Competing risks and the Fine-Gray model

Terry Therneau

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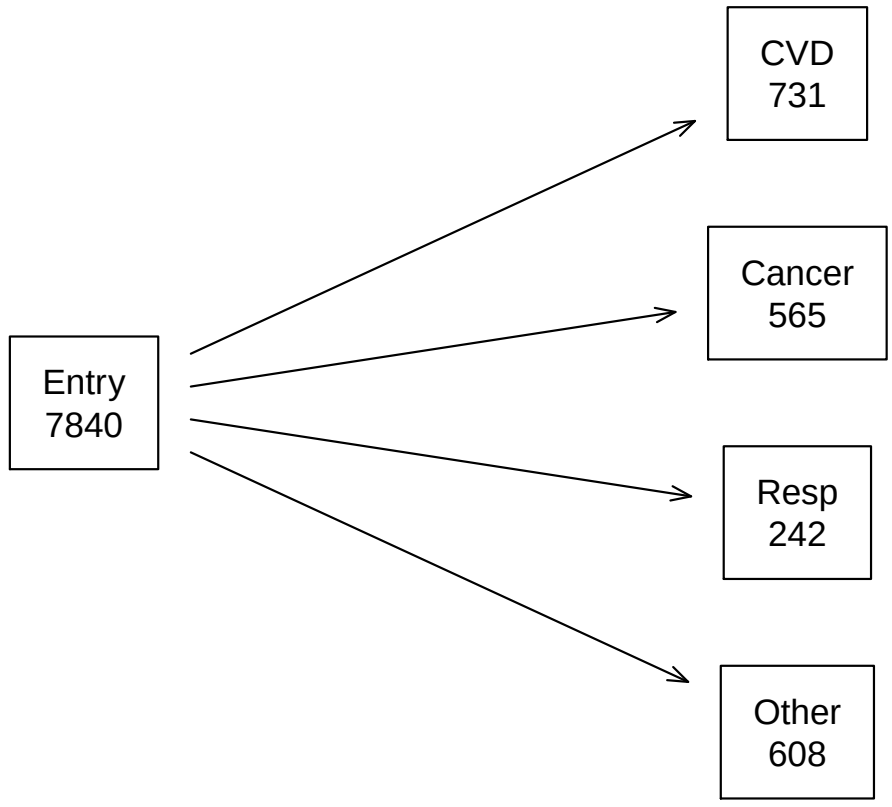
Free light chain

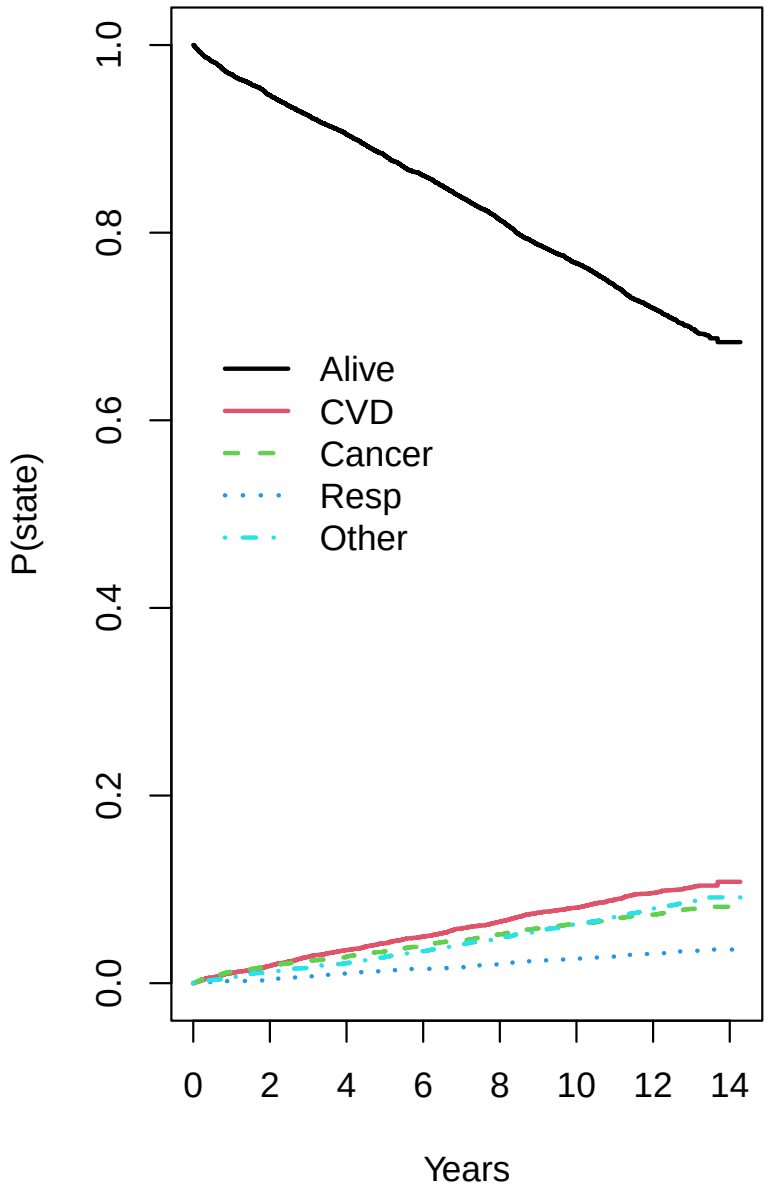


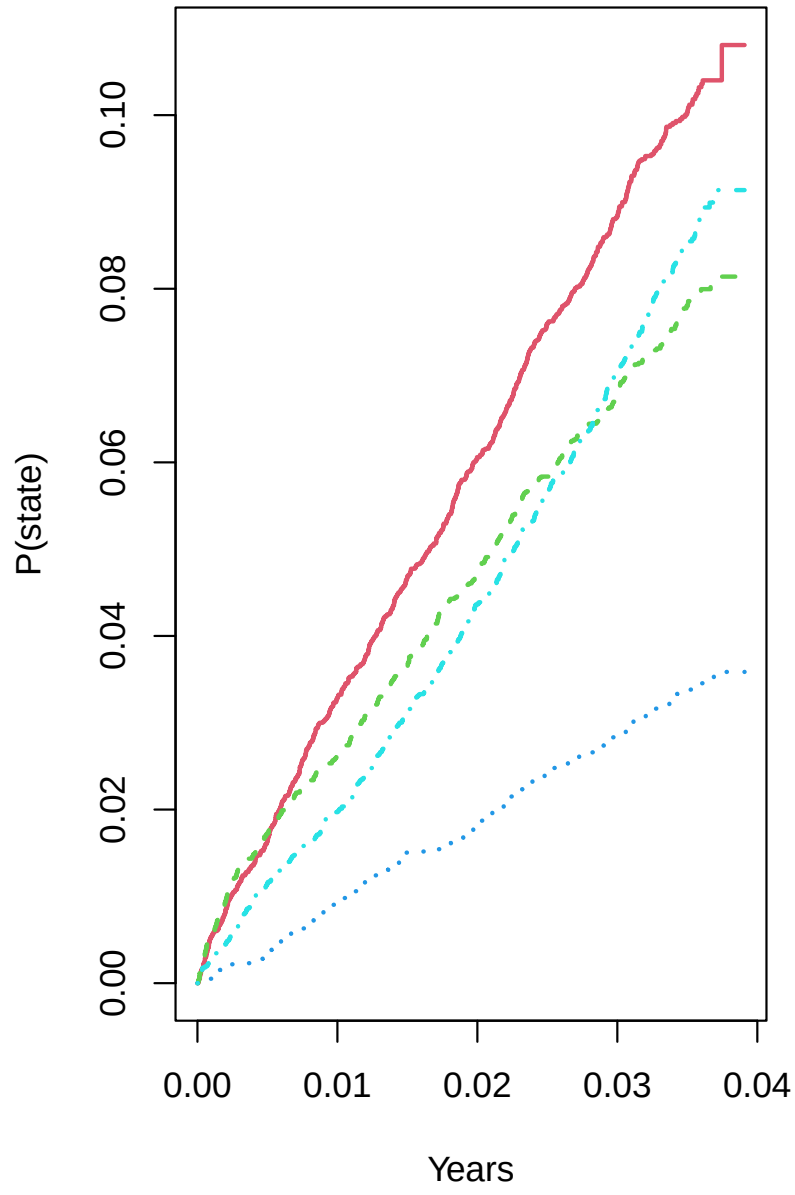
```r
# create a factor (class) variable (hidden)
table(fdata$state)
```

```
censor     CVD Cancer    Resp   Other
  5694     731     565     242     608
```

```r
# Aalen-Johansen
fsurv <- survfit(Surv(years, state) ~1, data=fdata, id=id)

# Multi-state hazard model
fcox  <- coxph(Surv(years, state) ~ age + sex + flc10,
               data= fdata, id = id)
```


P(state)
1.0
0.8
0.6
0.4
0.2
0.0
Alive
CVD
Cancer
Resp
Other
0
2
4
6
8
10
12
14
Years


P(state)
0.10
0.08
0.06
0.04
0.02
0.00
0.00
0.01
0.02
0.03
0.04
Years

The coxph call produces a multi-state hazard model fit. One set of coefficients for each transition (arrow) in the diagram

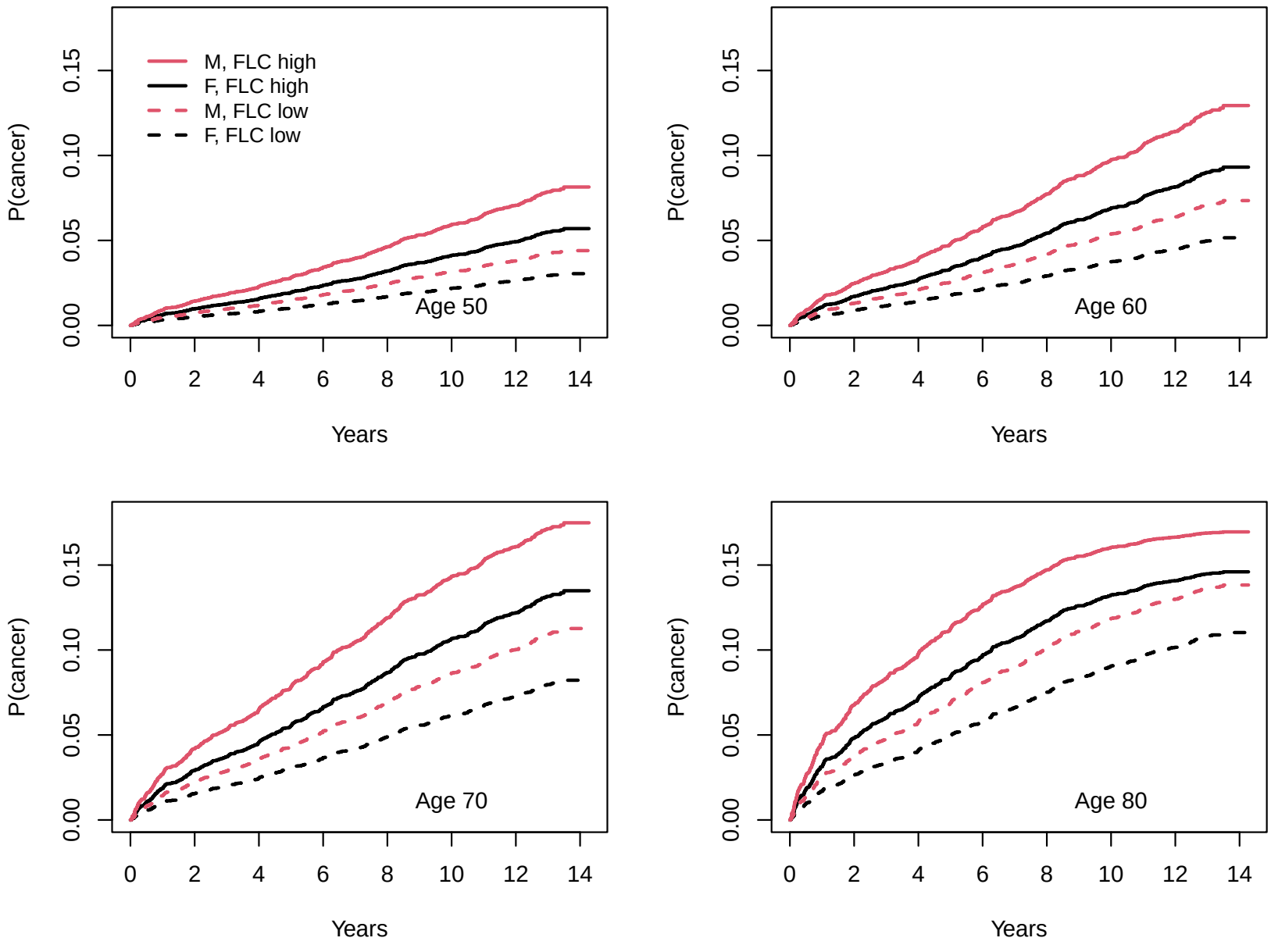
	CVD	Cancer	Resp	Other
age	1.13(28.5)	1.06(12.8)	1.12(16.8)	1.14(27.1)
male	1.52(5.6)	1.46(4.4)	1.73(4.1)	1.23(2.5)
FLC	2.32(9.1)	1.92(5.4)	1.63(2.7)	2.29(7.9)

What is the effect of FLC on *cancer* death?

Create predicted curves based on the fitted model.

```
dummy <- expand.grid(flc10 = 0:1,  sex = c("F", "M"),
                     age= c(50,60, 70, 80))
predsurv <- survfit(fcox, newdata=dummy)
dim(predsurv)
```

```
  data states
    16      5
```


M, FLC high
F, FLC high
M, FLC low
F, FLC low
P(cancer)
0.00
0.05
0.10
0.15
0
2
4
6
8
10
12
14
Years
Age 50
Age 60
Age 70
Age 80

	7 year	14 year
Age 50, Female	1.29	2.65
Age 50, Male	1.86	3.74
Age 60, Female	2.16	4.16
Age 60, Male	3.06	5.59
Age 70, Female	3.36	5.27
Age 70, Male	4.50	6.22
Age 80, Female	4.05	3.57
Age 80, Male	4.68	3.13

But the investigator wants a 1 number summary.

Additive models

- The three most popular models in statistics
  - Linear: $E(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots$
  - GLM: $E(y) = g\left(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots\right)$
  - Cox: $\lambda(t) = \exp\left(\beta_0(t) + \beta_1 x_1 + \beta_2 x_2 + \ldots\right)$
- Why? Simplicity.
  - If `x1= FLC+`, then β_1 is *THE* effect of FLC, independent of any other variables in the model.
  - Statisticians like this.
  - Investigators really like this (a single p-value)
- (Generalized additive models will replace one of the βx terms with $s(x)$, but retain the separability.)

3 criteria for a successful statistical model

1. Simplicity: in the sense described above, leading to simple explanations for the effect of key predictors.
2. Statistical validity: the model must describe the data adequately. "All models are wrong. The practical question is whether a model is wrong enough to not be useful." George Box
3. Numerical stability: the code to fit a model does not require hand-holding or fiddling with tuning parameters: it just runs.

The transform g gets chosen to fit criteria 3; if it helps with criteria 2 that is mostly luck. (It nearly always impedes interpretability).

Fine-Gray: key idea

For an ordinary 2 state Cox model:

$$P(death) = g(\beta_0(t) + \beta_1 x_1 + \beta_2 x_2 + \ldots)$$

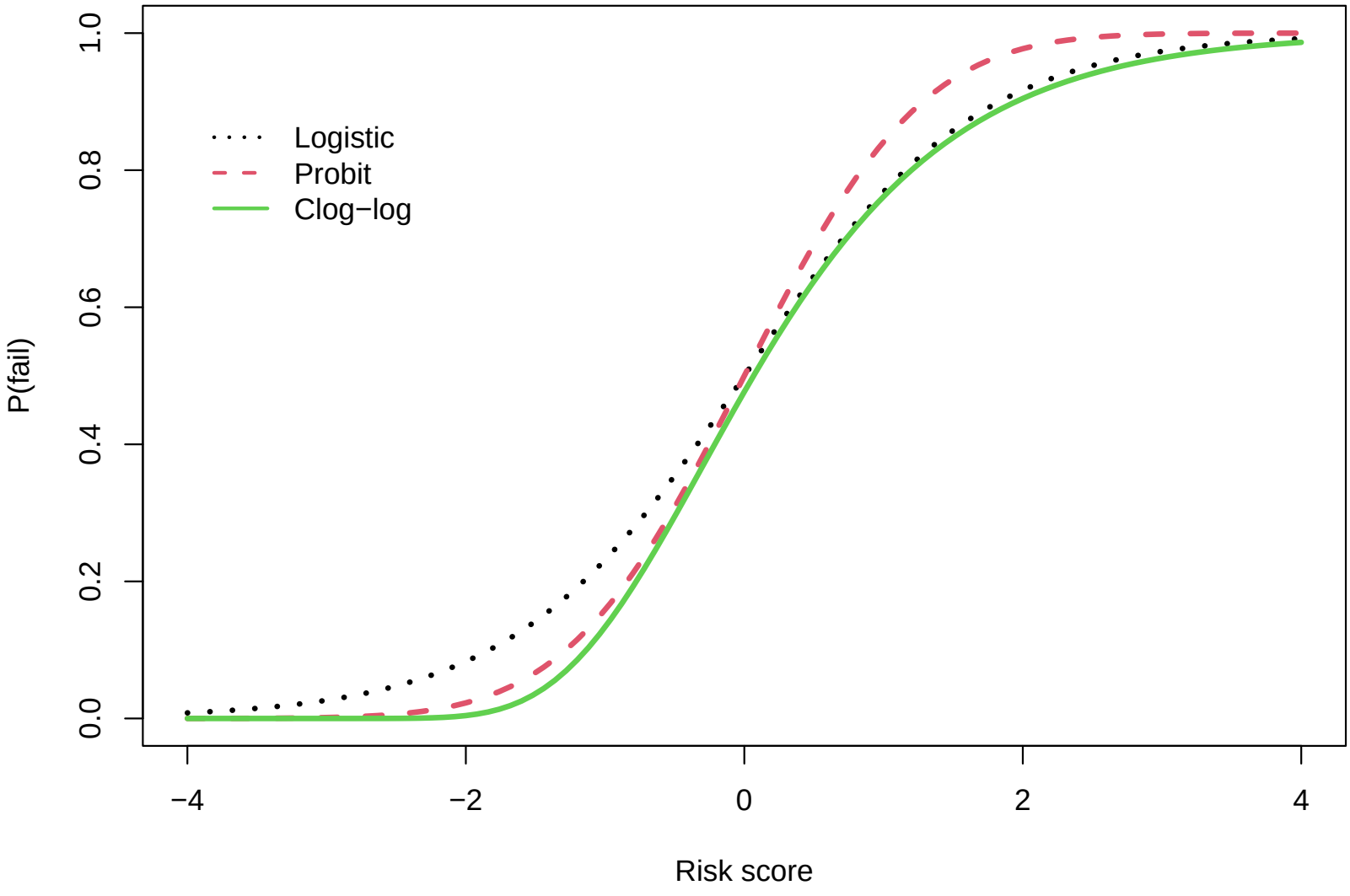
where g = complementary log-log

Assume that for outcome k

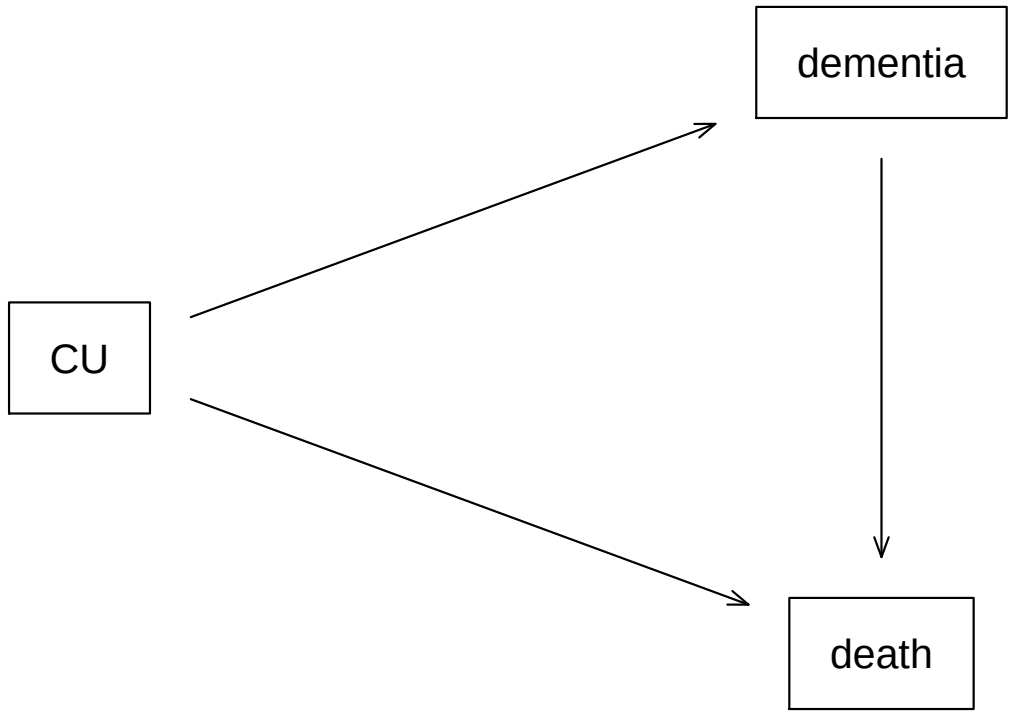
$$p_k(t) = g(\beta_{k0}(t) + \beta_{k1} x_1 + \beta_{k2} x_2 + \ldots)$$

Issues - *how* to fit this (censored data) - is it a sensible model?

Transforms

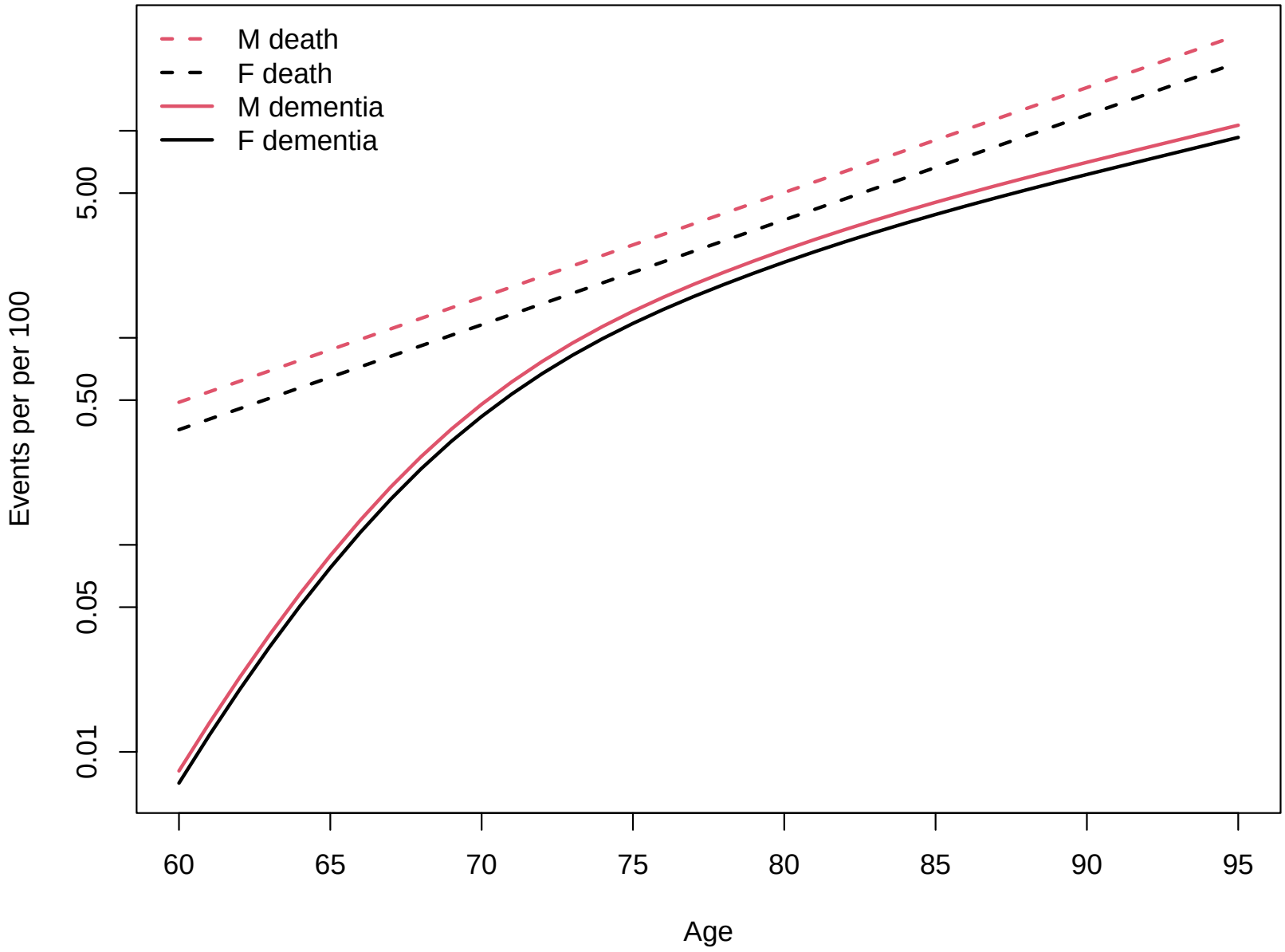

Logistic
Probit
Clog−log
P(fail)
0.0
0.2
0.4
0.6
0.8
1.0
−4
−2
0
2
4
Risk score

Example

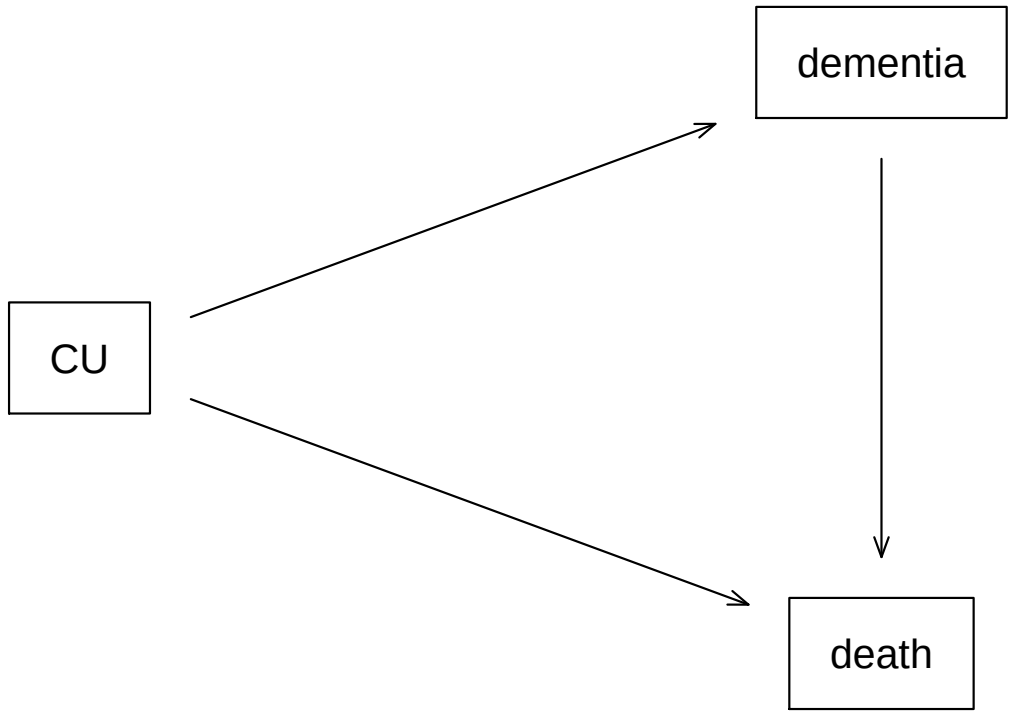


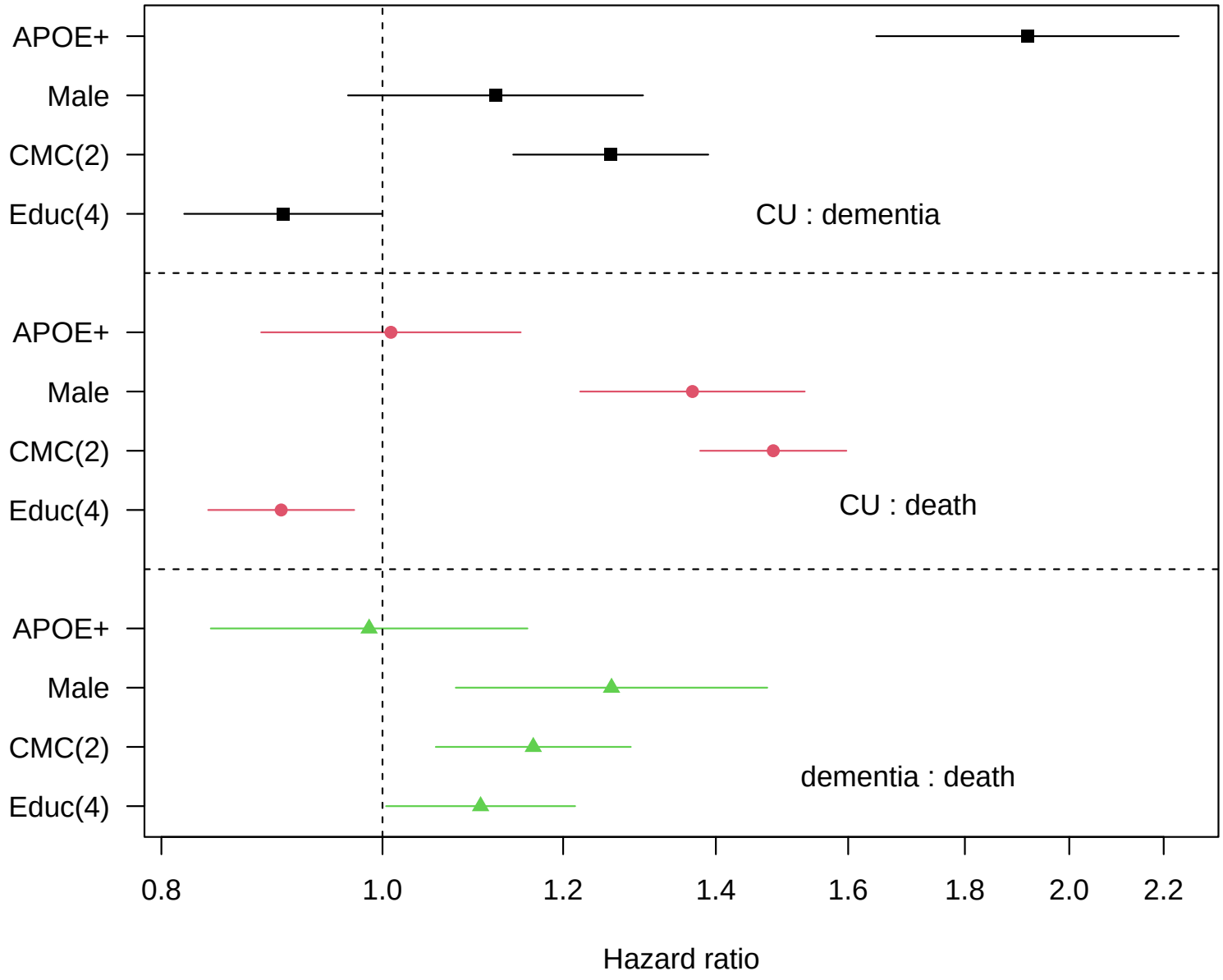
Predictors of dementia and death

- 6258 subjects
- 726 dementia, 1990 deaths, 1/2 the dementias occur after active participation
- Taken from the MCSA, an age/sex stratified random sample from Olmsted County, Minnesota
- REP infrastructure
- Covariates
  - APOE e4 allele: risk factor for amyloidosis
  - CMC score: 0-7, count of morbidities

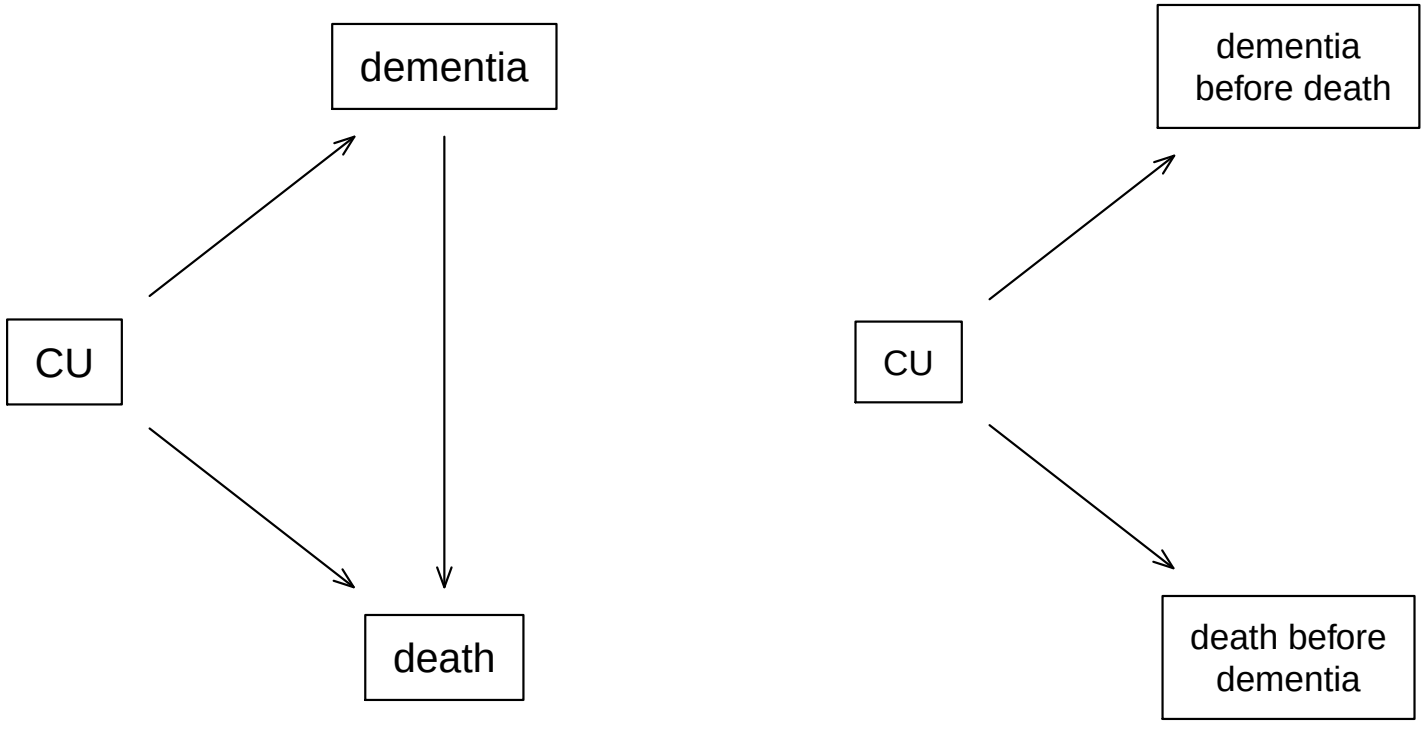

M death
F death
M dementia
F dementia
Events per per 100
0.01
0.05
0.50
5.00
60
65
70
75
80
85
90
95
Age

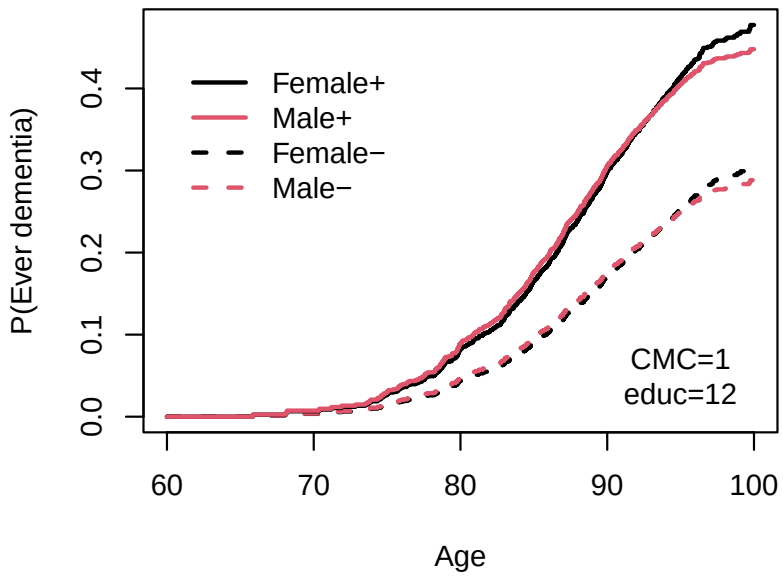
Multistate

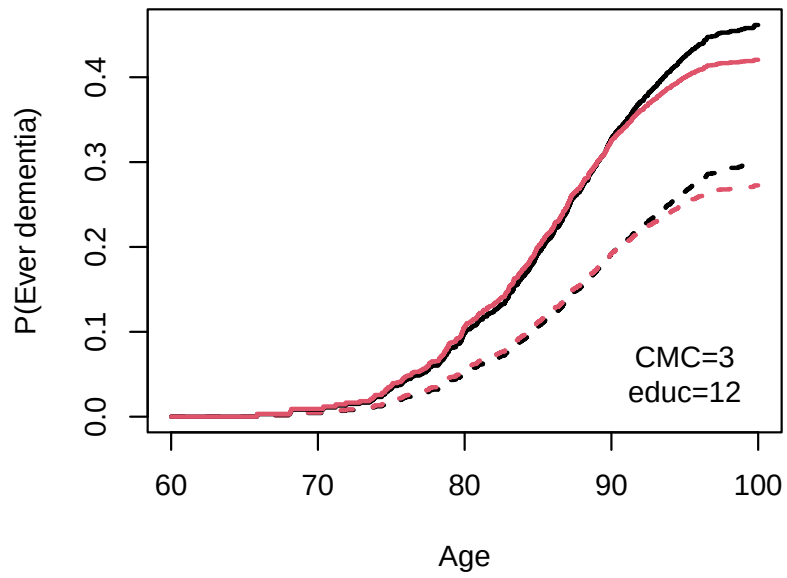


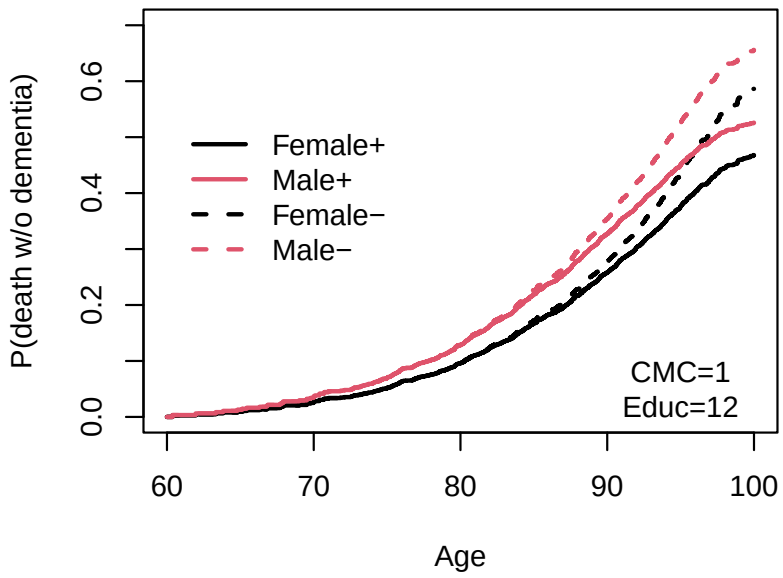

APOE+
Male
CMC(2)
Educ(4)
CU : dementia
APOE+
Male
CMC(2)
Educ(4)
CU : death
APOE+
Male
CMC(2)
Educ(4)
dementia : death
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
Hazard ratio

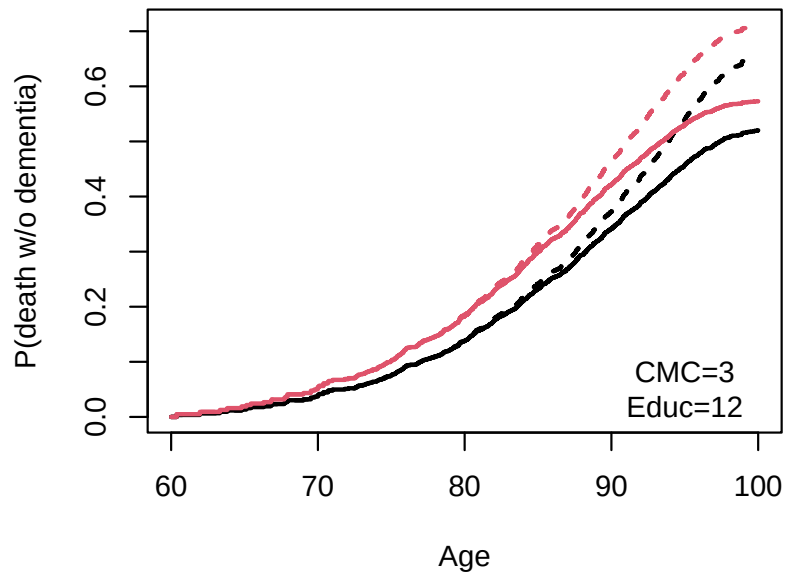
Competing risks




P(Ever dementia)
0.0
0.1
0.2
0.3
0.4
Female+
Male+
Female−
Male−
CMC=1
educ=12
60
70
80
90
100
Age


P(Ever dementia)
0.0
0.1
0.2
0.3
0.4
CMC=3
educ=12
60
70
80
90
100
Age


P(death w/o dementia)
0.0
0.2
0.4
0.6
Female+
Male+
Female−
Male−
CMC=1
Educ=12
60
70
80
90
100
Age


P(death w/o dementia)
0.0
0.2
0.4
0.6
CMC=3
Educ=12
60
70
80
90
100
Age

Fine-Gray

- The effect of sex on P(dementia) depends on the levels of all the other covariates, and on time.
- There is no single p-value.
-
- Model the two outcomes directly:
  - P(dementia before death) $= g(\beta_0(t) + X\beta)$
  - P(death before dementia) $= g(\alpha_0(t) + X\alpha)$
  - $g =$ the complimentary log log
- Technical challenge.
  - Treating survival as binomial

Geskus' formulation

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- Create a special data set for each outcome.
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- Weights decrease based on $F(t)$ and $G(t)$.
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- Apply an ordinary Cox model program to the new data set.

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- Advantage: all the Cox model checks are available.

Geskus' formulation

- Create a special data set for each outcome.
- Subjects who are censored persist, but with diminished case weights.
- Weights decrease based on $F(t)$ and $G(t)$.
- (You can't have time-dependent covariates.)
- Apply an ordinary Cox model program to the new data set.
- Advantage: all the Cox model checks are available.
- For the dementia dataset, subjects who die also persist, but with diminished case weights.

Geskus

```
fdata1 <- finegray(Surv(age1, age2, state) ~., data=data3,
                   id= clinic, etype= "dementia")
fdata2 <- finegray(Surv(age1, age2, state) ~., data=data3,
                   id= clinic, etype= "death")
#
rbind(data3 = dim(data3), fdata1 = dim(fdata1), fdata2= dim
```

```
         [,1] [,2]
data3   12110   13
fdata1 334555   14
fdata2 293461   14
```

```
fcox1 <- coxph(Surv(fgstart, fgstop, fgstatus) ~ apoepos +
                male + cmc + edu4, weight = fgwt, fdata1)
fcox2 <- coxph(Surv(fgstart, fgstop, fgstatus) ~ apoepos +
                male + cmc + edu4, weight = fgwt, fdata2)
```

	apoepos	male	cmc	edu4
multi, CU:dementia	0.651	0.114	0.230	-0.100
multi, CU:death	0.009	0.313	0.394	-0.102
FG, dementia before death	0.501	-0.096	0.047	-0.115
FG, death before dementia	-0.326	0.164	0.143	-0.099

cox.zph on fcox1

	chisq	df	p
apoepos	14.137	1	0.00017
male	5.680	1	0.01716
cmc	20.329	1	6.5e-06
edu4	0.751	1	0.38622
GLOBAL	37.154	4	1.7e-07

How well does it work?

- If cause 2 has low prevalence ($< 1/4$) and/or cause 2 has no strong covariates, then all is well for the cause 1 model
  - Coefficients for outcome 1 hardly change from the Cox model
  - The predicted curves have the same shape, but are attenuated
- Examples
  - Revision after hip fracture
  - Epidemic

Otherwise

1. The model often does not fit very well. It fails our 'good enough' criteria.
2. There is no physical system that satisfies the FG model.
3. Users interpret coefficients as though it were a Cox model, and it is not.
4. It encourages bad science: most examples (and users) fit only one of the endpoints, ignoring the other.
5. If there are moderately strong covariates, and $> 80\%$ reach one of the two endpoints, it is common to have $\hat{P}$(dementia before death) + $\hat{P}$(death before dementia) > 1 for high risk subjects.
6. In the guts of the code, people who die are still at risk for dementia.

What to do?

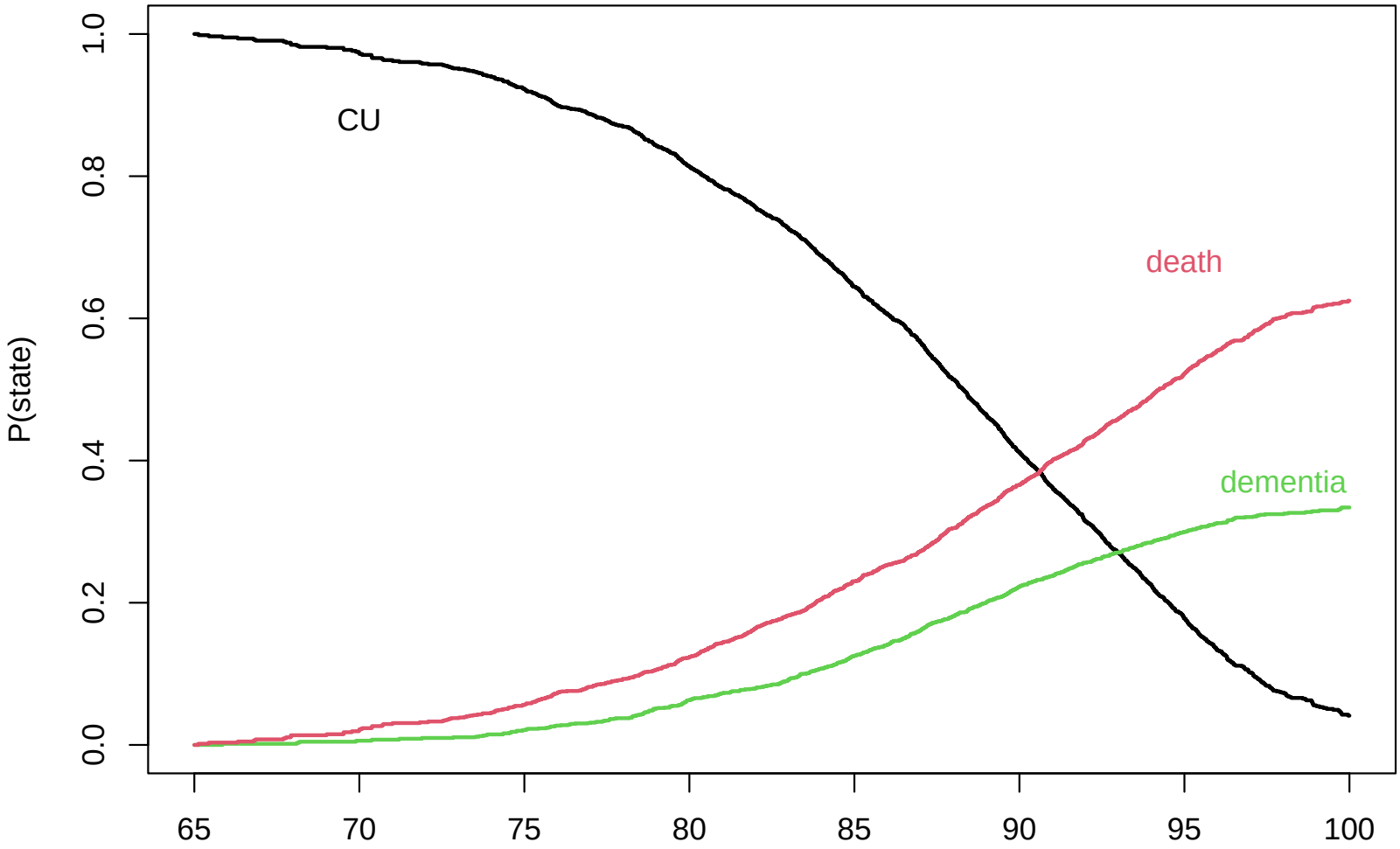
1. Intentionally report both hazards and absolute risk
   - Biology + the consequences of that biology
   - A two number summary of (APOE hazard, APOE risk), true for all time, for all combinations of other covariates, is an impossible dream.
   - For absolute risk, choose 1 (or 2) timepoints of interest.
   - Use pseudovalues or marginal estimates for those time points.
2. Marginal estimates
   - If APOE is the variable of interest, average over the others
     - dummy data set with n rows, everyone APOE-
     - get all n predicted curves, take the average
     - repeat for APOE+
   - g-estimation
3. Pseudovalues
   - From the appropriate KM or Aalen-Johansen (CI) curve
   - Select one or more time points, and create the matrix of *pseudovalues*
   - Essentially, the influence of each observation on $p(t)$
   - Use these in a regression model

```
ajfit <- survfit(Surv(age1, age2, state) ~ 1, id = clinic,
                 data=data3, start.time = 65)
pdat <- pseudo(ajfit, times= c(70, 80, 90, 100))
dim(pdat)
```

```
[1] 6157    4    3
```

```
d100 <- pdat[,4,2]  # influence on dementia at age 100

# data with one obs per subject
base <- subset(data3, !duplicated(clinic))
pfit1 <- glm(d100 ~ apoepos + male + cmc +edu4, base,
             family= gaussian(link = blogit()))
pfit2 <- glm(d100 ~ apoepos + male + cmc +edu4, base,
             family= gaussian(link = bcloglog()))
```


P(state)
0.0
0.2
0.4
0.6
0.8
1.0
65
70
75
80
85
90
95
100
CU
death
dementia

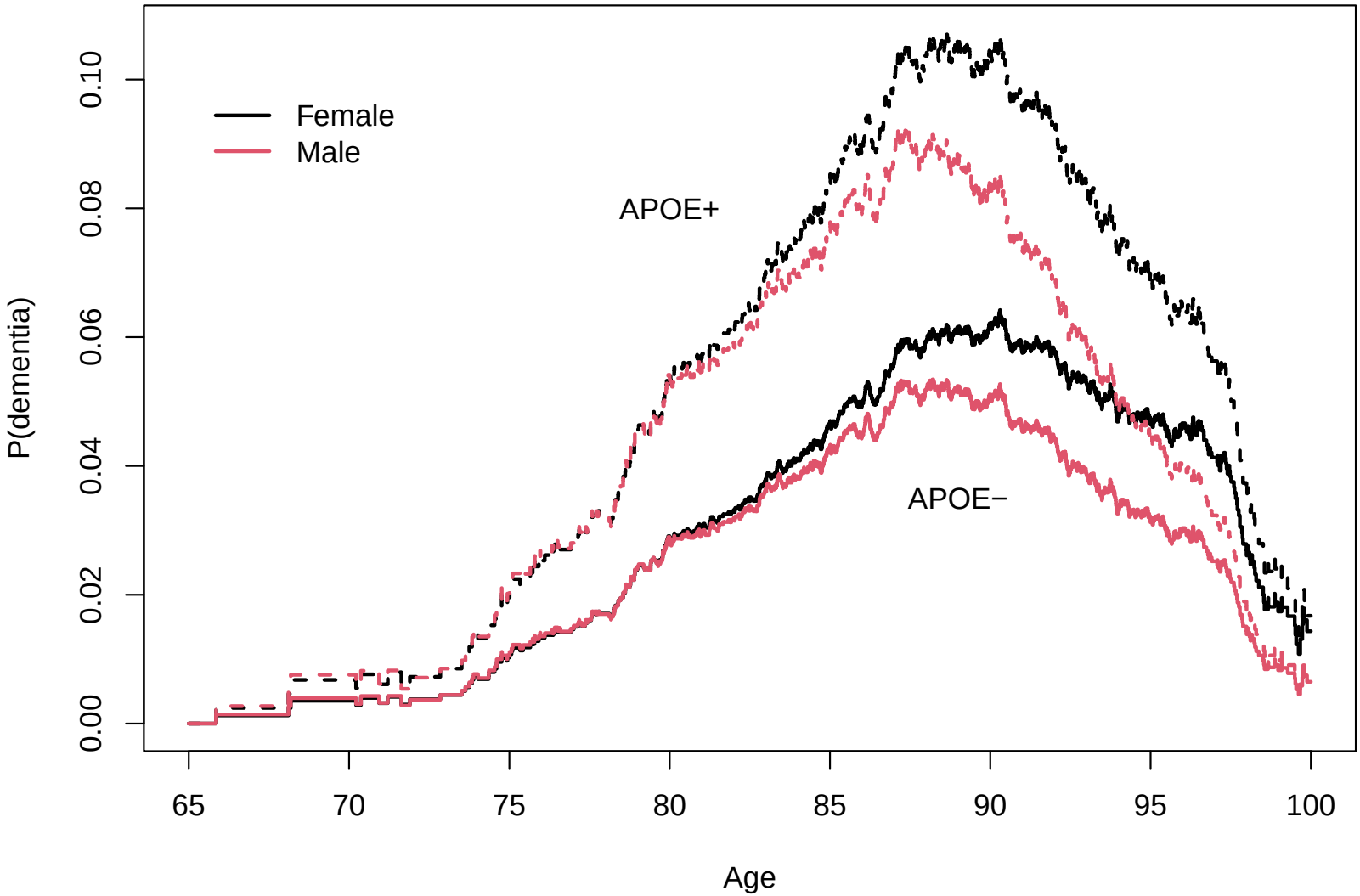
	(Intercept)	apoepos	male	cmc	edu4
pseudo, logit	-0.60	0.67	-0.09	-0.07	-0.03
pseudo, cloglog	-0.83	0.54	-0.09	-0.05	-0.02
FineGray, dem		0.50	-0.10	0.05	-0.12
multistate HR		0.65	0.11	0.23	-0.10

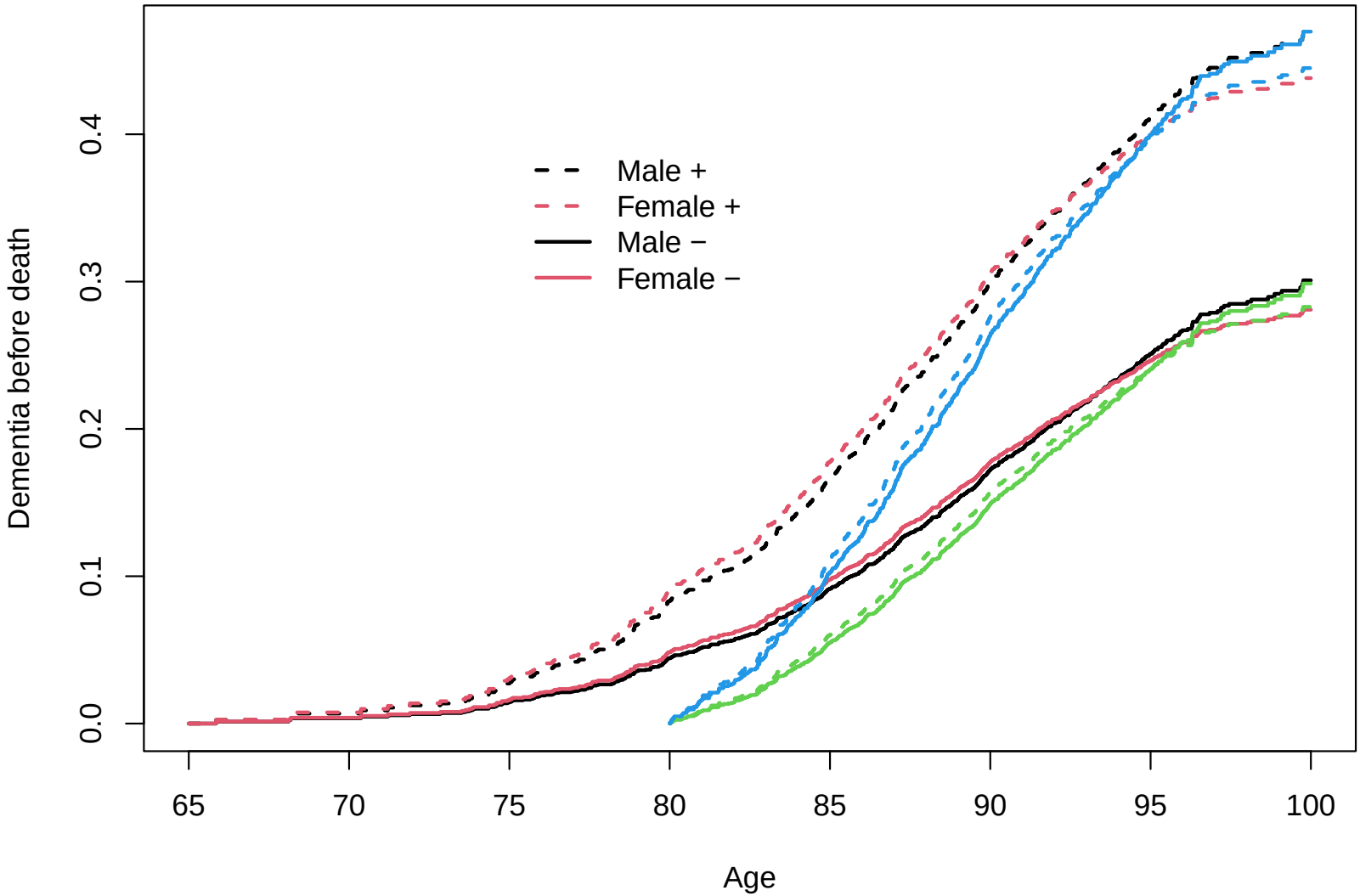
Multiple time points

- For multiple time points at once:
  - A bit more work to set up.
  - Add `factor(time)` to the fit: one intercept per time point.
  - Robust variance is necessary, fit using GEE instead of glm.
- Closely related to ordinal logistic regression
- With many time points, result will approach the FG
  - Coefficients will be nearly identical, se a small bit larger
  - Adding time*covariate interactions is a test for 'proportional cloglog'
  - A good way to more deeply understand the Fine Gray model

Final

- Multi-state models are important
  - No one outcome is dominant
  - Want to understand the trajectory of disease
  - Both rates and outcomes are necessary summaries
- We like additive models.
- Additive on hazard scale $\neq$ additive on absolute risk scale
- FG was an early attempt to address this. Credible at the time, but has not aged well.
- It works when you don't need it, and fails when you do.


Female
Male
APOE+
APOE−
P(dementia)
0.00
0.02
0.04
0.06
0.08
0.10
65
70
75
80
85
90
95
100
Age


Dementia before death
0.0
0.1
0.2
0.3
0.4
65
70
75
80
85
90
95
100
Age
Male +
Female +
Male −
Female −