Extensions to linear and logistic regressions

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Conditional logistic regression

- **When?**
- **What?**
- **How?**

Other methods for analyzing binary data

Models for **relative risks**
Models for **risk differences**

Clustered data / data with **several random components**

Continuous outcome
Dichotomous outcome

Clustered binary data with **one random components**

Nonlinear regression models

Conditional logistic regression
When

Used in two situations:

1. **Matched** studies (binary response).
2. **Unmatched** studies with a **confounder** with **many distinct values**.

In **1.** the models correspond to **the way data was collected**.

In **2.** the method adjust for a '**mathematical**' **flaw** in the unconditional method.

An example of situation **2.** the confounder is "*kommune*" having 275 distinct values.

Conditional logistic regression
What

The logistic regression model (outcome disease yes/no):

$$\ln(odds) = \alpha + \sum_{i=1}^{k}(\beta_i \cdot x_i)$$

ln(odds) in reference ln(odds ratios)

Suppose the model above hold in each strata:

$$\ln(odds) = \alpha_s + \sum_{i=1}^{k}(\beta_i \cdot x_i)$$

ln(odds) in reference **different in each strata**
ln(odds ratios) **the same in each strata**

Conditional logistic regression
What

$$\ln(odds) = \alpha_s + \sum_{i=1}^{k}(\beta_i \cdot x_i)$$

ln(odds) different in each strata

We are not interested in these !

In a **matched** study these are 'controlled'.

In a **conditional** logistic regression one '**condition on the odds in each strata**' , i.e. these case/control ratio.

In the conditional model the α's **disappear** !

The β's , the log OR's, are still in and **can be estimated**.

Conditional logistic regression
How

It is easy !

You need a statistical software package.

A package made for **research in epidemiology**

Not in social science

Not *SPSS*

But ***STATA***, *EPICURE, EPILOG, EGRET, EPIINFO(2000) and SAS can do it.*

Conditional logistic regression
How

An example using *STATA*

A study of cancer in the oral cavity

Matched on **gender** and **10 years age groups**

Ten strata (`genage`)

Here we focus on

`textile-worker` and

`life time consumption of alcohol` (three groups)

Conditional logistic regression How

logistic regression in *STATA*

```
xi:logit cancer textile i.alkcon i.genage
```

Part of the output:

cancer	Coef.	Std. Err.	z	P>|z|	CI	
textile	**.5022**	**.4141**	**1.213**	**0.225**	**-.3094**	**1.3139**
_Ialkcon_1	**.4628**	**.2823**	**1.639**	**0.101**	**-.0905**	**1.0163**
_Ialkcon_2	**2.7165**	**.3232**	**8.404**	**0.000**	**2.0829**	**3.3501**
_Igenage_2	.2450	1.2514	0.196	0.845	-2.2075	2.6977
_Igenage_3	-.4940	.5503	-0.898	0.369	-1.5726	.5846
_Igenage_4	.1798	.6406	0.281	0.779	-1.0758	1.4353
_Igenage_5	-.2899	.5482	-0.529	0.597	-1.3644	.7844
_Igenage_6	.2127	.6282	0.340	0.734	-1.0147	1.4401
_Igenage_7	-.2305	.5355	-0.431	0.667	-1.2802	.8190
_Igenage_8	.5507	.5263	1.046	0.295	-.4809	1.5825
_Igenage_9	.0315	.5884	0.054	0.957	-1.1217	1.1847
_Igenage_10	.5572	.5595	0.996	0.319	-.53954	1.6539
_cons	-1.4692	.4762	-3.085	0.002	-2.4027	-.5356

Conditional logistic regression in *STATA*

The syntax:

```
xi:clogit cancer textile i.alkcon,group(genage)
```

Part of the output:

cancer	Coef.	Std. Err.	z	P>|z|	CI	
textile	**.4929**	**.4103**	**1.201**	**0.230**	**-.3112**	**1.2971**
_Ialkcon_1	**.452**	**.27923**	**1.621**	**0.105**	**-.094**	**.9999**
_Ialkcon_2	**2.660**	**.31936**	**8.332**	**0.000**	**2.034**	**3.2868**

```
xi:clogit cancer textile i.alkcon, group(genage) or
```

cases	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
textile	1.63708	.6717022	1.20	0.230	.732517	3.658661
_Ialkcon_1	1.572508	.4390957	1.62	0.105	.909724	2.718168
_Ialkcon_2	14.30908	4.569879	8.33	0.000	7.651811	26.75835

Other methods to analysis of binary response data Relative Risk models

Logistic regression model focus on the **Odds Ratios**

This is the correct thing to do in **case-control** studies.

In **follow-up** studies **Relative Risk** is often the appropriate measure of association, (personal risk).

I.e. a model like this might be more relevant:

$$\Pr(\text{event}) = p_0 \times RR_1 \times RR_2 \times RR_3$$

$$\ln\{\Pr(\text{event})\} = \ln(p_0) + \ln(RR_1) + \ln(RR_2) + \ln(RR_3)$$

$$\ln\{\Pr(\text{event given the covariates})\} = \alpha + \sum_{i=1}^{p}(\beta_i \cdot x_i)$$

That is linear on **log-probability** scale

Other methods to analysis of binary response data Relative Risk models

$$\ln\{\Pr(\text{event given the covariates})\} = \alpha + \sum_{i=1}^{p}(\beta_i \cdot x_i)$$

Such a model **modelling the relative risk** can easily be fitted by many programs (not SPSS).

Logistic regression in STATA:

```
xi: logit obese age i.sex
```

or

```
xi: glm obese age i.sex, fam(bin) link(logit)
```

Relative risk model:

```
xi: glm obese age i.sex, fam(bin) link(log)
```

The `link` is **log** instead of **logit**

Other methods to analysis of binary response data Risk difference models

Logistic regression model focus on the **Odds Ratios**

This is the correct thing to do in **case-control** studies.

In **follow-up** studies **Risk Difference** is often the appropriate measure of association, (community effect).

I.e. a model like this might be more relevant:

$$\Pr(\text{event}) = p_0 + RD_1 + RD_2 + RD_3$$

$$\Pr(\text{event given the covariates}) = \alpha + \sum_{i=1}^{p}(\beta_i \cdot x_i)$$

That is linear on **probability** scale

Other methods to analysis of binary response data Risk difference models

$$\Pr(\text{event given the covariates}) = \alpha + \sum_{i=1}^{p}(\beta_i \cdot x_i)$$

Such a model **modelling the risk difference** can easily be fitted by many programs (not SPSS).

Logistic regression in STATA:

```
xi: logit obese age i.sex
```

or

```
xi: glm obese age i.sex, fam(bin) link(logit)
```

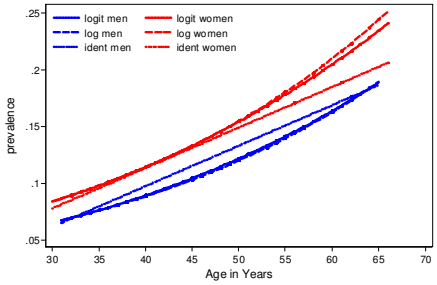
Risk difference model:

```
xi: glm obese age i.sex, fam(bin) link(id)
```

The `link` is **identity** instead of **logit**

Other methods to analysis of binary response data

Three different links for Obese "=" sex "+" age



Other methods to analysis of binary response data Problems

$$\Pr(\text{event}) = p_0 \times RR_1 \times RR_2 \times RR_3$$

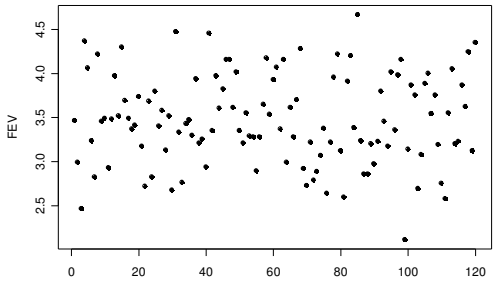
As the relative risk can be **larger** than one the product might be **larger than one** !

$$\Pr(\text{event}) = p_0 + RD_1 + RD_2 + RD_3$$

The sum might **negative** and be **larger than one** !

Clustered data / data with several random components

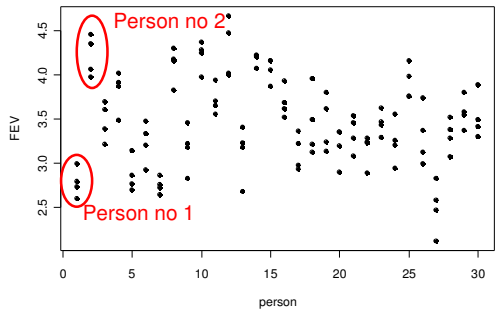
120 measurements of FEV:



Some variation in the data.

Clustered data / data with several random components

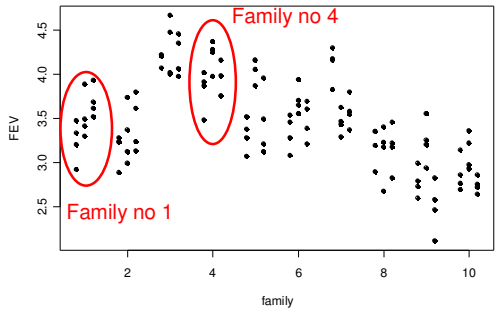
But it is on only **30** persons:



Some of the variation is due to **variation between persons** and some within person.

Clustered data / data with several random components

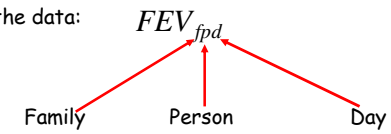
From **10** families:



Some of the variation between persons is due to **variation between families and some within family.**

Clustered data / data with several random components

Structure of the data:



Three sources of random variation:

Variation between families

Variation between persons (variation within family)

Variation between days (variation within person)

Clustered data / data with several random components

Factors of interest:

household **I**ncome	Constant within **family**
Urbanization	Constant within **family**
Age	Constant within **person**; varies within family
Sex	Constant within **person**; varies within family
Grass pollen	Constant within **day**; varies within person

A model:

$$FEV = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G$$
+random variation

Clustered data / data with several random components

$$FEV = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G$$
+random variation

If the **three** levels/sources of **random** variation **are not** taken into account :

- The **precision** of the β_I and β_Y are **highly overestimated**
- The **precision** of the β_A and β_Σ are **overestimated**
- The **estimates** of the β_I and β_Y will be **biased** if the not all families are represented by the **same number of persons** and each person is measured the **same number of times**.
- The **estimates** of the β_A and β_Σ will be **biased** if the not all persons are measured the **same number of times**.

Clustered data / data with several random components

$$FEV = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G + F_f + P_{fp} + E_{fpd}$$

variance

F_f	: Random family contribution	σ_F^2
P_{fp}	: Random person contribution	σ_P^2
E_{fpd}	: Random day contribution	σ_E^2

$$\text{var}(FEV_{fpd}) = \sigma_F^2 + \sigma_P^2 + \sigma_E^2$$

Variance components

Assumed to be normal distributed

Clustered data / data with several random components

Systematic part

$$FEV = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G + F_f + P_{fp} + E_{fpd}$$

Random part

$\beta_0, \beta_I, \beta_U, \beta_A, \beta_S$ and β_G Quantify the **systematic** variation

σ_F^2, σ_P^2 and σ_E^2 Quantify the **random** variation

This is a:

- **Variance component** model
- **Mixed** model (both systematic and random variation)
- **Multilevel** model

The theory behind and the understanding of such models is well **established!!!**

Clustered data / data with several random components
Dichotomous outcome

A different outcome:

$$H_{fpd} = \begin{cases} 1 & \text{if the person has hayfewer} \\ 0 & \text{else} \end{cases}$$

A statistical model:

Systematic part

$$\text{logit}(H_{fpd}=1) = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G + F_f + P_{fp} + \cancel{E_{fpd}}$$

Random part

This is not needed due to the binomial error

Clustered data / data with several random components
Dichotomous outcome

$$\text{logit}(H_{fpd}=1) = \beta_0 + \beta_I \cdot I + \beta_U \cdot U + \beta_A \cdot A + \beta_S \cdot S + \beta_G \cdot G + F_f + P_{fp}$$

That is, an ordinary logistic regression + **random components**.

- **A generalized linear mixed model**
- **A multilevel model for dichotomous outcome**

Comments 1:

- It is **important** to include the **relevant random** components in the model.
- 'Multilevel models' is **essential** in medical/epidemiological research.

Clustered data / data with several random components Dichotomous outcome

Comments 2:

- The theory and insight into the models for non-normal data are **not yet fully developed**.
- The main problem being that it is not known how to obtain **valid (unbiased) estimates**.
- Several software programs **falsely claim** to estimate the models. (SAS, STATA, SUDAAN, NLwin)
- The programs/algorithms are not able give 'the correct' estimates.

Advice:

At the moment, do not trust results based on multilevel models.

Wait and see, the statisticians **might** solve the problems.

Clustered data / data with one random components Dichotomous outcome

If the models only involves **one random components**, e.g. **variation between families** or between **GP's**.

then methods exists which can **adjust the standards errors**.

Remember that if the **data contains clusters,** then the precision of the estimates overestimated, that is the reported **standard errors is too small**.

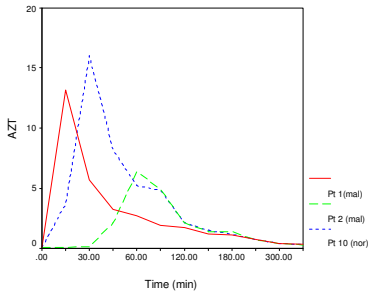
So called **robust methods** or **sandwich estimates** of the standard errors will (try) adjust for this problem.

Only a **few** programs have this option – STATA does!

Nonlinear regression models

Concentration in the blood of zidovudine (AZT) after administration of the drug.

One person with normal fat absorption and two with malabsorption.



Clearly non linear.

Nonlinear regression models

The is **no way** that the above data can be described by a linear regression.

Furthermore **pharmaco kinetic** theory specify a simple model for the **expected concentration** as a function of time:

$$\text{concentration}(t) = d\,\frac{k_A}{k_A - k_E}\left(\exp(-k_E \cdot t) - \exp(-k_A \cdot t)\right)$$

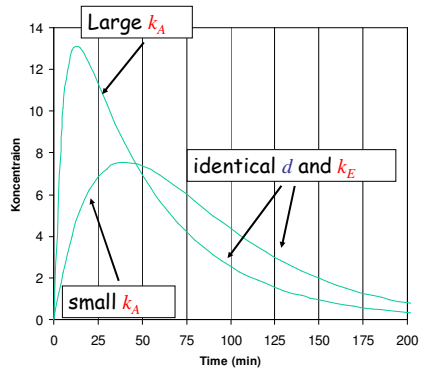
Where:

d : dose (per kg bodyweigth)

k_A : absorptionsrate

k_E : eliminationsrate

Nonlinear regression models



Nonlinear regression models

How do persons with malabsorption differ from normal in k_E and k_A ?

One type of analysis:

1. Fit this pharmaco-kinetic model to the data for each person.
2. Extract the estimates of k_E and k_A from each analysis.
3. Compare the distributions of k_E and k_A from the two types for persons.