Poisson and Logistic Regression

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Finnish Cancer Registry

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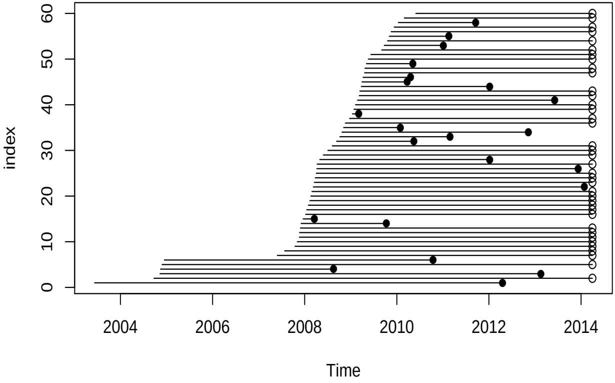
Points to be covered

- Incidence rates, rate ratios and rate differences from *follow-up studies* can be computed by fitting *Poisson regression models*.
- Odds ratios can be computed from binary data by fitting *Logistic regression models*.
- Odds-ratios can be estimated from case-control studies.
- Both models are special instances of *Generalized linear models*.
- There are various ways to do these tasks in R.

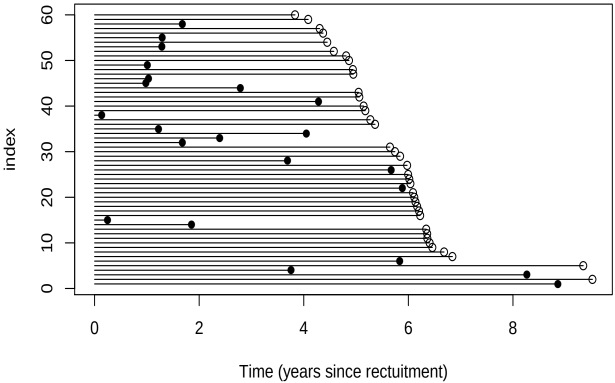
The Estonian Biobank cohort: survival among the elderly

Follow-up of 60 random individuals aged 75-103 at recruitment, until death (•) or censoring (o) in April 2014 (linkage with the Estonian Causes of Death Registry).



The Estonian Biobank cohort: survival among the elderly

Follow-up time for 60 random individuals aged 75-103 at recruitment (time-scale: time in study).



Events, dates and risk time

- Mortality as the outcome:

  `d`: indicator for **status** at exit:

  1: death observed

  0: censored alive

- Dates:

$$\texttt{doe} = \text{date of } \textbf{E}\text{ntry to follow-up},$$
$$\texttt{dox} = \text{date of e}\textbf{X}\text{it, end of follow-up.}$$

- Follow-up time (years) computed as:

$$\texttt{y} = \texttt{(dox - doe)/365.25}$$

Crude overall rate computed by hand and model

Total no. cases, person-years & rate (/1000 y):

```
> D <− sum( d ); Y <− sum(y) ; R <− D/(Y/1000)
>  round( c(D=D, Y=Y, R=R), 2)
    D        Y          R
  884.00 11678.24     75.70
```

Two R-implementations of the rate estimation with Poisson regression:

```
A model with  offset  term
> m1 <− glm( D ~ 1,
     family=poisson, offset=log(Y))

> coef(m1)
( Intercept )
  −2.581
```

```
A model with poisreg−family
> glm(cbind(D, Y) ~1,
      family=poisreg)

 Coefficients :
( Intercept )
       −2.581
```

Why do we get the same results?

Constant hazard — Poisson model

Let $Y \sim exp(\lambda)$, then $f(y;\lambda) = \lambda e^{-\lambda y} I(y > 0)$
Constant rate: $\lambda(y) = \frac{f(y;\lambda)}{S(y;\lambda)} = \lambda$
Observed data $\{(y_i, \delta_i); i = 1, ..., n\}$.
The likelihood $L(\lambda) = \prod_{i=1}^{n} \lambda^{\delta_i} e^{-\lambda y_i}$ and

$$log(L) = \sum_{i=1}^{n} [\delta_i log(\lambda) - \lambda y_i]$$

Solving the *score equations*: $\frac{\partial \log L(\lambda)}{\partial \lambda} = \sum \left[\frac{\delta_i}{\lambda} - y_i\right]$
$= \frac{D}{\lambda} - Y = 0$ and $D - \lambda Y = 0$

→ **maximum likelihood estimator** (MLE) of λ:

$$\widehat{\lambda} = \frac{D}{Y} = \frac{\text{number of cases}}{\text{total person-time}} = \text{ empirical rate!}$$

offset term — Poisson model

- Previous model without offset: Intercept 6.784=log(884)
- We should use an offset if we suspect that the underlying **population sizes (person-years) differ** for each of the observed counts – For example varying person-years by tratment group, sex,age,...
- We need a term in the model that "scales" the likelihood, but does not depend on model parameters (include a **term with reg. coef. fixed to 1**) – offset term is log(y)

$$log(\frac{\mu}{y}) = \beta_0 + \beta_1 x_1$$
$$log(\mu) = 1 \times log(y) + \beta_0 + \beta_1 x_1$$

Comparing rates: The Thorotrast Study

- Cohort of seriously ill patients in Denmark on whom angiography of brain was performed.
- Exposure: `contrast` medium used in angiography,
  1. `thor` = thorotrast (with ^{232}Th), used 1935-50
  2. `ctrl` = other medium (?), used 1946-63
- Outcome of interest: death

$$\begin{aligned}\texttt{doe} &= \text{date of } \textbf{E}\text{ntry to follow-up},\\ \texttt{dox} &= \text{date of e}\textbf{X}\text{it, end of follow-up.}\end{aligned}$$

- `data(thoro)` in the `Epi` package.

Comparing rates: thorotrast vs. control

Tabulating cases, person-years & rates by group

```
> stat.table( contrast,
+             list ( N = count(),
+                    D = sum(d),
+                    Y = sum(y),
+                 rate = ratio(d,y,1000) ) )
 ----------------------------------------------
 contrast        N       D        Y      rate
 ----------------------------------------------
  ctrl        1236  797.00 30517.56    26.12
  thor         807  748.00 19243.85    38.87
 ----------------------------------------------
```

Rate ratio, RR $= 38.89/26.12 = 1.49$,
Std. error of log-RR, SE $= \sqrt{1/748 + 1/797} = 0.051$,
Error factor, EF $= \exp(1.96 \times 0.051) = 1.105$,
95% confidence interval for RR:
$(1.49/1.105, 1.49 \times 1.105) = (1.35, 1.64)$.

Rate ratio estimation with Poisson regression

- Include `contrast` as the explanatory variable (factor).
- Insert person years in units that you want rates in

```
> m2 <- glm( d ~ contrast, offset=log(y/1000),
+                  family  = poisson )
> round( summary(m2)$coef, 4)[, 1:2]
```

```
               Estimate Std. Error
(Intercept)      3.2626     0.0354
contrast thor    0.3977     0.0509
```

- Rate ratio and CI?
  Call function `ci.exp()` in `Epi`

```
> round( ci.exp( m2 ), 3 )
```

```
              exp(Est.)   2.5%  97.5%
(Intercept)      26.116 24.364 27.994
contrast thor     1.488  1.347  1.644
```

Rates in groups with Poisson regression

- Include `contrast` as the explanatory variable (factor).
- Remove the intercept (−1)
- Insert person-years in units that you want rates in

```
> m3 <- glm( d ~ contrast - 1,
               offset=log(y/1000),
+              family = poisson )
> round( summary(m3)$coef, 4)[, 1:2]

             Estimate Std. Error
contrast ctrl  3.2626    0.0354
contrast thor  3.6602    0.0366

> round( ci.exp( m3 ), 3 )

             exp(Est.)  2.5% 97.5%
contrast ctrl   26.116 24.364 27.994
contrast thor   38.870 36.181 41.757
```

Rates in groups with Poisson regression

- You can have it all in one go:

```
> CM <- rbind( c(1,0), c(0,1), c(-1,1) )
> rownames(CM) <- c("Ctrl","Thoro","Th vs.Ct")
> colnames(CM) <- names( coef(m3) )
> CM
         contrast ctrl contrast thor
Ctrl                1            0
Thoro               0            1
Th vs. Ct          -1            1


> round( ci.exp( m3, ctr.mat=CM ),3 )


         exp(Est.)  2.5% 97.5%
Ctrl        26.116 24.364 27.994
Thoro       38.870 36.181 41.757
Th vs. Ct    1.488 1.347 1.644
```

Rate ratio estimation with Poisson regression

- Response may also be specified as individual *rates*: `d/y` `weights=` instead of `offset=` are needed.

```
> m4<-glm( d/(y/1000)~contrast, weights=y/1000,
+            family=poisson)
> round( ci.exp(m4), 3 )
```

```
             exp(Est.)  2.5% 97.5%
(Intercept)     26.116 24.365 27.994
contrast thor    1.488  1.347  1.644
```

Rate difference estimation with Poisson regression

- The approach with `d/y` enables additive rate models too:

```
> m5 <-glm(d/(y/1000) ~contrast,weights=y/1000,
+           family=poisson(link="identity") )
> round( ci.exp(m5,Exp=F), 3 )
```

```
              Estimate  2.5% 97.5%
(Intercept)     26.116 24.303 27.929
contrast thor  12.753 9.430 16.077
```

Rates difference

- As before you can have it all:

```
> m6 <- glm( d/(y/1000) ~ contrast -1,
+  family = poisson(link="identity"),
+  weights = y/1000)
> round(ci.exp(m6, ctr.mat=CM, Exp=F ), 3)

         Estimate  2.5% 97.5%
Ctrl       26.116 24.303 27.929
Thoro      38.870 36.084 41.655
Th vs. Ct  12.753 9.430 16.077

> round( ci.exp( m3, ctr.mat=CM), 3 )

         exp(Est.)  2.5% 97.5%
Ctrl        26.116 24.364 27.994
Thoro       38.870 36.181 41.757
Th vs. Ct    1.488  1.347  1.644
```

Binary data: Treatment success Y/N

85 diabetes-patients with foot-wounds:

- Dalterapin (Dal)
- Placebo (Pl)

Treatment/Placebo given to diabetes patients, the design is prospective and outcome is measured better(Y)/worse(N). Is the probability of outcome more than 15% – yes, then use the risk difference or risk ratio (RR)

	Treatment group	
	Dalterapin	Placebo
Better	29	20
Worse	14	22
Total	43	42

$$\hat{p}_{\mathrm{Dal}} = \frac{29}{43} = 67\% \qquad \hat{p}_{\mathrm{Pl}} = \frac{20}{42} = 47\%$$

The difference between the probabilities is the fraction of the patients that benefit from the treatment: $p_{\mathrm{Dal}} - p_{\mathrm{Pl}}$

```
> library(Epi)
> dlt <- rbind( c(29,14), c(20,22) )
> colnames( dlt ) <- c("Better","Worse")
> rownames( dlt ) <- c("Dal","Pl")
> kable(twoby2( dlt ),"latex")
```

```
2 by 2 table analysis :
     Better Worse     P(Better) 95% conf. interval
Dal      29    14        0.6744    0.5226   0.7967
Pl       20    22        0.4762    0.3316   0.6249

                                            95% conf. interval
                  Relative Risk: 1.4163      0.9694   2.0692
             Sample Odds Ratio: 2.2786       0.9456   5.4907
Conditional MLE Odds Ratio: 2.2560       0.8675   6.0405
         Probability  difference : 0.1982    −0.0110   0.3850

                      Exact P−value: 0.0808
              Asymptotic P−value: 0.0665
```

Logistic regression for binary data

For grouped binary data, the response is a two-column matrix with columns (successes,failures).

```
 trt  <- factor(c("Dal","Pl"))
 trt  <- relevel( trt , 2 )
b1 <- glm( dlt ~ trt,  family=binomial )
round(  ci.exp(  b1  ),  4  )


              exp(Est.)     2.5%  97.5%
(Intercept)      0.9091 0.4962 1.6657
trtDal           2.2786 0.9456 5.4907
```

- The default parameters in logistic regression are **odds** (the intercept: $20/22 = 0.9090$) and the **odds-ratio** ($(29/14)/(20/22) = 2.28$).
- This is **NOT** what you want, because odds ratio is biased estimate of the risk ratio.(recall if p>10% $\frac{p}{1-p} \not\approx p$)

Logistic regression for binary data - Risk ratio (Relative risk)

```
> library(Epi)
> library(xtable)
> dlt <- rbind( c(29,14), c(20,22) )
> diab<-expand.grid(dlt)
> colnames(diab)[1]<-"d"
> diab$out <- c("Better","Better","Worse","Worse")
> diab$trt <- as.factor(c("Dal","Pl","Dal","Pl"))
> diab$totals<-rep(rowSums(dlt),2)
> diab$trt<-relevel( diab$trt, 2 )
> print(xtable(diab,digits=c(0,0,0,0,0)),include.rownames = F)
```

d	out	trt	totals
29	Better	Dal	43
20	Better	Pl	42
14	Worse	Dal	43
22	Worse	Pl	42

Logistic regression for binary data - risk ratio

```
> library(Epi)
> library(xtable)
> b2 <- glm(d/totals˜trt,
+           weights=totals,
+           family=binomial(link="log"),
+           data=diab[c(1,2),])
> xtable(round( ci.exp( b2 ), digits=6 ))
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.48	0.35	0.65
trtDal	1.42	0.97	2.07

Diabetics with Dalterapin treatment are 1.4 times likely to get better than those treated with placebo

Case-control study: Food-poisoning outbreak

- An outbreak of acute gastrointestinal illness (AGI) occurred in a psychiatric hospital in Dublin in 1996.
- Out of all 423 patients and staff members, 65 were affected during 27 to 31 August, 1996.
- 65 cases and 62 randomly selected control subjects were interviewed.
- Exposure of interest: chocolate mousse cake.
- 47 cases and 5 controls reported having eaten the cake.

Ref: `http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=188` – here original numbers somewhat modified.

Outbreak: crude summary of data

- Target population information
  - N = 423, size of the whole study population
  - D = 65, no. of cases of AGI
  - B = 358, no. of non-cases
- Case-control data
  - C = 62, no. of controls, random sample from 358 non-cases
  - f = 62/358 = 0.173, sampling fraction of non-cases
  - D1 = 47 cases exposed to chocolate mousse
  - D0 = 18 unexposed cases
  - C1 = 5 controls exposed to chocolate mousse
  - C0 = 57 unexposed controls

Outbreak: results of analysis

Overall incidence proportion (IP) of AGI in the population

```
> D <- 65; N <- 423; IP <- D/N
> round(IP, 3)
[1] 0.154
```

Analysis of case-control data

```
> D1 <- 47; D0 <- D - D1;
> C <- 62 ; C1 <- 5; C0 <- C - C1
```

Case-control ratios by exposure (not as useful as the following!)

```
> round( c( D1/C1, D0/C0 ), 2)
[1] 9.40 0.32
```

Exposure odds in cases and controls

```
> round( c( D1/D0, C1/C0 ), 2)
[1] 2.61 0.09
```

Outbreak: results of analysis

Estimation of the incidence odds ratio (IOR) = exposure odds ratio

```
> IOR <- (D1/D0)/(C1/C0)
> SE.logIOR <- sqrt(1/D1 + 1/D0 + 1/C1 + 1/C0 )
> CI.IOR <- IOR * exp( c(-1,1)*1.96*SE.logIOR )
> round( c(IOR, SE.logIOR, CI.IOR ), 2)
```

```
[1] 29.77  0.54 10.28 86.21
```

Same with glm model

```
> count<-c(D1,D0,C1,C0)
> cc<-c(1,1,0,0)
> exposed<-c(1,0,1,0)
> mousse<-data.frame(cbind(cc,exposed,count))
> ci.exp(glm(cc~exposed,weights=count,family="binomial",data=mousse))
```

```
              exp(Est.)       2.5%      97.5%
(Intercept)  0.3157895  0.1858913  0.5364586
exposed     29.7666667 10.2778305 86.2102603
```

Logistic regression in case-control studies

- Model for disease occurrence in the target population:
$$\ln\left[\tfrac{p}{1-p}\right] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$
- Sampling fractions: P(inclusion in study | control) = s_{ctr}
P(inclusion in study | case) = s_{case}
- Model for observed case-control data:

$$\ln[\text{odds (case} \mid \text{incl.)]} = \ln\left[\frac{p}{1-p}\right] + \ln\left[\frac{s_{\text{cas}}}{s_{\text{ctr}}}\right]$$

$$= \left(\ln\left[\frac{s_{\text{cas}}}{s_{\text{ctr}}}\right] + \beta_0\right) + \beta_1 x_1 + \beta_2 x_2$$

Logistic regression in case-control studies

Analysis of $P(case|inclusion)$ — *i.e.* binary observations:

$$Y = \begin{cases} 1 & \sim \text{ case} \\ 0 & \sim \text{ control} \end{cases}$$

$$\ln[\text{odds (case } | \text{ incl.) }] = \left(\ln \left[\frac{s_{\text{cas}}}{s_{\text{ctr}}} \right] + \beta_0 \right) + \beta_1 x_1 + \beta_2 x_2$$

- Effect of covariates is estimated correctly.
- Intercept is meaningless

  depends on s_{cas} and s_{ctr} that are often unknown.

Conclusion: What did we learn?

- Poisson regression models.
- In Poisson models the response can be either:
  - case indicator `d` with `offset = log(y)`, or
  - rate `d/y` with `weights = y` or
  - case and person-years `c(d,y)` as response in glm with poisreg-family (Epi-package)
- Both may be fitted on either grouped data, or individual records.
- Binary outcome can be modeled with odds.
- Case-control studies:
  Odds-ratios can be computed by logistic regression models, but **Intercept** from model is **meaningless**.