Multi-state Models and the Survival package

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Sept 2019

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Background

- I am a medical statistician in a tertiary care center
- Most of the questions are time until ...
  - waiting time on the liver transplant list
  - failure of a hip replacement (if ever)
  - clinical trial: chemotherapy to relapse
  - CN $\rightarrow$ MCI $\rightarrow$ Dementia
    none vs. mild vs. moderate/severe neurodegeneration
    none/mild vs. moderate amyloid deposition
- Naturally fell into survial analysis.

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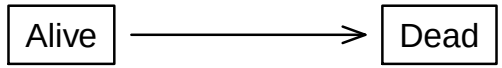

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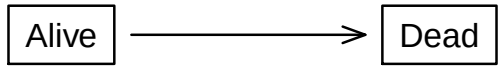

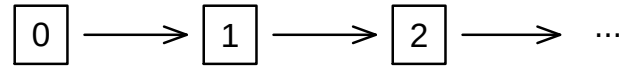

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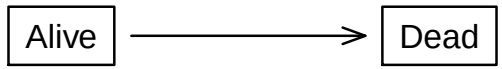

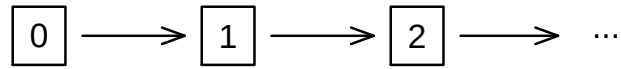

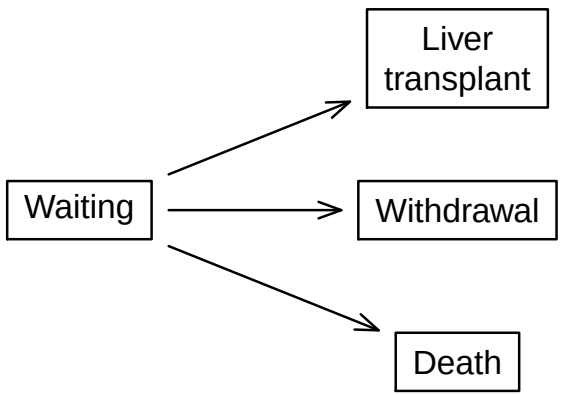

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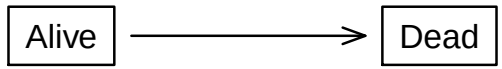
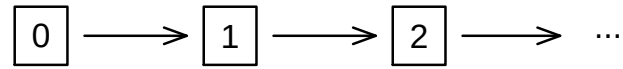
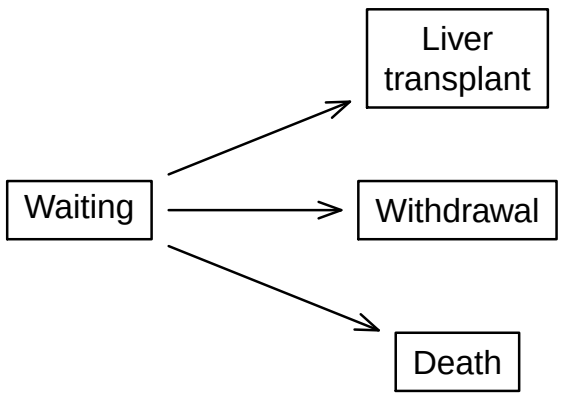
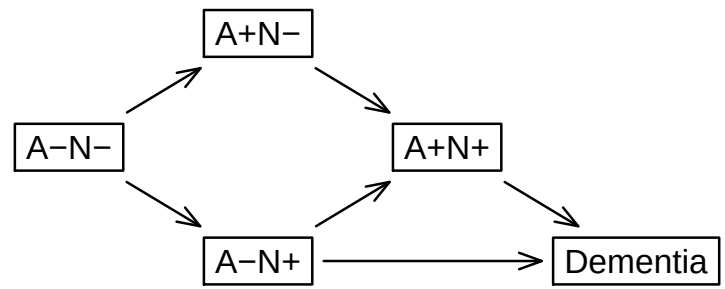

Alive
Dead


0
1
2
...


Liver transplant
Waiting
Withdrawal
Death


A+N−
A−N−
A+N+
A−N+
Dementia

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Outline

- Three research studies
  - MGUS
  - Leukemia
  - Fatty liver disease
- R code along the way

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Outline

- Three research studies
  - MGUS
  - Leukemia
  - Fatty liver disease
- R code along the way
- Main points
  - Multi-state approach is very useful
  - It ain't that hard

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The survival package

- Does what I need it to do
- Building block for others (666 dependencies on 9/10)

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The survival package

- Does what I need it to do
- Building block for others (666 dependencies on 9/10)
- survival3 went to CRAN on Wed
- Major change/enhancement: multistate

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MGUS

- Observation of Dr Robert Kyle
  - semi-abnormal lab test in normal people (PE)
  - reminiscent of multiple myeloma results
  - are these subjects at risk of MM?
  - note every one he sees, and follow them
- mgus2 data set in R
  - 1384 sequential subjects
  - 5–35 years of follow-up
  - Death, PCM, age, sex, + 3 labs

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Data

	id	age	sex	creat	futime	death	ptime	pstat
79	79	96	M	1.8	33	1	33	0
80	80	80	M	1.1	68	1	68	0
81	81	91	F	1.0	21	1	14	1
82	82	71	M	1.1	65	1	65	0
83	83	77	F	0.8	233	1	228	1

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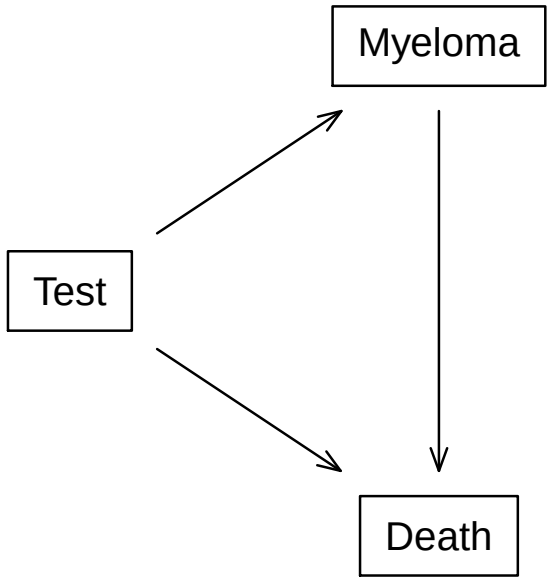

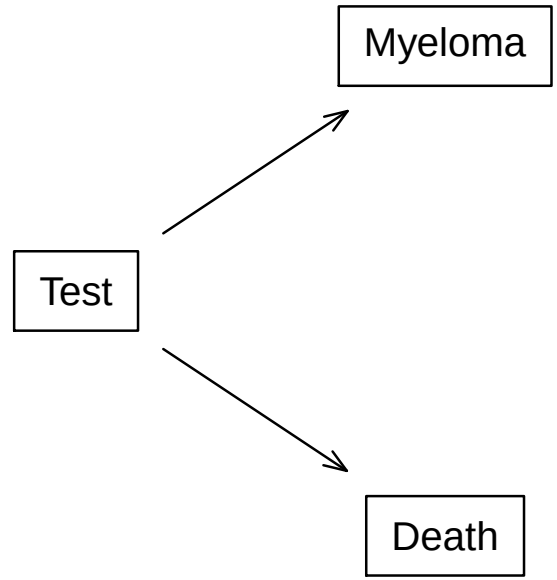

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```
    id tstart tstop event age sex  hgb enum
80 79      0    33 Death  96   M  9.6    1
81 80      0    68 Death  80   M 14.1    1
82 81      0    14   PCM  91   F  5.9    1
83 81     14    21 Death  91   F  5.9    2
84 82      0    65 Death  71   M 15.6    1
85 83      0   228   PCM  77   F 12.2    1
86 83    228   233 Death  77   F 12.2    2
87 84      0    78 Death  89   M 14.3    1
```

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```
# Kaplan-Meier
kmfit <- survfit(Surv(futime, death) ~ sex, data=mgus2)

# Competing risks
crdata <- subset(mdata, enum==1)
crfit <- survfit(Surv(tstop, event) ~ sex, data=crdata)
```

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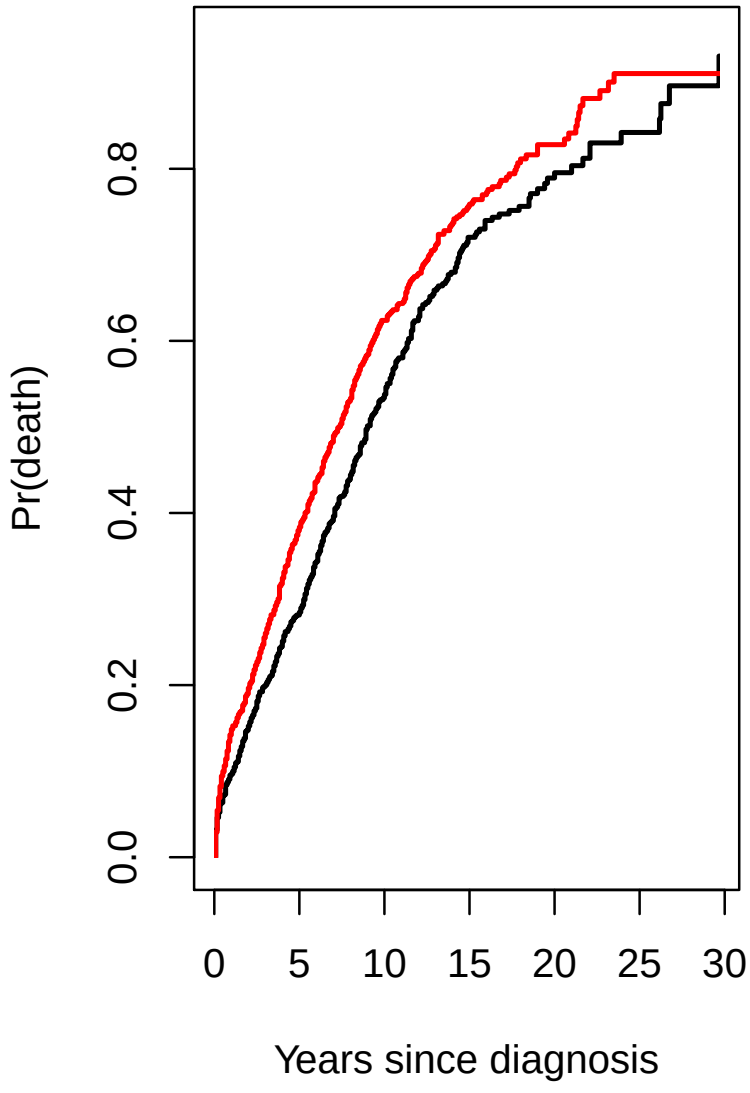
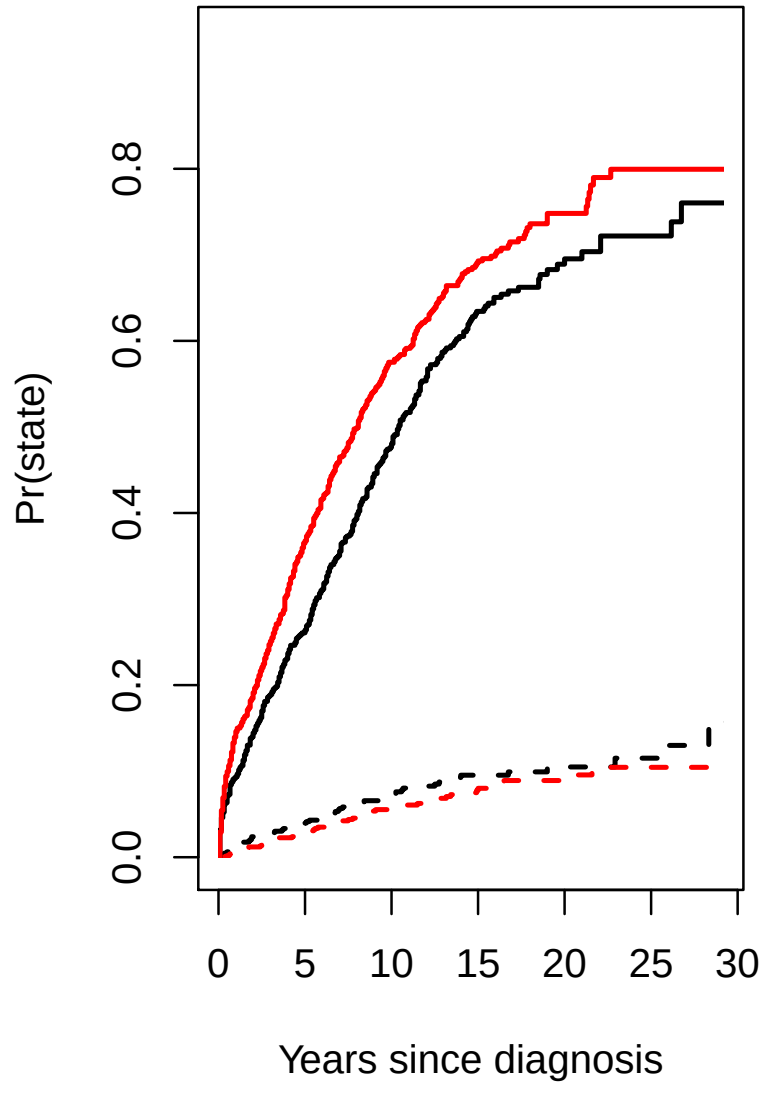

Pr(death)
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
25
30
Years since diagnosis


Pr(state)
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
25
30
Years since diagnosis

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```
# Kaplan-Meier and Cox model
kmfit <- survfit(Surv(futime, death) ~ sex, data=mgus2)
cfit  <- coxph(Surv(futime, death) ~ sex + age, data=mgus2)

# Competing risks and Cox model
crfit <- survfit(Surv(tstop, event) ~ sex, data=crdata)
cfit2 <- coxph(Surv(tstop, event) ~ sex + age10, data=crdata, id=id)
```

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```
Call:
coxph(formula = Surv(tstop, event) ~ sex + age10, data = crdata,
    id = id)


1:2        coef exp(coef) se(coef) robust se    z    p
  sexM   -0.025     0.975    0.188     0.189 -0.1 0.89
  age10   0.130     1.139    0.083     0.067  1.9 0.05


1:3        coef exp(coef) se(coef) robust se    z       p
  sexM   0.393     1.482    0.070     0.066  5.9  3e-09
  age10 0.648     1.912    0.036     0.037 17.6 <2e-16

 States:  1= (s0), 2= PCM, 3= Death

Likelihood ratio test=390  on 4 df, p=<2e-16
n= 1384, number of events= 975
```

MGUS

- Sex has absolutely no effect on the instantaneous risk of PCM
- Females *do* have an increased lifetime risk of PCM, however.
  - The malignancy rate is 1% per year
  - Females live longer

```
dummy <- expand.grid(sex= c("M", "F"), age10 = c(6, 8))
sfit <- survfit(cfit2, newdata=dummy)   # dimension (4, 3)
plot(sfit[1:2,])
plot(sfit[3:4,])
```

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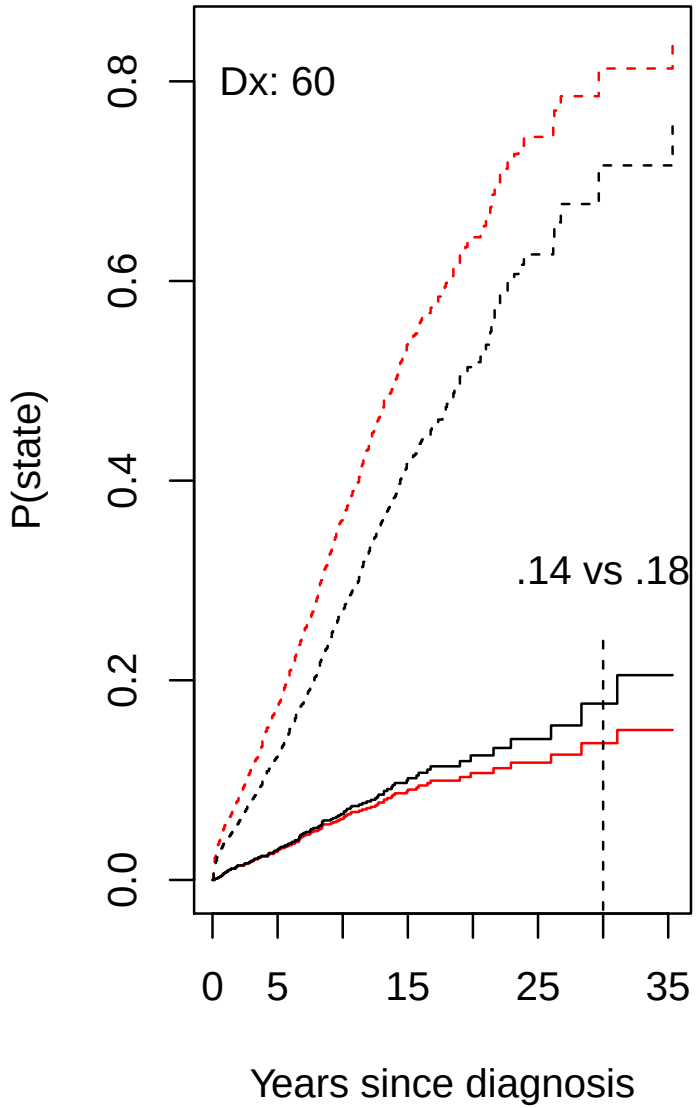
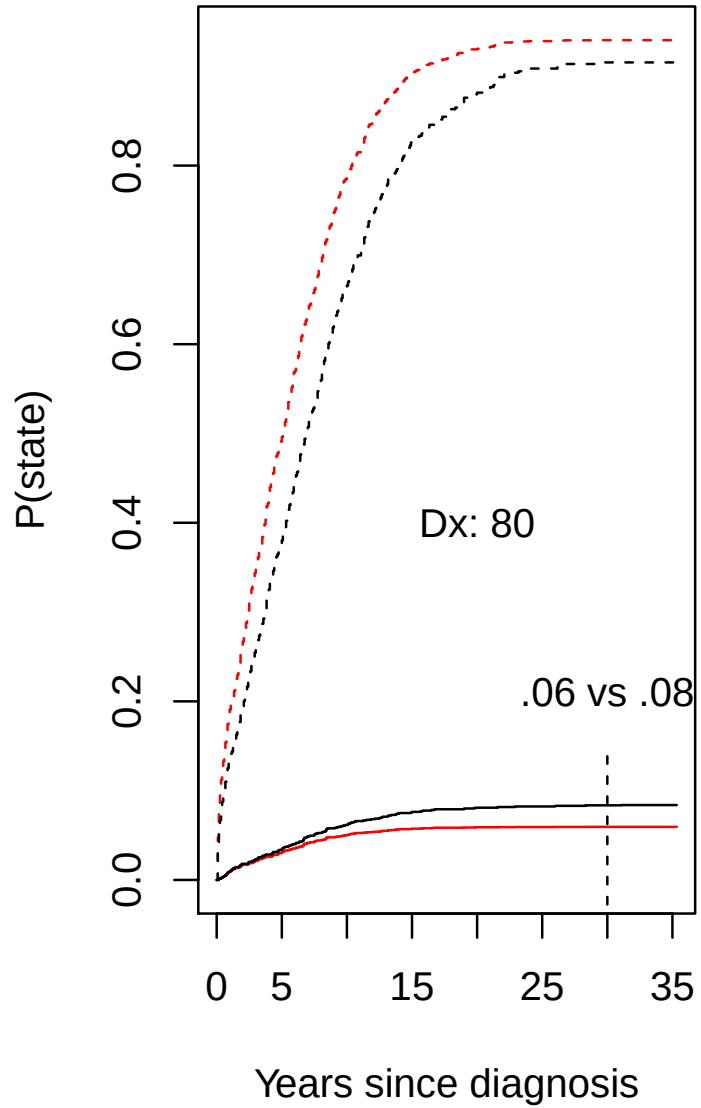

Dx: 60
.14 vs .18
P(state)
0.0
0.2
0.4
0.6
0.8
0
5
15
25
35
Years since diagnosis


Dx: 80
.06 vs .08
P(state)
0.0
0.2
0.4
0.6
0.8
0
5
15
25
35
Years since diagnosis

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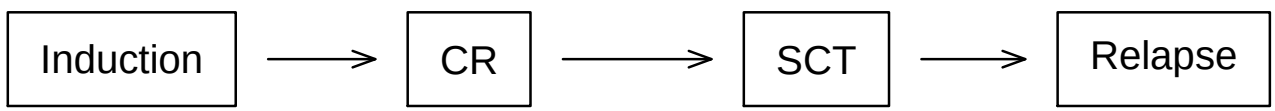
Acute Myeloid Leukemia

- Clinical trial of two induction therapies
- Surprising interaction in the data
- "Can we sort this out?"



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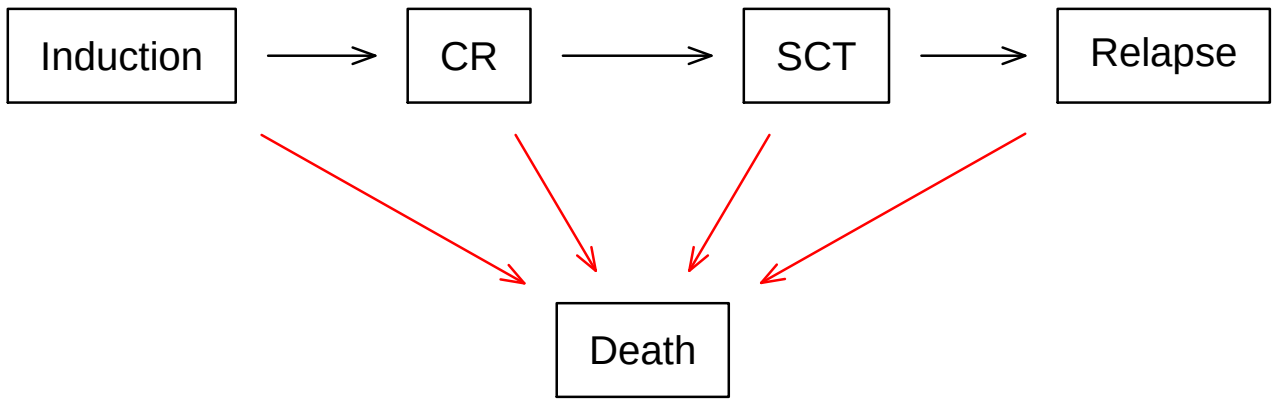
Acute Myeloid Leukemia



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	id	trt	tstart	tstop	event
1	1	B	0	44	CR
2	1	B	44	113	relapse
3	1	B	113	235	death
4	2	A	0	200	SCT
5	2	A	200	286	death
6	3	A	0	38	CR
7	3	A	38	1983	none

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Data

- `event` is a multi-level factor variable.
  - The first level must correspond to "no event at this time"
  - Otherwise unrestricted.
- An `id` variable identifies multiple rows per subject.
- Consistent
  - If at risk, you should be some state: (0,50,CR) (90,210,SCT)
  - But only one place at a time: (0,50,CR) (30,210,SCT)

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Data check

```
check <- survcheck(Surv(tstart, tstop, event) ~ 1,
                   data=mdata, id=id)
check$transitions
         to
from        CR SCT relapse death (censored)
  (s0)     443 106      13    55         29
  CR         0 159     168    17        110
  SCT       11   0      45   149        158
  relapse    0  99       0    99         28
  death      0   0       0     0          0
#
check$flag
 overlap       gap      jump teleport
       0         0         0        0
```

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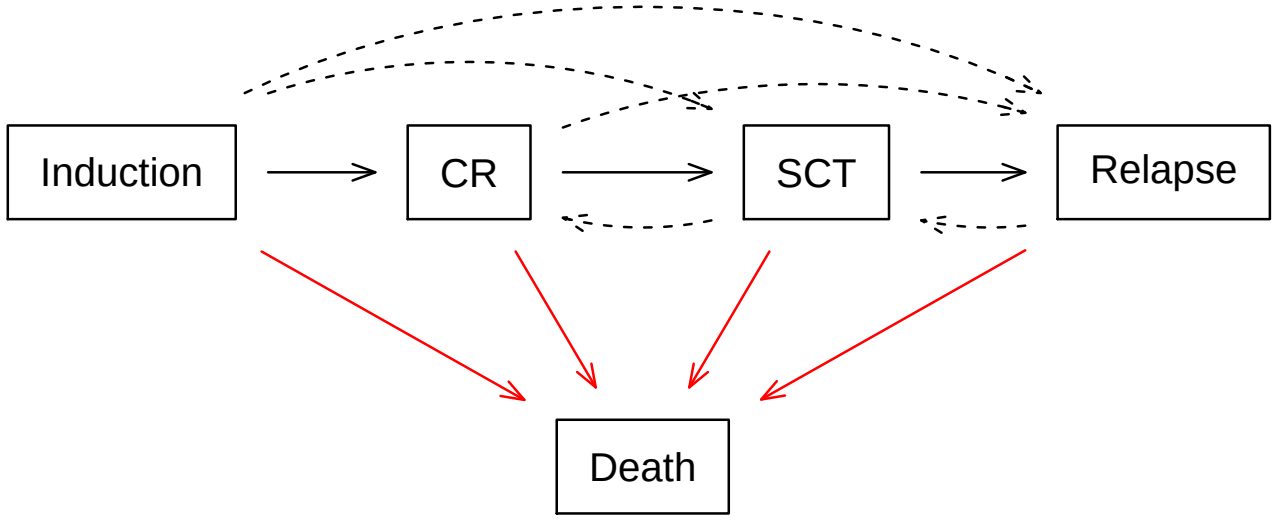

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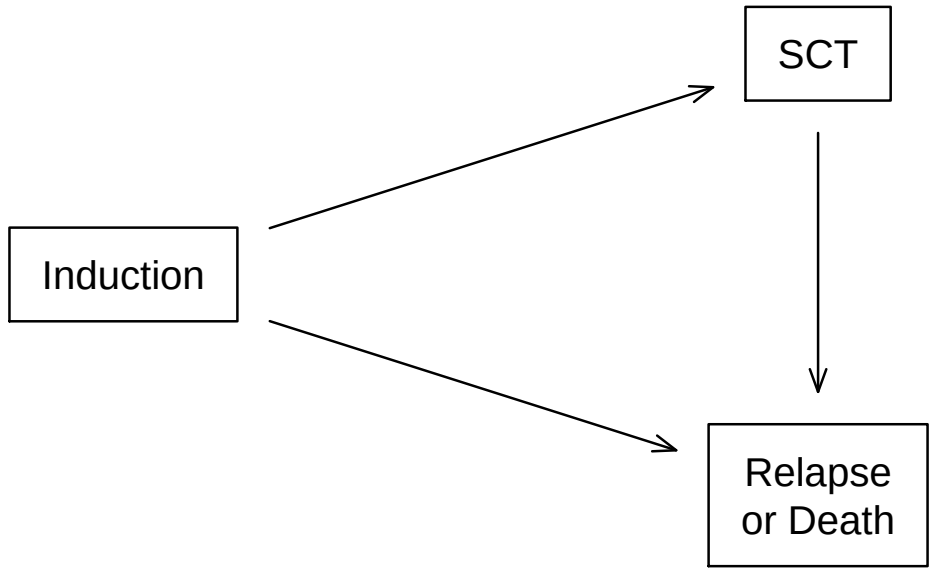

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	id	trt	tstart	tstop	event	e2
1	1	B	0	44	CR	none
2	1	B	44	113	relapse	Fail
3	1	B	113	235	death	none
4	2	A	0	200	SCT	SCT
5	2	A	200	286	death	Fail
6	3	A	0	38	CR	none
7	3	A	38	1983	none	none

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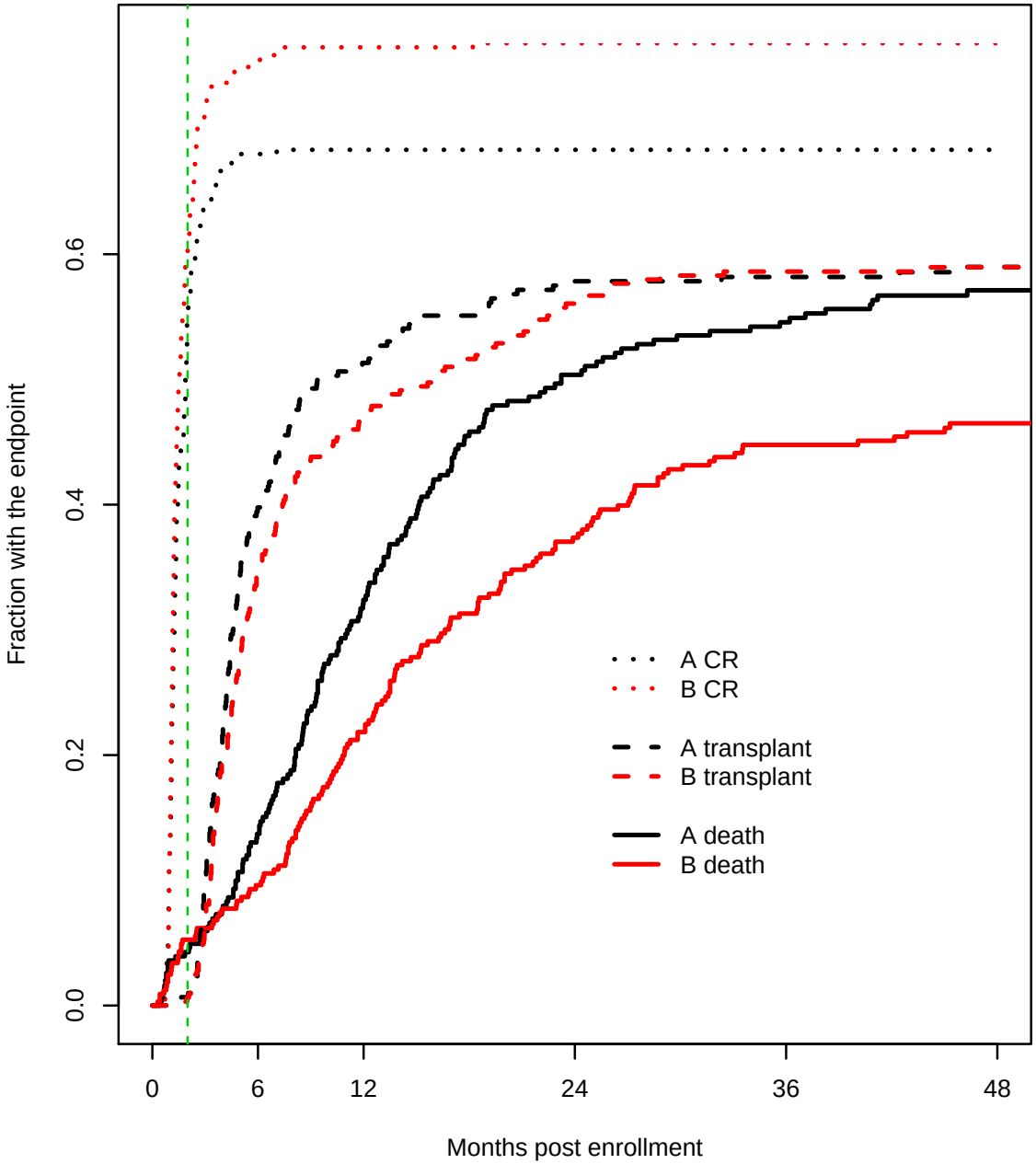
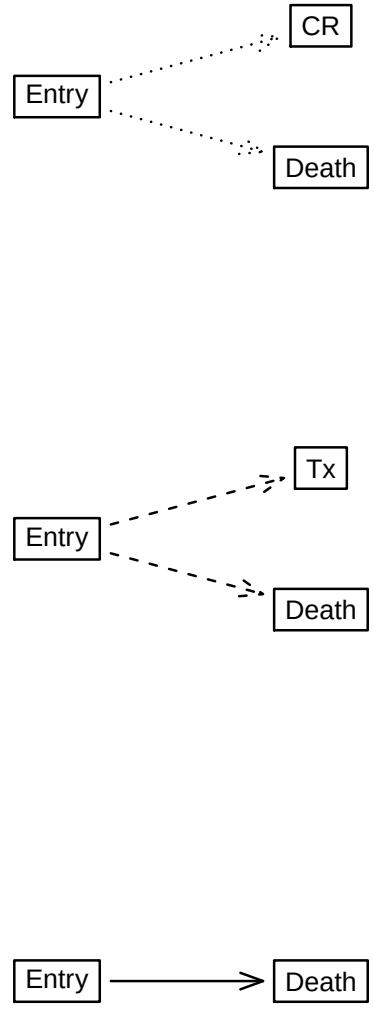

Fraction with the endpoint
0.0
0.2
0.4
0.6
0
6
12
24
36
48
Months post enrollment
A CR
B CR
A transplant
B transplant
A death
B death


Entry
CR
Death
Entry
Tx
Death
Entry
Death

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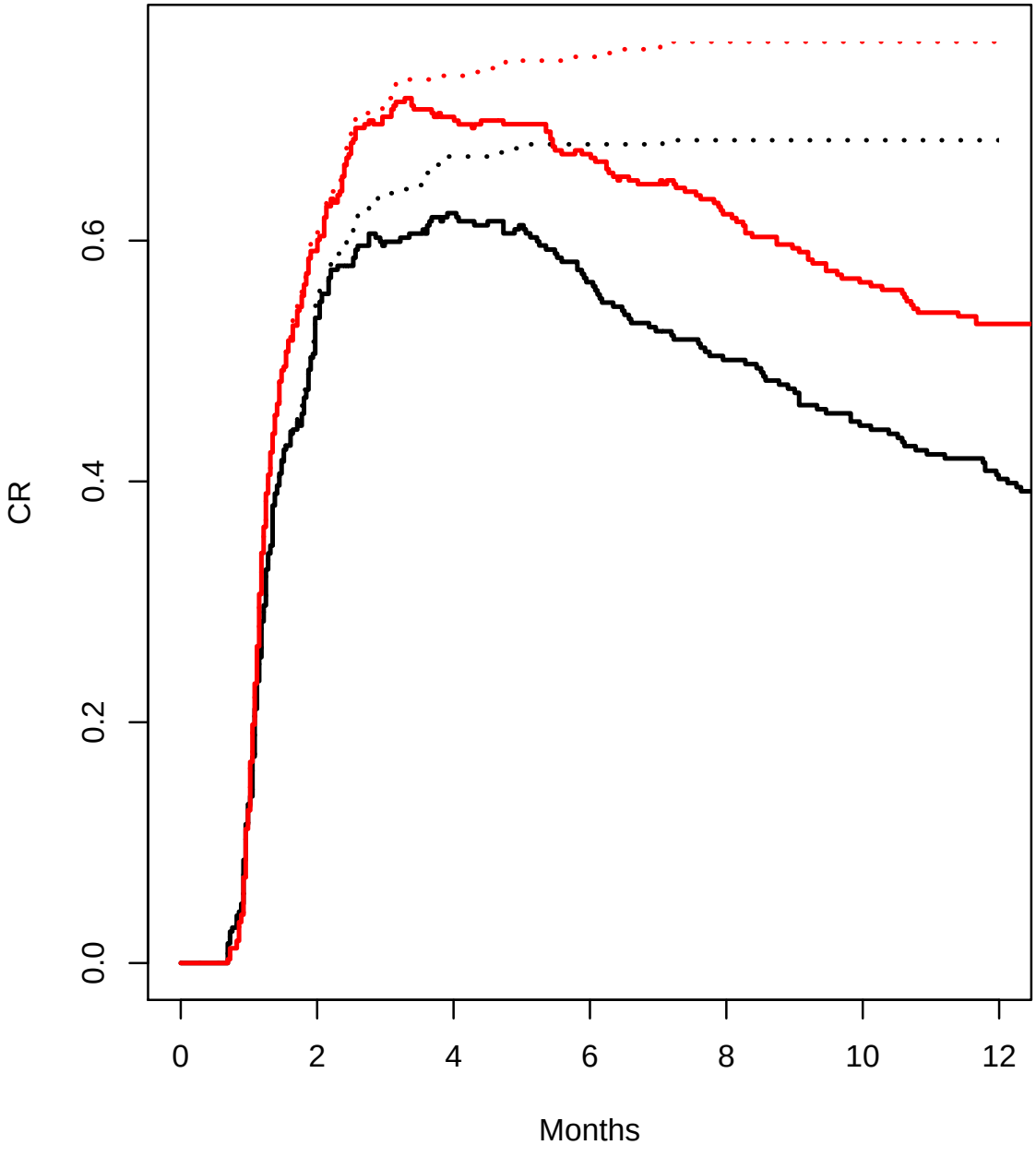
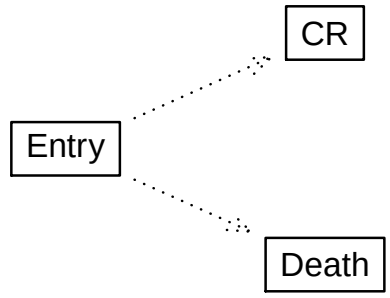
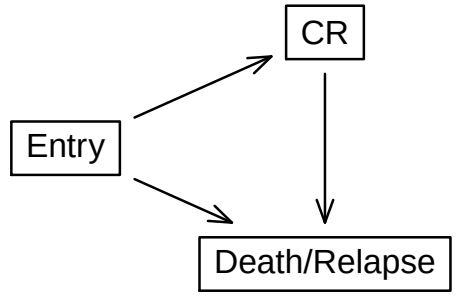

CR
0.0
0.2
0.4
0.6
0
2
4
6
8
10
12
Months


CR
Entry
Death


CR
Entry
Death/Relapse

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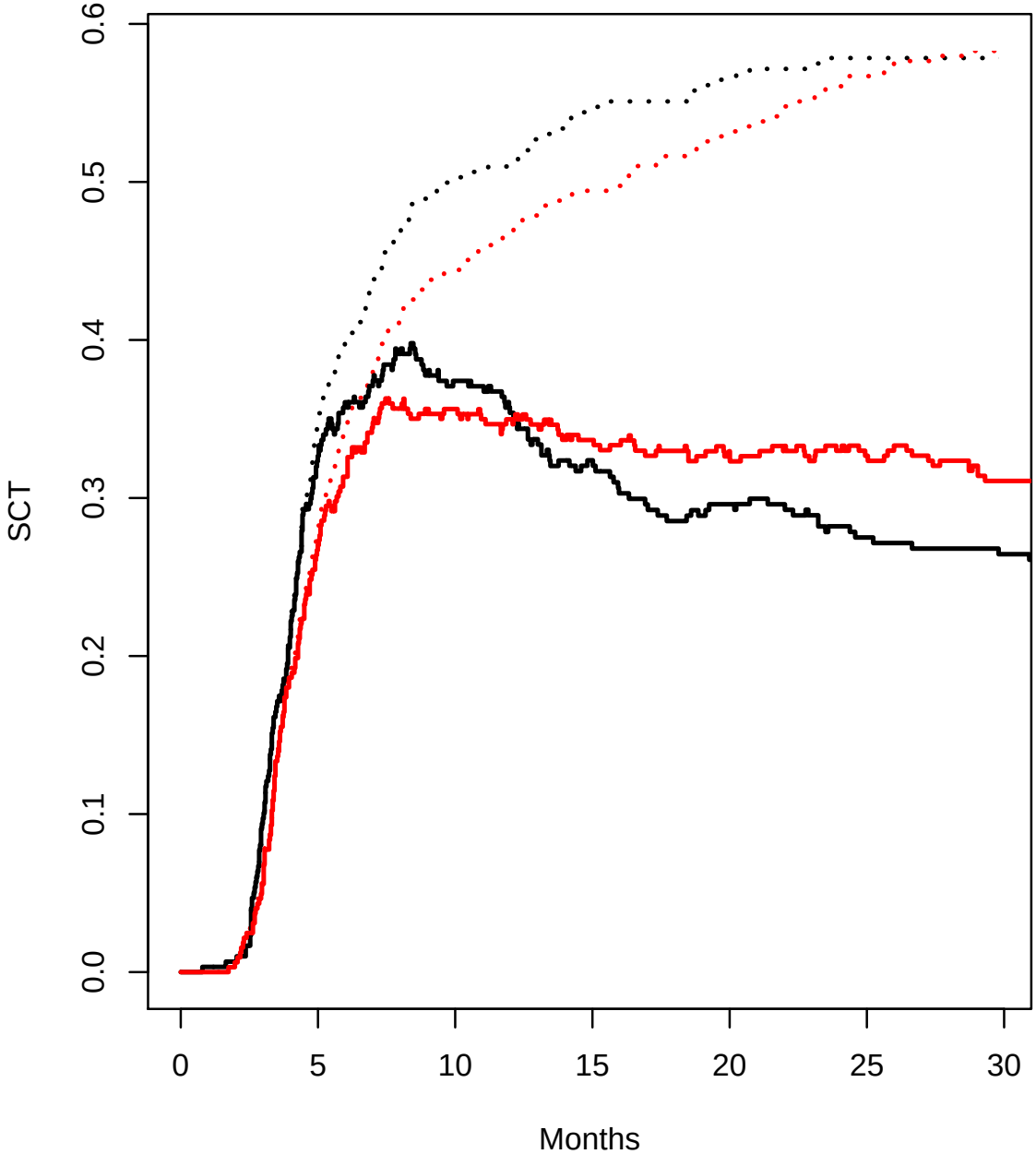
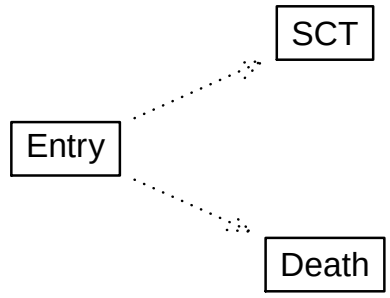
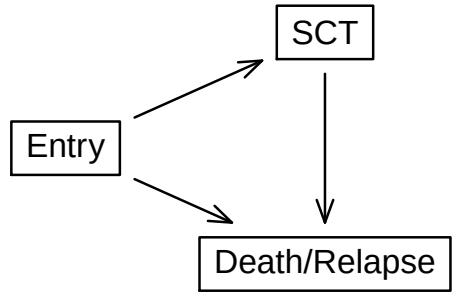

SCT
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
5
10
15
20
25
30
Months


SCT
Entry
Death


SCT
Entry
Death/Relapse

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Possible questions

- Does the time from CR to progression/death differ?
- Does the rate of SCT after CR differ?
- How do all of these interact with sex?

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Possible questions

- Does the time from CR to progression/death differ?
- Does the rate of SCT after CR differ?
- How do all of these interact with sex?
- Why would you settle for a single (boring) KM?

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AJ estimator

- The survfit routine caculates the Aalen-Johansen estimate of $p(t)$
  $p_j(t)$ =Pr(in state j at time t)
- $\sum_j p_j(t) = 1$
- IJ variance
- Kaplan-Meier = special case of AJ
- Cumulative incidence = special case of the AJ

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Fatty liver disease (NAFLD)

- Definition
  - presence of $> 5\%$ fat in the liver (steatosis)
  - absence of other indications (alcohol or certain medications)
  - no other liver disease
- Why would you care?
  - responsible for $1/3$ of liver transplants
  - prevalence is growing with obesity

"Nonalcoholic fatty liver disease, metabolic syndrome, and the fight that will define clinical practice for a generation of hepatologists." Tapper and Loomba, Hepatology 2018.

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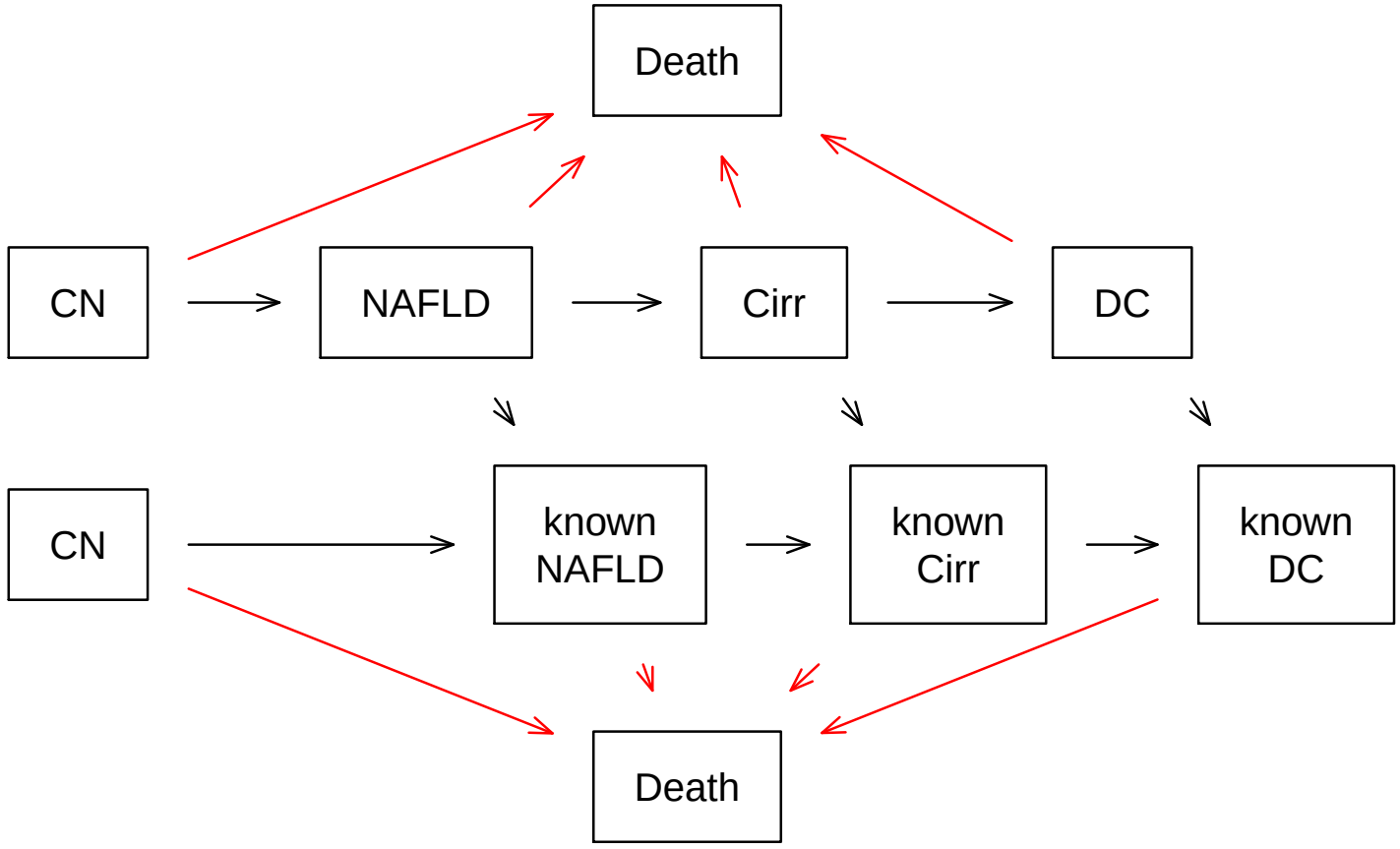
Death
CN
NAFLD
Cirr
DC
CN
known
NAFLD
known
Cirr
known
DC
Death

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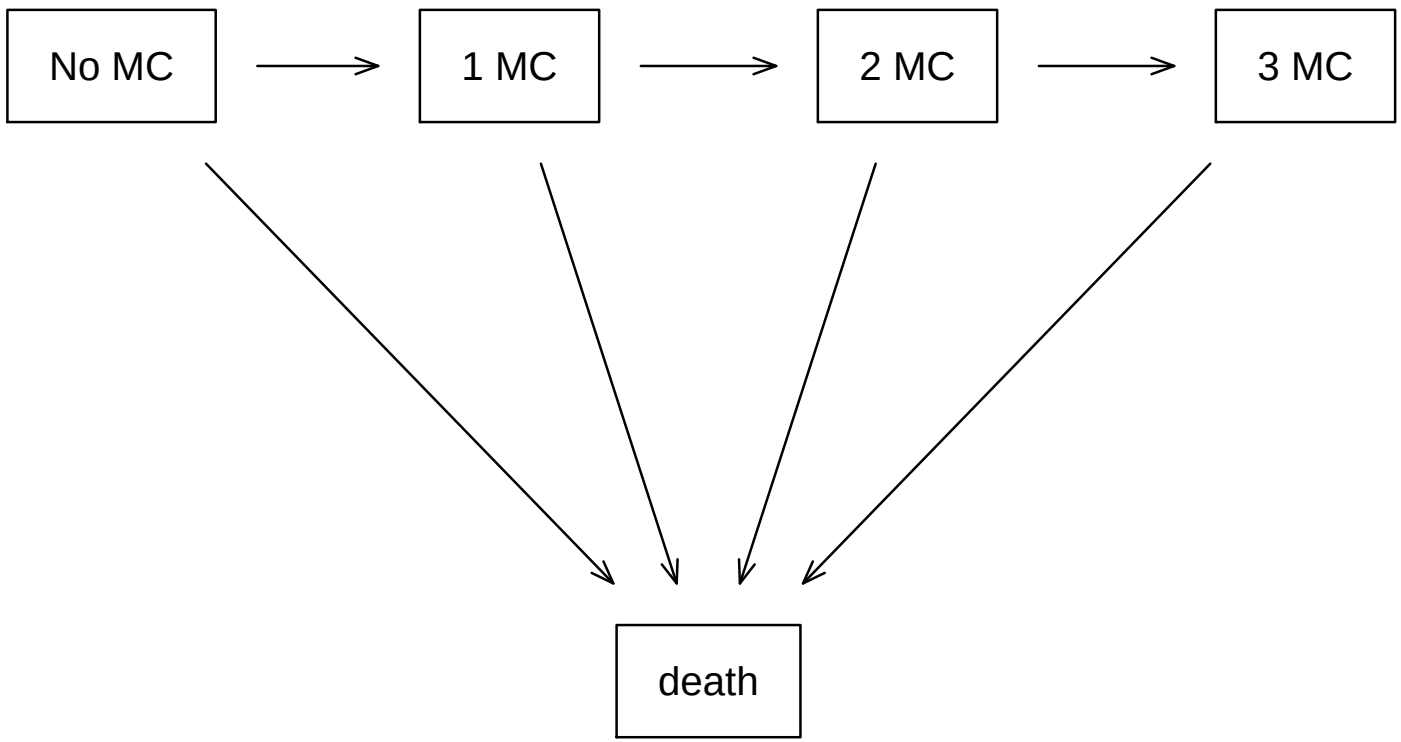
- NAFLD as a covariate
- Outcome of 0–3 “metabolic syndrome” comorbidities
  - diabetes
  - dyslipidemia
  - hypertension



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Data

- 3514 NAFLD cases
- 14004 age/sex matched controls

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Data

- 3514 NAFLD cases
- 14004 age/sex matched controls
- Use age scale
- "Duration of NAFLD" not possible

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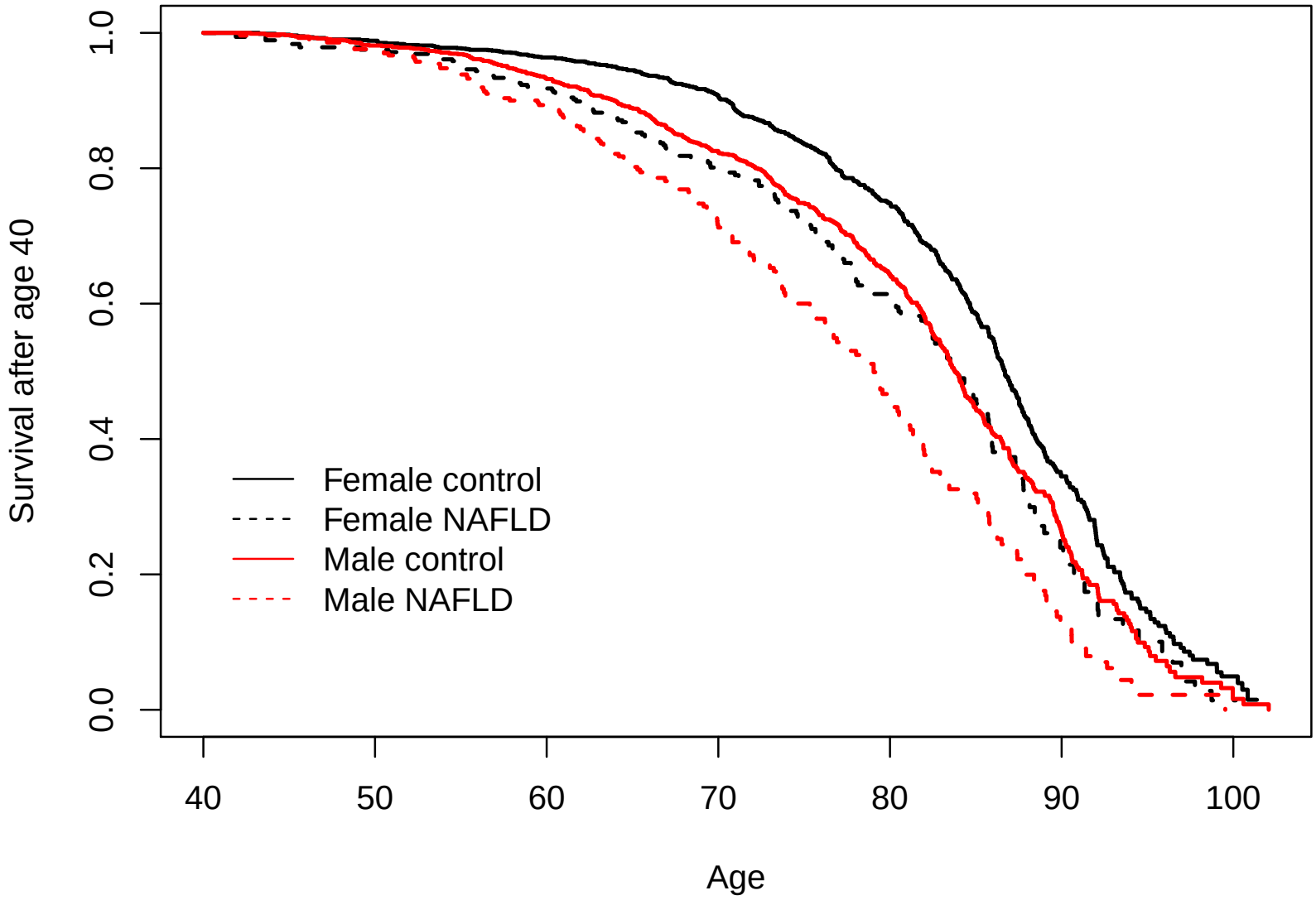
Survival after age 40
1.0
0.8
0.6
0.4
0.2
0.0
40
50
60
70
80
90
100
Age
Female control
Female NAFLD
Male control
Male NAFLD

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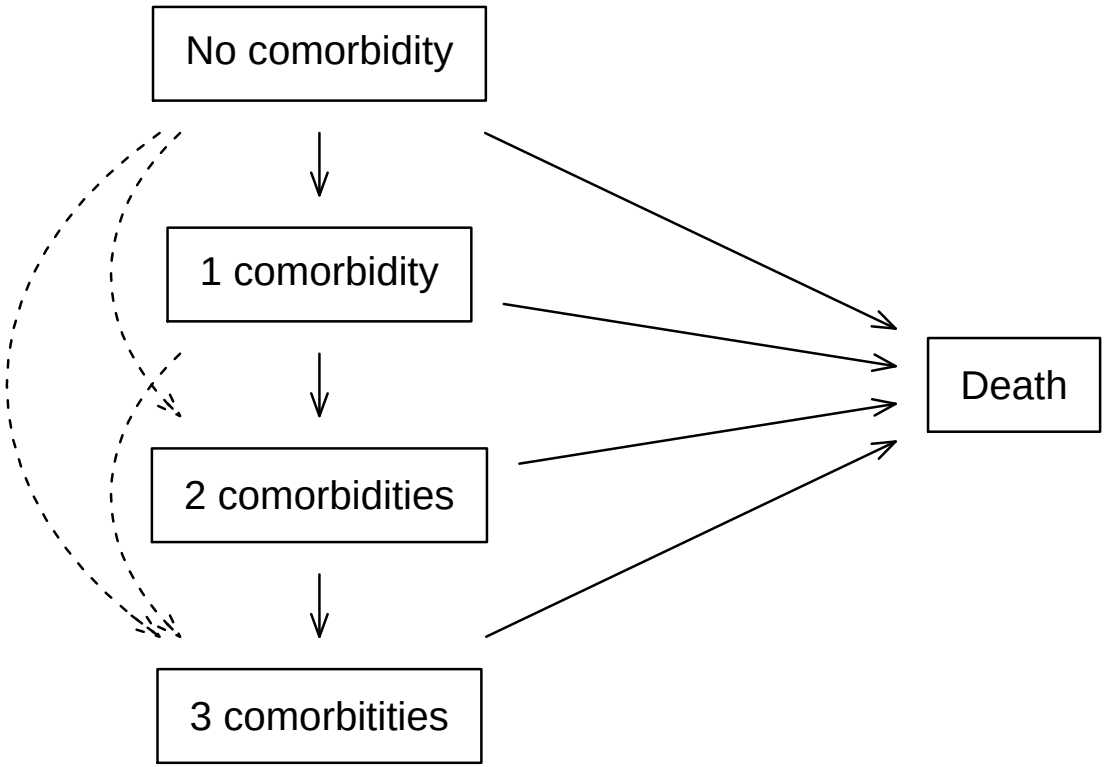
Multistate



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```
check <- survcheck(Surv(age1, age2, event) ~ 1, data=data1,
          istate=cstate, id = id)
check$transitions
       to
from      1mc  2mc  3mc death (censored)
  0mc    1829   70    4   263        5705
  1mc       0 1843   28   243        4567
  2mc       0    0 1048   417        3687
  3mc       0    0    0   441        2220
  death     0    0    0     0           0
```

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Analysis

- Hazard ratios
- Absolute risk
  - current state $p(t)$
  - E(time in state)
  - E(number of visits to each state)
    lifetime risk
  - E(time in state, per visit)

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Hazard model

- Default
  - separate baseline for each transition
  - separate coefficients for each transition
- 0mc:3mc has 4 cases, 1:3 only has 28
- Collapse 0:1, 0:2, 0:3 = "worsening"
- x:death as a single baseline + covariates?
- Many choices possible

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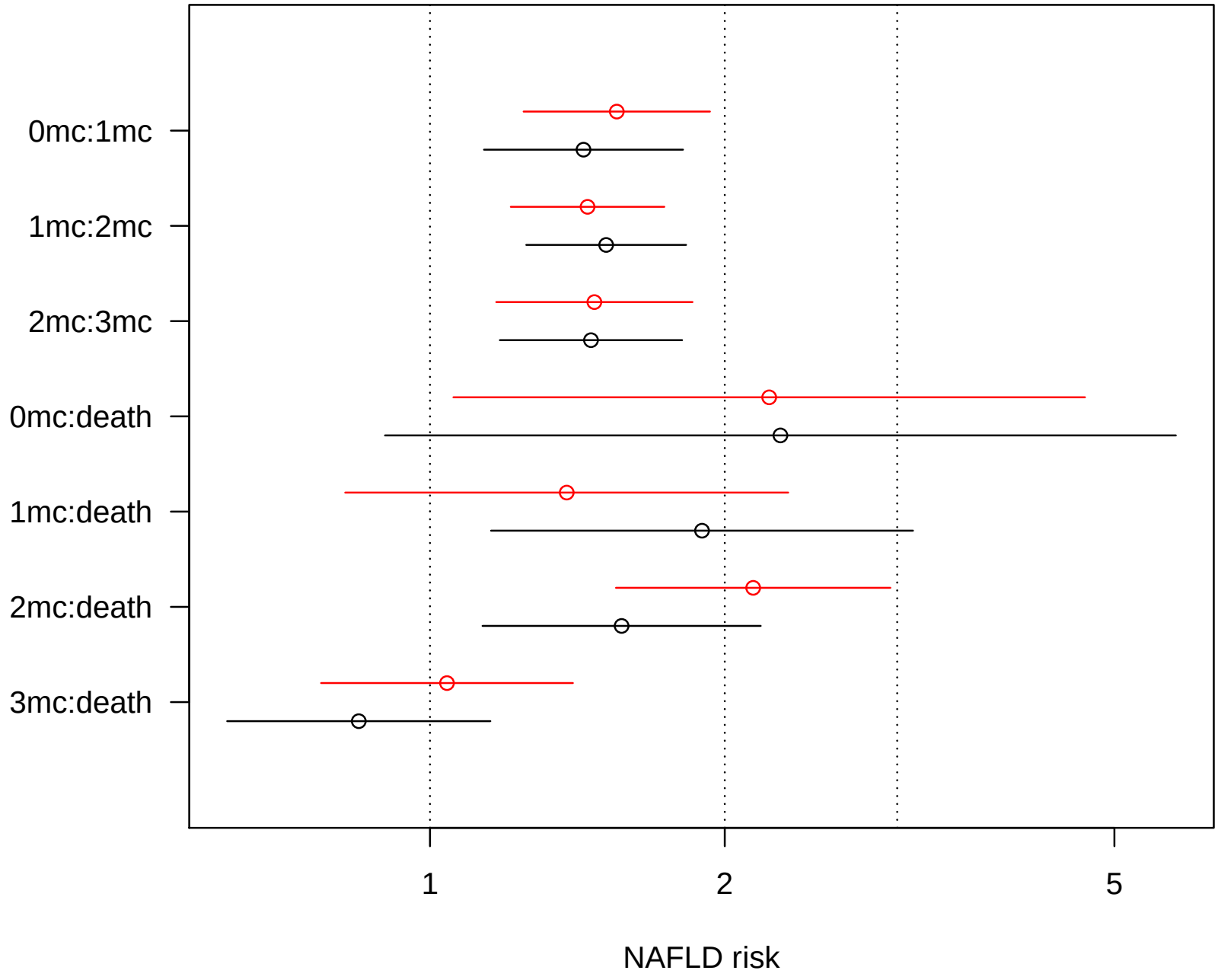
Cox fits

```
cform <- list(Surv(age1, age2, event) ~ nafld + bmi,
              "0mc":c("1mc", "2mc", "3mc") ~ nafld +bmi/ common,
              "1mc":c("2mc", "3mc")        ~ nafld +bmi/ common)

coxm <- coxph(cform, istate=cstate, id= id,
                 data1, subset= (male==1))
coxf <- coxph(cform, istate=cstate, id = id,
                data1, subset= (male==0))
coxm$cmap
           1:2 1:3 2:3 1:4 2:4 3:4 1:5 2:5 3:5 4:5
(Baseline)   1   2   3   4   5   6   7   8   9  10
nafld        1   1   3   1   3   5   7   9  11  13
bmi          2   2   4   2   4   6   8  10  12  14
j <- unique(coxm$cmap[2,])
temp <- rbind(male=coef(coxm)[j], female= coef(coxf)[j])
colnames(temp) <- c("0:1", "1:2", "2:3", paste(0:3, 'death', sep=':'))
round(exp(temp),2)
        0:1  1:2  2:3 0:death 1:death 2:death 3:death
male   1.55 1.45 1.47    2.22    1.38    2.14    1.04
female 1.43 1.51 1.46    2.28    1.90    1.57    0.85
```


0mc:1mc
1mc:2mc
2mc:3mc
0mc:death
1mc:death
2mc:death
3mc:death
1
2
5
NAFLD risk

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State at enrollment

	cstate			
nafld0	0mc	1mc	2mc	3mc
0	51	27	16	7
1	22	31	28	19

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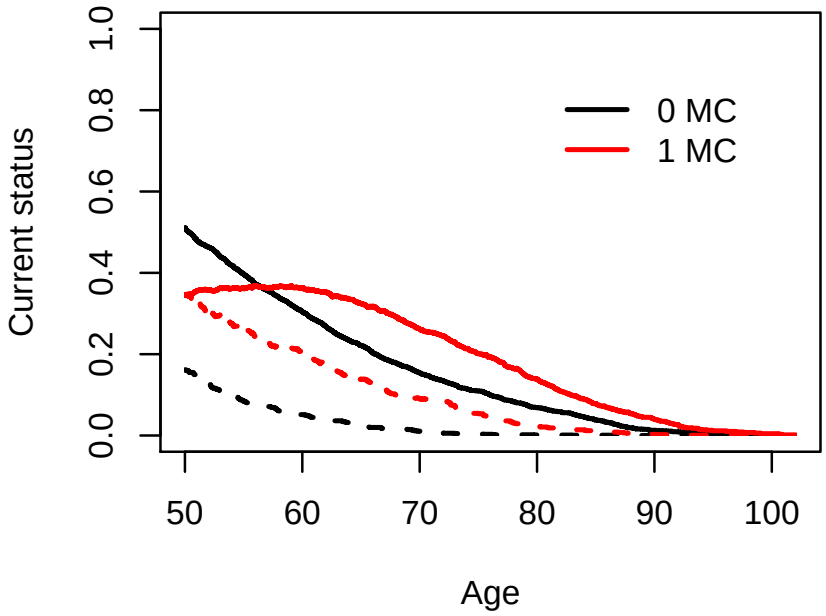
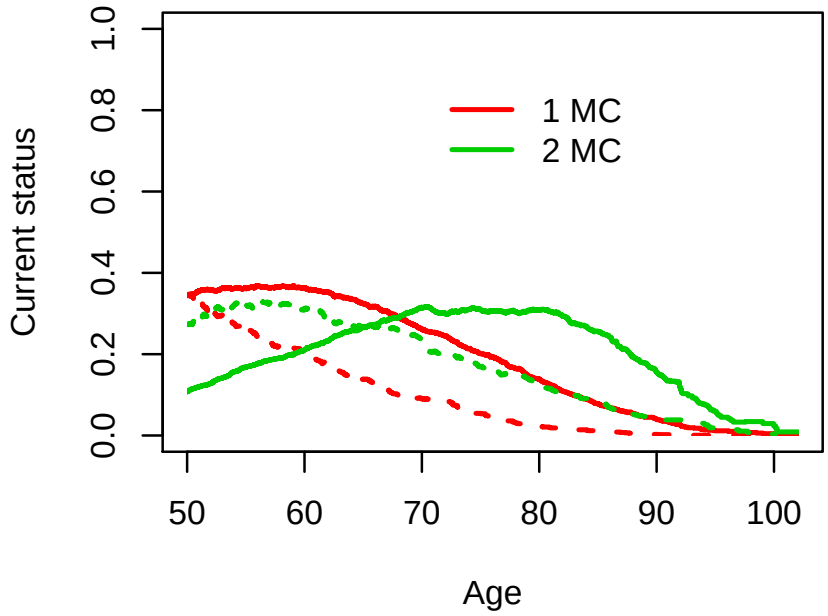
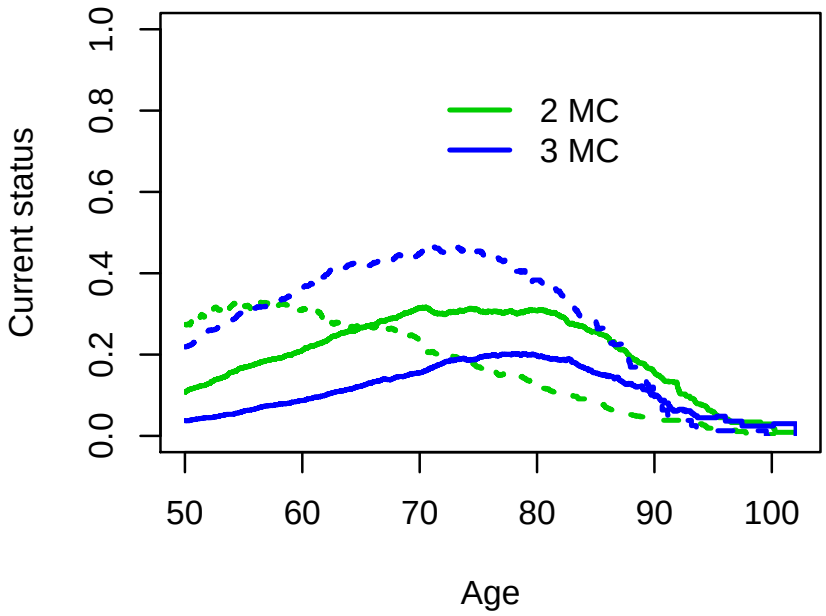
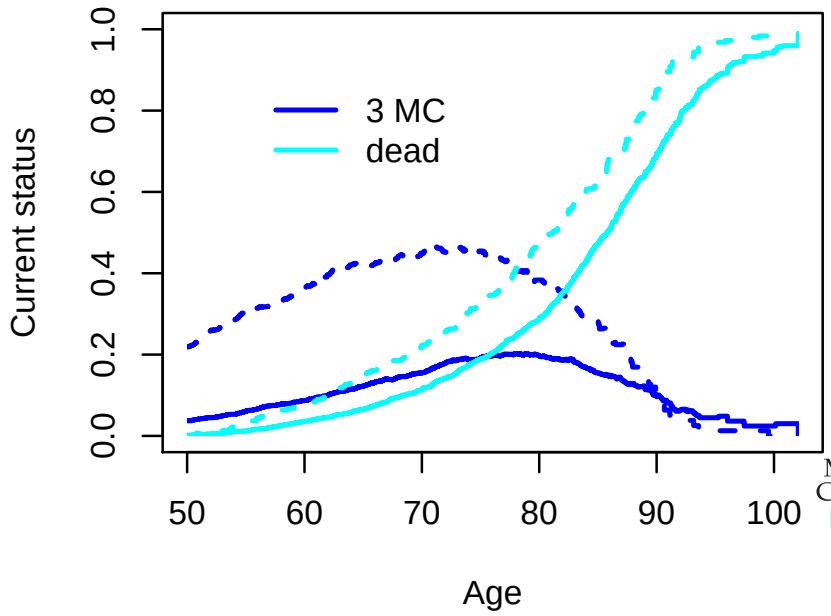
Current status as a function of age









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Expected future for a 50 year old with no comorbidities

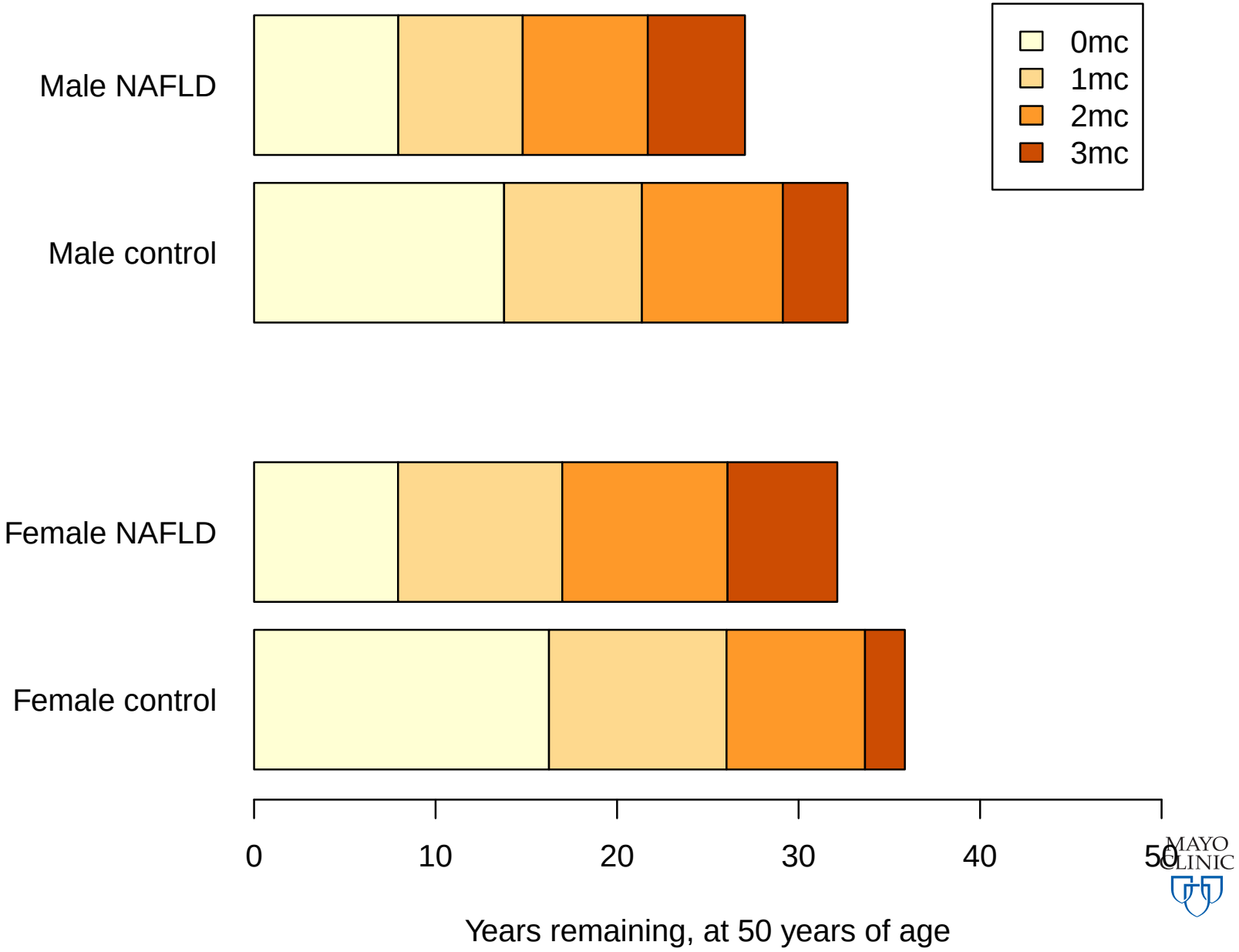
```
s50a <-  survfit(Surv(age1, age2, event) ~ nafld0, data=data1,
                 istate=cstate,
                 id=id, start.time=50)

s50b <- survfit(Surv(age1, age2, event) ~ nafld0, data=data1,
                istate=cstate,
                id=id, start.time=50,
                p0=c(1,0,0,0,0))

print(s50b, rmean=100, digits=2)
Call: survfit(formula = Surv(age1, age2, event) ~ nafld0, data = data1,
    id = id, istate = cstate, start.time = 50, p0 = c(1, 0, 0,
        0, 0))

                     n nevent rmean*
nafld0=0, 0mc    13309      0   15.2
nafld0=1, 0mc     3283      0    7.8
nafld0=0, 1mc    13309    980    8.9
nafld0=1, 1mc     3283    129    8.2
nafld0=0, 2mc    13309   1143    7.7
nafld0=1, 2mc     3283    327    8.2
nafld0=0, 3mc    13309    575    2.7
```

Time in state



Summary

- Multi-state problems are common
- Rich analysis possibilities
- Tools are getting better
- Just don't get carried away with the wrong things . . .

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Software goals

- Multi-state fits are as easy as `coxph`
- Curves of $P(\text{state} \mid t)$ are as easy as `survfit`
- Secondary summaries (time in state, E(visits to state), . . .)
- Better data tools
  - Rules for data
    - Cannot be in two places at once
    - If at risk, must be someplace
    - Gaps and teleports are viewed with suspicion
    - Don't make the user break the rules
  - Immortal time bias is everywhere.
- These are the tools that I use.

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  - Immortal time bias is everywhere.
- These are the tools that I use.
- Don't bugger it up

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