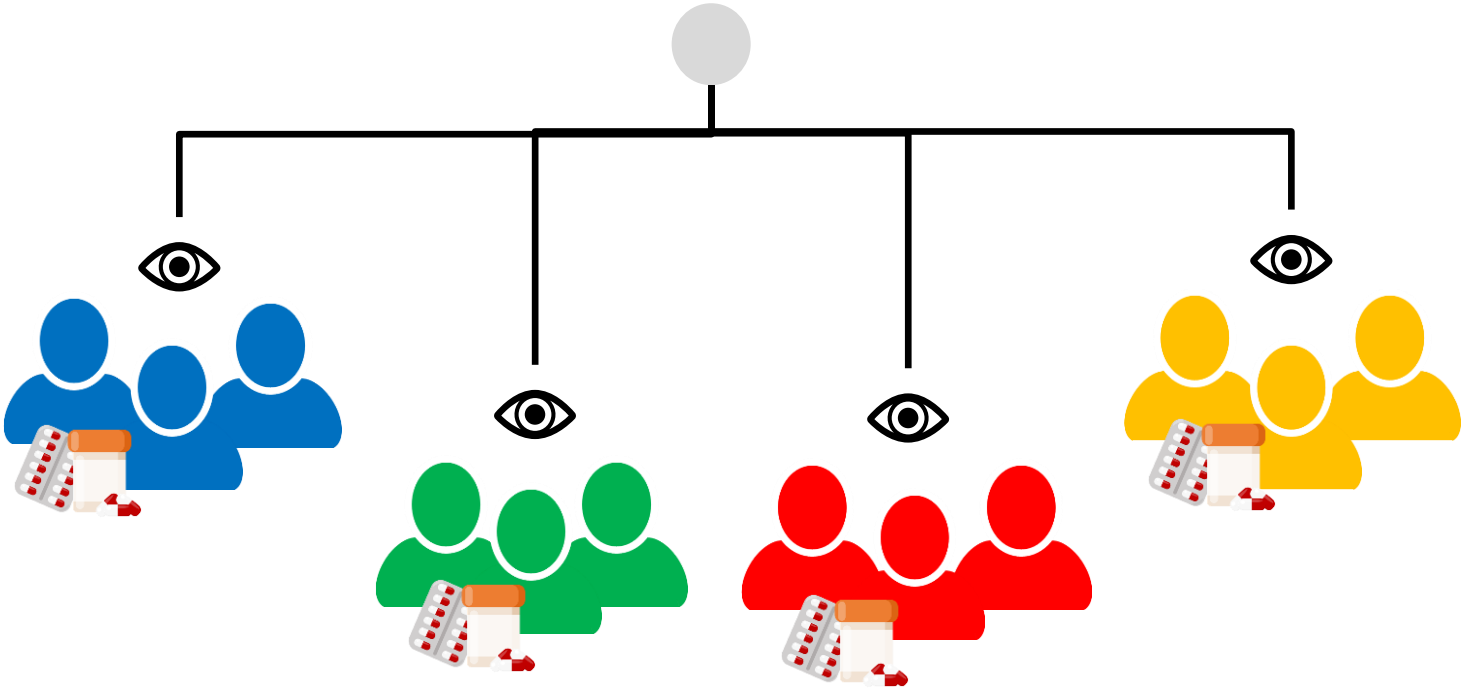
Repeated measures data

- Longitudinal study design, time series data (panel data in econometrics)
- Studying changes in an outcome over time, increase precision of estimates and power to detect effects.
- Parallel vs. cross-over design: account for interindividual and interoccasion variability.
- Medical research, pharmaceutics, psychology and much more.



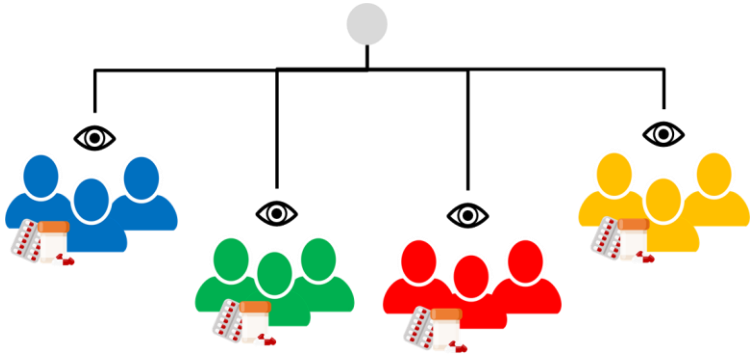
Ref: Schober et al. 2018

Cross-sectional data



Cross-sectional study design

- Carried out at one time point (or short interval) to estimate the prevalence of an outcome of interest.
- Aims to describe a population, or subgroup, with respect to a set of risk factors.
- Give no indication of sequence of events (see causal inference).
- Commonly used in for example public health.



Ref: Levin 2006


It's Complicated...

Real-world data
non-interventional, retrospective, single/multi-centre study

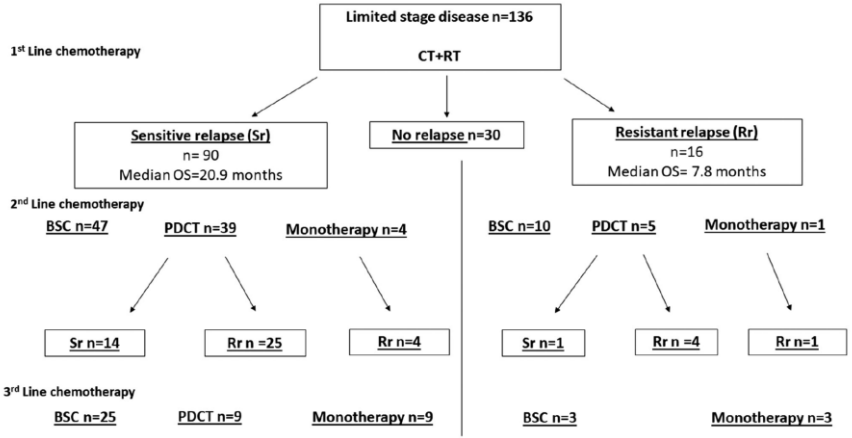


Figure 2. Treatment patterns for patients with limited disease treated with chemo- and radio-therapy (CT + RT).

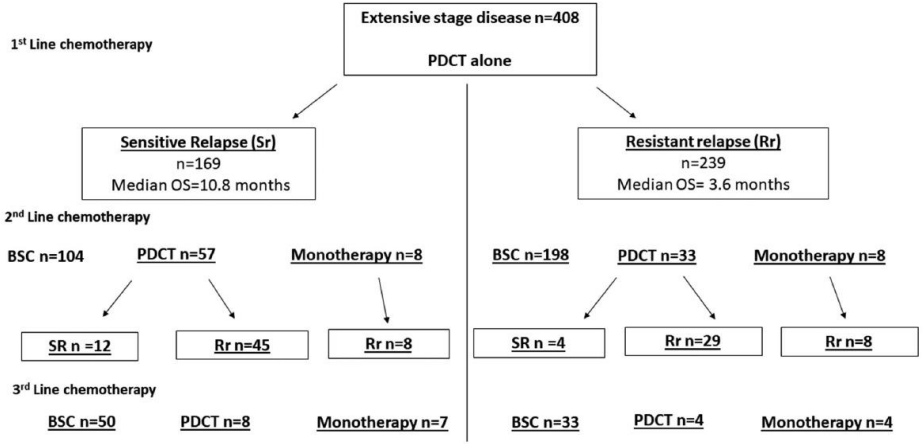
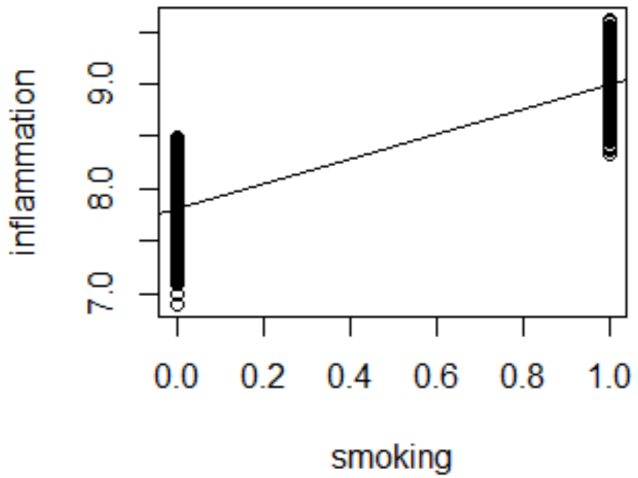


Figure 1. Treatment patterns for patients with extensive disease treated with platinum-doublet chemotherapy (PDCT alone).

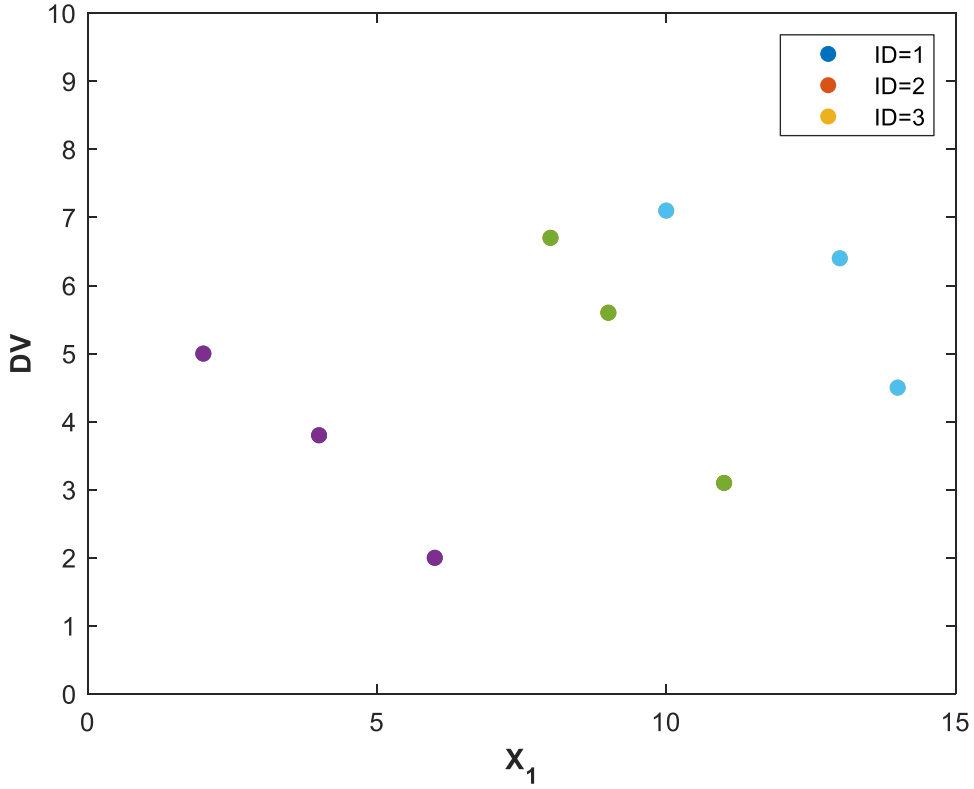
Ref: Tendler et al. 2020



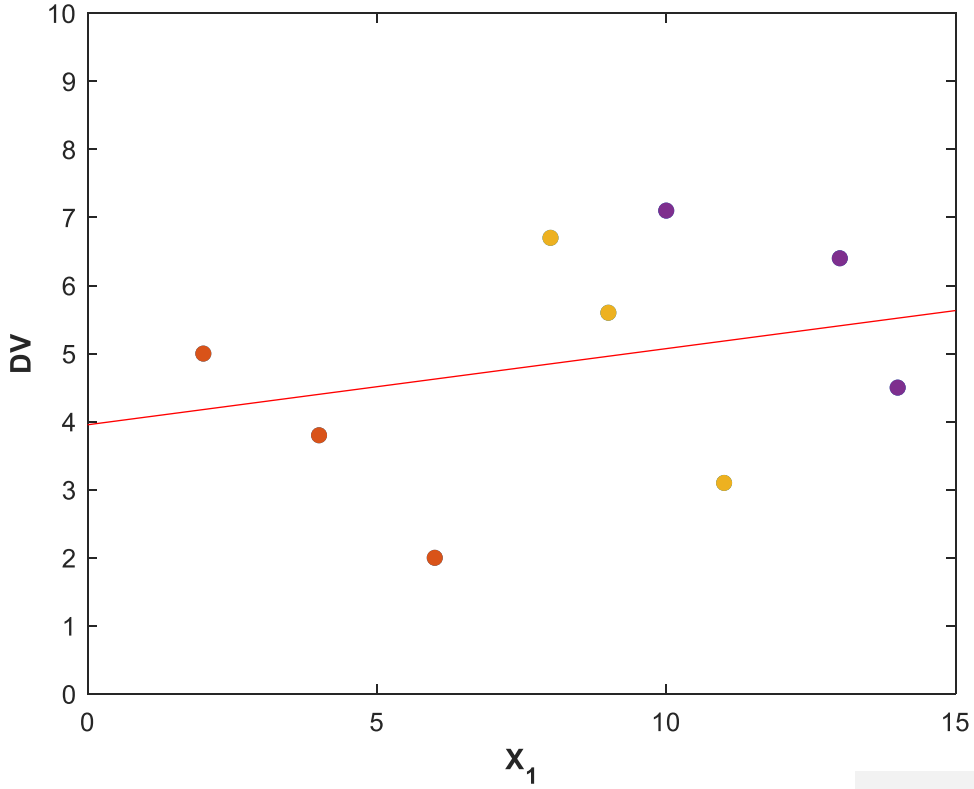
What can and cannot be learnt from this approach?

$$y = \alpha + x \cdot \beta + \epsilon$$

ID	DV	X1
1	5	2
1	3.8	4
1	2	6
2	6.7	8
2	5.6	9
2	3.1	11
3	7.1	10
3	6.4	13
3	4.5	14

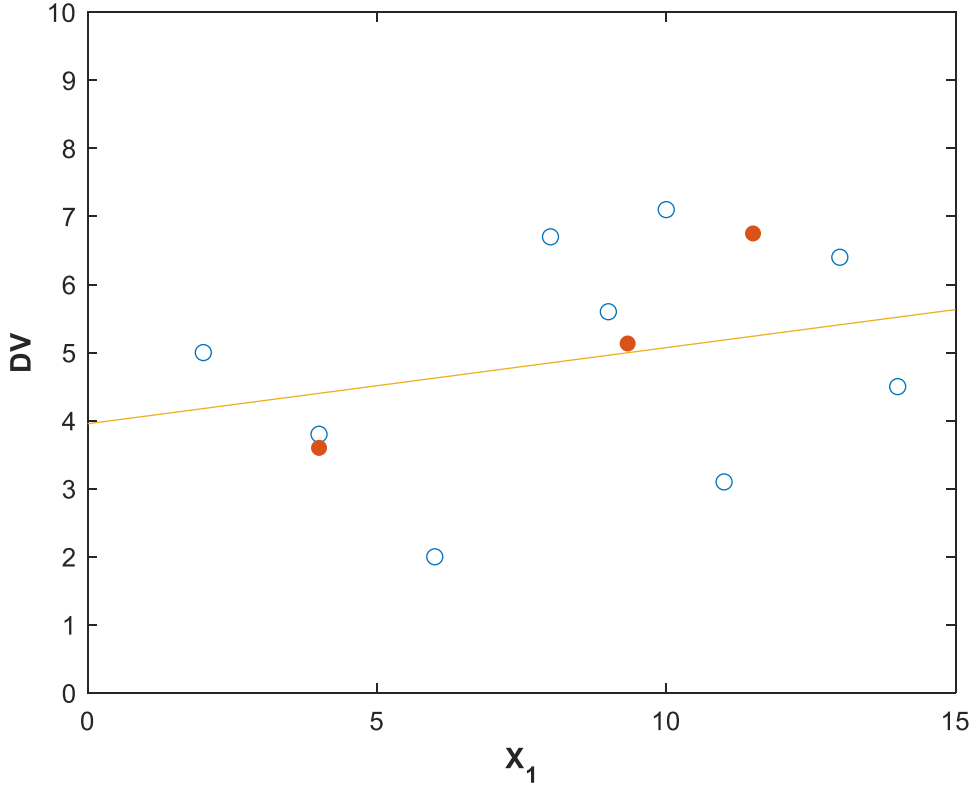

ID=1
ID=2
ID=3
DV
X1
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15

Naïve pooling: each data point is independent

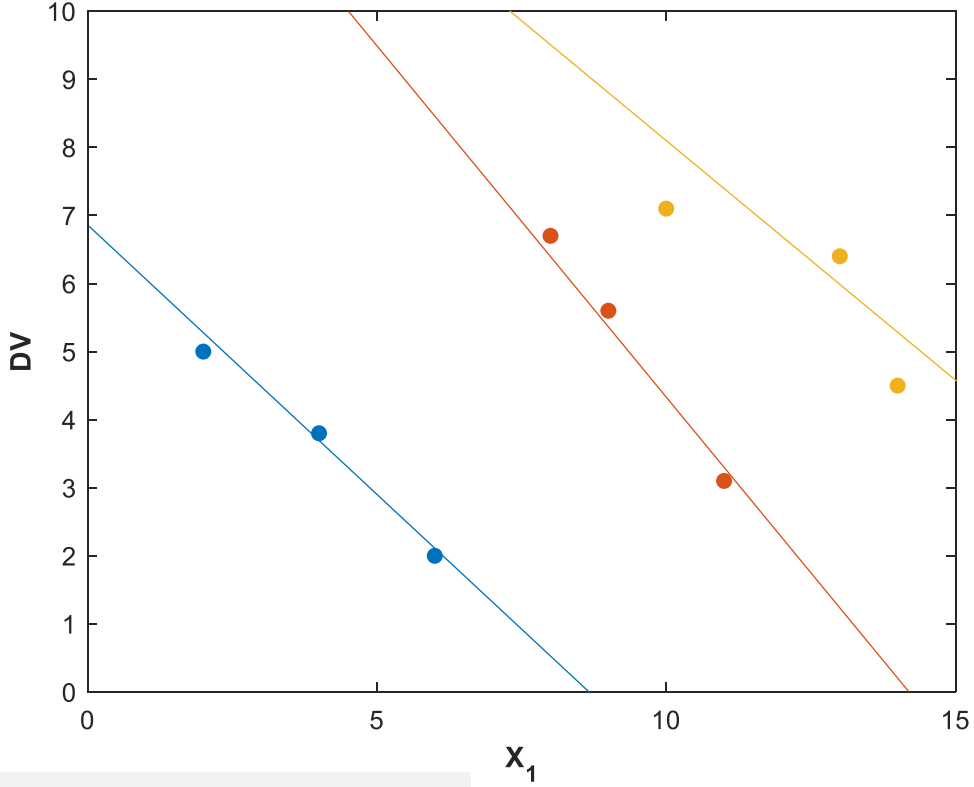



```
fit <- lm(DV ~ X1)
```

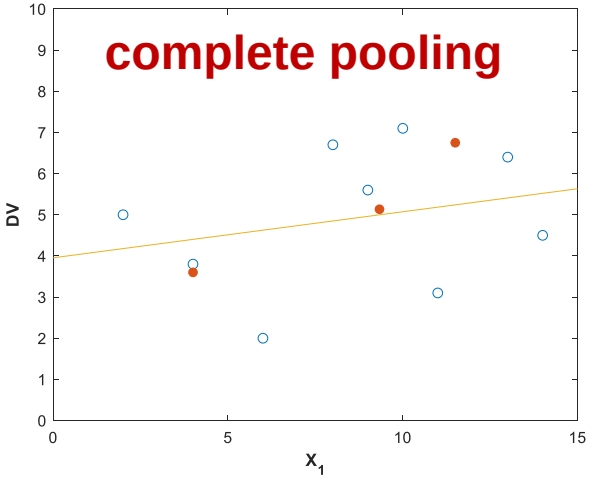
Complete or average pooling: loosing features of the dataset



no pooling

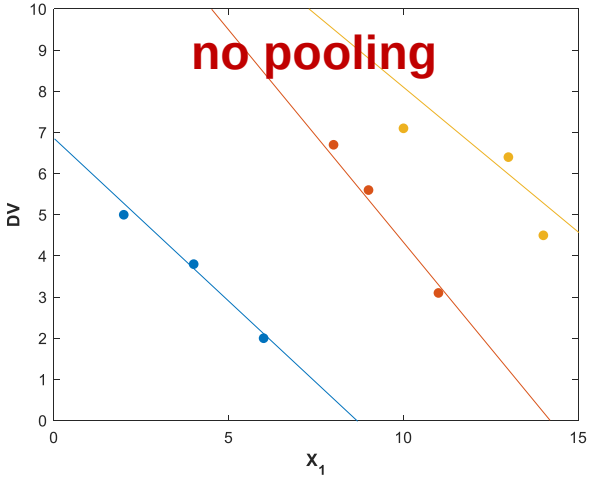



```
fit <- lm(DV ~ X1 + factor(ID) -1)
```




```
fit <- lm(DV ~ Xav)
```

$$\sigma_{\propto} \to 0$$




```
fit <- lm(DV ~ X1 +
factor(ID) -1)
```

$$\sigma_{\propto} \to \infty$$

$$\propto_j \sim N\left(\mu_\alpha, \sigma_\propto^2\right), for\ j = 1, \ldots, J$$

There used to be something called a repeated-measure ANOVA

- It handles missing DV data through listwise deletion.
- It treats each response as a different variable.
- Can only account for categorical repeats, not continuous time.

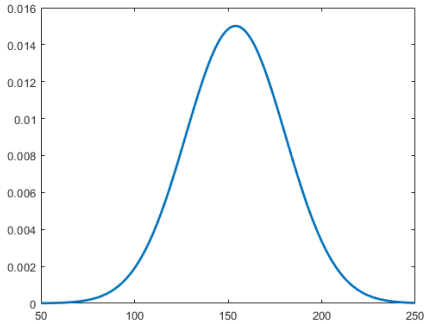
……

Partial pooling or shrinkage of group coefficients α_j

$$\propto_j \sim N\left(\mu_\alpha, \sigma_\propto^2\right), for\ j = 1, \dots, J$$

$$\propto_j \approx \frac{\frac{n_j}{\sigma_y^2}}{\frac{n_j}{\sigma_y^2} + \frac{1}{\sigma_\propto^2}} \cdot \left(\bar{y}_j - \beta \bar{x}_j\right) + \frac{\frac{1}{\sigma_\propto^2}}{\frac{n_j}{\sigma_y^2} + \frac{1}{\sigma_\propto^2}} \cdot \mu_\propto$$

Maximum likelihood (ML) or restricted/residual maximum likelihood estimation (REML)



ML

- Estimate the mean then estimate the variance of the mean.
- In small sample sizes ML is biased in estimating the standard deviation of variance.

REML

- Variation of normal likelihood.
- Corrects for the bias in the variance component.
- Less biased in small samples relative to ML.
- Cannot use in likelihood ratio test to compare models.

Let’s try this one out really quickly in R

- Linear mixed-effects package: lme4
- Some other useful libraries: jtools, lmerTest

```
# load library
library(lme4)
library(jtools)
library(lmerTest)

# import dataset
exdata <- read.table(file="exdata0.csv", header=TRUE, sep = ",")
attach(exdata)

# mixed-effects fit model
fit1 <- lmer(DV ~ 1 + X1 + ( 1 | ID), exdata)
summary(fit1) # default lme4
summ(fit1) # jtools
ranova(fit1) # lmerTest
plot(fit1)
```

Let’s take a look at the output

```
Linear mixed model fit by REML. t-tests use Satterthwaite's
  method [lmerModLmerTest]
Formula: DV ~ 1 + X1 + (1 | ID)
   Data: exdata

REML criterion at convergence: 29.4

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.1875 -0.3720 -0.1376  0.3366  1.3387

Random effects:
 Groups   Name        Variance Std.Dev.
 ID       (Intercept) 18.6018  4.3130
 Residual              0.4695  0.6852
Number of obs: 9, groups:  ID, 3

Fixed effects:
            Estimate Std. Error      df t value Pr(>|t|)
(Intercept)  11.1383     2.7927  2.7780   3.988   0.0325 *
X1           -0.7279     0.1453  5.3369  -5.008   0.0034 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
   (Intr)
X1 -0.445
```

Let's take a look at the output

```
Linear mixed model fit by REML. t-tests use Satterthwaite's
  method [lmerModLmerTest]
Formula: DV ~ 1 + X1 + (1 | ID)
   Data: exdata

REML criterion at convergence: 29.4

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.1875 -0.3720 -0.1376  0.3366  1.3387

Random effects:
 Groups   Name        Variance Std.Dev.
 ID       (Intercept) 18.6018  4.3130
 Residual              0.4695  0.6852
Number of obs: 9, groups:  ID, 3

Fixed effects:
            Estimate Std. Error      df t value Pr(>|t|)
(Intercept)  11.1383     2.7927  2.7780   3.988   0.0325 *
X1           -0.7279     0.1453  5.3369  -5.008   0.0034 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
   (Intr)
X1 -0.445
```

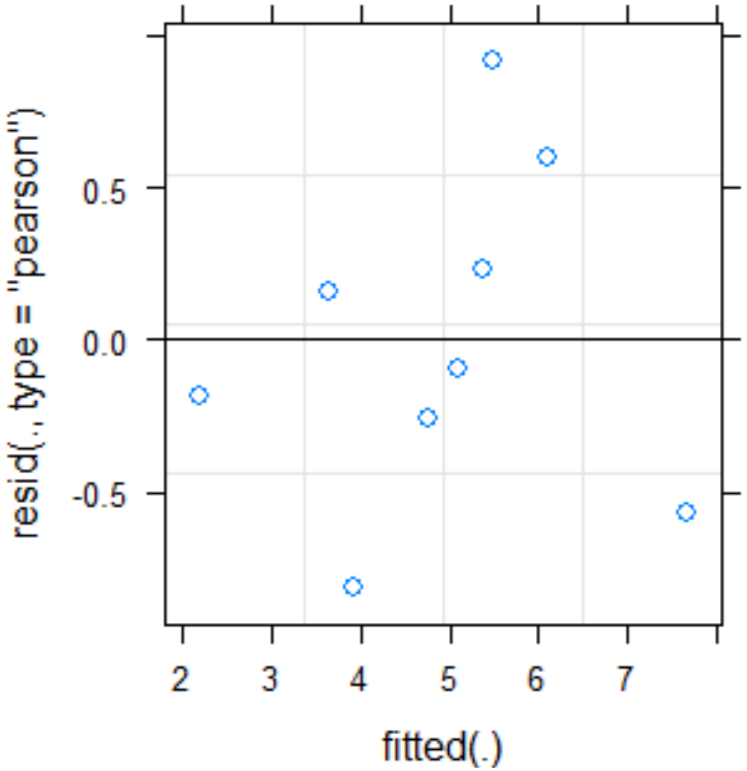
model converged successfully

distribution of residual errors

estimates of random effects

estimates of fixed effects

Residual errors vs. predictions



We have produced a mixed-effects model. Also known as a multi-level or hierarchical model.

Let’s revisit the definition of fixed vs. random effects?

- Fixed effects are constant across individuals and random effects vary.
- Effects are fixed if they of interest or random if there is interest in the underlying population.
- When a sample is small its variable is random, whereas if it exhausts the population it becomes fixed.
- If an effect is a value of a random variable it is a random effect.
- Fixed effects are estimated using least squares, random effect with shrinkage.
- Bayesian view: fixed effect β_j^m is estimated conditional on $\sigma_m=\infty$, random effect β_j^m is estimated conditional on σ_m from the posterior distribution.

Ref: Gelman 2005

Mixed-effects modelling

How carry out model building

What to consider before fitting a model:

- Study your data carefully
- Collinearity, combine or remove variables from dataset?

```
library(corrplot)
data.cor <- cor(data)
corrplot(data.cor)
```

- Transforming distributions (for example, normalise DV)
- Centering and standardising
- Linear transformation

How carry out model building

Constructing the model:

- Include all input variables that, for substantive reasons, might be expected to be important in predicting the outcome.
- Inputs can be combined into total scores if needed.
- For inputs with large effect, consider also adding interaction effects.


THE SACRAMENTO BEE © 2015
THE RONALD
TEAR DOWN THIS WALL!!!
BERLIN
THE DONALD
BUILD UP THIS WALL!!!
MEXICO

How carry out model building

How remove variables:

- If a predictor is significant and has the expected sign, keep it in.
- If a predictor is not statistically significant, with the expected sign, keep in. This will not make a huge difference either way and certainly will not hurt.
- If the coefficient of a variable has the wrong expected sign, consider removing it (equivalent to setting the coefficient to zero).
- If predictor is significant with wrong sign, think hard about what this can mean.

Assessing goodness-of-fit

- **Plotting the residual errors vs. predicted values.** This gives a good indication of model bias and any heteroscedasticity (or non-uniformity of errors). It is useful to plot this for the overall model and individual groups.
- **Distribution of residuals.** Checking normality of residual errors.
- **Predicted vs. observed.** Overall and individually.
- **Validation.** Involves for example bootstrapping techniques.

Model selection

- **Logical reasoning.** What makes the most sense biologically/physically/mechanistically/etc? What is the purpose, question your are trying to answer?
- **Compare goodness-of-fit plots.** residuals vs. predictions, predicted vs. observed.
- **Likelihood ratio test.** Assess goodness-of-fit of two competing models. If there is a significant difference between two likelihoods then we reject the null model. Remember that this requires switching from REML to ML estimation procedure.
- **AIC.** The Akaike Information Criterion assesses the quality of one, or series of, models given the set of data.

Likelihood ratio test

$$LR = 2\left(logL|\hat{\theta}_{ML}\right) - logL(\theta_{H0})$$

- Maximised log-likelihood measures how well the objective function has achieved, objective function value (OFV).
- A measure of relative model adequacy. The higher the better.
- If there is a significant difference between the two values, the ratio is relatively large and we reject the H0 model.

AIC: Akaike Information Criterion

$$AIC = N \cdot \ln\left(\frac{SS_{error}}{N}\right) + 2 \cdot K$$

- Trade-off between goodness-of-fit of the model and model complexity.

  N: number of observations,

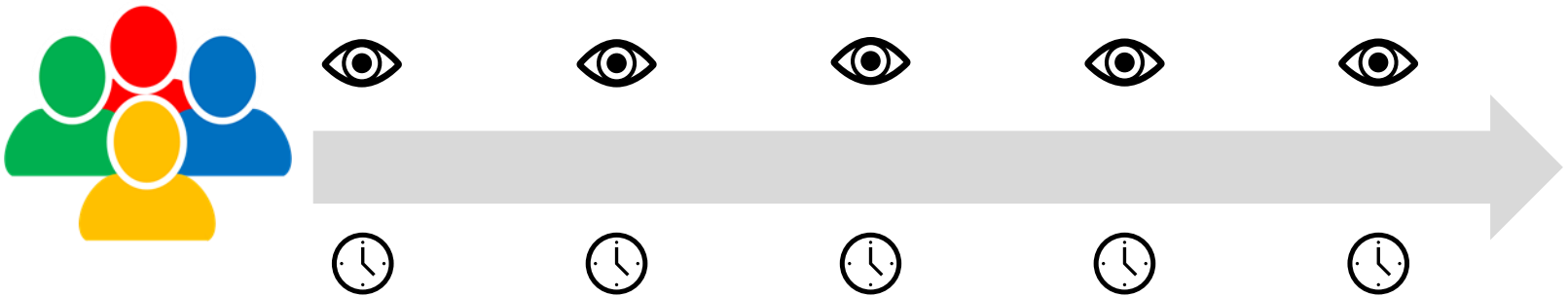
  SS_{error}: sum of squares of error,

  K: N parameters + 1

- The lower the value of AIC the better is the goodness-of-fit relative to model complexity.
- Bayesian Information Criterion (BIC): penalises N parameters to a higher extent than the AIC.

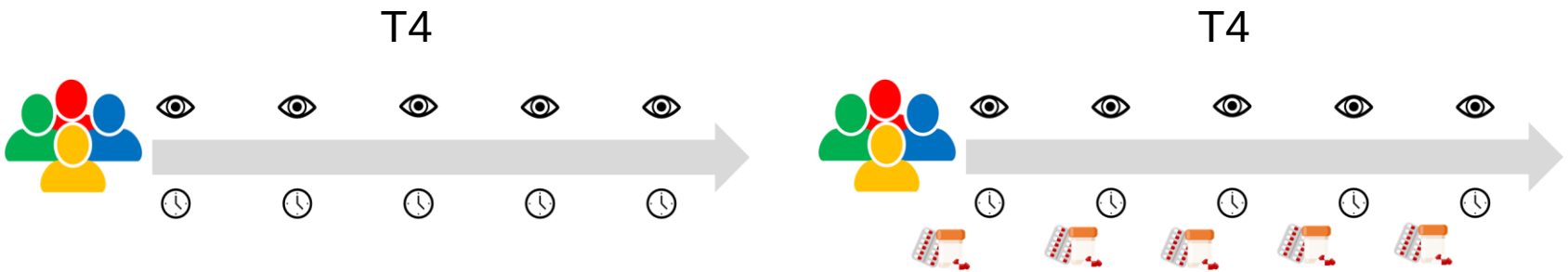
figure: https://www.verywellhealth.com/overview-of-hypothyroidism-4164534

Study design



Study design and dataset

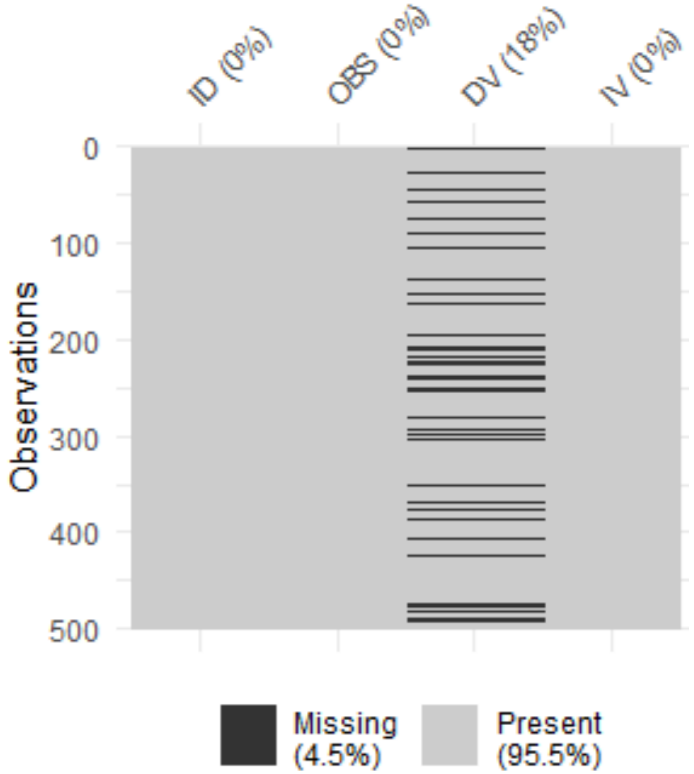
ID: subject ID,
OBS: time point of observation,
DV: dependent variable, treatment effect,
IV: intervention - drug treatment,
~5% random missingness



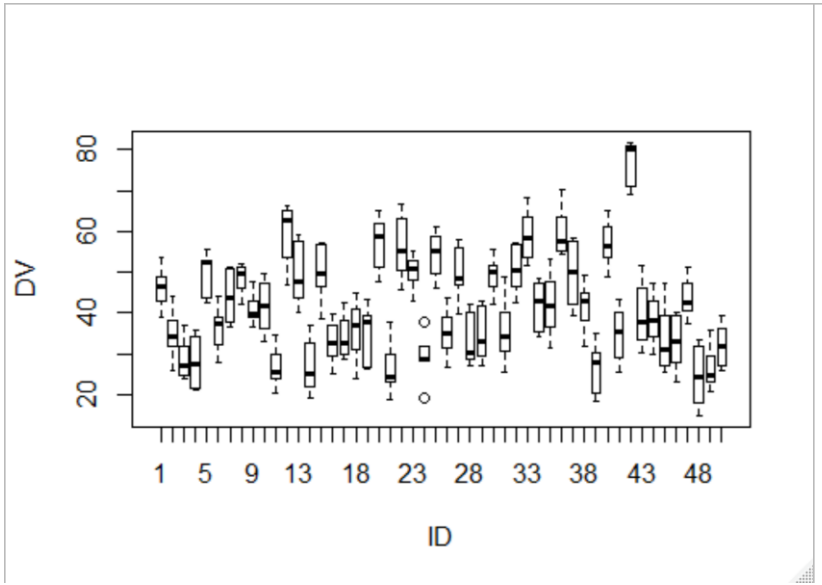
treatment dosed to steady state

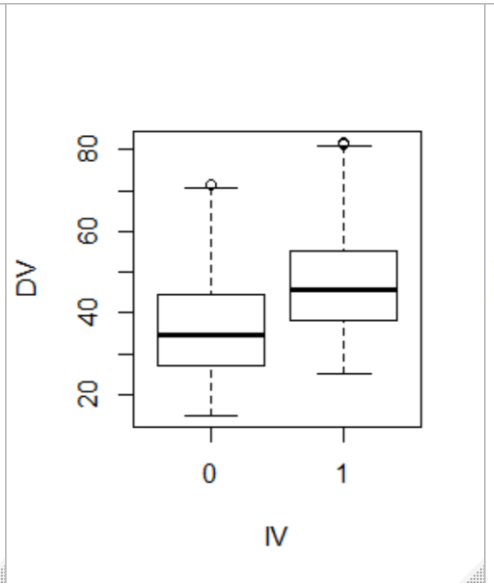
R libraries

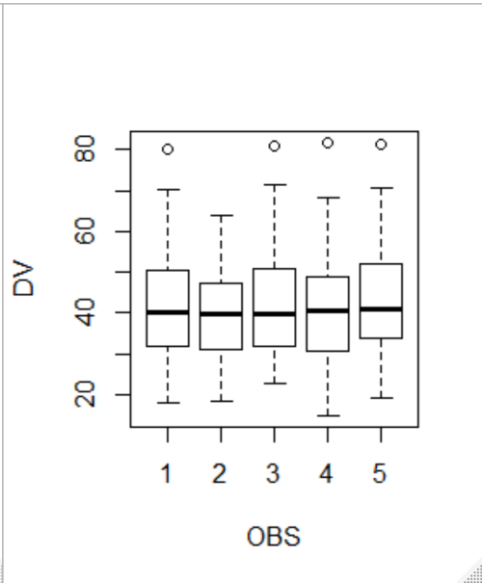
```
library(lme4)
library(jtools)
library(lmerTest)
library(corrplot)
library(naniar)
```



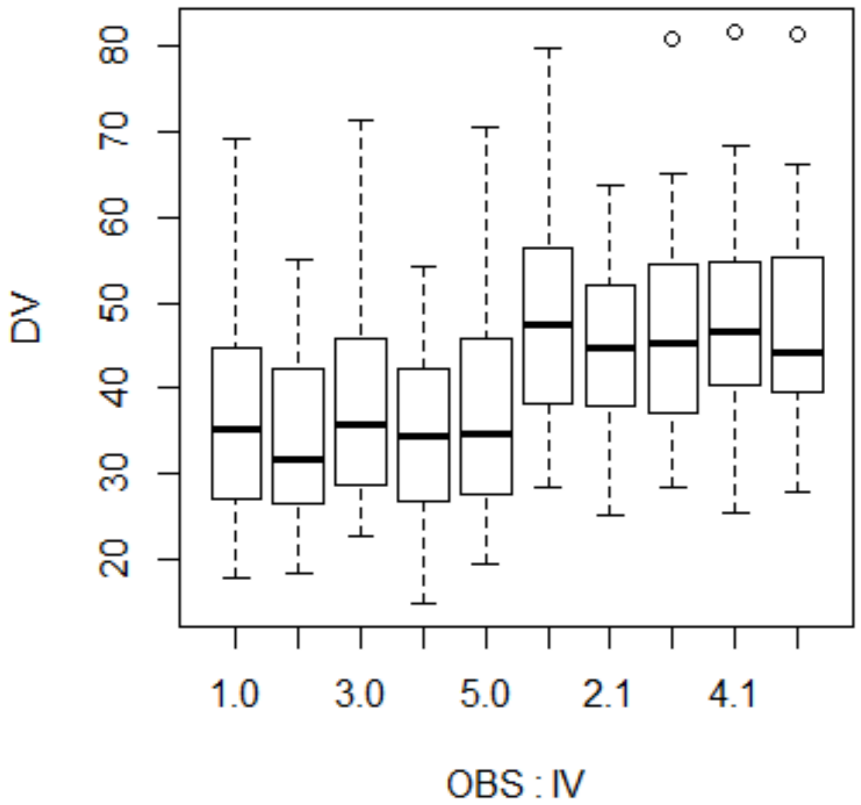

```
library(naniar)
vis_mis(exdata)
```


DV
20
40
60
80
1
5
9
13
18
23
28
33
38
43
48
ID


DV
20
40
60
80
0
1
IV

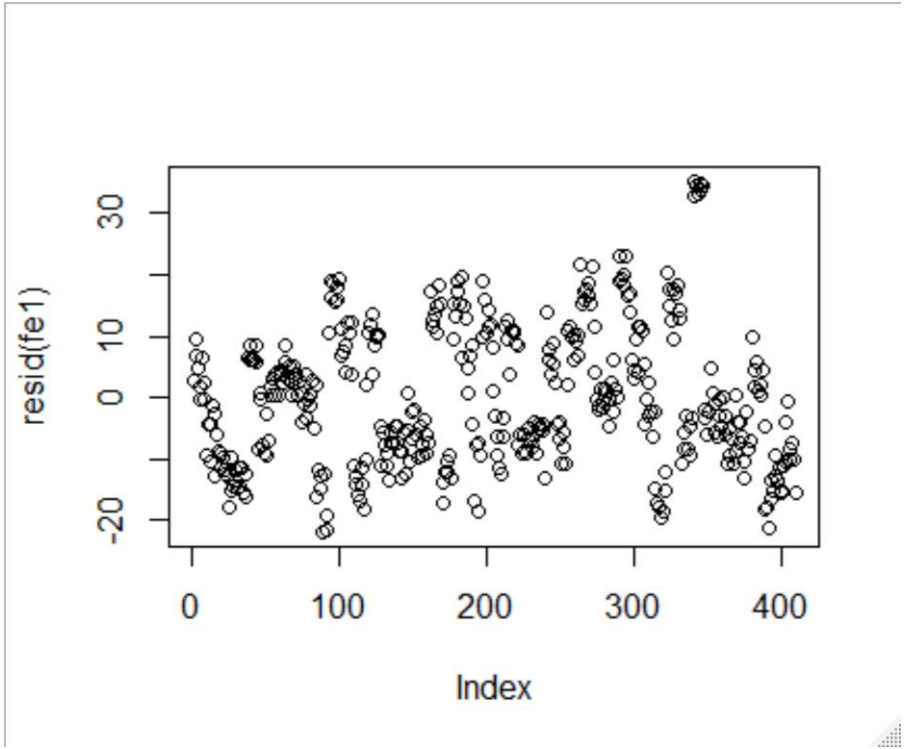

DV
20
40
60
80
1
2
3
4
5
OBS

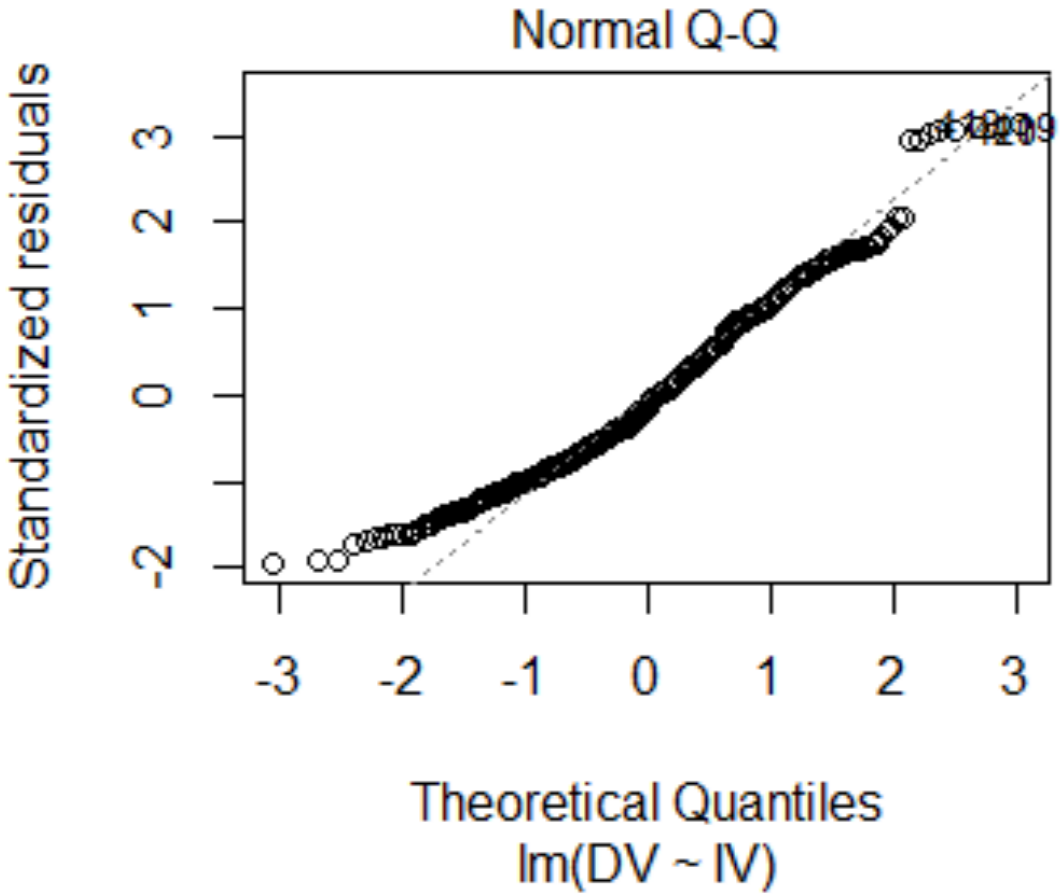
```
# boxplots
boxplot(DV ~ ID, data=exdata)
boxplot(DV ~ ID + IV, data=exdata)
boxplot(DV ~ OBS, data=exdata)
boxplot(DV ~ OBS + IV, data=exdata)
```



fixed-effects model: complete pooling

```
# fixed effects fit: complete
# pooling
fe1 <- lm(formula = DV ~ IV)
plot(fe1)
```

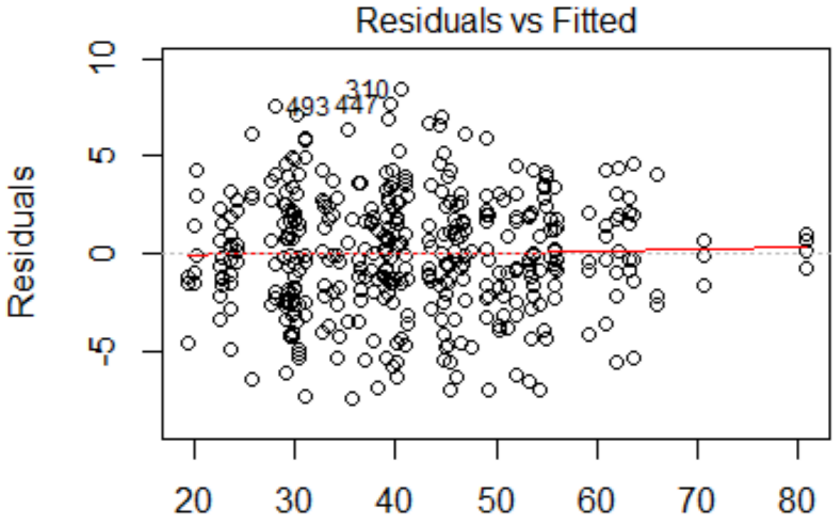


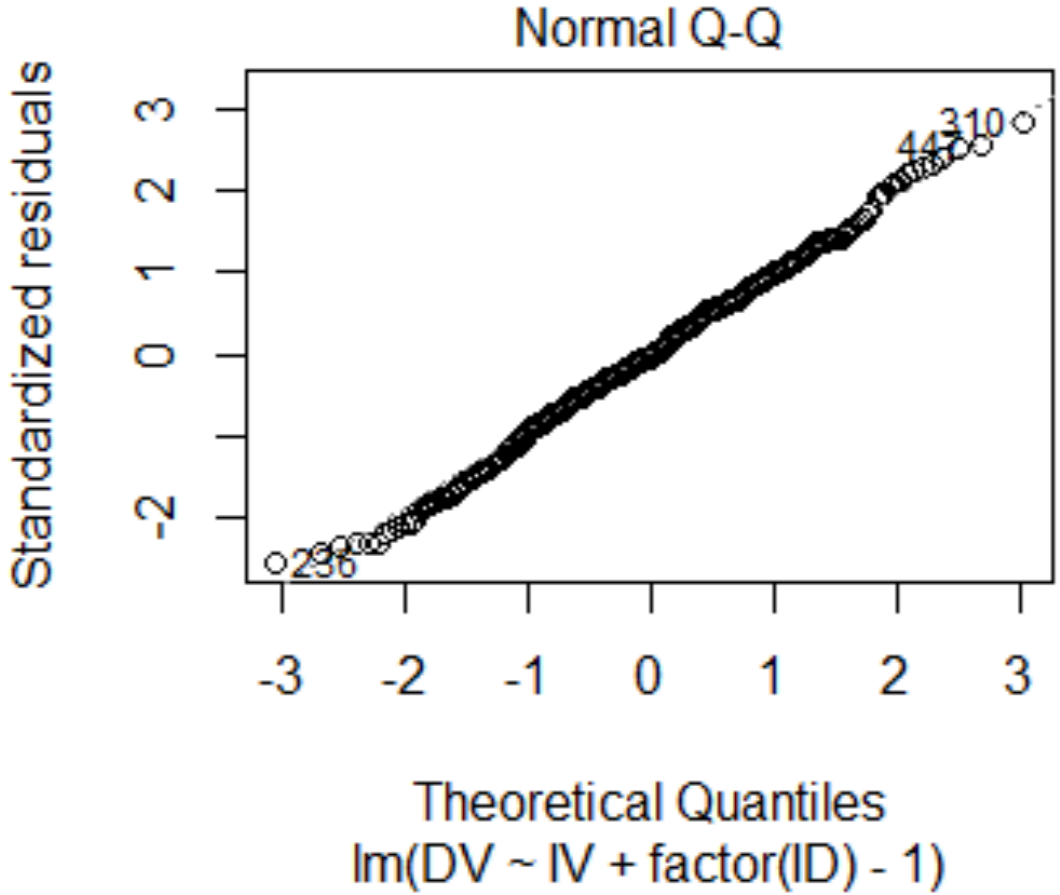

Normal Q-Q
Standardized residuals
-2
0
1
2
3
-3
-2
-1
0
1
2
3
Theoretical Quantiles
lm(DV ~ IV)

```
> summary(fe1)

Call:
lm(formula = DV ~ IV)

Residuals:
    Min      1Q  Median      3Q     Max
-21.796  -8.863  -1.488   8.399  35.142

Coefficients:
            Estimate Std. Error t value
(Intercept)  36.1619     0.7814  46.277
IV           10.7020     1.1133   9.613
            Pr(>|t|)
(Intercept)   <2e-16 ***
IV            <2e-16 ***
---
Signif. codes:
  0 '***' 0.001 '**' 0.01 '*' 0.05
  '.' 0.1 ' ' 1

Residual standard error: 11.27 on 408 degrees of freedom
  (90 observations deleted due to missingness)
Multiple R-squared:  0.1847,     Adjusted R-squared:  0.1827
F-statistic: 92.41 on 1 and 408 DF,  p-value: < 2.2e-16
```

fixed-effects model: no pooling

```
# fixed effects fit: no
# pooling
fe2 <- lm(formula = DV ~ IV +
factor(ID) - 1)
plot(fe2)
```




Normal Q-Q
Standardized residuals
-2
0
1
2
3
310
44
236
-3
-2
-1
0
1
2
3
Theoretical Quantiles
lm(DV ~ IV + factor(ID) - 1)

```
> summary(fe2)

Call:
lm(formula = DV ~ IV + factor(ID) - 1)

Residuals:
    Min      1Q  Median      3Q     Max
-7.4353 -1.9040 -0.1054  1.9683  8.4838

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
IV            10.0337     0.3199   31.36   <2e-16 ***
factor(ID)1   40.3414     1.0792   37.38   <2e-16 ***
factor(ID)2   29.7712     1.0740   27.72   <2e-16 ***
factor(ID)3   24.2284     1.0740   22.56   <2e-16 ***
...
factor(ID)50  28.1311     1.1354   24.77   <2e-16 ***
---
Signif. codes:
0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 3.194 on 359 degrees of freedom
  (90 observations deleted due to missingness)
Multiple R-squared:  0.9952,    Adjusted R-squared:  0.9946
F-statistic:  1468 on 51 and 359 DF,  p-value: < 2.2e-16
```

mixed-effects model: null

```
# mixed-effects model null
# pooling
fit1 <- lmer(DV ~ 1 + (1 | ID), exdata)
summary(fit1)
summ(fit1)
ranova(fit1)
plot(fit1)
```

mixed-effects model: treatment

```
# mixed-effects model treatment
# pooling
fit1 <- lmer(DV ~ 1 + IV + (1 | ID), exdata)
summary(fit1)
summ(fit1)
ranova(fit1)
plot(fit1)
```

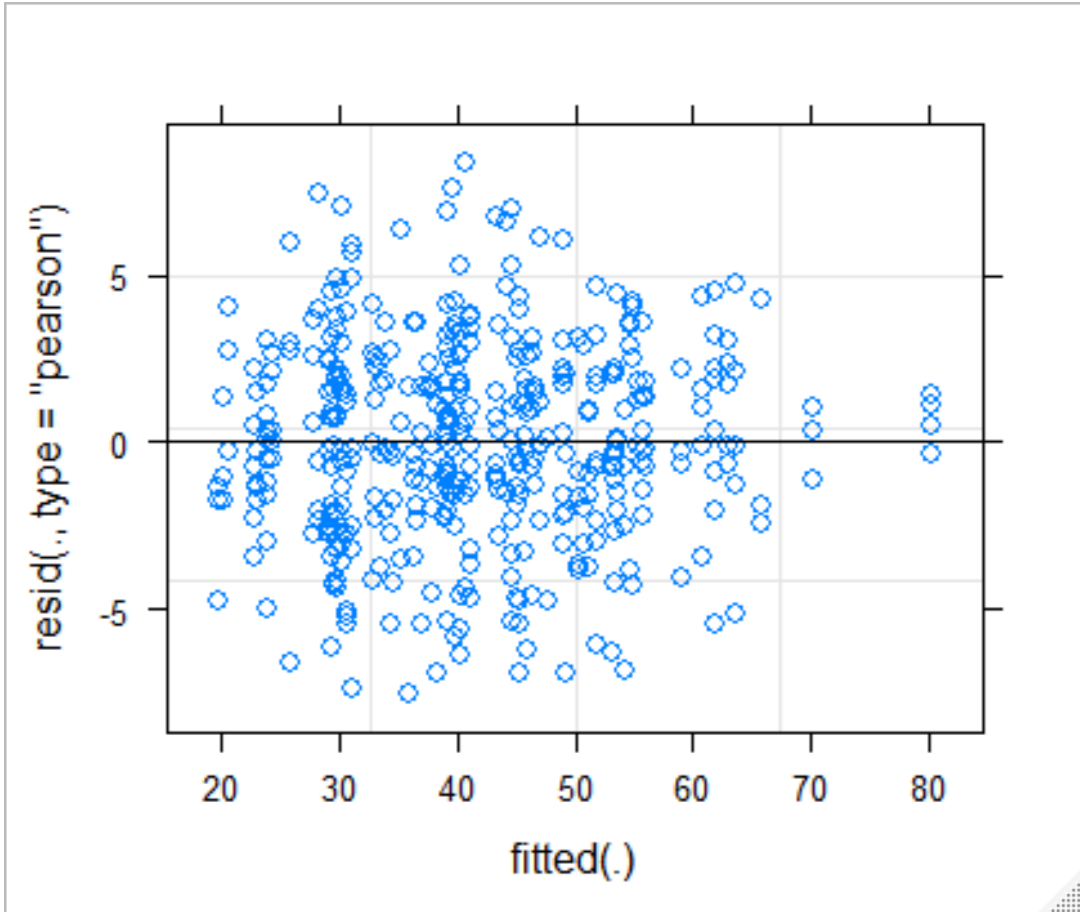
```
> summary(fit2)
Linear mixed model fit by REML. t-tests use Satterthwaite's
method ['lmerModLmerTest']
Formula: DV ~ 1 + IV + (1 | ID)
   Data: exdata

REML criterion at convergence: 2340.9

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.3760 -0.6038 -0.0386  0.6275  2.6359

Random effects:
 Groups   Name        Variance Std.Dev.
 ID       (Intercept) 122.4    11.062
 Residual              10.2     3.194
Number of obs: 410, groups:  ID, 50

Fixed effects:
            Estimate Std. Error       df t value Pr(>|t|)
(Intercept)  36.4495     1.5803  49.9485   23.07   <2e-16 ***
IV           10.0421     0.3199 359.1928   31.39   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
   (Intr)
IV -0.100
```

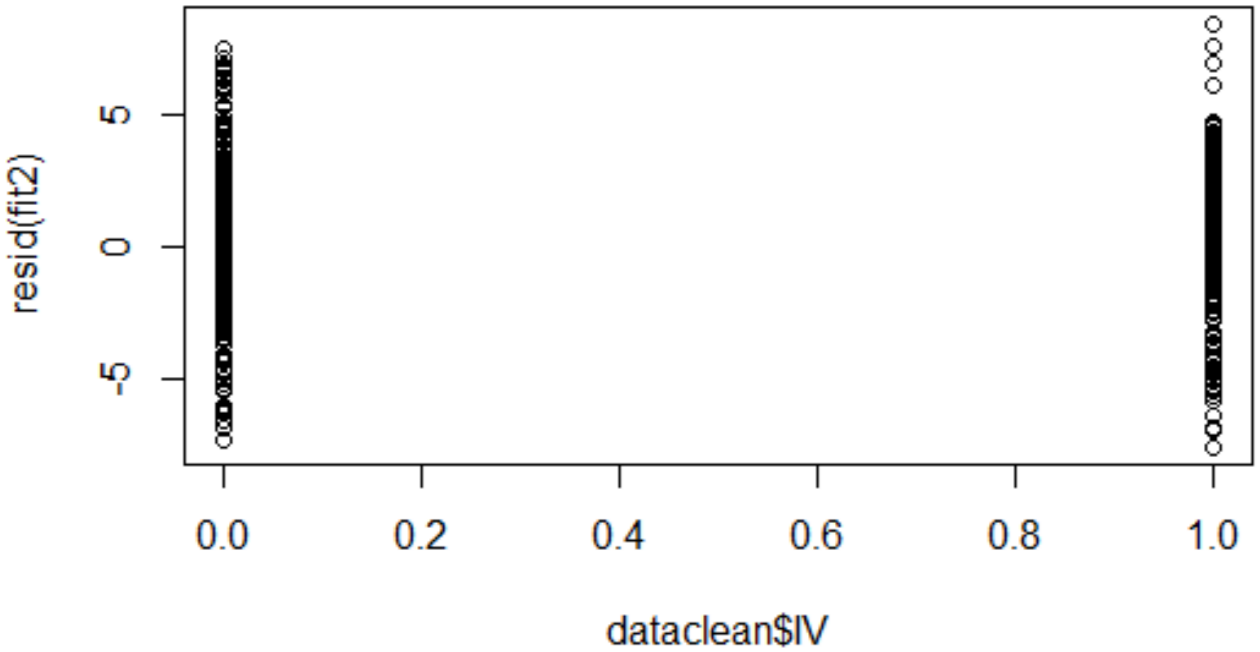
```
> summ(fit2)
MODEL INFO:
Observations: 410
Dependent Variable: DV
Type: Mixed effects linear regression

MODEL FIT:
AIC = 2348.93, BIC = 2364.99
Pseudo-R² (fixed effects) = 0.16
Pseudo-R² (total) = 0.94

FIXED EFFECTS:
----------------------------------------------------------
                      Est.   S.E.   t val.      d.f.      p
----------------- ------- ------ -------- -------- ------
(Intercept)          36.45   1.58    23.07    49.95   0.00
IV                   10.04   0.32    31.39   359.19   0.00
----------------------------------------------------------

p values calculated using Satterthwaite d.f.

RANDOM EFFECTS:
-------------------------------------
  Group      Parameter    Std. Dev.
---------- ------------- -----------
    ID       (Intercept)     11.06
 Residual                    3.19
-------------------------------------

Grouping variables:
-------------------------
 Group   # groups   ICC
------- ---------- ------
  ID        50      0.92
-------------------------
```

mixed-effects model: likelihood ratio test

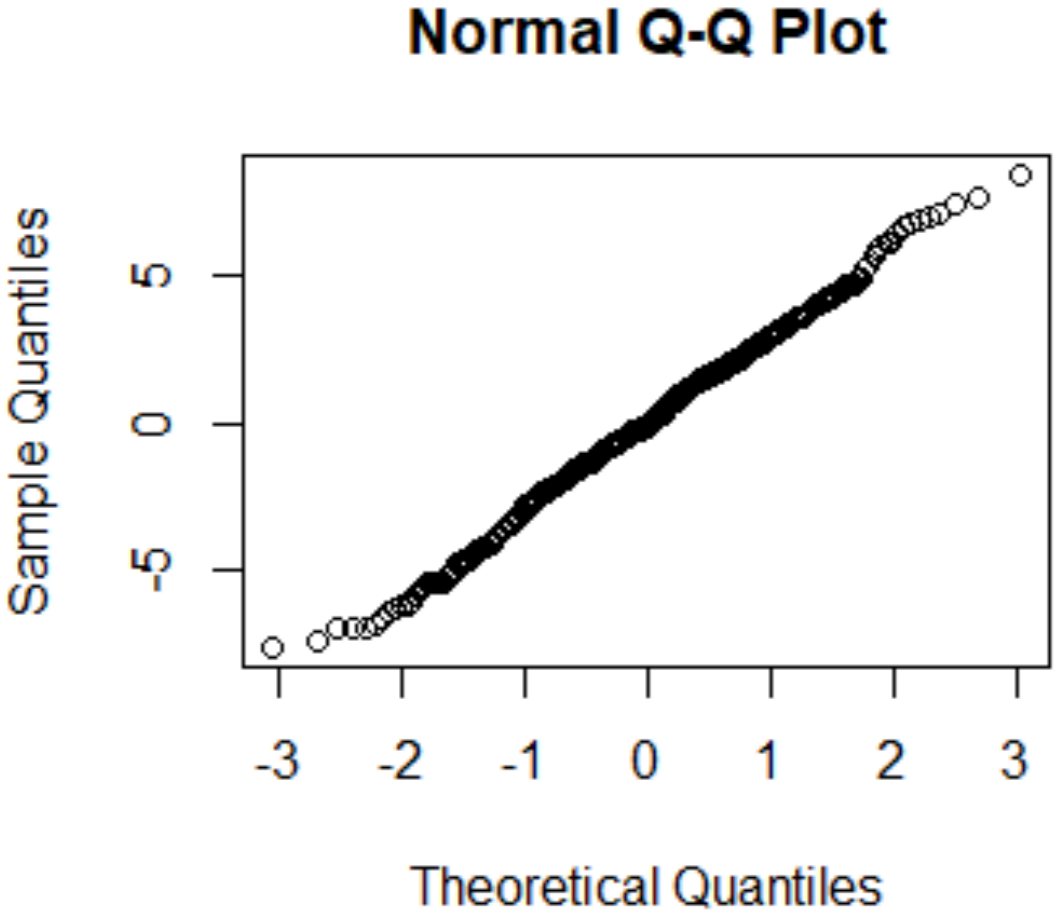
```
# likelihood ratio test
m_null <- lmer(DV ~ 1 + (1 | ID), exdata, REML = FALSE)
m_treat <- lmer(DV ~ 1 + IV + (1 | ID), exdata, REML = FALSE)
anova(m_null,m_treat)
```

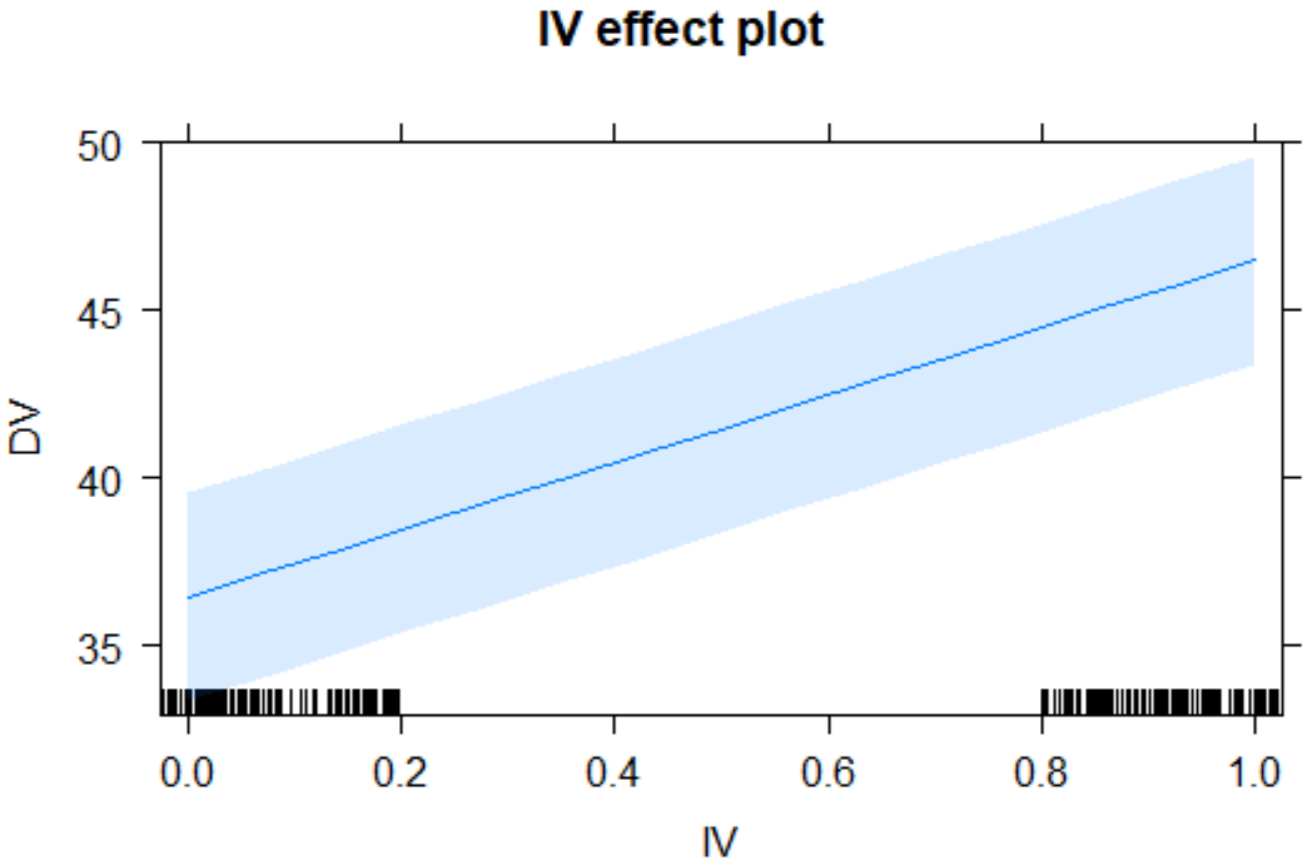
```
> anova(m_null,m_treat)
Data: exdata
Models:
m_null: DV ~ 1 + (1 | ID)
m_treat: DV ~ 1 + IV + (1 | ID)
        npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
m_null     3 2826.0 2838.0 -1410.0   2820.0
m_treat    4 2351.2 2367.3 -1171.6   2343.2 476.74  1  < 2.2e-16
***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```


resid(., type = "pearson")
5
0
-5
20
30
40
50
60
70
80
fitted(.)

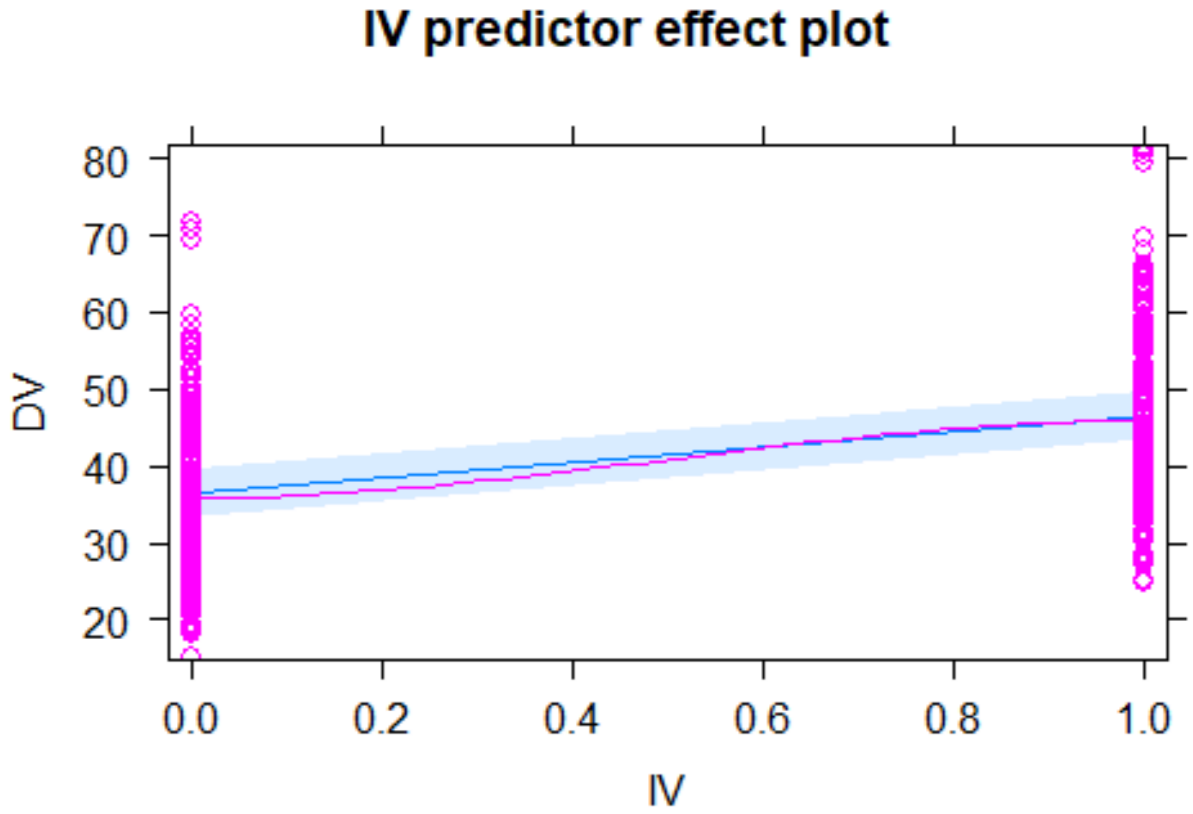



```
dataclean <- exdata[!is.na(exdata$DV), ] # remove rows with NA
plot(dataclean$IV,resid(fit2)) # plot residuals vs. treatment
```


Normal Q-Q Plot
Sample Quantiles
5
0
-5
-3
-2
-1
0
1
2
3
Theoretical Quantiles




```
# plot effects
Plot(allEffects(fit2))
```

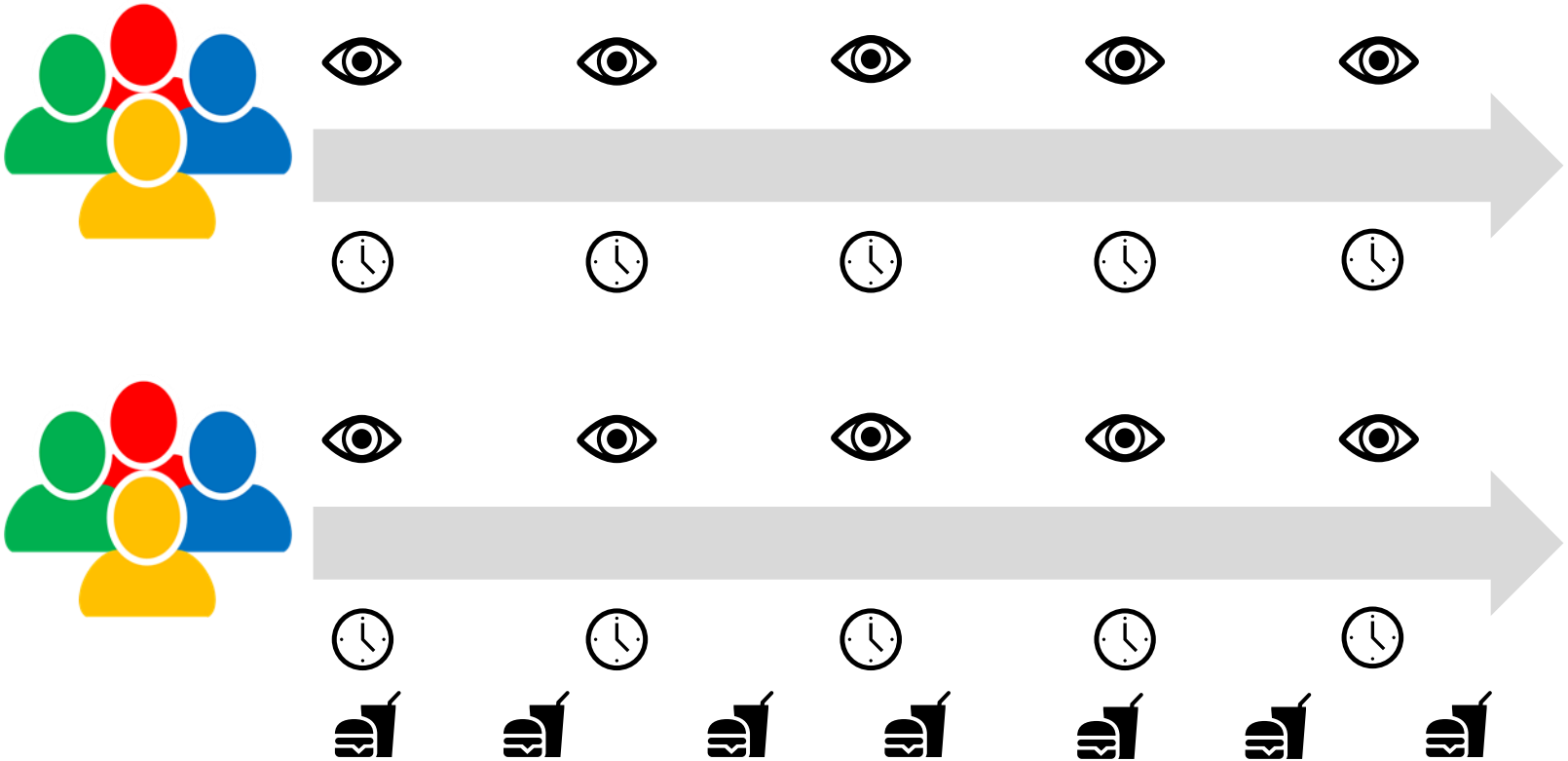



```
plot(predictorEffects(fit2,~IV,partial.residuals=TRUE))
```

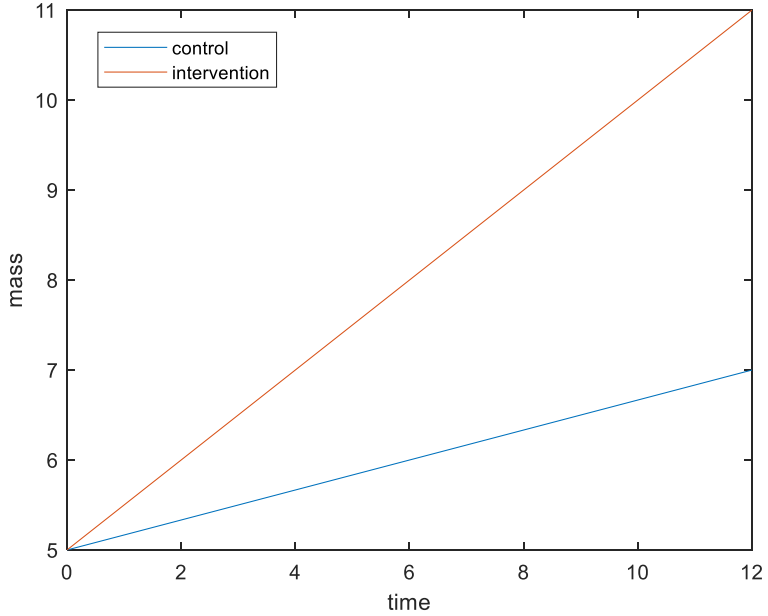
bootstrap

```
> library(boot)
> confint(fit2,parm=c(3,4),method="boot",nsim=1000,boot.type="perc")
Computing bootstrap confidence intervals ...
                2.5 %   97.5 %
(Intercept) 33.28305 39.58972
IV           9.39840 10.62247
```

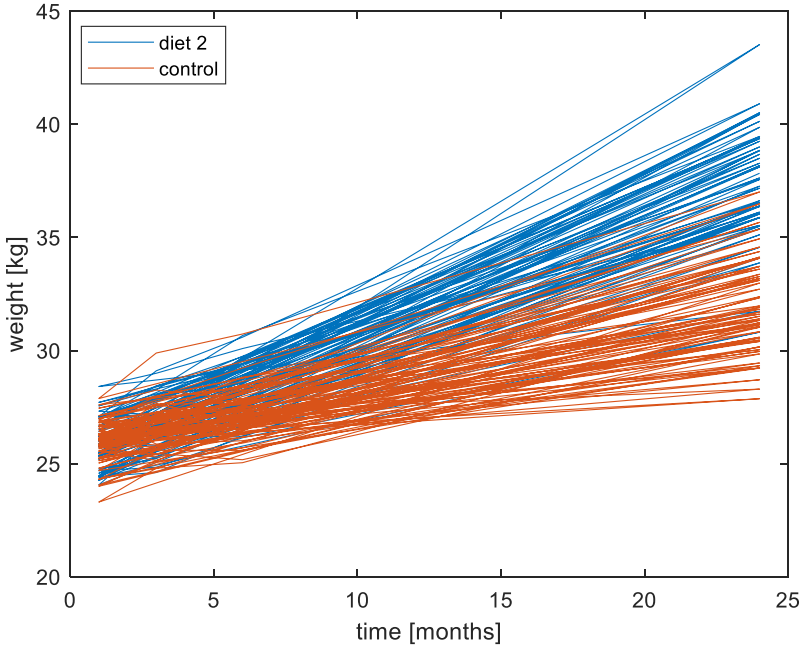
Diet and body weight paediatric dataset



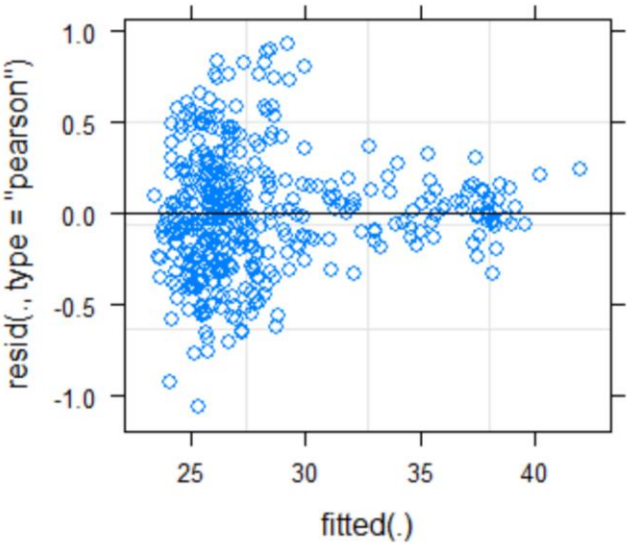
Conditional growth model

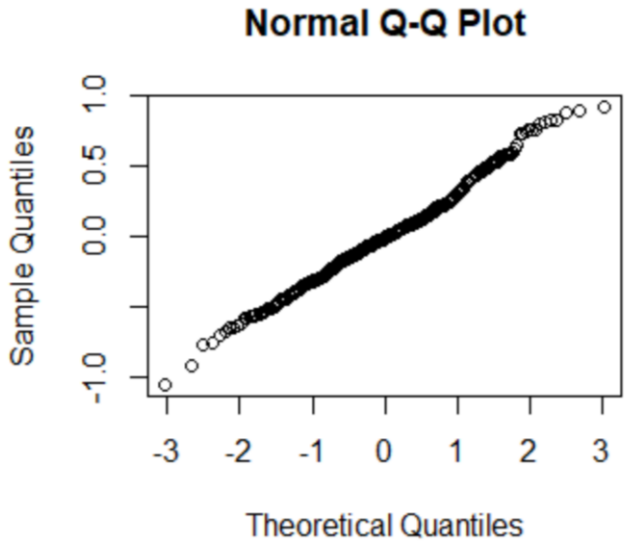


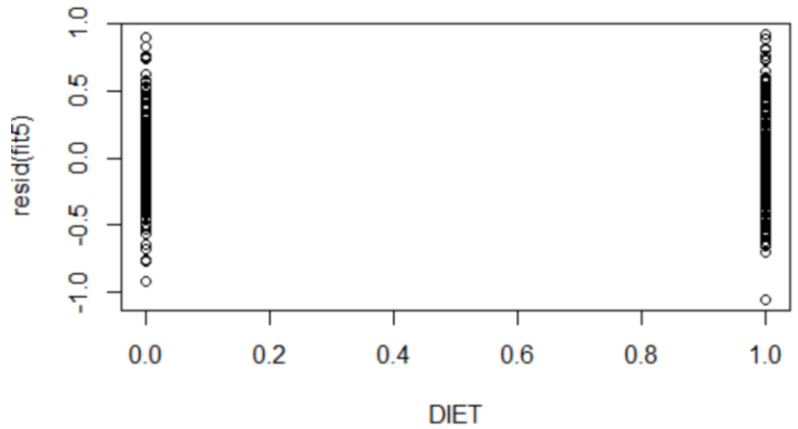
$$Y = \beta_0 + \beta_1 \cdot time + \varepsilon$$

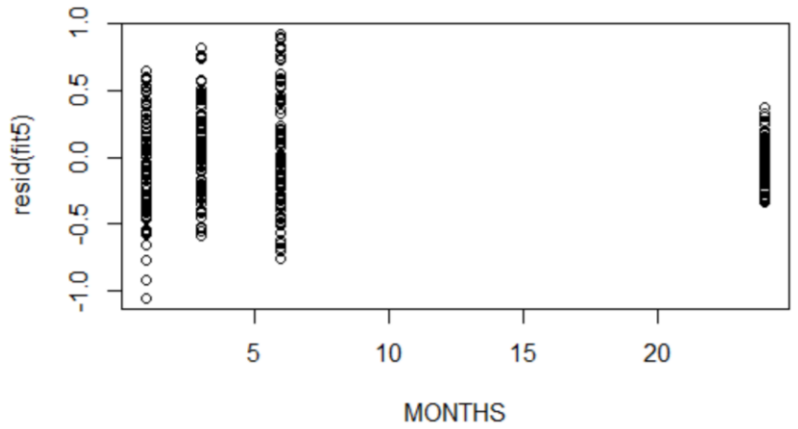



```
# conditional growth model
model <- lmer(BW ~ 1 + Months*Diet + (Months | ID), data)
```

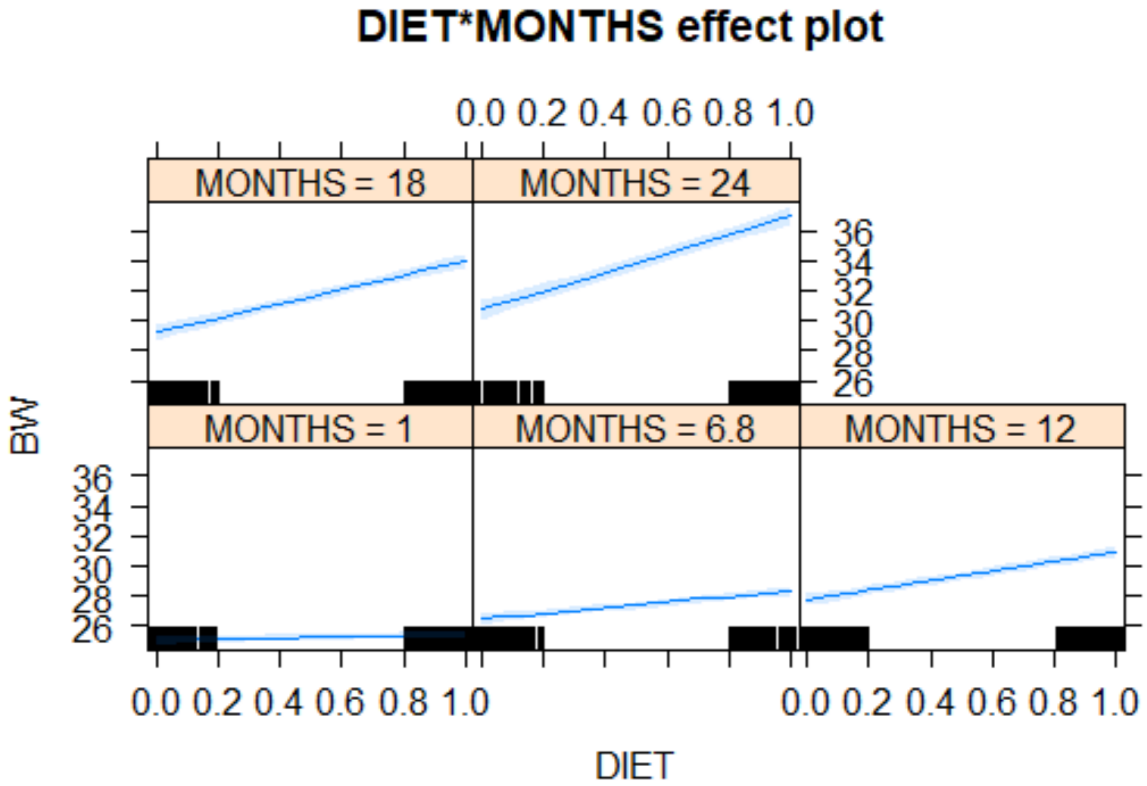

resid(., type = "pearson")
1.0
0.5
0.0
-0.5
-1.0
25
30
35
40
fitted(.)


Normal Q-Q Plot
Sample Quantiles
1.0
0.5
0.0
-1.0
-3
-2
-1
0
1
2
3
Theoretical Quantiles






```
plot(DIET,resid(fit5))
plot(MONTHS,resid(fit5))
```

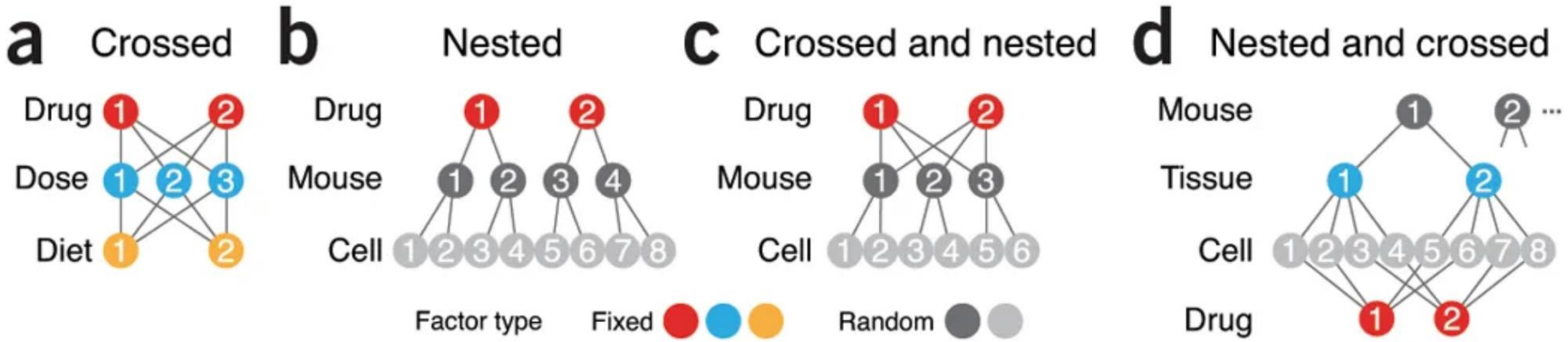



```
# plot effects
Plot(allEffects(model))
```

```
> summary(model)
Linear mixed model fit by REML. t-tests use Satterthwaite's method
['lmerModLmerTest']
Formula: BW ~ DIET * MONTHS + (MONTHS | ID)
   Data: dietdata

REML criterion at convergence: 1032.4

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.37610 -0.47912 -0.01658  0.41414  2.08534

Random effects:
 Groups   Name        Variance Std.Dev. Corr
 ID       (Intercept) 0.877062 0.93652
          MONTHS      0.005634 0.07506  0.05
 Residual             0.196379 0.44315
Number of obs: 400, groups:  ID, 100

Fixed effects:
            Estimate Std. Error       df t value Pr(>|t|)
(Intercept) 24.80192    0.14838 98.01430 167.149   <2e-16 ***
DIET         0.14432    0.19828 98.01430   0.728    0.468
MONTHS       0.24656    0.01189 97.99779  20.731   <2e-16 ***
DIET:MONTHS  0.25396    0.01589 97.99779  15.980   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) DIET   MONTHS
DIET        -0.748
MONTHS      -0.015  0.011
DIET:MONTHS  0.011 -0.015 -0.748
```

```
> summ(model)
MODEL INFO:
Observations: 400
Dependent Variable: BW
Type: Mixed effects linear regression

MODEL FIT:
AIC = 1048.41, BIC = 1080.34
Pseudo-R² (fixed effects) = 0.88
Pseudo-R² (total) = 0.99

FIXED EFFECTS:
----------------------------------------------------------
                      Est.   S.E.   t val.     d.f.      p
----------------- ------- ------ -------- ------- ------
(Intercept)         24.80   0.15   167.15   98.01   0.00
DIET                 0.14   0.20     0.73   98.01   0.47
MONTHS               0.25   0.01    20.73   98.00   0.00
DIET:MONTHS          0.25   0.02    15.98   98.00   0.00
----------------------------------------------------------

p values calculated using Satterthwaite d.f.

RANDOM EFFECTS:
-------------------------------------
  Group      Parameter    Std. Dev.
---------- ------------- -----------
    ID      (Intercept)     0.94
    ID        MONTHS        0.08
 Residual                   0.44
-------------------------------------

Grouping variables:
-------------------------
 Group   # groups   ICC
------- ---------- ------
  ID       100      0.82
-------------------------
```

nested and crossed mixed effects




```
# crossed random effects
fit <- lmer(DV ~ 1 + (1 | A) +
(1 | B), data)
```

```
# nested random effects
fit <- lmer(DV ~ 1 + (1 | A/B),
data)
```

Figure: Zablotski - https://yury-zablotski.netlify.app/post/mixed-effects-models-2/

Summary

- We reviewed:
  - The limits of fixed effects linear regression modelling.
  - When and why you should consider mixed-effects/multi-level modelling.
  - The theory behind mixed-effects/multi-level modelling.
  - A basic workflow for mixed-effects modelling to get you started and learn more.
  - A couple of practical examples and case studies.
- Mixed-effects modelling can do far more than what we covered today.
- Hopefully it came across that this is a powerful approach for unravelling effects hidden away behind variability.

darwich@kth.se