Analysis of repeated measurements (KLMED8008)

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Day 5

- Practical issues …?
  - Lectures
  - Textbook
  - Software
  - Exam
- Brief review of exercise 1
- Cluster randomized trials – sample size dtermination
- Linear mixed effects models: models with random intercept (Textbook chapter 3)
- Sample size

Repeated measurements

Ignoring dependency between observations may lead to…

- p-values becoming too small when doing between-patient comparisons (i.e. yield false positive results)

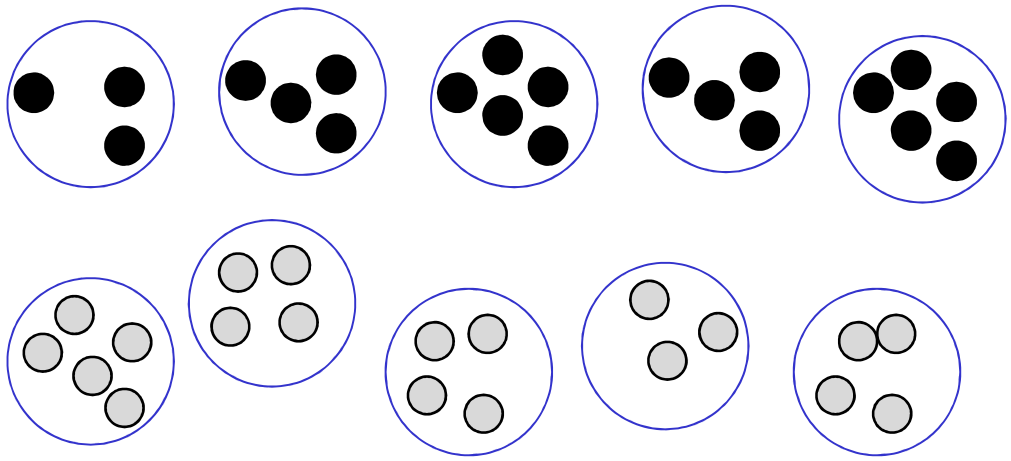
Textbook 3.10.2 (p. 167), *Veierød et al.* 7.1 (p. 231)

Observations:

● Treatment, n=20

○ Control, n=20

○ Patients



Repeated measurements

Ignoring dependency between observations may lead to…

- p-values becoming too large when doing within-patient comparisons (i.e. yield false negative results)

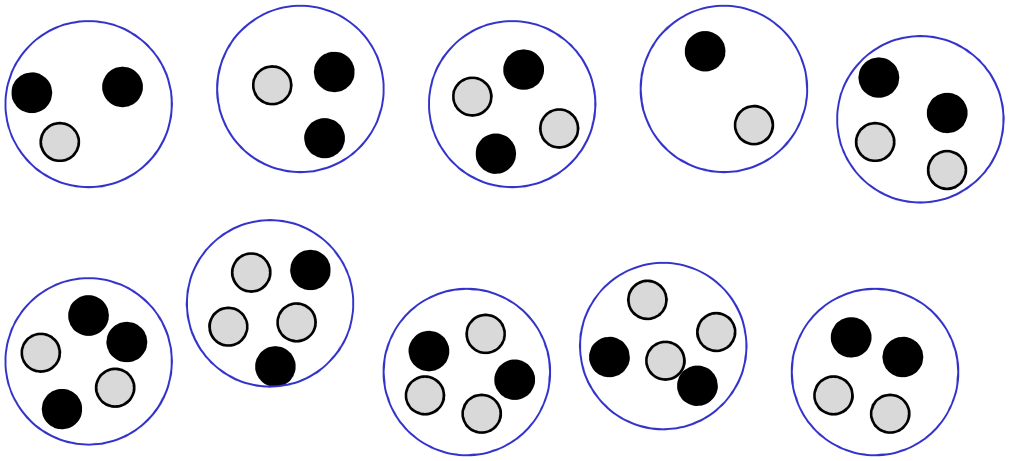
Textbook 3.10.2 (p. 167), *Veierød et al.* 7.1 (p. 231)

Observations:

● Treatment,n=20

○ Control, n=20

○ Individual



Cluster-randomized design

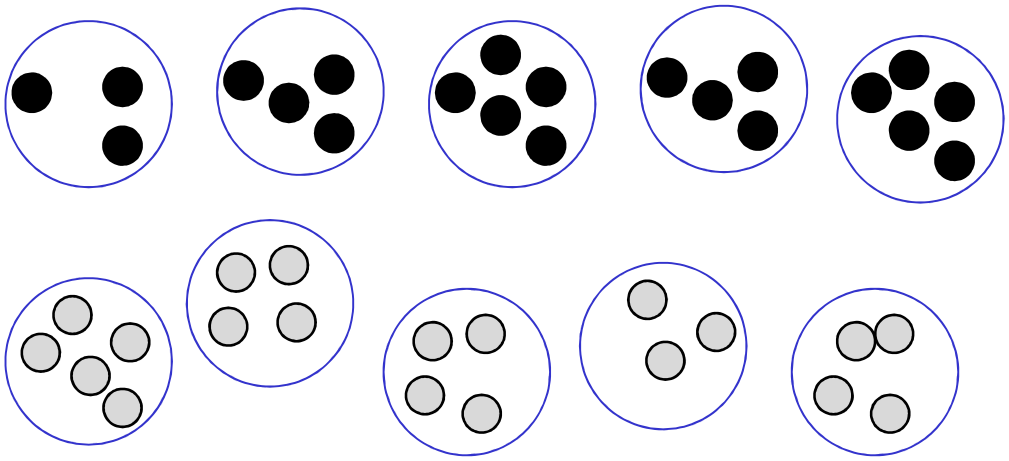
- Sometimes impossible to allocate treatment/ control to individual subjects:
  - ”contamination” within general practice, household, school
  - Practical limitations within geographical areal etc.
- Allocation of treatment must therefore be made to clusters of subjects:
- p-values become too small when doing between-patient comparisons (i.e. yield false positive results)

Subjects:

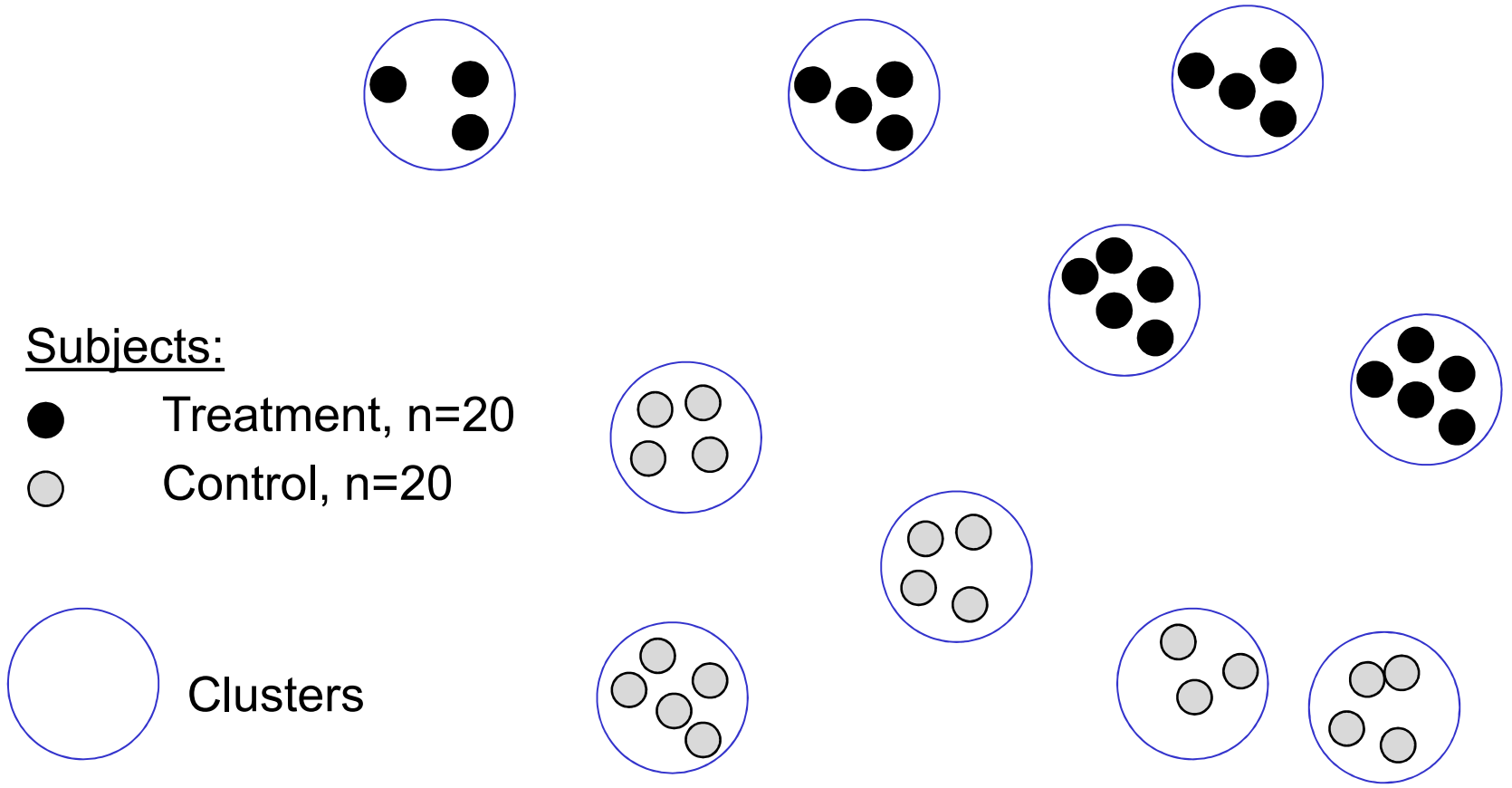
● Treatment, n=20

○ Control, n=20

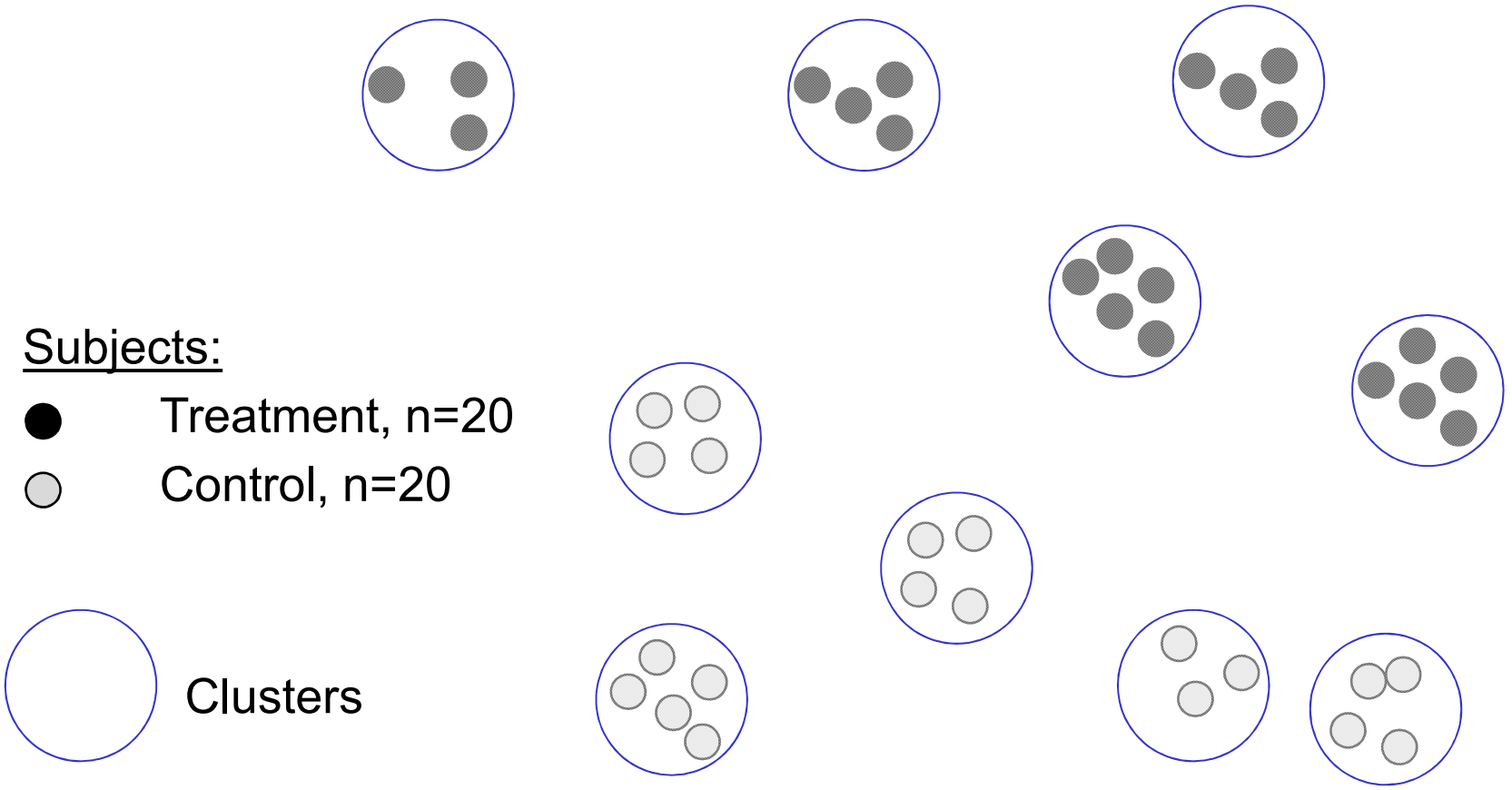
Clusters



So… how large is ”n” in each group? 20?



Or perhaps 5…?



It depends… on the ICC!

- ICC = intra-class (cluster) correlation
- ICC summarizes the extent that the *subjects within a cluster* are similar, relative to the clusters

$$\text{ICC} = \frac{\sigma_j^2}{\sigma_j^2 + \sigma_{ij}^2}$$

$$\text{Total variance} = \sigma_j^2 + \sigma_{ij}^2$$

$$\sigma_j^2 = \text{ cluster variance}$$

$$\sigma_{ij}^2 = \text{ residual variance (subject)}$$

- If subjects within a cluster are dissimilar, $\sigma^2_j = 0$ and $ICC = 0$
- If subjects within a cluster are identical, $\sigma^2_j = 1$, $\sigma_{ij}^2 = 0$ and $ICC = 1$

Some aspects …

- Ignoring clusters during trial planning may lead to increased type II error (i.e. lower power than required)
- Ignoring clusters during trial analysis may lead to increased type I error (”to sensitive”)

- Power does not increase substantially when the cluster size *k* exceeds *1/ICC*

Some examples:

$ICC = 0.01, \quad k = 1/0.01 = 100$ (i.e. max reasonable cluster size is 100)

$ICC = 0.05, \quad k = 1/0.05 = 20$

$ICC = 0.1, \quad k = 1/0.1 = 10$

Campbell, M. J., A. Donner, et al. (2007). *Stat Med* 26(1): 2-19.

Machin D, Campbell M, Tan SB, Tan SH. Sample Size Tables for Clinical Studies. 3 ed. Oxford: Wiley-Blackwell; 2009.

Cluster randomization – sample size

Starting point:

$m_{cluster} = c \cdot k$ = total number of subjects in each group (treatment/ control)

c = number of clusters

k = number of subjects in each cluster (i.e. cluster size)

Three problems:

1. Given n in each group [from usual calculations], how large is $m_{cluster}$?
2. Given $m_{cluster}$ and k, how many clusters (c) are required?
3. Given n [from usual calculations] and c, what is the cluster size (k)?

Cluster randomized trial – ICC adjustment

Principle:

- Low ICC: every subject within cluster adds information
- High ICC: each subject adds little information

In practice, guess the ICC, and calculate the ”Design Effect” (DE).
(DE is a multiplication factor for increasing the sample size)

$$DE = 1 + (k - 1) \cdot ICC$$

k = number of subjects within each cluster

Examples:

$ICC = 0,\ k = 5 \quad DE = 1+(5-1)\cdot 0 = 1+0 = 1$ *(reference)*

$ICC = 0.2,\ k = 5 \quad DE = 1+(5-1)\cdot 0.2 = 1+4\cdot 0.2 = 1+0.8 = 1.8$ *(80 % increase)*

$ICC = 0.5,\ k = 5 \quad DE = 1+(5-1)\cdot 0.5 = 1+4\cdot 0.5 = 1+2 = 3$ *(300 % increase)*

Cluster randomization – sample size

1. If n is the (originally) calculated sample size in each group, how many subjects do you really need in each group:

$$m_{cluster} = DE \cdot n = c \cdot k$$

2. Given $m_{cluster}$ and k, how many clusters (c) are required?

$$c = \frac{DE \cdot n}{k} = \frac{m_{cluster}}{k}$$

3. Given n and c, how large do the clusters become (k)?

$$k = \frac{n \cdot (1 - ICC)}{(c - ICC \cdot n)}$$

”Design Effect”

for different values of k (cluster size) and ICC

	ICC								
k	0.01	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4
1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2	1.0	1.1	1.1	1.1	1.2	1.2	1.3	1.4	1.4
3	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8
4	1.0	1.1	1.3	1.5	1.6	1.8	1.9	2.0	2.2
5	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6
15	1.1	1.7	2.4	3.1	3.8	4.5	5.2	5.9	6.6
25	1.2	2.2	3.4	4.6	5.8	7.0	8.2	9.4	10.6
35	1.3	2.7	4.4	6.1	7.8	9.5	11.2	12.9	14.6
45	1.4	3.2	5.4	7.6	9.8	12.0	14.2	16.4	18.6
55	1.5	3.7	6.4	9.1	11.8	14.5	17.2	19.9	22.6
65	1.6	4.2	7.4	10.6	13.8	17.0	20.2	23.4	26.6
75	1.7	4.7	8.4	12.1	15.8	19.5	23.2	26.9	30.6
85	1.8	5.2	9.4	13.6	17.8	22.0	26.2	30.4	34.6
95	1.9	5.7	10.4	15.1	19.8	24.5	29.2	33.9	38.6

Example

$$k = \frac{n \cdot (1 - ICC)}{(c - ICC \cdot n)}$$

k = number of individuals in each cluster

- $n = 25, ICC = 0.05, c = 10$ $\quad k = 25 \cdot (1 - 0.05)/(10 - 0.05 \cdot 25) = 2.7$
- $n = 25, ICC = 0.05, k = 3$ $\quad m_{cluster} = DE \cdot n = (1+(4-1) \cdot 0.05) \cdot 25 = 28$
- $m_{cluster} = 28, k = 3$ $\quad c = 28/3 = 9$

Linear mixed effects model

Example

```
. regress post pre
```

Source	SS	df	MS	
Model	6323.33822	1	6323.33822	
Residual	12970.9695	50	259.419389	$\hat{\sigma}^2$
Total	19294.3077	51	378.319759	

Number of obs	= 52
F(1, 50)	= 24.37
Prob > F	= 0.0000
R-squared	= 0.3277
Adj R-squared	= 0.3143
Root MSE $\hat{\sigma}$	= 16.107

post		Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
pre	$\hat{\beta}_1$	.8252027	.1671432	4.94	0.000	.4894858	1.16092
_cons	$\hat{\beta}_0$	23.54709	9.79174	2.40	0.020	3.8798	43.21438

Linear model

$$y_{ij} = \beta_0 + \beta_1 \cdot x_{1ij} + ... + \beta_p \cdot x_{pij} + \xi_{ij}$$

$x_{1ij} ... x_{pij}$ covariates (predictor variables, possibly categorical)

ξ_{ij} error term, $\xi_{ij} \sim N(0, \sigma^2)$

Linear mixed effects model

But unrealistic that ξ_{ij} is independent of x_{ij}

Define $\xi_{ij} = \varsigma_j + \varepsilon_{ij} \quad \varsigma_j \sim \mathrm{N}(0, \psi) \quad \varepsilon_{ij} \sim \mathrm{N}(0, \theta)$

$$y_{ij} = \beta_0 + \beta_1 \cdot x_{2ij} + \ldots + \beta_p \cdot x_{pij} + \varsigma_j + \varepsilon_{ij}$$
$$y_{ij} = (\beta_0 + \varsigma_j) + \beta_2 \cdot x_{2ij} + \ldots + \beta_p \cdot x_{pij} + \varepsilon_{ij}$$

Compare variance components

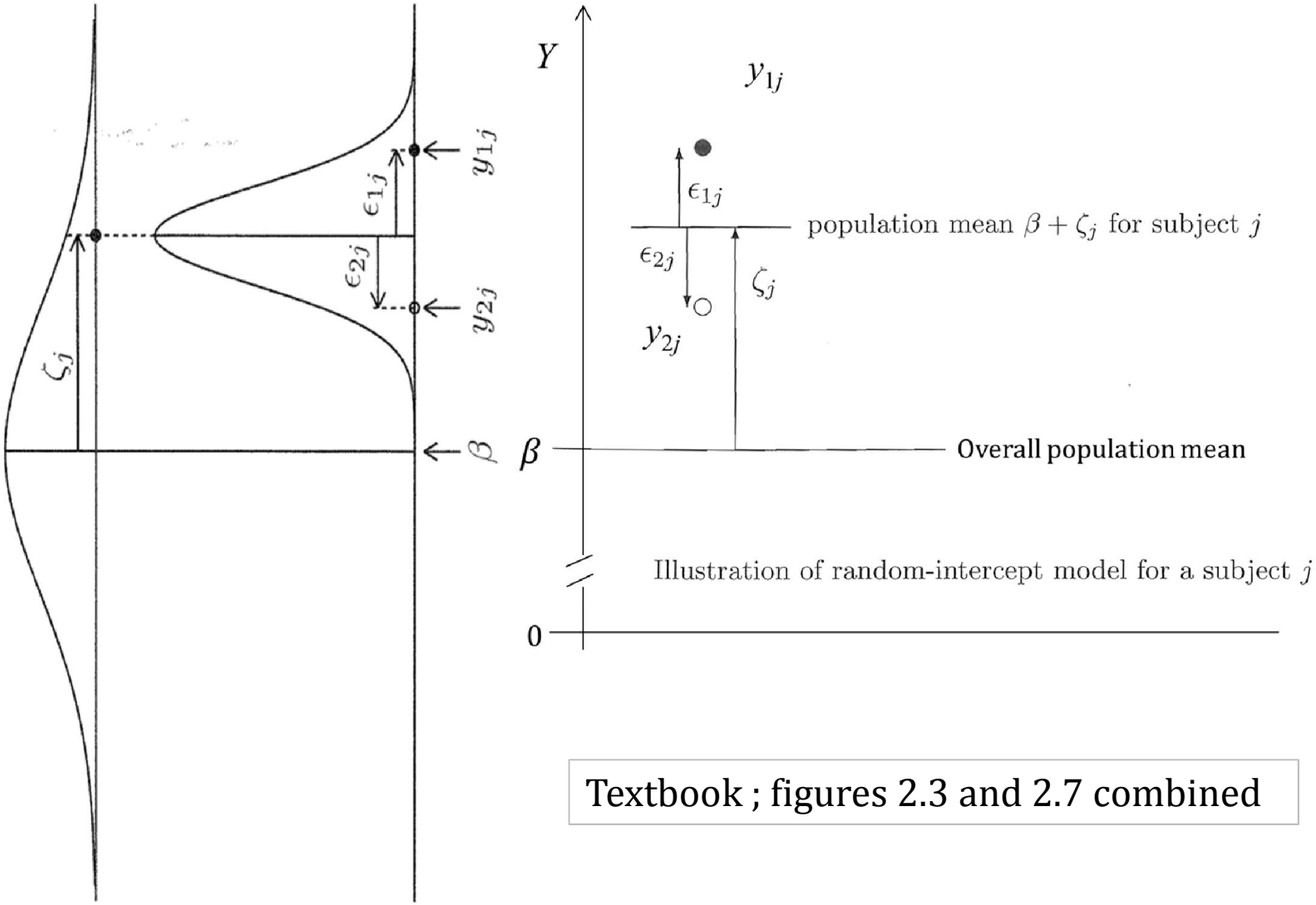
$$y_{ij} = \beta + \varsigma_j + \varepsilon_{ij}$$

$i =$ children nested within mother

$j =$ mother

$\varsigma_j \sim N(0, \psi)$ $\quad$ ψ : between-subject variance

$\varepsilon_i \sim N(0, \theta)$ $\quad$ θ : within-subject variance



Textbook ; figures 2.3 and 2.7 combined

Linear mixed effects model

- Involves both fixed and random factors/ effects; is thus *mixed*
- A starting point: grouped or clustered observations of a continuous outcome variable
- The groups are ”internally similar”: observations within the group are correlated
- Groups are ”drawn” at random from the population of similar groups or clusters
- It is the intention to generalize to this population
- Examples:
  - Repeated observations on the same subject
  - Observations on different schools, hospitals, cities, countries…

Winer revisited

- Linear model
- Robust linear model (but this *really* requires large «n»)
- Linear *mixed* model

Winer revisited

- Reaction time (score) with four drugs was measured repeatedly in the same 5 persons:

	person	score_1	score_2	score_3	score_4
1.	1	30	28	16	34
2.	2	14	18	10	22
3.	3	24	20	18	30
4.	4	38	34	20	44
5.	5	26	28	14	30

Winer 1991 in Stata manual: [R] anova

```
. use winer, clear
(T4.3 -- Winer, Brown, Michels)

. list
```

	person	drug	score
1.	1	1	30
2.	1	2	28
3.	1	3	16
4.	1	4	34
5.	2	1	14
6.	2	2	18
7.	2	3	10
8.	2	4	22
9.	3	1	24
10.	3	2	20
11.	3	3	18
12.	3	4	30
13.	4	1	38
14.	4	2	34
15.	4	3	20
16.	4	4	44
17.	5	1	26
18.	5	2	28
19.	5	3	14
20.	5	4	30

```
. regress score i.drug
```

Source	SS	df	MS		
Model	698.2	3	232.733333	Number of obs	20
Residual	793.6	16	49.6	F(3, 16)	4.69
				Prob > F	0.0155
				R-squared	0.4680
				Adj R-squared	0.3683
Total	1491.8	19	78.5157895	Root MSE	7.0427

score	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
drug						
2	-.8	4.454211	-0.18	0.860	-10.24251	8.642507
3	-10.8	4.454211	-2.42	0.028	-20.24251	-1.357493
4	5.6	4.454211	1.26	0.227	-3.842507	15.04251
_cons	26.4	3.149603	8.38	0.000	19.72314	33.07686

```
. margins i.drug

Adjusted predictions                            Number of obs   =         20
Model VCE    : OLS

Expression   : Linear prediction, predict()
```

	Delta-method Margin	Std. Err.	z	P>|z|	[95% Conf.	Interval]
drug						
1	26.4	3.149603	8.38	0.000	20.22689	32.57311
2	25.6	3.149603	8.13	0.000	19.42689	31.77311
3	15.6	3.149603	4.95	0.000	9.426891	21.77311
4	32	3.149603	10.16	0.000	25.82689	38.17311

```
. regress score i.drug, robust cluster(person)

Linear regression                               Number of obs =         20
                                                F(  3,     4) =      47.85
                                                Prob > F      =     0.0014
                                                R-squared     =     0.4680
                                                Root MSE      =     7.0427

                                    (Std. Err. adjusted for 5 clusters in person)
------------------------------------------------------------------------------
             |               Robust
       score |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        drug |
          2  |        -.8   1.770593    -0.45   0.675    -5.715955    4.115955
          3  |      -10.8   2.808024    -3.85   0.018    -18.59633   -3.003675
          4  |         5.6   .8154753     6.87   0.002     3.335878    7.864122
             |
       _cons |        26.4   4.270831     6.18   0.003     14.54227    38.25773
------------------------------------------------------------------------------

. margins i.drug

Adjusted predictions                            Number of obs   =         20
Model VCE    : Robust

Expression   : Linear prediction, predict()

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        drug |
          1  |        26.4   4.270831     6.18   0.000     18.02932    34.77068
          2  |        25.6    3.18826     8.03   0.000     19.35113    31.84887
          3  |        15.6   1.874833     8.32   0.000     11.92539    19.27461
          4  |          32   3.898718     8.21   0.000     24.35865    39.64135
------------------------------------------------------------------------------
```

```
. xtmixed score i.drug || person:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -55.795093
Iteration 1:   log likelihood = -55.795093

Computing standard errors:

Mixed-effects ML regression                     Number of obs      =         20
Group variable: person                          Number of groups   =          5

                                                Obs per group: min =          4
                                                               avg =        4.0
                                                               max =          4


                                                Wald chi2(3)       =      92.85
Log likelihood = -55.795093                     Prob > chi2        =     0.0000
```

score	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
drug						
2	-.8	1.734358	-0.46	0.645	-4.19928	2.59928
3	-10.8	1.734358	-6.23	0.000	-14.19928	-7.40072
4	5.6	1.734358	3.23	0.001	2.20072	8.99928
_cons	26.4	2.817092	9.37	0.000	20.8786	31.9214

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
person: Identity				
sd(_cons)	5.670981	1.899121	2.941741	10.93231
sd(Residual)	2.742261	.5006661	1.91735	3.922078

LR test vs. linear regression: chibar2(01) = 18.78 Prob >= chibar2 = 0.0000

```
. margins i.drug

Adjusted predictions                                  Number of obs   =         20

Expression   : Linear prediction, fixed portion, predict()
```

	Delta-method Margin	Std. Err.	z	P>|z|	[95% Conf.	Interval]
drug						
1	26.4	2.817092	9.37	0.000	20.8786	31.9214
2	25.6	2.817092	9.09	0.000	20.0786	31.1214
3	15.6	2.817092	5.54	0.000	10.0786	21.1214
4	32	2.817092	11.36	0.000	26.4786	37.5214

Birthweight and smoking

Dataset «smoking»,Textbook pp. 91 →