Statistical Analysis in the Lexis Diagram: Age-Period-Cohort models

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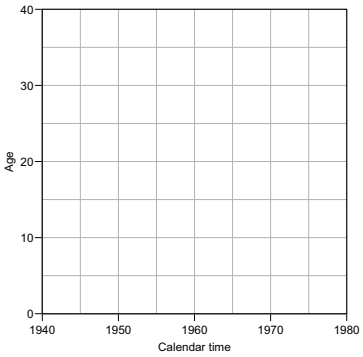
Lexis diagram [1]

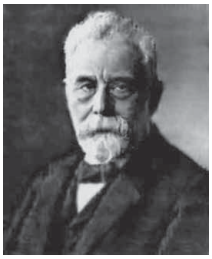


Disease registers record events.

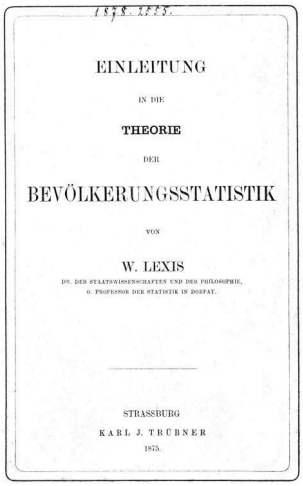
Official statistics collect population data.

[1] Named after the German statistician and economist **William Lexis** (1837–1914), who devised this diagram in the book "Einleitung in die Theorie der Bevölkerungsstatistik" (Karl J. Trübner, Strassburg, 1875).

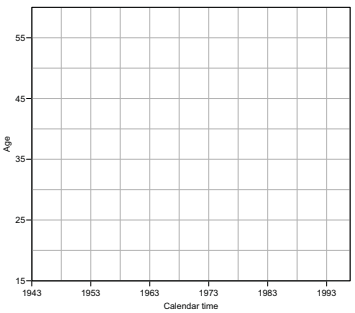
Wilhelm Lexis



Wilhelm Lexis (1837–1914)
German statistician and economist.


EINLEITUNG
IN DIE
THEORIE
DER
BEVÖLKERUNGSSTATISTIK
VON
W. LEXIS
STRASSBURG
KARL J. TRÜBNER

Lexis diagram



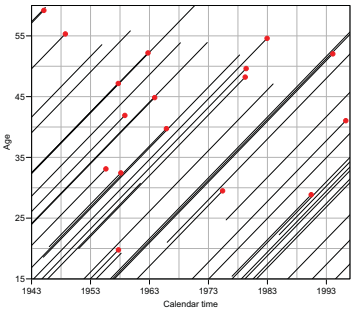
Registration of:

cases (D)

risk time, person-years (Y)

in subsets of the Lexis diagram.

Lexis diagram



Registration of:

cases (D)

risk time, person-years (Y)

in subsets of the Lexis diagram.

Rates available in each subset.

Register data

Classification of **cases** (D_{ap}) by age at diagnosis and date of diagnosis, and **population** (Y_{ap}) by age at risk and date at risk, in compartments of the Lexis diagram, e.g.:

	Seminoma cases				Person-years			
Age	1943	1948	1953	1958	1943	1948	1953	1958
15	2	3	4	1	773812	744217	794123	972853
20	7	7	17	8	813022	744706	721810	770859
25	28	23	26	35	790501	781827	722968	698612
30	28	43	49	51	799293	774542	769298	711596
35	36	42	39	44	769356	782893	760213	760452
40	24	32	46	53	694073	754322	768471	749912

Reshape data to analysis form:

	A	P	D	Y
1	15	1943	2	773812
2	20	1943	7	813022
3	25	1943	28	790501
4	30	1943	28	799293
5	35	1943	36	769356
6	40	1943	24	694073
1	15	1948	3	744217
2	20	1948	7	744706
3	25	1948	23	781827
4	30	1948	43	774542
5	35	1948	42	782893
6	40	1948	32	754322
1	15	1953	4	794123
2	20	1953	17	721810
3	25	1953	26	722968
4	30	1953	49	769298
5	35	1953	39	760213
6	40	1953	46	768471
1	15	1958	1	972853
2	20	1958	8	770859
3	25	1958	35	698612

Tabulated data

Once data are in tabular form, models are restricted:

- Rates must be assumed constant in each cell of the table / subset of the Lexis diagram.
- With large cells it is customary to put a separate parameter on each level of the classifying factors.
- Output from the model will be rates and rate-ratios.
- Since we use multiplicative Poisson, usually the log rates and the log-RRs are reported

Register data - rates

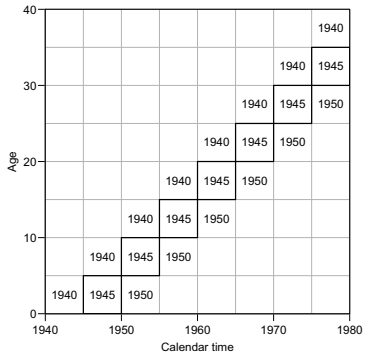
Rates in "tiles" of the Lexis diagram:

$$\lambda(a,p) = D_{ap}/Y_{ap}$$

Descriptive epidemiology based on disease registers:
How do the rates vary across by age and time?

- Age-specific rates for a given period.
- Age-standardized rates as a function of calendar time.
  (Weighted averages of the age-specific rates).

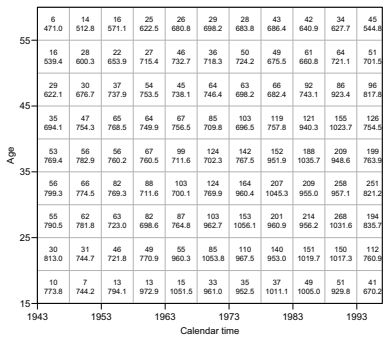
Synthetic cohorts



Events and risk time in cells along the diagonals are among persons with roughly same date of birth.

Successively overlapping 10-year periods.

Lexis diagram: data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Data matrix: Testis cancer cases

Number of cases

	Date of diagnosis $(year - 1900)$							
Age	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87
15–19	7	13	13	15	33	35	37	49
20–24	31	46	49	55	85	110	140	151
25–29	62	63	82	87	103	153	201	214
30–34	66	82	88	103	124	164	207	209
35–39	56	56	67	99	124	142	152	188
40–44	47	65	64	67	85	103	119	121
45–49	30	37	54	45	64	63	66	92
50–54	28	22	27	46	36	50	49	61
55–59	14	16	25	26	29	28	43	42

Data matrix: Male risk time

1000 person-years

	Date of diagnosis $(year - 1900)$							
Age	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87
15–19	744.2	794.1	972.9	1051.5	961.0	952.5	1011.1	1005.0
20–24	744.7	721.8	770.9	960.3	1053.8	967.5	953.0	1019.7
25–29	781.8	723.0	698.6	764.8	962.7	1056.1	960.9	956.2
30–34	774.5	769.3	711.6	700.1	769.9	960.4	1045.3	955.0
35–39	782.9	760.2	760.5	711.6	702.3	767.5	951.9	1035.7
40–44	754.3	768.5	749.9	756.5	709.8	696.5	757.8	940.3
45–49	676.7	737.9	753.5	738.1	746.4	698.2	682.4	743.1
50–54	600.3	653.9	715.4	732.7	718.3	724.2	675.5	660.8
55–59	512.8	571.1	622.5	680.8	698.2	683.8	686.4	640.9

Data matrix: Empirical rates

Rate per 1000,000 person-years

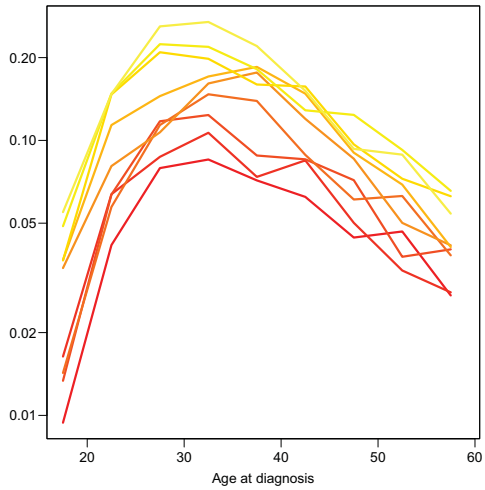
	Date of diagnosis $(year - 1900)$							
Age	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87
15–19	9.4	16.4	13.4	14.3	34.3	36.7	36.6	48.8
20–24	41.6	63.7	63.6	57.3	80.7	113.7	146.9	148.1
25–29	79.3	87.1	117.4	113.8	107.0	144.9	209.2	223.8
30–34	85.2	106.6	123.7	147.1	161.1	170.8	198.0	218.8
35–39	71.5	73.7	88.1	139.1	176.6	185.0	159.7	181.5
40–44	62.3	84.6	85.3	88.6	119.8	147.9	157.0	128.7
45–49	44.3	50.1	71.7	61.0	85.7	90.2	96.7	123.8
50–54	46.6	33.6	37.7	62.8	50.1	69.0	72.5	92.3
55–59	27.3	28.0	40.2	38.2	41.5	40.9	62.6	65.5

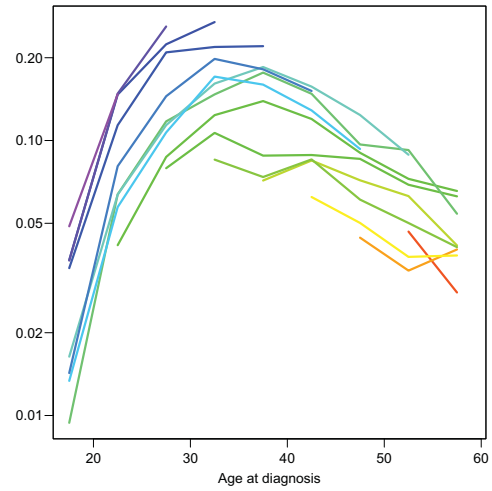
The classical plots

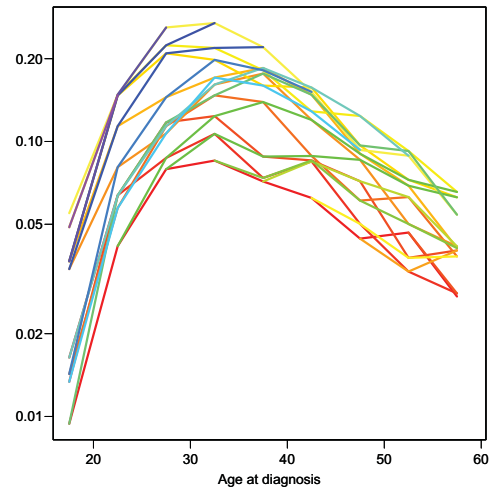
Given a table of rates classified by age and period, we can do 4 "classical" plots:

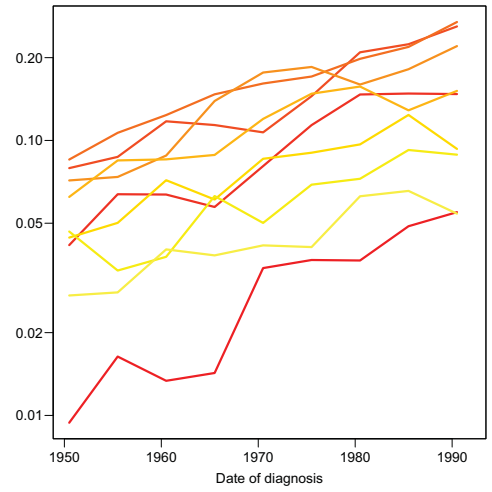
- Rates versus age at diagnosis (period):
  — rates in the same period connected.
- Rates versus age at diagnosis:
  — rates in the same birth-cohort connected.
- Rates versus date of diagnosis:
  — rates in the same ageclass connected.
- Rates versus date of date of birth:
  — rates in the same ageclass connected.

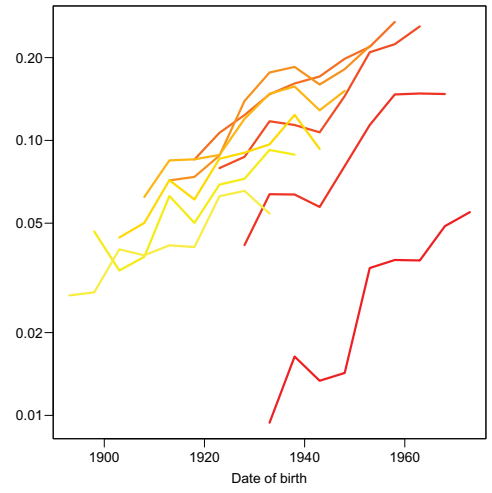
These plots can be produced by the R-function `rateplot`.











Age-period model

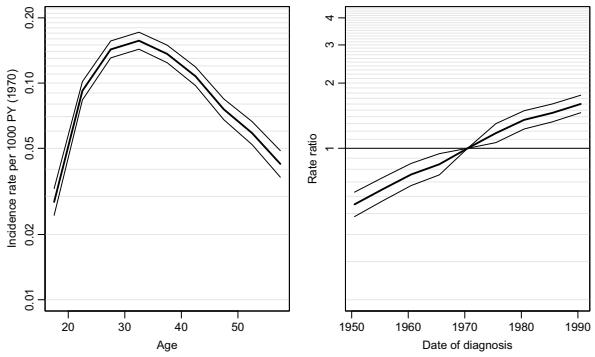
Rates are proportional between periods:

$$\lambda(a,p) = a_a \times b_p \qquad \text{or} \qquad \log[\lambda(a,p)] = \alpha_a + \beta_p$$

Choose p_0 as reference period, where $\beta_{p_0} = 0$

$$\log[\lambda(a,p_0)] = \alpha_a + \beta_{p_0} = \alpha_a$$

Estimates with confidence intervals



Age-cohort model

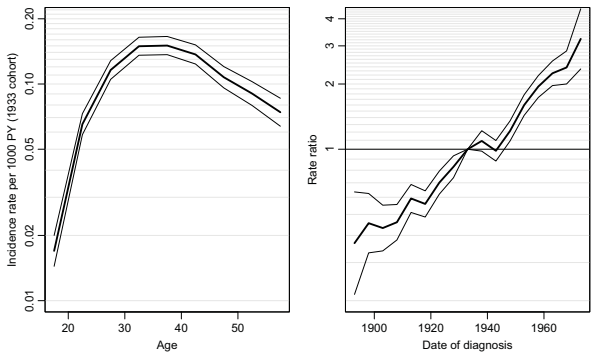
Rates are proportional between cohorts:

$$\lambda(a,c) = a_a \times c_c \qquad \text{or} \qquad \log[\lambda(a,p)] = \alpha_a + \gamma_c$$

Choose c_0 as reference cohort, where $\gamma_{c_0} = 0$

$$\log[\lambda(a,c_0)] = \alpha_a + \gamma_{c_0} = \alpha_a$$

Estimates with confidence intervals



Linear effect of period:

$$\log[\lambda(a,p)] = \alpha_a + \beta_p = \alpha_a + \beta(p - p_0)$$

that is, $\beta_p = \beta(p - p_0)$.

Linear effect of cohort:

$$\log[\lambda(a,p)] = \tilde{\alpha}_a + \gamma_c = \tilde{\alpha}_a + \gamma(c - c_0)$$

that is, $\gamma_c = \gamma(c - c_0)$

Age and linear effect of period:

```
> apd <- glm( D ~ factor( A ) - 1 + I(P-1970.5) +
+             offset( log( Y ) ),
+             family=poisson )
> summary( apd )

Call:
glm(formula = D ~ factor(A) - 1 + I(P - 1970.5) + offset(log(Y))

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-2.97593  -0.77091   0.02809   0.95914   2.93076

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
factor(A)17.5 -3.58065    0.06306  -56.79   <2e-16
...
factor(A)57.5 -3.17579    0.06256  -50.77   <2e-16
I(P - 1970.5)  0.02653    0.00100   26.52   <2e-16

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 89358.53  on 81  degrees of freedom
Residual deviance:   126.07  on 71  degrees of freedom
```


Age and linear effect of cohort:

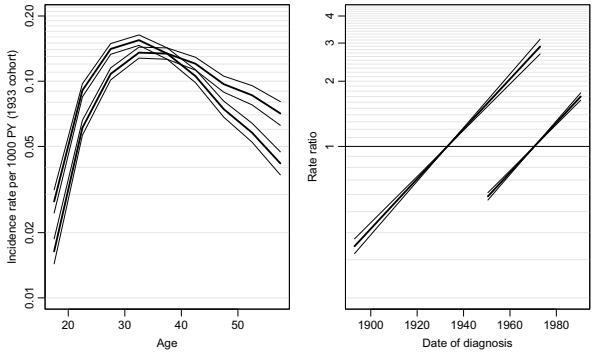
```
> acd <- glm( D ~ factor( A ) - 1 + I(C-1933) +
+             offset( log( Y ) ),
+             family=poisson )
> summary( acd )

Call:
glm(formula = D ~ factor(A) - 1 + I(C - 1933) + offset(log(Y)),

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-2.97593  -0.77091   0.02809   0.95914   2.93076

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
factor(A)17.5 -4.11117    0.06760  -60.82   <2e-16
...
factor(A)57.5 -2.64527    0.06423  -41.19   <2e-16
I(C - 1933)    0.02653    0.00100   26.52   <2e-16

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 89358.53  on 81  degrees of freedom
Residual deviance:   126.07  on 71  degrees of freedom
```


What goes on?

$$\begin{aligned}\alpha_a + \beta(p - p_0) &= \alpha_a + \beta\big(a + c - (a_0 + c_0)\big) \\ &= \underbrace{\alpha_a + \beta(a - a_0)}_{\text{cohort age-effect}} + \beta(c - c_0)\end{aligned}$$

The two models are the same.
The **parametrization** is different.

The age-curve refers either
- to a period (cross-sectional rates) or
- to a cohort (longitudinal rates).



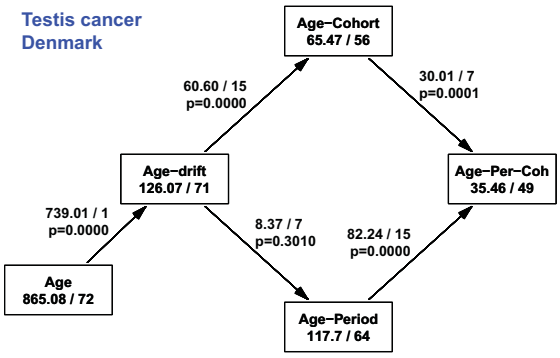
Which age-curve is period and which is cohort?

The age-period-cohort model

$$\log[\lambda(a,p)] = \alpha_a + \beta_p + \gamma_c$$

- Three effects:
  - Age (at diagnosis)
  - Period (of diagnosis)
  - Cohort (of birth)
- Modelled on the same *scale*.
- No assumptions about the *shape* of effects.

Relationship of models



Smooth functions

$$\log[\lambda(a,p)] = f(a) + g(p) + h(c)$$

Possible choices for parametric functions describing the effect of the three continuous variables:

- Polynomials / fractional polynomials.
- Linear / quadratic / cubic splines.
- Natural splines.

All of these contain the linear effect as special case,. . .

The identifiability problem still exists:

$$c = p - a \quad \Leftrightarrow \quad p - a - c = 0$$

$$\begin{aligned}
\lambda_{ap} &= f(a) + g(p) + h(c) \\
&= f(a) + g(p) + h(c) + \gamma(p - a - c) \\
&= f(a) - \mu_a - \gamma a + \\
&\quad g(p) + \mu_a + \mu_c + \gamma p + \\
&\quad h(c) - \mu_c - \gamma c
\end{aligned}$$

A decision on parametrization is needed.
It must be **external to the model**.

Parametrization of effects

There are still three "free" parameters:

$$\begin{aligned}
\check{f}(a) &= f(a) - \mu_a - \gamma a \\
\check{g}(p) &= g(p) + \mu_a + \mu_c + \gamma p \\
\check{h}(c) &= h(c) - \mu_c - \gamma c
\end{aligned}$$

Choose μ_a, μ_c and γ according to some criterion for the functions.

Parametrization principle

1. The age-function should be interpretable as log age-specific rates in cohort c_0 after adjustment for the period effect.
2. The cohort function is 0 at a reference cohort c_0, interpretable as log-RR relative to cohort c_0.
3. The period function is 0 on average with 0 slope, interpretable as log-RR relative to the age-cohort prediction. (residual log-RR).

Longitudinal or cohort age-effects.

Biologically interpretable — what happens during the lifespan of a cohort?

Implementation:

1. Obtain any set of parameters $f(a)$, $g(p)$, $h(c)$.
2. Extract the trend from the period effect:

$$\tilde{g}(p) = \hat{g}(p) - (\mu + \beta p)$$

3. Use the functions:

$$\begin{aligned}
\tilde{f}(a) &= \hat{f}(a) + \mu + \beta a + \hat{h}(c_0) + \beta c_0 \\
\tilde{g}(p) &= \hat{g}(p) - \mu - \beta p \\
\tilde{h}(c) &= \hat{h}(c) + \beta c - \hat{h}(c_0) - \beta c_0
\end{aligned}$$

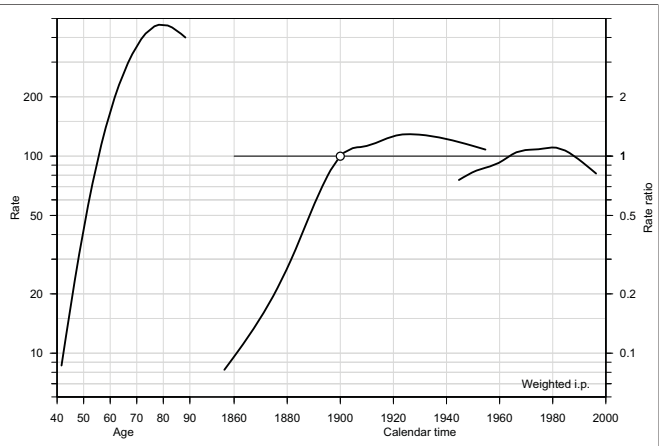
These functions fulfill the criteria.

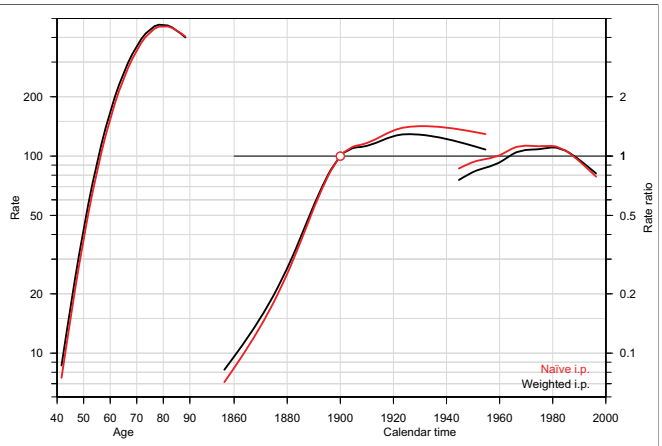
How to?

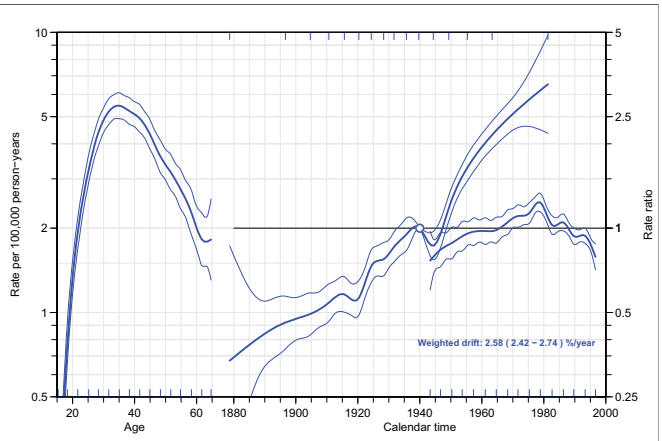
Implemented in `apc.fit`:

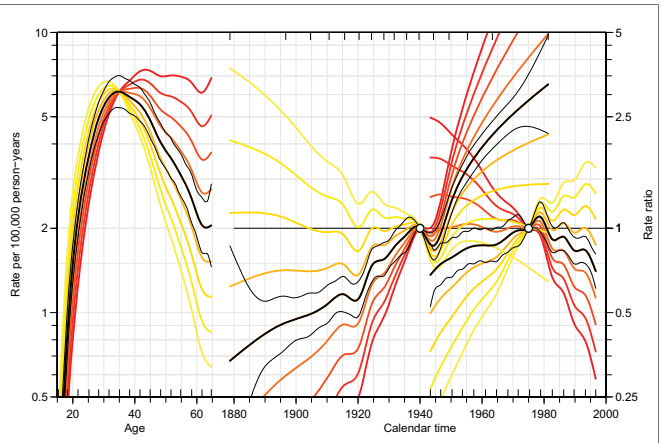
```
m1 <- apc.fit( A=lungDK$Ax,
               P=lungDK$Px,
               D=lungDK$D,
               Y=lungDK$Y/10^5,
           ref.c=1900 )
apc.plot( m1 )
```

Consult the help page for details.







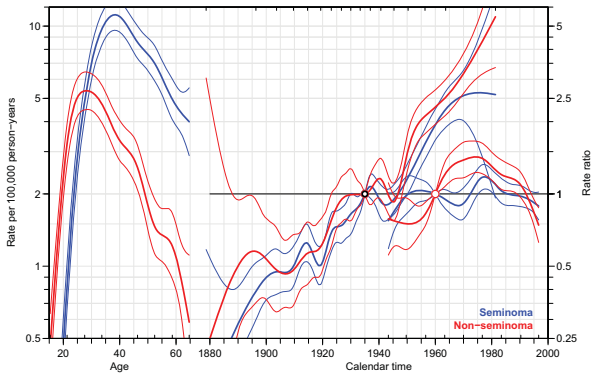


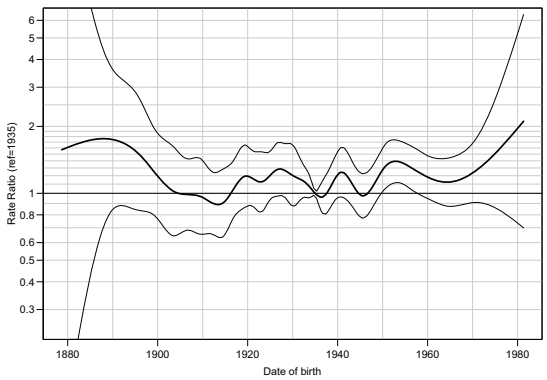
Two sets of data

Example: Testis cancer in Denmark, Seminoma and non-Seminoma cases.

```
> stat.table( list( Histology=hist ),
+             list( D=sum(d), Y=sum(y/10^6) ),
+             margins = TRUE )
 ----------------------------
 Histology         D       Y
 ----------------------------
 1           4708.00  127.53
 2           3632.00  127.53
 3            466.00  127.53

 Total       8806.00  382.58
 ----------------------------
```

First step is separate analyses for each subtype.





Conclusions

- Categorization is a bad thing to do:
  - for data it's throwing away data
  - for modelling it's ignoring data
  - . . . or making silly assumptions
- **A**ge, **P**eriod and **C**ohort are **continuous** variables and should be treated as such:
- we want to see the continuous effct of these.
- Constraints needed **externally**,
- . . . just like it is needed to use a reference group if e.g. different occupational groups are compared.

Conclusions

- There is no solution to the identifiability problem,
- . . . only ways to cope with it.

Thanks for you attention.