Methodological challenges in research on consequences of sickness absence and disability pension?

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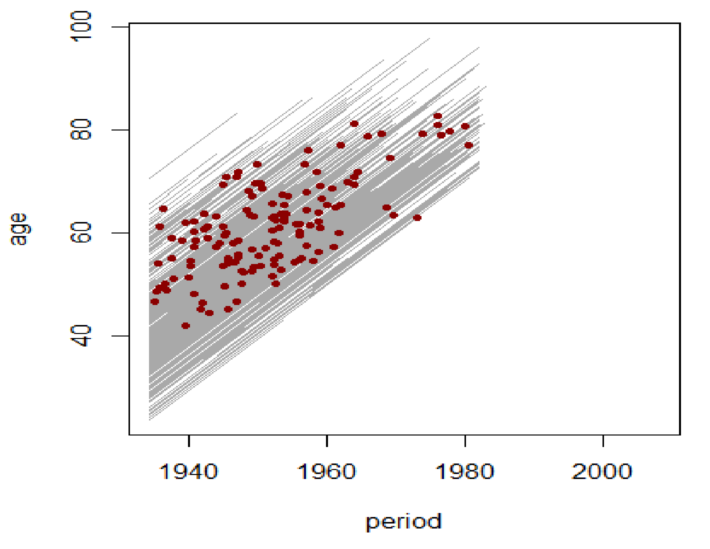
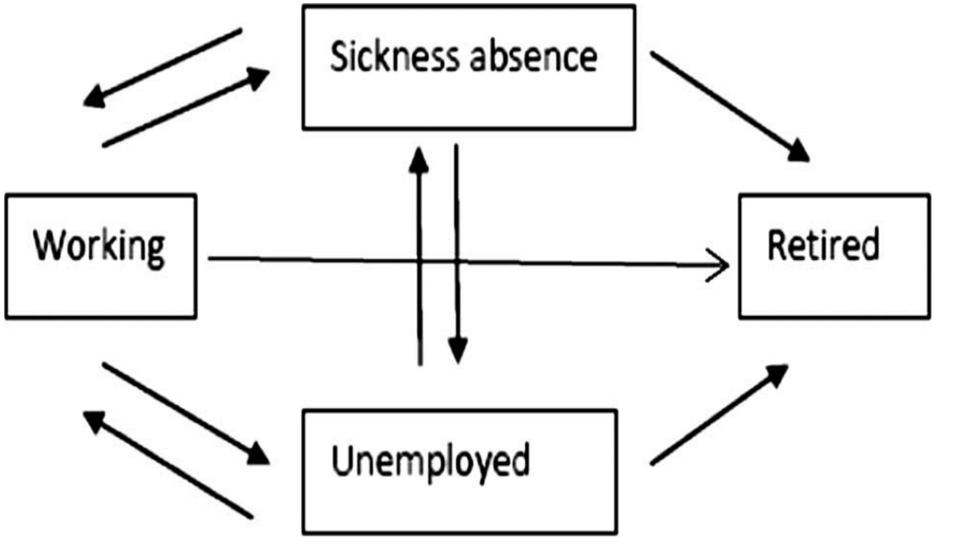
Two methodological approaches

Lexis diagrams and

Poisson regression



Multi state modeling



Poisson regression

- The Cox proportional hazards model use <u>only one time scale</u>
- Alternative is to use Poisson regression with a piecewise-constant hazard
- Typically 5-years timebands of age and calendar year are used.

Poisson regression

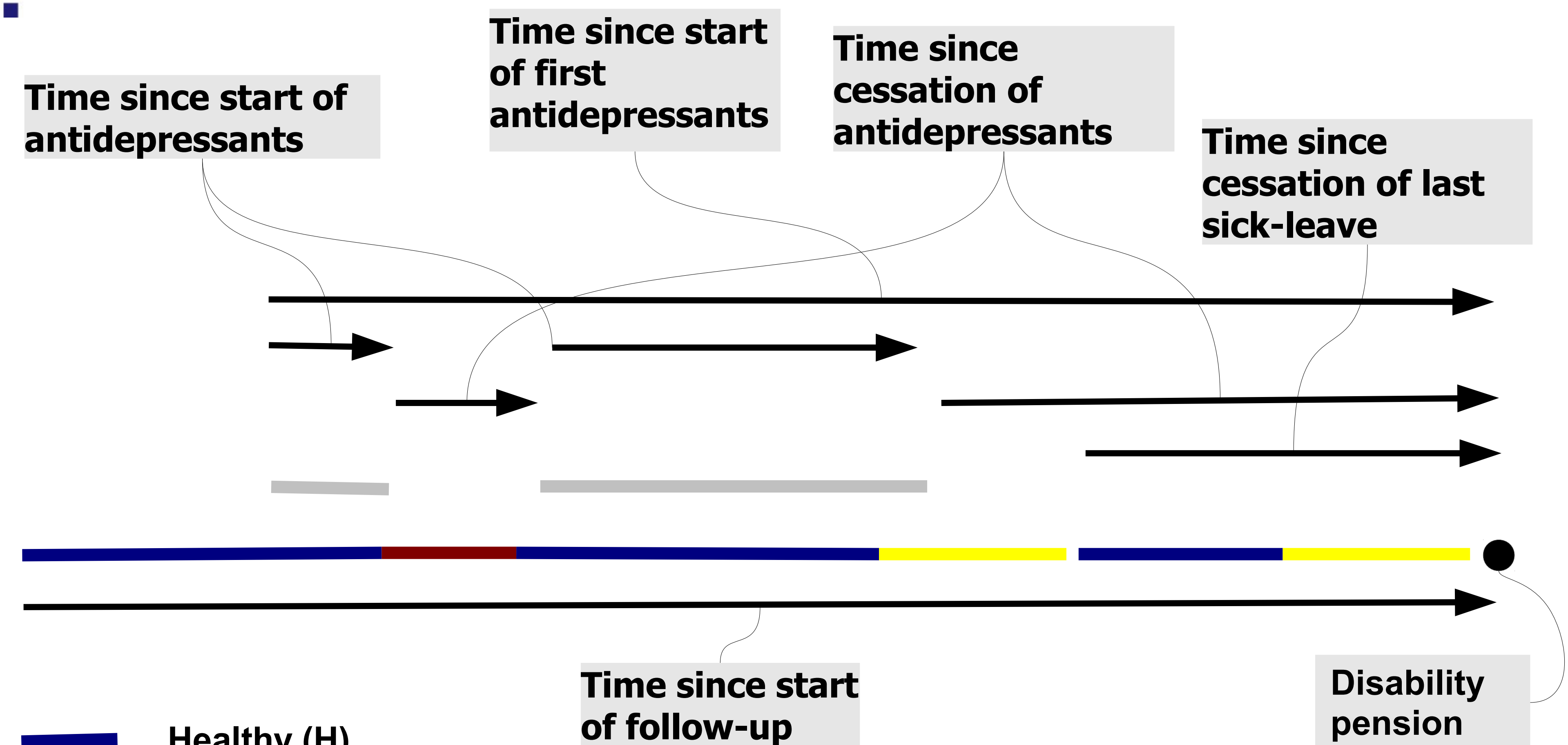
- Quite sophisticated analysis could be carried out by Poisson regression
- Follow-up time could be split by event in interest e.g.:
  - E.g. by first prescrition of certain drug
  - first long sickness leave
  - first hospitalization
- Times could be modeled using splines that provides good tools for data-analysis

Sick-leave data time scales

- Time since start of follow-up
- Time since start of antidepressants
- Time since cessation of antidepressants
- Time since cessation of last sick-leave
- Age
- Calendar time

Lexis and multiple time scales
Two sample individuals

Time-scales

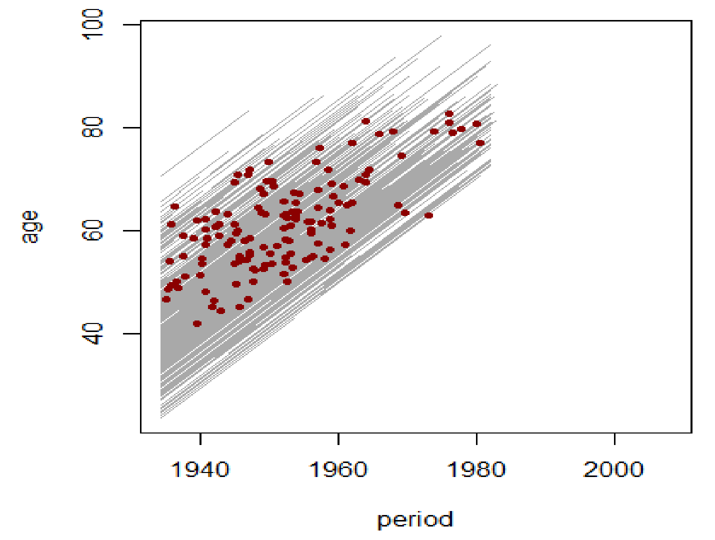


- Healthy (H)
- Sickness absence
- Mental disorder (hospitalisation)
- Antidepressant medication (AD)

<u>Other time scales:</u>

Age, Calendar time, Time since stop of hospitalization

Lexis diagrams



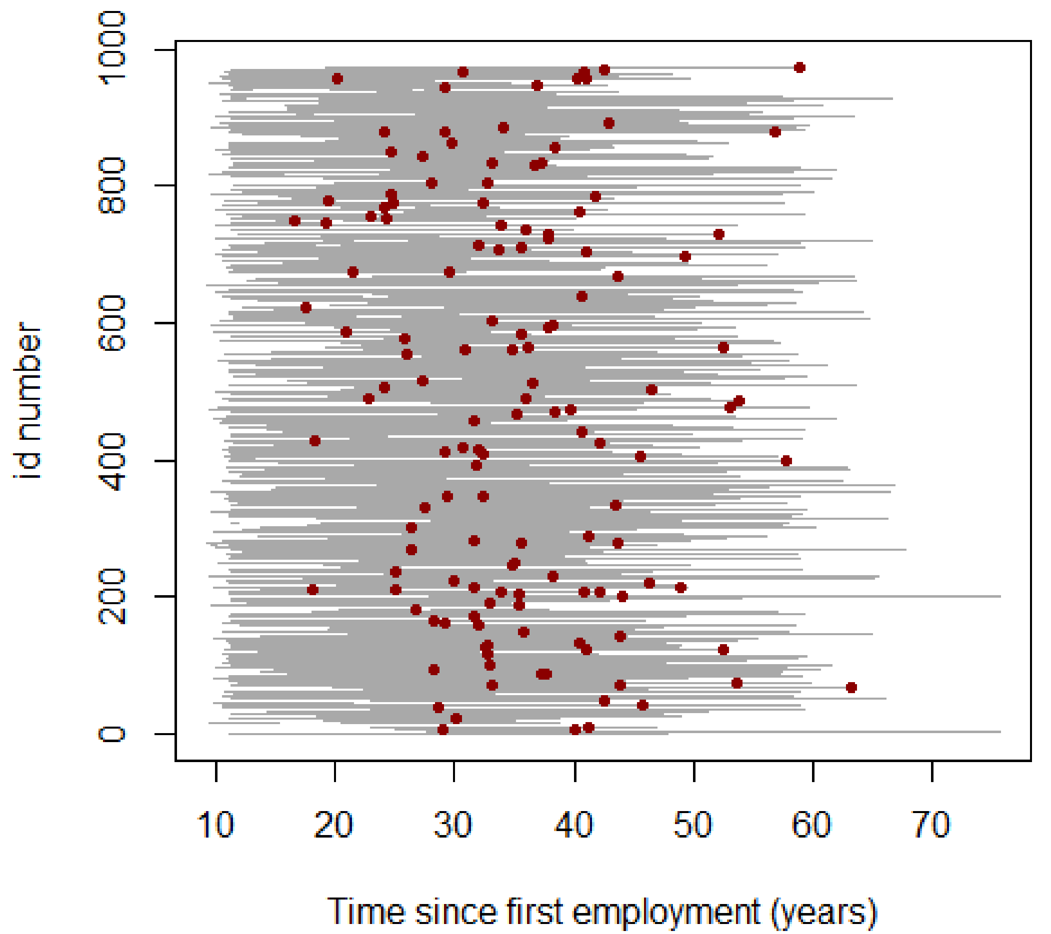
- Examples from :
  - Carstensen B, Plummer M. Using Lexis Objects for Multi-State Models in R. Journal of Statistical Software 2011;38:1–18.
  - Carstensen B. Age–period–cohort models for the Lexis diagram. Statistics in Medicine 2007;26:3018–45.
  - Plummer M, Carstensen B. Lexis: An R Class for Epidemiological Studies with Long-Term Follow-Up. Journal of Statistical Software 2011;38:1–12.
- Example data: The data concern a cohort of nickel smelting workers in South Wales and are taken from Breslow and Day, Volume 2. For comparison purposes, England and Wales mortality rates (per 1,000,000 per annum) from lung cancer (ICDs 162 and 163), nasal cancer (ICD 160), and all causes, by age group and calendar period, are supplied in the dataset ewrates.

Nickel data

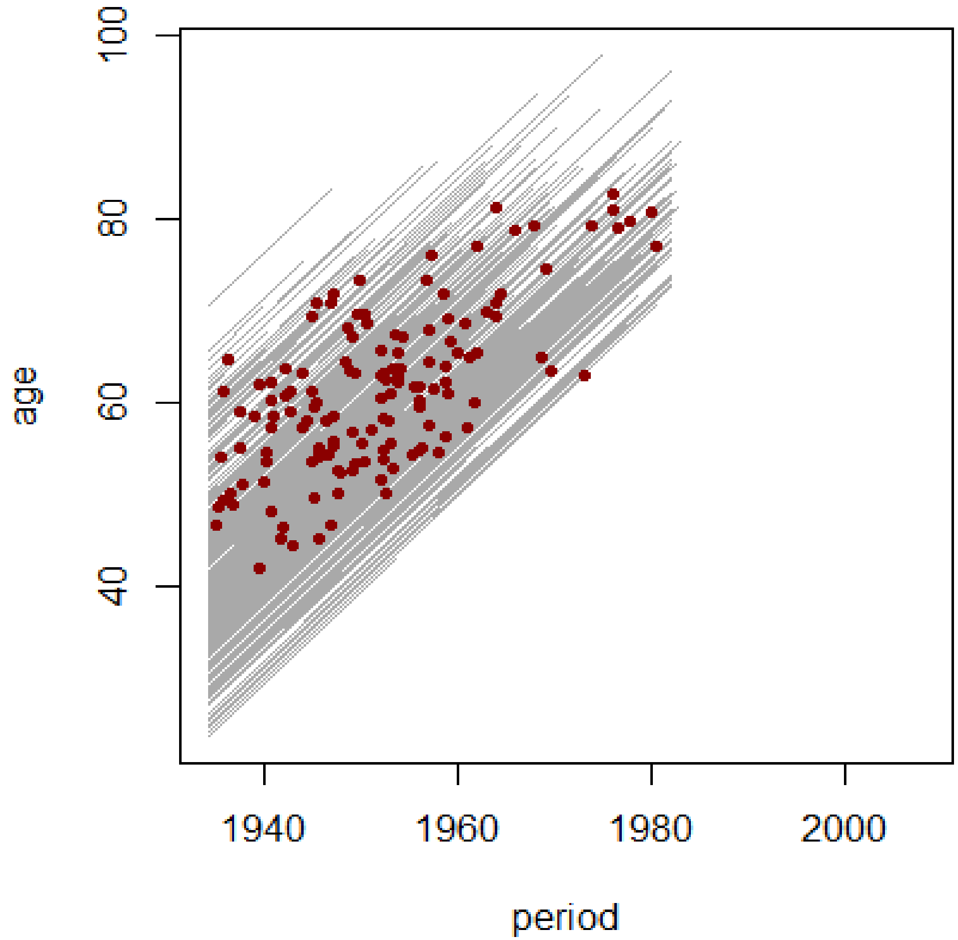
- Example data

```
> head(nickel)
  id icd exposure      dob  age1st   agein  ageout
1  3   0        5 1889.019 17.4808 45.2273 92.9808
2  4 162        5 1885.978 23.1864 48.2684 63.2712
3  6 163       10 1881.255 25.2452 52.9917 54.1644
4  8 527        9 1886.340 24.7206 47.9067 69.6794
5  9 150        0 1879.500 29.9575 54.7465 76.8442
6 10 163        2 1889.915 21.2877 44.3314 62.5413
>
```

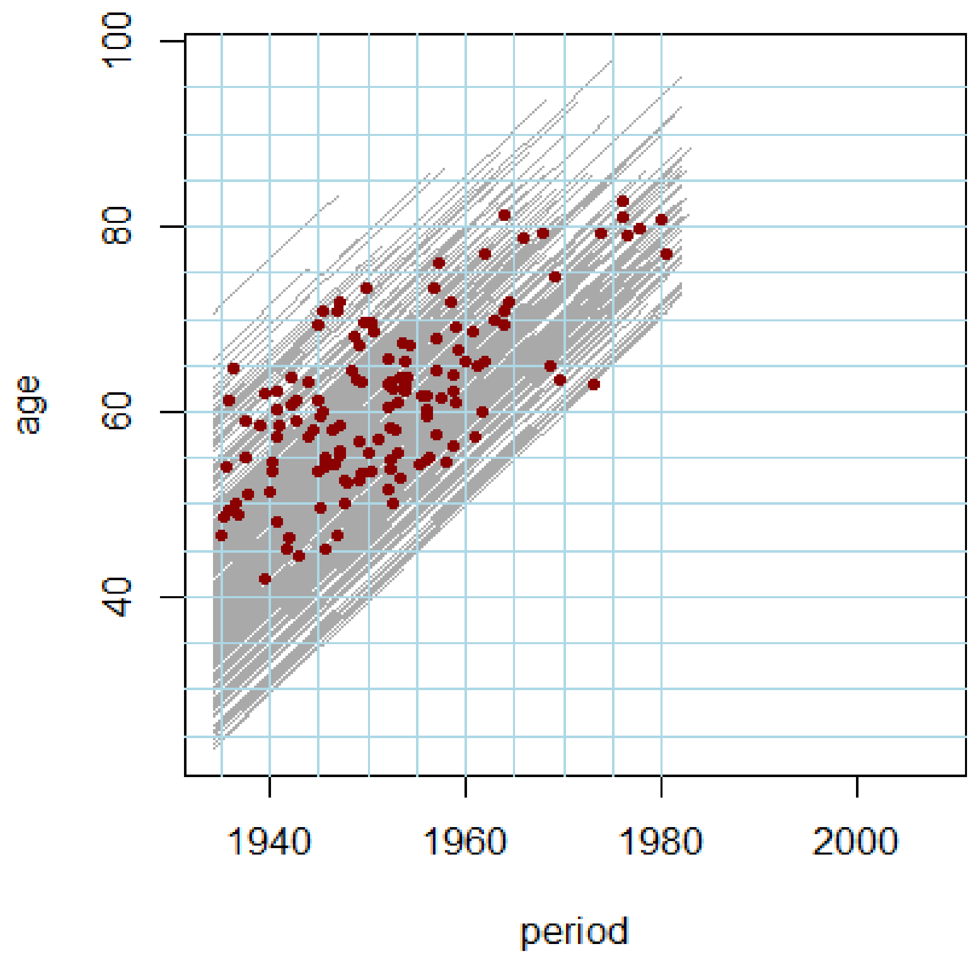
Lexis, one time scale



Lexis, two time scales



Lexis, two time scales, 5 yrs



Modeling data (1)

- Variables for three time scale, viz. period, age and time since first exposure

```
> subset(nicS2,id==4,select = c("case","period","age",
"tfe", "lex.dur"))

    case   period     age     tfe lex.dur
7  FALSE 1934.246 48.2684 25.0820  1.7316
8  FALSE 1935.978 50.0000 26.8136  3.1864
9  FALSE 1939.164 53.1864 30.0000  6.8136
10  TRUE 1945.978 60.0000 36.8136  3.2712
```

Modeling data (2)

```
library( Hmisc )
library( rms )
library(Epi)
# Model with age and time since first exposure
# NOTE!
# function "rcs" applies restricted cubic spline with
# user specified knots

tmp.m1.2<-glm(case ~
      rcs(age,parms=c(30,50,70)) +
      rcs(tfe,parms=c(10,20,30,40)) +
      offset(log(pyar)),
      family = poisson(),
      subset = (age >= 40), data = nicS2)
```

Modeling data (3)

```
> (tmp.m1.2)
Call:  glm(formula = case ~ rcs(age, parms = c(30, 50, 70)) + rcs(tfe,
    parms = c(10, 20, 30, 40)) + offset(log(pyar)), family = poisson(),
    data = nicS2, subset = (age >= 40))

Coefficients:
                                (Intercept)
                                  -13.23426
      rcs(age, parms = c(30, 50, 70))age
                                    0.13467
     rcs(age, parms = c(30, 50, 70))age'
                                   -0.09365
  rcs(tfe, parms = c(10, 20, 30, 40))tfe
                                    0.11148
 rcs(tfe, parms = c(10, 20, 30, 40))tfe'
                                   -0.10678
rcs(tfe, parms = c(10, 20, 30, 40))tfe''
                                    0.08234

Degrees of Freedom: 2757 Total (i.e. Null);  2752 Residual
Null Deviance:     999.4
Residual Deviance: 968.7  AIC: 1255
```

Interpretation of spline parameters is difficult.

->
Present results as graphs

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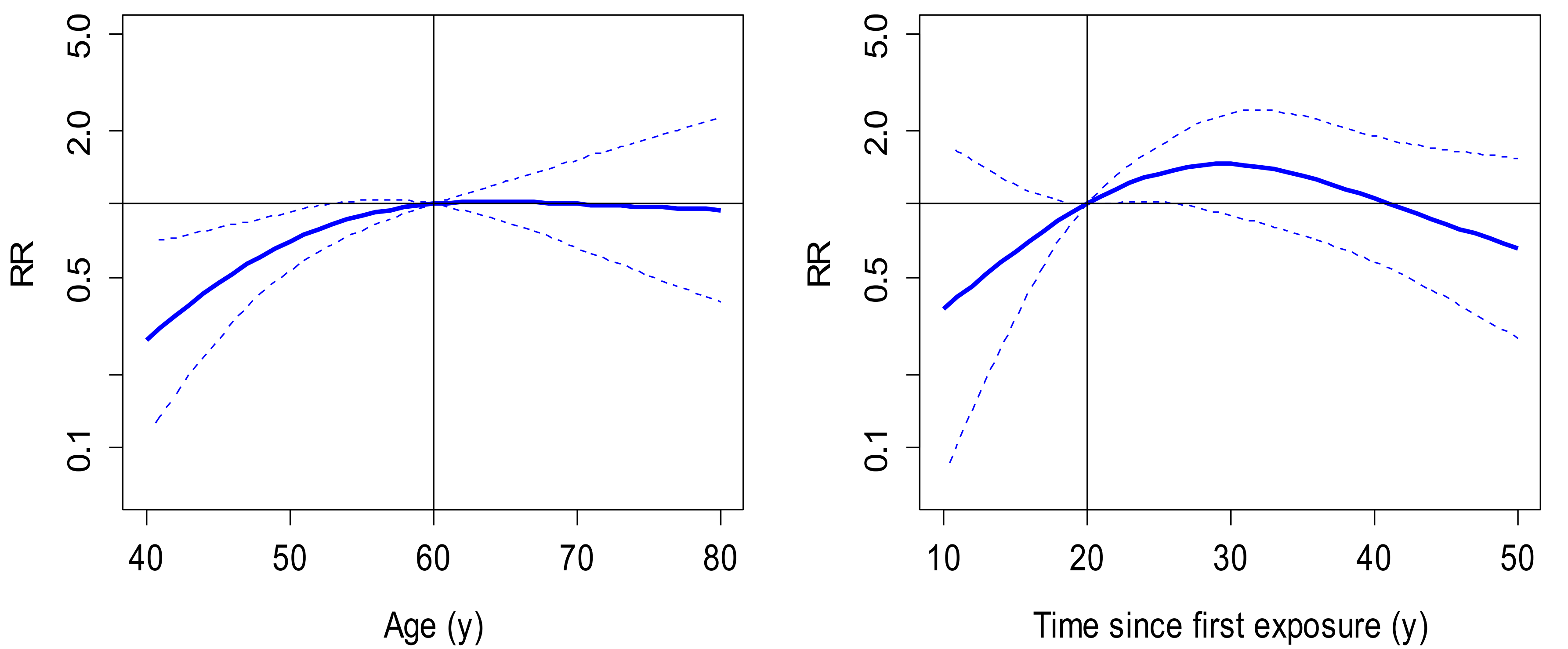
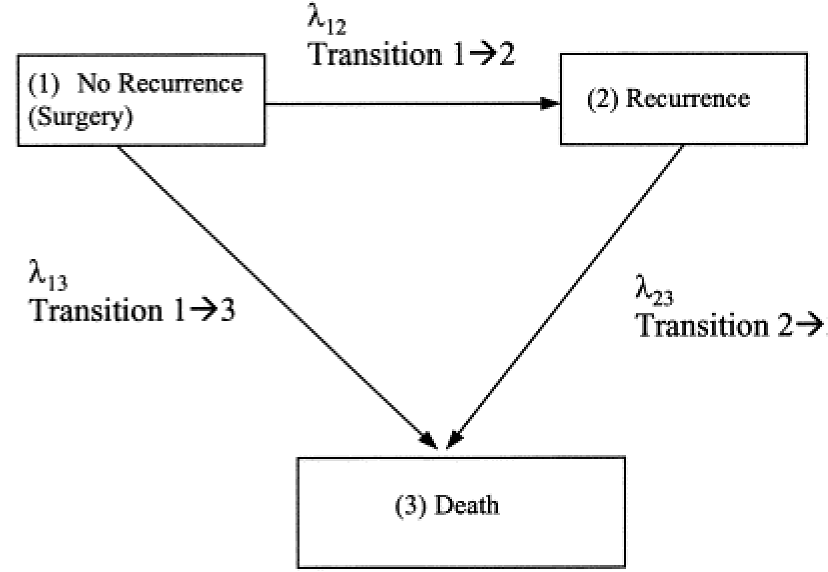
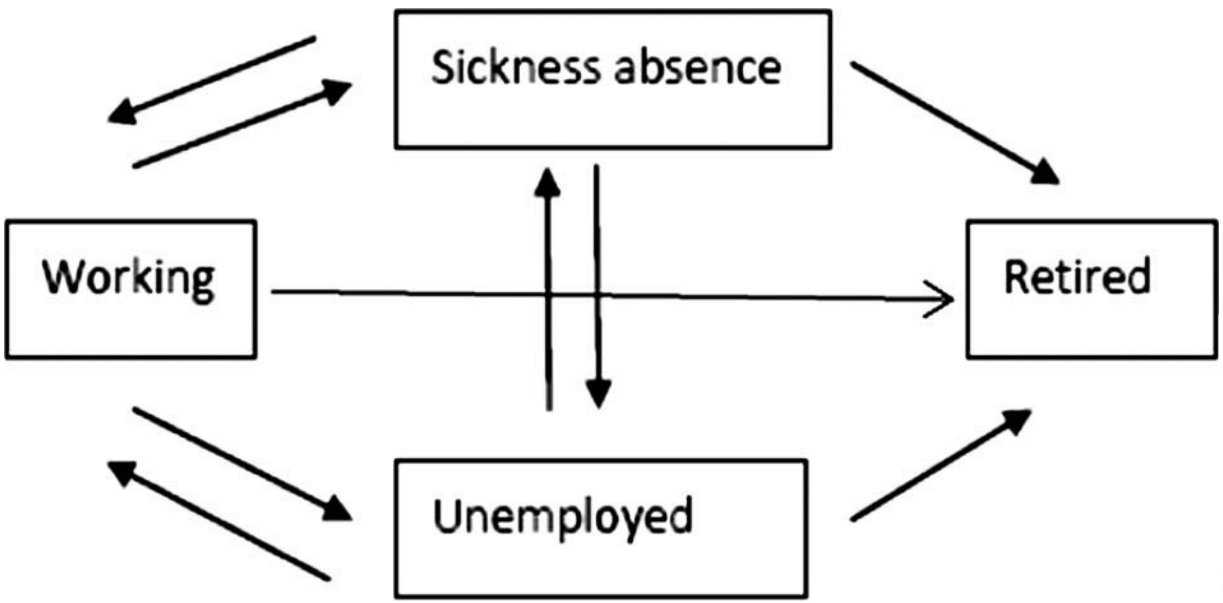
Modeling data (4)

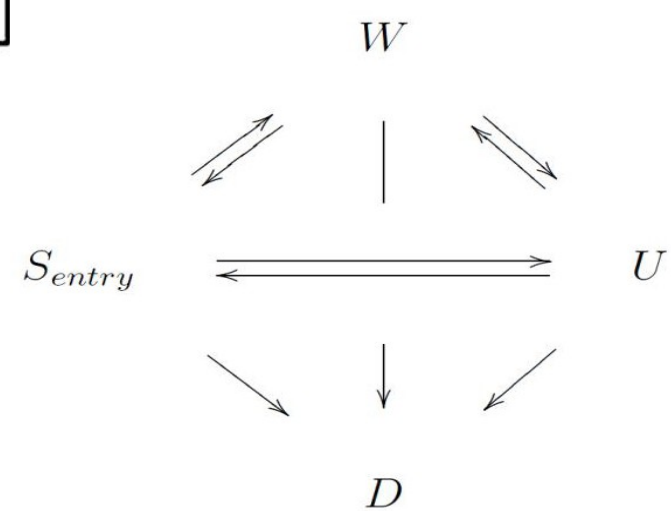
Rate ratios (RR) with 95% CI presented in graphics.



Multi state modeling







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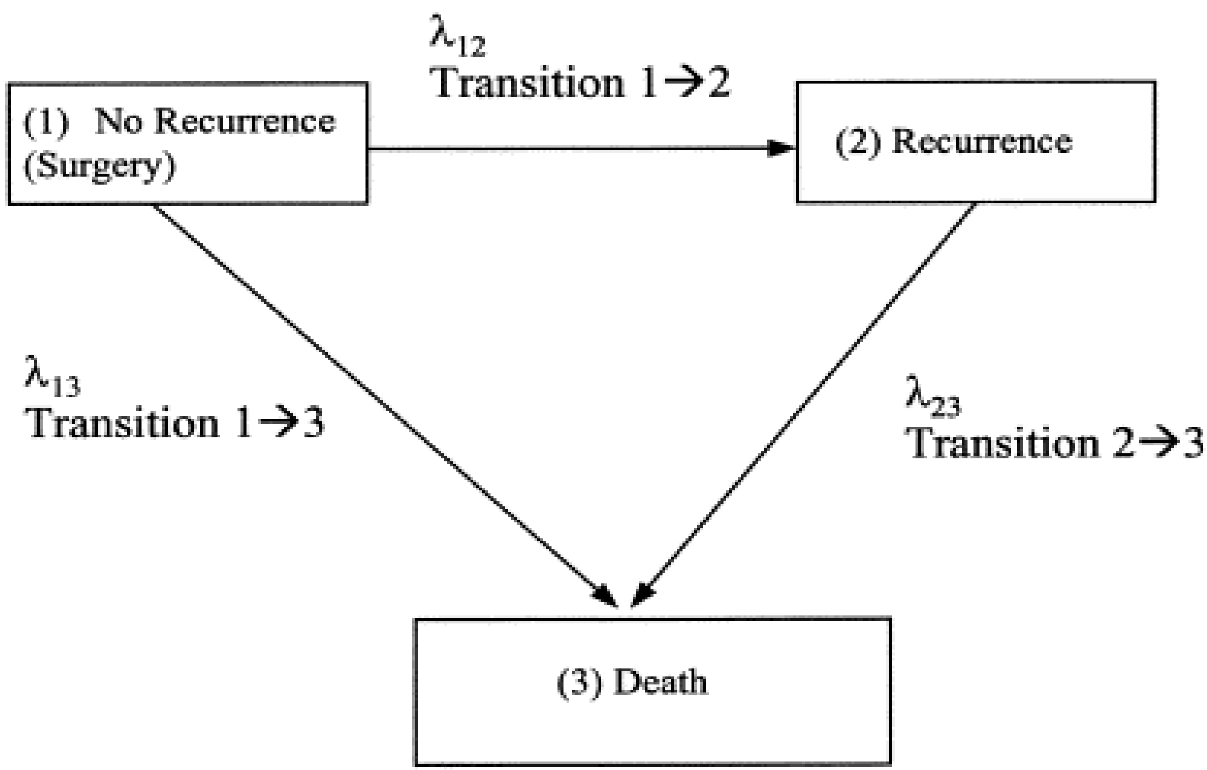
Multi state modeling

- Multi state models describe how individual moves between <u>series of states</u> in continuous time



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Multi state modeling

- Multi state models describe how individual moves between series of states in continuous time

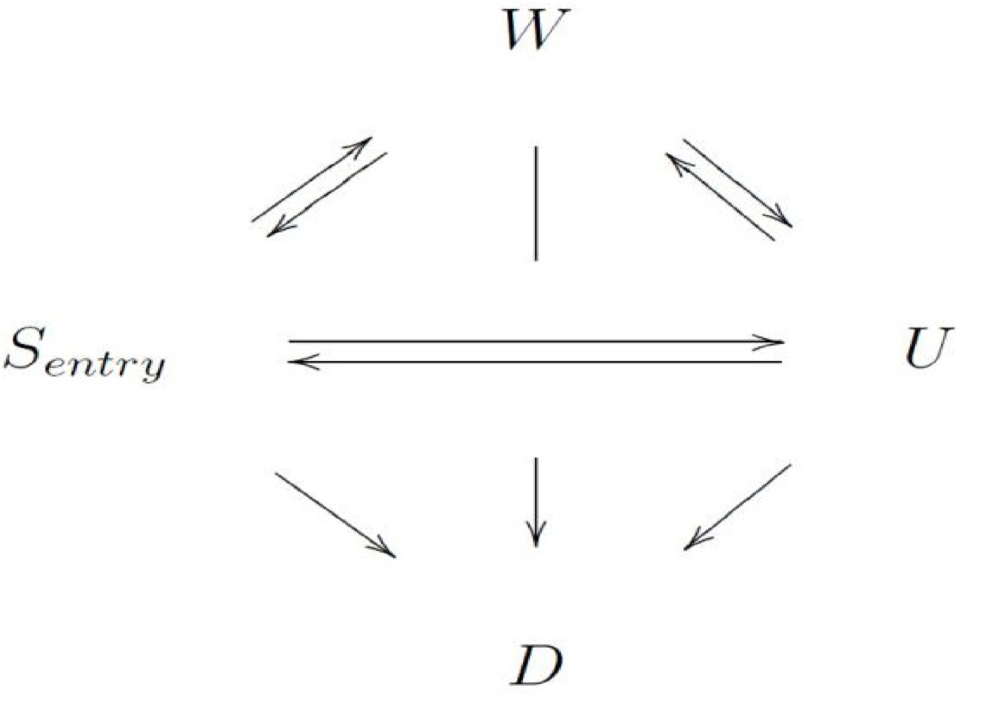

Figure 1. Model for transitions between the four states: **working (W)**, **sickness absence (S)**, **unemployment (U)** and **disability pension (D)**. The sickness absence state is labeled “entry”, to indicate that only sick-listed persons enter the study. (*Pedersen J, Bjorner JB, Burr H, et al. Transitions between sickness absence, work, unemployment, and disability in Denmark 2004-2008. Scand J Work Environ Health 2012;38:516–26.*)

Analysing multi-state data (1)

- One approach is that we are interested in transition pattern between states. We apply Markov model, where transition intensities between states are presented in matrix **Q**

$$Q=\begin{pmatrix} q_{11} & q_{12} & q_{13} \\ q_{21} & q_{22} & q_{23} \\ q_{31} & q_{32} & q_{33} \end{pmatrix}$$

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Transition example (1)

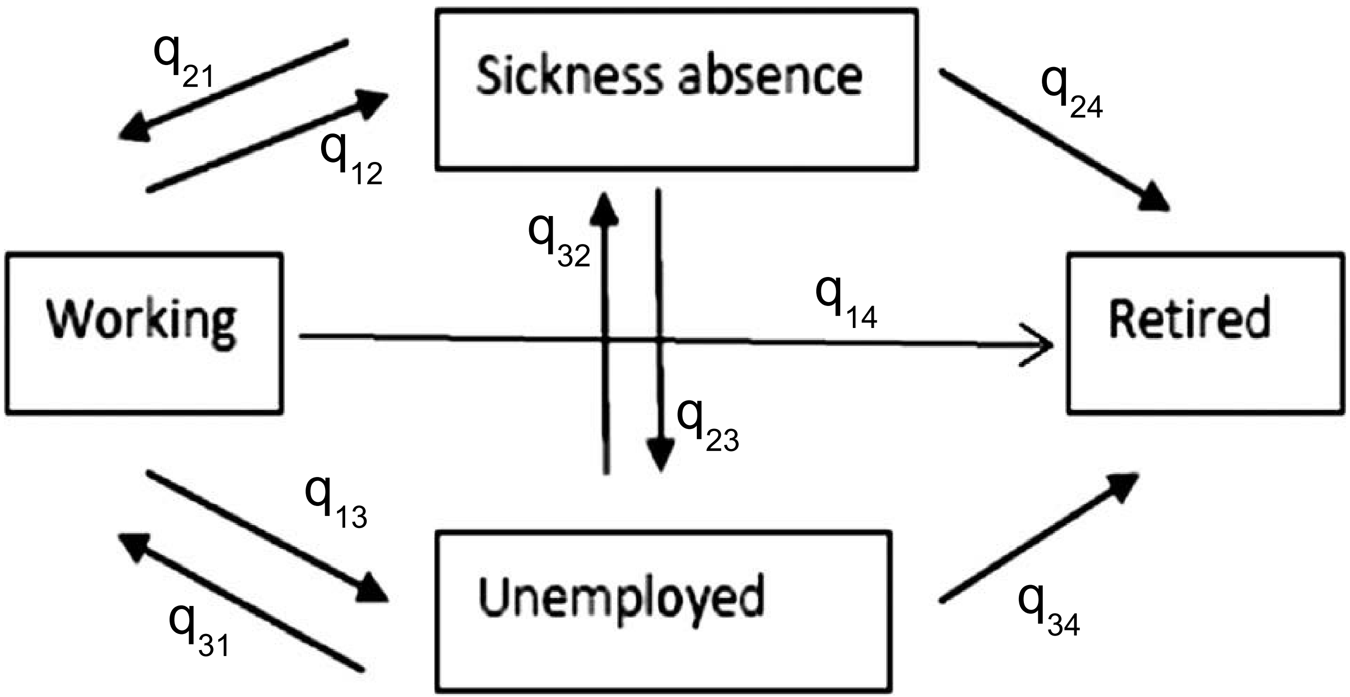


Figure 1 Transition states between labour market outcomes in Denmark. Work, sickness absence and unemployment covers persons in the workforce while retirement independent of the reason (disability or age) is an irreversible state, where persons are considered to leave the workforce forever. (*Carlsen K, Harling H, Pedersen J, et al. The transition between work, sickness absence and pension in a cohort of Danish colorectal cancer survivors. BMJ Open 2013;3. doi:10.1136/bmjopen-2012-002259*)

Q with some constrains

1. Working
2. Sickness absense
3. Unemployed
4. Retired

$$Q = \begin{pmatrix} q_{11} & q_{12} & q_{13} & q_{14} \\ q_{21} & q_{22} & q_{23} & q_{24} \\ q_{31} & q_{32} & q_{33} & q_{34} \\ 0 & 0 & 0 & q_{44} \end{pmatrix}$$

Intensity matrix for Carlsen K, Harling H, Pedersen J (2013)

Analysing multi-state data

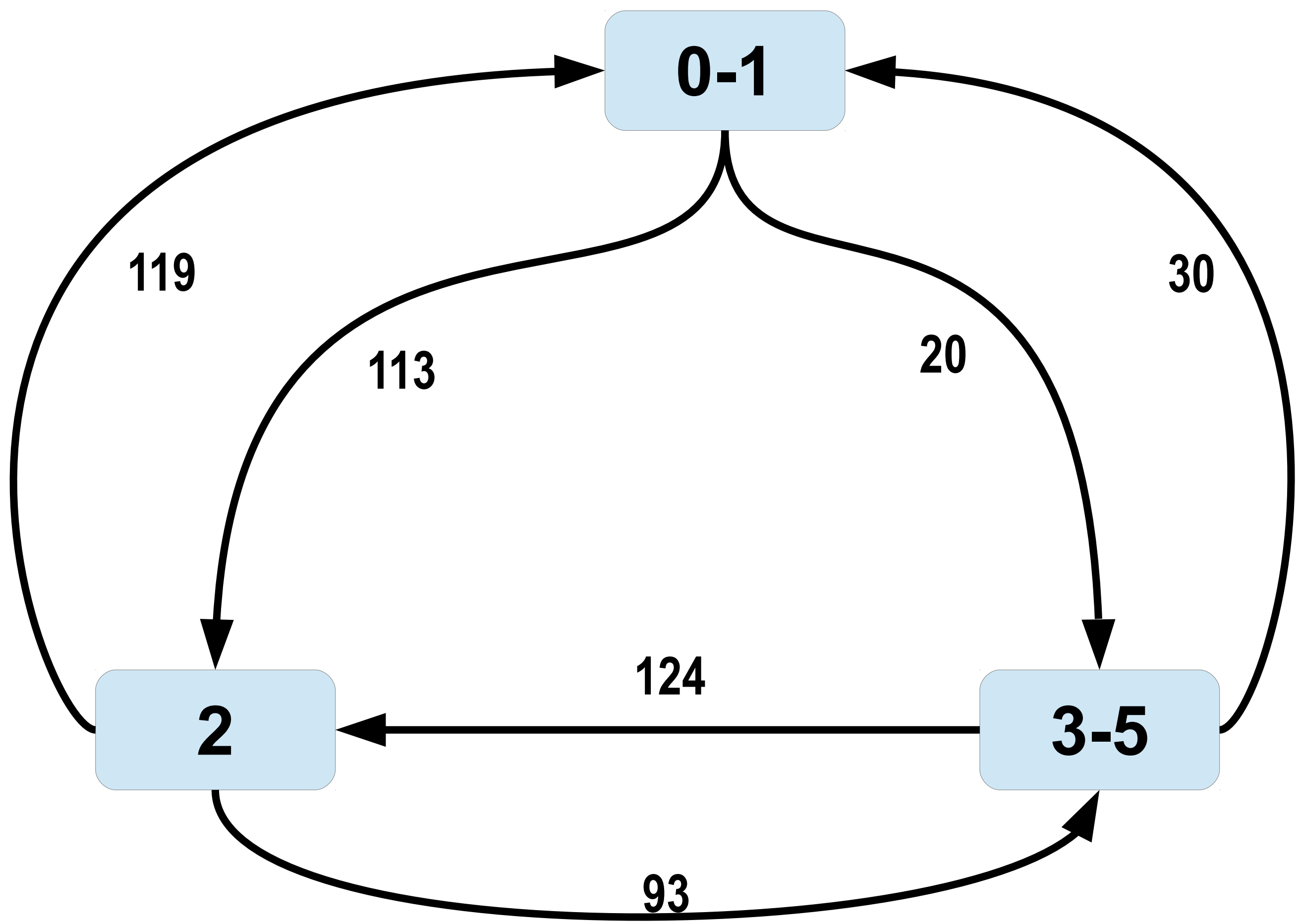
- Using matrix **Q** we are able to calculate <u>transition matrix</u> **P** between states.
- p_{ij} describes probability to be in state j after certain time when starting state is i

$$Q=\begin{pmatrix} q_{11} & q_{12} & q_{13} & q_{14} \\ q_{21} & q_{22} & q_{23} & q_{24} \\ q_{31} & q_{32} & q_{33} & q_{34} \\ 0 & 0 & 0 & q_{44} \end{pmatrix} \qquad P=\begin{pmatrix} p_{11} & p_{12} & p_{13} & p_{14} \\ p_{21} & p_{22} & q_{23} & p_{24} \\ p_{31} & p_{32} & q_{33} & p_{34} \\ p_{41} & p_{42} & p_{43} & p_{44} \end{pmatrix} ¿$$

Intensity matrix for Carlsen K, Harling H, Pedersen J (2013)

States in nocturia data

```
     to
from 0-1   2 3-5
   1 333 113  20
   2 119 272  93
   3  30 124 432
```



NOTE!
All transitions between states are possible. Here are number of transitions

Example

- We use R package ”msm” for analysis

```
# Initial values for Q matrix
> twoway2.q
       0-1      2   3-5
0-1 0.000 0.166 0.166
2   0.166 0.000 0.166
3-5 0.166 0.166 0.000

# Model without covariates
tmp.m1.msm <- msm(Noct.3.num ~ Week.num,
   subject = PATIENT, gen.inits = TRUE,
   qmatrix = twoway2.q,
   data = pla.data.1.V2,
   obstype = 1, analyticp = TRUE,
   opt.method = "optim",
   control = list(maxit = 1000,
                  trace = 0, fnscale = 2000))
```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Simple model results

```
##
## Call:
## msm(formula = Noct.3.num ~ Week.num, subject = PATIENT, data =
pla.data.1.V2,     qmatrix = twoway2.q, gen.inits = TRUE, obstype
= 1, opt.method = "optim",     analyticp = TRUE, control =
list(maxit = 1000, trace = 0,         fnscale = 2000))
##
## Maximum likelihood estimates:
## Transition intensity matrix
##
##     0-1                           2
## 0-1 -0.05529 (-0.0685,-0.04463) 0.05298 (0.042,0.06682)
## 2   0.05591 (0.04434,0.07049)   -0.09766 (-0.1153,-0.0827)
## 3-5 0.00321 (0.001195,0.008623) 0.04537 (0.04053,0.05078)
##     3-5
## 0-1 0.002316 (0.0005702,0.009405)
## 2   0.04176 (0.03352,0.05203)
## 3-5 -0.04858 (-0.05445,-0.04333)
##
## -2 * log-likelihood:  2658
```


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Simple model, intensity matrix

Intensity matrix (**Q**)

	0-1	2	3-5
0-1	-0.0553	0.0530	0.0023
2	0.0559	-0.0977	0.0418
3-5	0.0032	0.0454	-0.0486

Adding covariates

- It is possible to add individual level covariates into model.
- We also might be interested in if transition intensities are stable or are they time-inhomogenius (not shown here).

```
msm(formula = Noct.3.num ~ Week.num,
    subject = PID, data = pla.data.2,
    qmatrix = twoway2.q, gen.inits = TRUE,
    obstype = 1, pci = c(27),
    opt.method = "optim",
    control = list(maxit = 1000, trace = 0,
   fnscale = 2000))
```

Model with covarites

```
# Add BMI as covariate

tmp.m2.msm <- msm(Noct.3.num ~ Week.num, subject = PATIENT,
   gen.inits = TRUE,
    qmatrix = twoway2.q, data = pla.data.1.V2[tmp.i., ],
   obstype = 1, covariates = ~BMI..kg.m2.,
    opt.method = "optim", control =
   list(maxit = 1000, trace = 0, fnscale = 2000))
```


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Model comparison

- Now we have two models, viz. "`tmp.m1.msm`" and "`tmp.m2.msm`".
- We use likelihood ratio test to check if covarite (BMI) should be included.
- It turns out that BMI as covariate should be included

```
# Check model, adding BMI as covariate gives better
#  model
lrtest.msm(tmp.m1.msm, tmp.m2.msm)

##              -2 log LR df       p
## tmp.m2.msm       20.19  6 0.00256
```


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Interpretation of results

- In order to interpret results it is usually sensible to calculate estimates **transition matrices (TM)**.
- In this example we calculate TM for two covariate values: BMI=25 and BMI=30
- Transition matrix is calculated for time period of 24 week (6 months)

Transition matrices estimates

- Predicted probability of transition (%) in 24 weeks.
- With two covariate values (BMI=25 and BMI=30)

BMI=25

	0-1	2	3-5
0-1	51 (45,57)	33 (28,37)	16 (13,21)
2	37 (32,42)	38 (33,42)	26 (22,31)
3-5	23 (20,28)	34 (30,37)	43 (37,48)

BMI=30

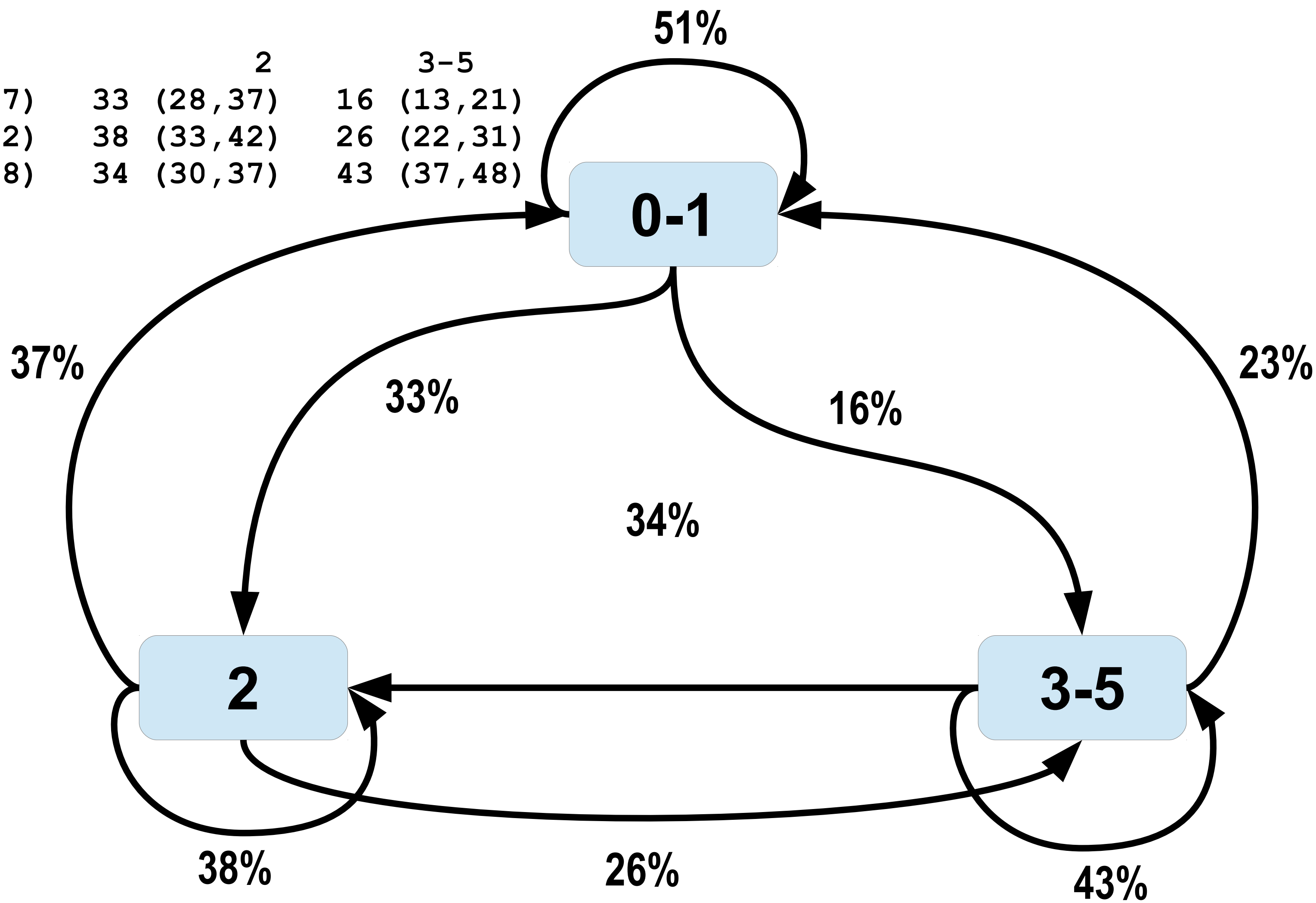
	0-1	2	3-5
0-1	45 (38,51)	32 (28,38)	23 (19,28)
2	33 (28,39)	35 (30,39)	32 (27,37)
3-5	22 (18,26)	31 (27,35)	47 (42,52)

Transition prob. to state ”3-5” is much higher for patients with higher BMI

24 weeks transitions

BMI=25

	0-1	2	3-5
0-1	51 (45,57)	33 (28,37)	16 (13,21)
2	37 (32,42)	38 (33,42)	26 (22,31)
3-5	23 (20,28)	34 (30,37)	43 (37,48)



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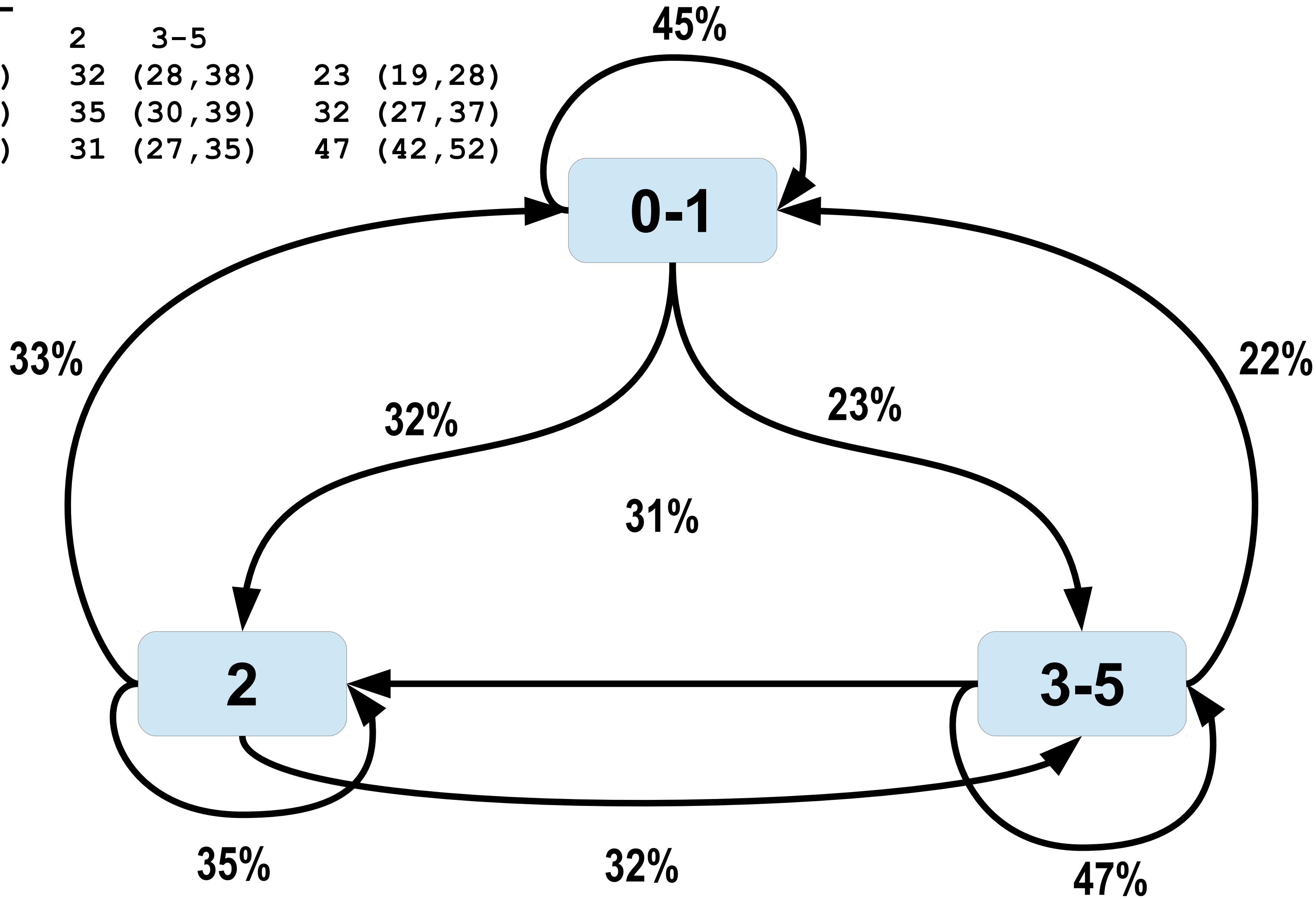
24 weeks transitions

BMI=30

	0-1	2	3-5
0-1	45 (38,51)	32 (28,38)	23 (19,28)
2	33 (28,39)	35 (30,39)	32 (27,37)
3-5	22 (18,26)	31 (27,35)	47 (42,52)



Model with covariate(s)

- Effect of covariate(s) could be presented as hazard ratios (HR) for each transition
- Here HR presented for five units of BMI

```
print(hazard.msm(tmp.m2.msm, hazard.scale = 5))
## $BMI..kg.m2.
##                  HR      L     U
## 0-1 - 2   1.1617 0.8475 1.593
## 0-1 - 3-5 1.8966 0.8879 4.051
## 2 - 0-1   1.0637 0.8199 1.380
## 2 - 3-5   1.2701 0.9502 1.698
## 3-5 - 0-1 1.0751 0.4494 2.572
## 3-5 - 2   0.9455 0.6939 1.288
```

Conclusion

Question was: Methodological challenges in research on consequences of sickness absence and disability pension?

Answer: Yes, there are such challenges. Two approaches,

- **Lexis** data with Poisson regression and
- **multi state** models,

might help researcher to have better grasp to data and the transitions of sickness absence and disability pension.

References

- Carlsen K, Harling H, Pedersen J, et al. The transition between work, sickness absence and pension in a cohort of Danish colorectal cancer survivors. BMJ Open 2013;3. doi:10.1136/bmjopen-2012-002259
- Carstensen B, Plummer M. Using Lexis Objects for Multi-State Models in R. Journal of Statistical Software 2011;38:1–18.
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- Plummer M, Carstensen B. Lexis: An R Class for Epidemiological Studies with Long-Term Follow-Up. Journal of Statistical Software 2011;38:1–12.