

Mortality and morbidity among T2D DN patients

SDC

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Chapter 1

Analysis of T2 patients' follow-up

```
> library( Epi )
> library( splines )
```

Initially we load the T2D patients from the datasets with the follow-up:

```
> load( file="./data/Base-Lexis.Rda" )
> L1 <- subset( L1, dm.type=="type2" )
> L7 <- subset( L7, dm.type=="type2" )
```

We can make a Lexis diagram of the follow-up with DN duration and age as timescales:

```
> ypi <- 7
> yl <- c(15,90)
> xl <- c(0,35)
> pdf( "./graph/DN2-tfn-Lexis.pdf",
+       height=1+diff(yl)/ypi,
+       width=1+diff(xl)/ypi )
> par( mai=c(3,3,1,1)/4, omi=c(0,0,0,0),
+       mgp=c(3,1,0)/1.6, las=1 )
> plsymb <- c(NA,16)[1+(substr(L7$lex.Xst,1,4)=="Dead")]
> plot( L7,
+       time.scale=c("tfn","age"), xlab="DN duration", ylab="Age",
+       col=clr[L7$lex.Cst],
+       xaxs="i", yaxs="i", xaxt="n", yaxt="n", xlim=xl, ylim=yl,
+       grid=seq(10,90,5), lty.grid=1 )
> axis( side=1, at=0:5*5, labels=rep("",6) )
> axis( side=1, at=0:5*10 )
> axis( side=2, at=0:20*5, labels=rep("",21) )
> axis( side=2, at=0:20*10 )
> points( L7, pch=pl symb, cex=0.7, col=clr[L7$lex.Cst] )
> dev.off()
null device
1

> xl <- c(0,15)+1998
> pdf( "./graph/DN2-per-Lexis.pdf",
+       height=1+diff(yl)/ypi,
+       width=1+diff(xl)/ypi )
> par( mai=c(3,3,1,1)/4, omi=c(0,0,0,0),
+       mgp=c(3,1,0)/1.6, las=1 )
> plsymb <- c(NA,16)[1+(substr(L7$lex.Xst,1,4)=="Dead")]
> plot( L7,
+       time.scale=c("per","age"), xlab="Date of FU", ylab="Age",
+       col=clr[L7$lex.Cst],
+       xaxs="i", yaxs="i", xaxt="n", yaxt="n", xlim=xl, ylim=yl,
+       grid=seq(10,90,5), lty.grid=1 )
> axis( side=1, at=0:5*5+2000, labels=rep("",6) )
```

```

> axis( side=1, at=0:5*10+2000 )
> axis( side=2, at=0:20*5, labels=rep("",21) )
> axis( side=2, at=0:20*10 )
> points( L7, pch=plsymb, cex=0.7, col=clr[L7$lex.Cst] )
> dev.off()

null device
1

> xl <- c(0,35)
> X7 <- subset( L7, !is.na(tfCVD) )
> pdf( "./graph/DN2-cvd-Lexis.pdf",
+      height=1+diff(y1)/ypi,
+      width=1+diff(x1)/ypi )
> par( mai=c(3,3,1,1)/4, omi=c(0,0,0,0),
+      mgp=c(3,1,0)/1.6, las=1 )
> plsymb <- c(NA,16)[1+(substr(X7$lex.Xst,1,4)=="Dead")]
> plot( X7,
+      time.scale=c("tfCVD","age"), xlab="CVD duration", ylab="Age",
+      col=clr[X7$lex.Cst],
+      xaxs="i", yaxs="i", xaxt="n", yaxt="n", xlim=xl, ylim=y1,
+      grid=seq(10,90,5), lty.grid=1 )
> axis( side=1, at=0:5*5, labels=rep("",6) )
> axis( side=1, at=0:5*10 )
> axis( side=2, at=0:20*5, labels=rep("",21) )
> axis( side=2, at=0:20*10 )
> points( X7, pch=plsymb, cex=0.7, col=clr[X7$lex.Cst] )
> dev.off()

null device
1

```

We also make a plot of the actual transitions between states for T2D patients:

```

> bp <- list( x = c( 10, 40, 43, 19, 90, 90, 90, 90 ),
+            y = c( 95, 65, 35, 5, 95, 65, 35, 5 ) )
> boxes( L7, boxpos=bp, cex=1.2, lwd=3, wmult=1.1, hmult=1.3,
+      show.BE="nz", BE.pre=c("", " ", ""),
+      scale.R=100, digits.R=1, DR.sep=c(" (", ")"),
+      col.bg=clx, col.txt=rep(c("white","black"),each=4),
+      col.border=c(clx[1:4],rep("black",4)),
+      col.arr=c(par("fg"),clr[c(2,1,4)])[c(1:3,2,3,4,1,4)],
+      pos.arr=c(0.4,0.6)[c(1,2,1,1,1,1,2,1)] )

```

1.1 Analysis of rates

In order to analyze the transition rates we split the follow-up in small pieces of 2 month duration along the timescale time since DN, called `tfn`:

```

> S7 <- splitLexis( L7, breaks=seq(0,100,1/6), time.scale="tfn" )
> summary( S7 )

```

Transitions:									
To									
From	DN	CVD	ESRD+CVD	ESRD	Dead(DN)	Dead(CVD)	Dead(ESRD+CVD)	Dead(ESRD)	
DN	8477	107	0	38	37	0	0	0	
CVD	0	8697	63	0	0	120	0	0	
ESRD+CVD	0	0	1333	0	0	0	43	0	
ESRD	0	0	16	602	0	0	0	1	
Sum	8477	8804	1412	640	37	120	43	1	

```

Transitions:
To
From      Records:  Events: Risk time:  Persons:

```

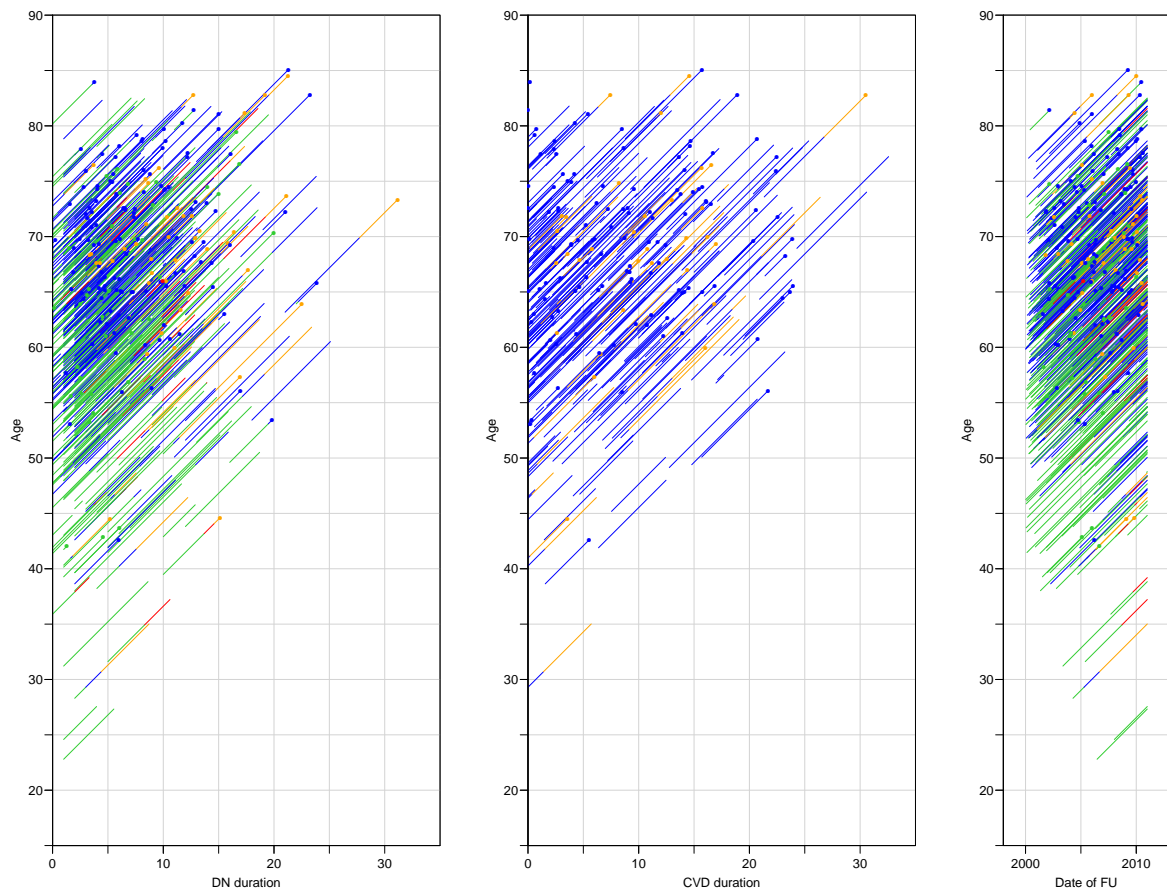


Figure 1.1: *Lexis diagrams for the follow-up of T2 patients by DN duration, CVD duration and calendar time versus age. DN state is green, CVD blue, ESRD after CVD orange and ESRD without CVD red. Dots indicate deaths.*

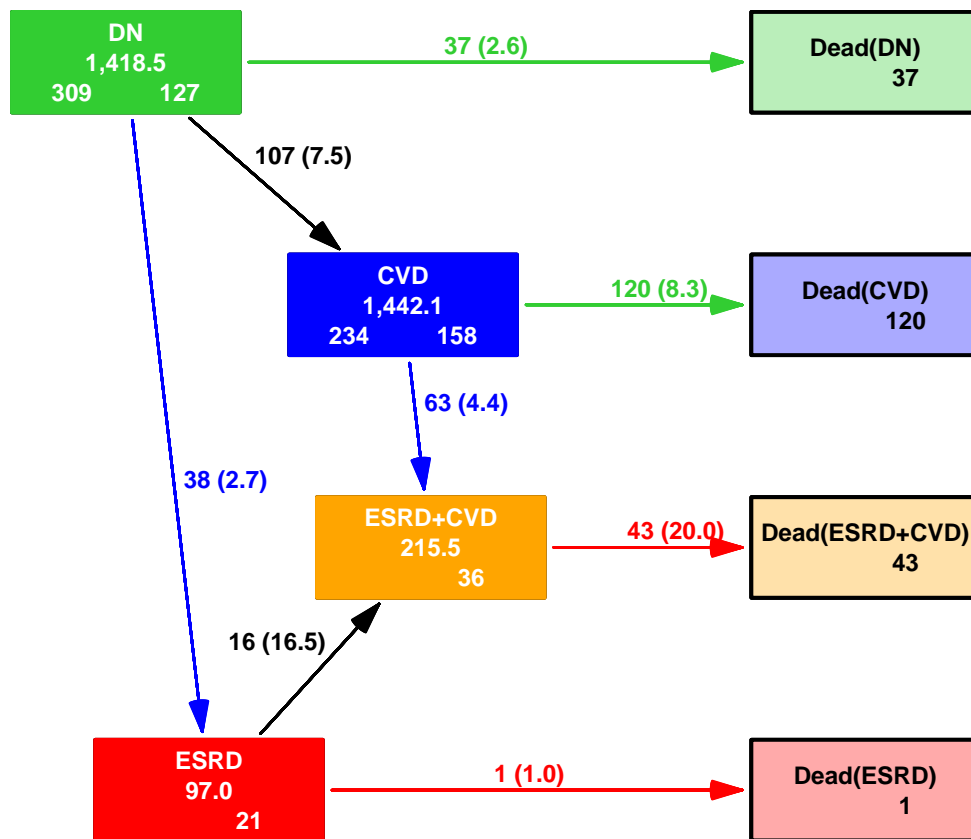


Figure 1.2: States and transitions between them in the analysis set-up for T2D patients. Numbers in the boxes are the person-years, and the number of persons starting, respectively ending in each state. The numbers on the arrows are the number of transitions (rate per 100 PY).

Note that some persons start their follow-up in the CVD state; these patients also suffer from DN.

```

      DN          8659      182      1418.51      309
      CVD         8880      183      1442.14      341
      ESRD+CVD    1376       43       215.51       79
      ESRD         619       17        96.97       38
      Sum        19534      425      3173.13      543

> addmargins(with(L7,table(table(lex.id))))
      1  2  3 Sum
353 156 34 543

> addmargins(with(S7,table(table(lex.id))))
      1  2  3  4  5  6  7  8  9 10 11 12 13 14 15 16 17 18 19 20
10  7  2  7  9  4  4  7  3  7 12  6  4  6  9  5  8  8  8  9
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
 5  9  5 12 11 14 10 14 15  6 11  4  7  6  9 17  3  9  4  5
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
12  7 13  4  3  5 10  8  6 10  4  5  5 10  6 10  9  8 10 11
61 62 63 64 65 66 67 68 Sum
11  9  8 10 14 16  6  2 543

```

We want to position the knots for the splines so that the number of events is the same between each pair of knots. We do this the same way for all transitions after inspection:

```

> nk <- 4
> ( n.kn <- with( subset( S7, substr(lex.Xst,1,4)=="Dead" ),
+               quantile( tfn+lex.dur, probs=(1:nk-0.5)/nk ) ) )
      12.5%   37.5%   62.5%   87.5%
3.306639 5.804928 9.611225 14.998631

> ( a.kn <- with( subset( S7, substr(lex.Xst,1,4)=="Dead" ),
+               quantile( age+lex.dur, probs=(1:nk-0.5)/nk ) ) )
      12.5%   37.5%   62.5%   87.5%
60.22998 66.23956 71.70157 76.57495

> ( d.kn <- with( subset( S7, substr(lex.Xst,1,4)=="Dead" ),
+               quantile( dur+lex.dur, probs=(1:nk-0.5)/nk ) ) )
      12.5%   37.5%   62.5%   87.5%
9.489391 16.574264 21.753593 27.902122

```

Since we are interested in modelling the transitions in figure 1.2, we make a stacked dataset and use this as the basis for modelling:

```

> St7 <- stack( S7 )
> dim( St7 )
[1] 46351 40

> xtabs( cbind(lex.dur,lex.Fail) ~ lex.Tr, data=St7 )
lex.Tr          lex.dur  lex.Fail
DN->CVD          1418.51335 107.00000
DN->ESRD          1418.51335  38.00000
DN->Dead(DN)      1418.51335  37.00000
CVD->ESRD+CVD    1442.14374  63.00000
CVD->Dead(CVD)   1442.14374 120.00000
ESRD+CVD->Dead(ESRD+CVD) 215.50719  43.00000
ESRD->ESRD+CVD    96.96646  16.00000
ESRD->Dead(ESRD)  96.96646   1.00000

```

We are not (initially) interested in the first and last two of these transitions, so we subset to the relevant 4 transitions; we want to look at mortality rates and rates of ESRD from the states DN and CVD. We just check that all is as expected:

```

> St4 <- subset( St7, lex.Tr %in% levels(St7$lex.Tr)[2:5] )
> St4$lex.Tr <- factor( St4$lex.Tr )
> with( St4, ftable( lex.Xst, lex.Tr, lex.Fail,col.vars=2:3 ) )

```

lex.Xst	lex.Tr	DN->ESRD		DN->Dead(DN)		CVD->ESRD+CVD		CVD->Dead(CVD)	
	lex.Fail	FALSE	TRUE	FALSE	TRUE	FALSE	TRUE	FALSE	TRUE
DN		8477	0	8477	0	0	0	0	0
CVD		107	0	107	0	8697	0	8697	0
ESRD+CVD		0	0	0	0	0	63	63	0
ESRD		0	38	38	0	0	0	0	0
Dead(DN)		37	0	0	37	0	0	0	0
Dead(CVD)		0	0	0	0	120	0	0	120
Dead(ESRD+CVD)		0	0	0	0	0	0	0	0
Dead(ESRD)		0	0	0	0	0	0	0	0

```

> dim( St4 )
[1] 35078 40

```


1.1.1 Simple proportional hazards model

We now set up a simple model that just models the 4 different transitions using the same dependency on time since DN, diabetes duration, sex and current age. Note that this model assumes that all 4 types of rates are proportional along the 3 chosen timescales:

```
> m0 <- glm( lex.Fail ~ lex.Tr + sex +
+           Ns( tfn, kn=n.kn ) +
+           Ns( age, kn=a.kn ) +
+           Ns( dur, kn=d.kn ),
+           offset=log(lex.dur), family=poisson,
+           data = St4 )
> round( ci.exp( m0 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)          0.019 0.013 0.030
lex.TrDN->Dead(DN)    0.974 0.619 1.531
lex.TrCVD->ESRD+CVD   1.436 0.954 2.163
lex.TrCVD->Dead(CVD)  2.736 1.885 3.970
sexM                  0.973 0.732 1.294
Ns(tfn, kn = n.kn)1  0.994 0.629 1.571
Ns(tfn, kn = n.kn)2  1.613 0.999 2.607
Ns(tfn, kn = n.kn)3  1.083 0.745 1.572
Ns(age, kn = a.kn)1  1.263 0.796 2.002
Ns(age, kn = a.kn)2  1.494 1.079 2.068
Ns(age, kn = a.kn)3  1.547 1.094 2.189
Ns(dur, kn = d.kn)1  1.651 1.093 2.496
Ns(dur, kn = d.kn)2  1.483 0.902 2.439
Ns(dur, kn = d.kn)3  1.540 1.073 2.209
> CM <- rbind(0,c(1,0,0),c(0,1,0),c(0,-1,1),c(-1,0,1))
> rownames( CM ) <- paste( c("",levels(St4$lex.Tr)[c(2:4,4)]),
+                          c("",rep(" vs. ",4)),
+                          levels(St4$lex.Tr)[c(1,1,1,3,2)], sep="" )
> colnames( CM ) <- levels(St4$lex.Tr)[-1]
> CM

              DN->Dead(DN)  CVD->ESRD+CVD  CVD->Dead(CVD)
DN->ESRD              0              0              0
DN->Dead(DN) vs. DN->ESRD      1              0              0
CVD->ESRD+CVD vs. DN->ESRD      0              1              0
CVD->Dead(CVD) vs. CVD->ESRD+CVD  0              -1              1
CVD->Dead(CVD) vs. DN->Dead(DN) -1              0              1
> round( ci.exp( m0, subset="lex.Tr" ), 2 )

              exp(Est.)  2.5% 97.5%
lex.TrDN->Dead(DN)    0.97 0.62  1.53
lex.TrCVD->ESRD+CVD   1.44 0.95  2.16
lex.TrCVD->Dead(CVD)  2.74 1.88  3.97
> round( ci.exp( m0, subset="lex.Tr", ctr.mat=CM ), 2 )

              exp(Est.)  2.5% 97.5%
DN->ESRD              1.00 1.00  1.00
DN->Dead(DN) vs. DN->ESRD      0.97 0.62  1.53
CVD->ESRD+CVD vs. DN->ESRD      1.44 0.95  2.16
CVD->Dead(CVD) vs. CVD->ESRD+CVD  1.90 1.40  2.58
CVD->Dead(CVD) vs. DN->Dead(DN)  2.81 1.93  4.09
```

This means that CVD influences the occurrence of ESRD by a factor of 1.5, whereas there is a 3.4-fold increase in the rate of death (prior to ESRD).

We can then test the proportionality of the rates on each of the three timescales:

```
> ma <- update( m0 , .~. + lex.Tr:Ns(age,kn=a.kn) )
> mna <- update( ma , .~. + lex.Tr:Ns(tfn,kn=n.kn) )
> mnad <- update( mna , .~. + lex.Tr:Ns(dur,kn=d.kn) )
> mad <- update( mnad, .~. - lex.Tr:Ns(tfn,kn=n.kn) )
> pr.test <- anova( m0, ma, mna, mnad, mad, ma, test="Chisq" )[-1,3:5]
> rownames( pr.test ) <- c("+i.age", "+i.tfn", "+i.dur", "-i.tfn", "-i.dur")
> round( pr.test, 3 )
```

	Df	Deviance	Pr(>Chi)
+i.age	9	23.314	0.006
+i.tfn	9	13.350	0.147
+i.dur	9	12.662	0.178
-i.tfn	-9	-10.686	0.298
-i.dur	-9	-15.327	0.082

If anything, the rates are non-proportional along the age-scale, but hardly along any of the other time scales. However, these tests are somewhat unspecific as they test for proportionality of 4 different transitions simultaneously; it is of more interest to see if there is proportionality between pairs of these. More precisely, it is more relevant to test the state×timescale interaction for one set of transitions at a time. Specifically we want to test proportionality between *pairs* of rates:

1. Death and ESRD rates from the DN state (`fromDN`)
2. Death and ESRD rates from the CVD state (`fromCVD`)
3. Death rates from the DN and CVD states (`toDeath`)
4. ESRD rates from the DN and CVD states (`toESRD`)

However we would also like to see if these non-proportionalities are confounded by the clinical variables of interest.

Each of these sets of proportionality assumptions are testable by fitting the same set of models as above, but varying the outcome and the dataset:

```
> log1.5 <- function(x) log(x)/log(1.5)
> mz <- update( m0, . ~ . + bmi
+               + I(sys.bt/10)
+               + I(-gfr/10)
+               + log2(alb)
+               + log1.5(pmax(ins.kg,0.03))
+               + hmgb
+               + hba1c
+               + tchol
+               + bmi
+               + smoke )
> mx <- update( mz, data=subset(St4,lex.Tr %in% c("DN->Dead(DN)","DN->ESRD") ) )
> ma <- update( mx , .~. + lex.Tr:Ns(age,kn=a.kn) )
> mna <- update( ma , .~. + lex.Tr:Ns(tfn,kn=n.kn) )
> mnad <- update( mna , .~. + lex.Tr:Ns(dur,kn=d.kn) )
> mad <- update( mnad, .~. - lex.Tr:Ns(tfn,kn=n.kn) )
> pr.fromDN <- anova( mx, ma, mna, mnad, mad, ma, test="Chisq" )[-1,3:5]
> rownames( pr.fromDN ) <- c("+i.age","+i.tfn","+i.dur","-i.tfn","-i.dur")
> mx <- update( mz, data=subset(St4,lex.Tr %in% c("CVD->Dead(CVD)","CVD->ESRD+CVD") ) )
> ma <- update( mx , .~. + lex.Tr:Ns(age,kn=a.kn) )
> mna <- update( ma , .~. + lex.Tr:Ns(tfn,kn=n.kn) )
> mnad <- update( mna , .~. + lex.Tr:Ns(dur,kn=d.kn) )
> mad <- update( mnad, .~. - lex.Tr:Ns(tfn,kn=n.kn) )
> pr.fromCVD <- anova( mx, ma, mna, mnad, mad, ma, test="Chisq" )[-1,3:5]
> rownames( pr.fromCVD ) <- c("+i.age","+i.tfn","+i.dur","-i.tfn","-i.dur")
> mx <- update( mz, data=subset(St4,lex.Tr %in% c("DN->Dead(DN)","CVD->Dead(CVD)") ) )
> ma <- update( mx , .~. + lex.Tr:Ns(age,kn=a.kn) )
> mna <- update( ma , .~. + lex.Tr:Ns(tfn,kn=n.kn) )
> mnad <- update( mna , .~. + lex.Tr:Ns(dur,kn=d.kn) )
> mad <- update( mnad, .~. - lex.Tr:Ns(tfn,kn=n.kn) )
> pr.toDeath <- anova( mx, ma, mna, mnad, mad, ma, test="Chisq" )[-1,3:5]
> rownames( pr.toDeath ) <- c("+i.age","+i.tfn","+i.dur","-i.tfn","-i.dur")
> mx <- update( mz , data=subset(St4,lex.Tr %in% c("DN->ESRD","CVD->ESRD+CVD") ) )
> ma <- update( mx , .~. + lex.Tr:Ns(age,kn=a.kn) )
```

```

> mna <- update( ma , .~. + lex.Tr:Ns(tfn, kn=n.kn) )
> mnad <- update( mna , .~. + lex.Tr:Ns(dur, kn=d.kn) )
> mad <- update( mnad, .~. - lex.Tr:Ns(tfn, kn=n.kn) )
> pr.toESRD <- anova( mx, ma, mna, mnad, mad, ma, test="Chisq" )[-1,3:5]
> rownames( pr.toESRD ) <- c("+i.age", "+i.tfn", "+i.dur", "-i.tfn", "-i.dur")
> prop <- cbind( pr.fromDN, pr.fromCVD, pr.toDeath, pr.toESRD )
> colnames( prop )[0:3*3+1] <- c("fromDN", "fromCVD", "toDeath", "toESRD")
> round( prop[,1:6], 3 )
      fromDN Deviance Pr(>Chi) fromCVD Deviance.1 Pr(>Chi).1
+i.age      3   4.372   0.224      3   17.817   0.000
+i.tfn      3   5.936   0.115      3    4.957   0.175
+i.dur      3   8.841   0.031      3    3.302   0.347
-i.tfn     -3  -3.160   0.368     -3   -3.533   0.316
-i.dur     -3 -11.617   0.009     -3   -4.725   0.193
> round( prop[,1:6+6], 3 )
      toDeath Deviance Pr(>Chi) toESRD Deviance.1 Pr(>Chi).1
+i.age      3   1.618   0.655      3    1.875   0.599
+i.tfn      3   4.218   0.239      3    0.562   0.905
+i.dur      3   3.246   0.355      3    2.763   0.430
-i.tfn     -3  -3.995   0.262     -3   -1.131   0.770
-i.dur     -3  -3.468   0.325     -3   -2.195   0.533

```

From this it is pretty clear that rates of mortality and ESRD from DN, resp. CVD are not proportional along the age-scale. It seems that mortality rates as well as ESRD rates are reasonably proportional between patients with and without CVD

Thus the most appropriate model would be one with separate baseline intensities for rates of Death and ESRD, and CVD as a time-dependent covariate with proportional effects along the three time scales. So basically model the rates of Death and ESRD separately but with the same set of covariates —it seems that rates *into* the same state (Dead, resp. ESRD) are proportional, whereas rates to *different* states are not necessarily so.

1.1.2 CVD effect

There is no particular reason to assume that the covariates have the same effects for all the transitions, so the *a priori* model would one with all interactions present. So we start out with a base model with separate baselines for ESRD and Death rates. This also means that it is only the contrasts *within* rates of death and *within* rates of ESRD that are of relevance:

```

> mD <- glm( lex.Fail ~ lex.Tr + sex +
+           Ns( age, kn=a.kn ) +
+           Ns( dur, kn=d.kn ) +
+           Ns( tfn, kn=n.kn ),
+           offset = log(lex.dur),
+           family = poisson,
+           data = subset(St4, lex.Tr %in% c("DN->Dead(DN)", "CVD->Dead(CVD)") ) )
> mE <- update( mD, data = subset(St4, lex.Tr %in% c("DN->ESRD", "CVD->ESRD+CVD") ) )
> round( rbind( ci.exp( mD, subset="Tr" ),
+             ci.exp( mE, subset="Tr" ) ), 3 )
      exp(Est.)  2.5% 97.5%
lex.TrCVD->Dead(CVD)  2.550 1.748 3.721
lex.TrCVD->ESRD+CVD  1.656 1.083 2.531

```

So there is a strong effect of CVD occurrence on the rate of Death, but none on the rate of ESRD, pretty much what we saw in the simple model with all proportional hazards.

In principle we could check whether covariates have the same effect on rates of Death and rates of ESRD, but it would not make much sense as they are distinct outcomes, so we might as well *a priori* decide to model these transitions separately.

1.1.3 Covariate effects

Hence we make separate models for the two transitions based on subsets of the split dataset, *S7*. But we will only use the part of the dataset that relates to the transitions we are looking at, so the part where `lex.Cst %in% %c("DN", "CVD")`:

```
> S7d <- Relevel( subset( S7, lex.Cst %in% c("DN", "CVD") ),
+               list("Dead"=5:8), first=FALSE )
```

	type	old	new
1	lex.Cst	DN	DN
2	lex.Cst	CVD	CVD
3	lex.Cst	ESRD+CVD	
4	lex.Cst	ESRD	
5	lex.Cst	Dead(DN)	
6	lex.Cst	Dead(CVD)	
7	lex.Cst	Dead(ESRD+CVD)	
8	lex.Cst	Dead(ESRD)	
9	lex.Xst	DN	DN
10	lex.Xst	CVD	CVD
11	lex.Xst	ESRD+CVD	ESRD+CVD
12	lex.Xst	ESRD	ESRD
13	lex.Xst	Dead(DN)	Dead
14	lex.Xst	Dead(CVD)	Dead
15	lex.Xst	Dead(ESRD+CVD)	
16	lex.Xst	Dead(ESRD)	

```
> summary( S7d )
```

Transitions:							Records:	Events:	Risk time:	Persons:
	To	DN	CVD	ESRD+CVD	ESRD	Dead				
From	DN	8477	107	0	38	37	8659	182	1418.51	309
	CVD	0	8697	63	0	120	8880	183	1442.14	341
	Sum	8477	8804	63	38	157	17539	365	2860.66	543

```
> S7e <- Relevel( subset( S7, lex.Cst %in% c("ESRD", "ESRD+CVD") ),
+               list("Dead"=5:8), first=FALSE )
```

	type	old	new
1	lex.Cst	DN	
2	lex.Cst	CVD	
3	lex.Cst	ESRD+CVD	ESRD+CVD
4	lex.Cst	ESRD	ESRD
5	lex.Cst	Dead(DN)	
6	lex.Cst	Dead(CVD)	
7	lex.Cst	Dead(ESRD+CVD)	
8	lex.Cst	Dead(ESRD)	
9	lex.Xst	DN	
10	lex.Xst	CVD	
11	lex.Xst	ESRD+CVD	ESRD+CVD
12	lex.Xst	ESRD	ESRD
13	lex.Xst	Dead(DN)	
14	lex.Xst	Dead(CVD)	
15	lex.Xst	Dead(ESRD+CVD)	Dead
16	lex.Xst	Dead(ESRD)	Dead

```
> summary( S7e )
```

Transitions:							Records:	Events:	Risk time:	Persons:
	To	DN	CVD	ESRD+CVD	ESRD	Dead				
From	ESRD+CVD	0	0	1333	0	43	1376	43	215.51	79
	ESRD	0	0	16	602	1	619	17	96.97	38
	Sum	0	0	1349	602	44	1995	60	312.47	101

```
> # Base model:
> Bd <- glm( lex.Xst=="Dead" ~ Ns( age, kn=a.kn ) +
+          Ns( dur, kn=d.kn ) +
```

```

+           Ns( tfn, kn=n.kn ) +
+           I(lex.Cst=="CVD") + sex,
+       offset = log(lex.dur),
+       family = poisson,
+       data = S7d )
> # Extend model by adding covariates:
> Ed <- update( Bd, . ~ . + bmi +
+             + I(sys.bt/10)
+             + I(-gfr/10)
+             + log2(alb)
+             + log1.5(pmax(ins.kg,0.03))
+             + hmgb
+             + hba1c
+             + tchol
+             + bmi
+             + smoke )
> # Model for ESRD cocurrence
> Be <- update( Bd, substr(lex.Xst,1,4)=="ESRD" ~ . )
> Ee <- update( Ed, substr(lex.Xst,1,4)=="ESRD" ~ . )
> # Model for post-ESRD mortality
> Bed <- update( Bd, . ~ . - I(lex.Cst=="CVD") + I(lex.Cst=="ESRD+CVD"), data=S7e )
> Eed <- update( Ed, . ~ . - I(lex.Cst=="CVD") + I(lex.Cst=="ESRD+CVD"), data=S7e )

```

When looking at the results of the CVD-effects we should keep in mind that for most CVD patients the baseline values are measured *after* the CVD date as illustrated in figure 1.3.

```

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> with( L1,
+     hist( docvd-donra,
+         breaks=seq(-26,11,1), col="gray", main="",
+         xlab="Time from entry to CVD (years)",
+         ylim=c(0,35),xlim=c(-26,13) ) )
> abline( v=0, col="red" )
> text(-15, 12, paste("\nCVD: ",
+                   sum(!is.na(L1$docvd) ),
+                   "\nno CVD: ",
+                   sum( is.na(L1$docvd) ),
+                   sep=""),
+     adj=c(1,1) )

```

The effects on the rates of death are now extracted; the first line is the isolated effect of CVD, only taking duration of DN, duration of diabetes and age (=duration of life) into account, the second line is the CVD effect controlled for all the other covariates. The subsequent lines are the effects of the covariates.

```

> dd <- rbind( ci.exp(Bd,subset="CVD"),
+             ci.exp(Ed,subset=-(1:10)) )
> round( dd, 3 )

```

	exp(Est.)	2.5%	97.5%
I(lex.Cst == "CVD")TRUE	2.550	1.748	3.721
I(lex.Cst == "CVD")TRUE	3.008	1.806	5.012
sexM	0.911	0.541	1.534
bmi	1.029	0.981	1.080
I(sys.bt/10)	0.894	0.777	1.030
I(-gfr/10)	1.136	1.044	1.236
log2(alb)	1.063	0.945	1.195
log1.5(pmax(ins.kg, 0.03))	0.924	0.836	1.021
hmgb	1.012	0.786	1.302
hba1c	0.945	0.814	1.097
tchol	1.076	0.908	1.274
smoke4-20+20+	1.195	0.733	1.949

It seems that only smoking (RR=2.3 (1.3–3.9)), presence of CVD (RR=2.7 (1.6–4.4)) and GFR (RR per 10: 1.2 (1.1–1.3)) influence the mortality. There is also a significant effect of hemoglobin (RR per %: 1.3 (1.0–1.7)).

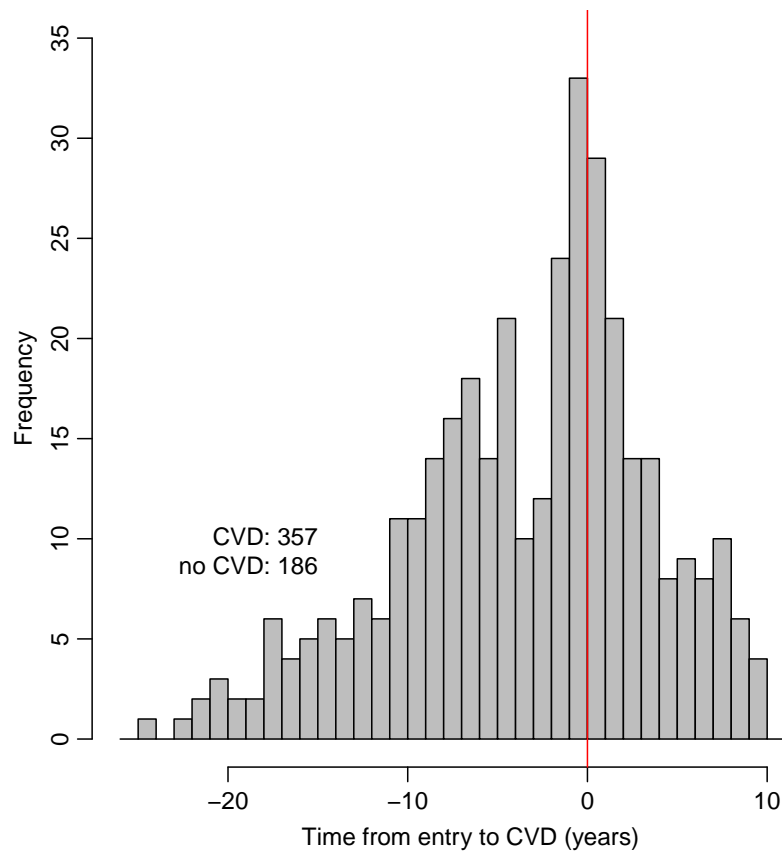


Figure 1.3: Histogram of time from entry (date of DN) to CVD; hence, negative numbers refer to patients with CVD prior to entry. Note that the numbers w/o CVD here is the total number in the database, also those 34 who have a recorded date of CVD after ESRD, and who thus do not appear in figure 1.2.

The same figures for the rates of ESRD and death subsequent to ESRD are:

```
> ee <- rbind( ci.exp(Be,subset="CVD"),
+             ci.exp(Ee,subset=-(1:10)) )
> round( ee, 3 )
```

	exp(Est.)	2.5%	97.5%
I(lex.Cst == "CVD")TRUE	1.656	1.083	2.531
I(lex.Cst == "CVD")TRUE	1.302	0.770	2.201
sexM	1.081	0.592	1.974
bmi	1.016	0.961	1.073
I(sys.bt/10)	0.981	0.824	1.169
I(-gfr/10)	1.095	0.997	1.202
log2(alb)	1.507	1.268	1.790
log1.5(pmax(ins.kg, 0.03))	0.935	0.824	1.061
hmgb	0.840	0.631	1.118
hba1c	1.223	1.045	1.432
tchol	1.110	0.924	1.333
smoke4-20+20+	0.591	0.312	1.119

```
> eed <- rbind( ci.exp(Bed,subset="CVD"),
+              ci.exp(Eed,subset=-(1:10)) )
> eed <- eed[c(1,nrow(eed),2:(nrow(eed)-1)),]
> round( eed, 3 )
```

	exp(Est.)	2.5%	97.5%
I(lex.Cst == "ESRD+CVD")TRUE	22.877	3.102	168.740
I(lex.Cst == "ESRD+CVD")TRUE	17.728	2.271	138.395
sexM	1.447	0.373	5.620
bmi	1.011	0.908	1.125
I(sys.bt/10)	0.988	0.659	1.481
I(-gfr/10)	1.116	0.924	1.347
log2(alb)	1.065	0.798	1.422
log1.5(pmax(ins.kg, 0.03))	1.419	1.068	1.886
hmgb	1.161	0.731	1.843
hba1c	1.068	0.807	1.413
tchol	1.217	0.786	1.885
smoke4-20+20+	2.974	0.883	10.015

The pattern of effects here is very different from the effects on the mortality rates; CVD is not a risk factor, but GFR and albumin are, along with HBA_{1c} and blood pressure.

Moreover, males have a higher ESRD rate than females. The pattern of risk is shown in forest plot in figures 1.4 and 1.5, the latter showing reasonably clearly that the risk factor pattern is pretty much the same for pre- and post-ESRD mortality, but different from that of ESRD occurrence.

These RRs are now compared in figure 1.4:

```
> new.names <- c("CVD-crude","Prior cardiovascular disease","Male vs. female",
+              "Body mass index (kg/m2)","Systolic blood pressure (10 mmHg)",
+              "GFR (10 ml/min/1.73 m2)",
+              "Albuminuria (per 100% incr.)","Insulin/kg (per 50% incr.)",
+              "Hemoglobin (mmol/l)","HbA1c (%)","Total cholesterol (mmol/l)","Smoker vs. non-smoker")
> data.frame( rownames( dd ), rownames( ee ), new.names )
```

	rownames.dd.	rownames.ee.
1	I(lex.Cst == "CVD")TRUE	I(lex.Cst == "CVD")TRUE
2	I(lex.Cst == "CVD")TRUE	I(lex.Cst == "CVD")TRUE
3	sexM	sexM
4	bmi	bmi
5	I(sys.bt/10)	I(sys.bt/10)
6	I(-gfr/10)	I(-gfr/10)
7	log2(alb)	log2(alb)
8	log1.5(pmax(ins.kg, 0.03))	log1.5(pmax(ins.kg, 0.03))
9	hmgb	hmgb
10	hba1c	hba1c
11	tchol	tchol


```

12          smoke4-20+20+          smoke4-20+20+
              new.names
1              CVD-crude
2      Prior cardiovascular disease
3              Male vs. female
4              Body mass index (kg/m2)
5      Systolic blood pressure (10 mmHg)
6              GFR (10 ml/min/1.73 m2)
7              Albuminuria (per 100% incr.)
8              Insulin/kg (per 50% incr.)
9              Hemoglobin (mmol/l)
10             HbA1c (%)
11      Total cholesterol (mmol/l)
12             Smoker vs. non-smoker

> data.frame( rownames( dd ), rownames( eed ), new.names )

              rownames.dd.              rownames.eed.
1      I(lex.Cst == "CVD")TRUE I(lex.Cst == "ESRD+CVD")TRUE
2      I(lex.Cst == "CVD")TRUE I(lex.Cst == "ESRD+CVD")TRUE
3              sexM              sexM
4              bmi              bmi
5              I(sys.bt/10)              I(sys.bt/10)
6              I(-gfr/10)              I(-gfr/10)
7              log2(alb)              log2(alb)
8      log1.5(pmax(ins.kg, 0.03))      log1.5(pmax(ins.kg, 0.03))
9              hmgb              hmgb
10             hba1c              hba1c
11             tchol              tchol
12             smoke4-20+20+              smoke4-20+20+
              new.names
1              CVD-crude
2      Prior cardiovascular disease
3              Male vs. female
4              Body mass index (kg/m2)
5      Systolic blood pressure (10 mmHg)
6              GFR (10 ml/min/1.73 m2)
7              Albuminuria (per 100% incr.)
8              Insulin/kg (per 50% incr.)
9              Hemoglobin (mmol/l)
10             HbA1c (%)
11      Total cholesterol (mmol/l)
12             Smoker vs. non-smoker

> rownames( dd ) <- rownames( ee ) <- rownames( eed ) <- new.names
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> rownames( dd )[c(4,6,10)] <- ""
> plotEst( dd[-1,1:3], xlog=TRUE, vref=1, y=c(11:1), txtpos=c(11:1),
+         lwd=3, cex=1.1, xlab="",
+         xtic=c(0.4,0.6,1,2,4), xlim=c(0.4,4*16^2),
+         grid=c(4:15/10,seq(2,4,0.5)),
+         restore.par=FALSE )
> axis( side=2, at=c(9,7,3),
+       labels=c( expression( "Body mass index (kg/"*m^2*)" ),
+                 expression( "GFR (-10 ml/min/1.73"*m^2*)" ),
+                 expression( HbA[1][c]*"%" ) ),
+       las=1, tick=FALSE )
> abline( v=c(4:15/10,seq(2,4,0.5))*16, col=gray(0.9) )
> abline( v=16 )
> axis( side=1, at=c(0.4,0.6,1,2,4)*16, labels=formatC(c(0.4,0.6,1,2,4),format="f",digits=1) )
> et <- pmax( ee, 0.4 )*16
> linesEst( et[-1,1:3], vref=1, y=11:1, lwd=3, cex=1.1 )
> abline( v=c(4:15/10,seq(2,4,0.5))*16^2, col=gray(0.9) )
> abline( v=16^2 )
> axis( side=1, at=c(0.4,0.6,1,2,4)*16^2, labels=formatC(c(0.4,0.6,1,2,4),format="f",digits=1) )
> et <- pmax( eed, 0.4 )*(16^2)
> linesEst( et[-1,1:3], vref=1, y=11:1, lwd=3, cex=1.1 )
> mtext( "RR of pre-ESRD death" , side=1, line=par("mgp")[1], at=sqrt(10)*0.4 )

```



```
> mtext( "RR of ESRD" , side=1, line=par("mgp")[1], at=sqrt(10)*0.4*16 )
> mtext( "RR of post-ESRD death", side=1, line=par("mgp")[1], at=sqrt(10)*0.4*16^2 )
```

We could also show the effects of the covariates on the same scale for comparability, using different colors:

```
> par( mar=c(5,3,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( dd[-1,1:3], xlog=TRUE, vref=1, y=c(11:1)+0.15, txtpos=c(11:1),
+         lwd=3, cex=1.1, xlab="",
+         xtic=c(0.4,0.6,1,2,4), xlim=c(0.4,4),
+         grid=c(4:15/10,seq(2,4,0.5)), col=clr[1],
+         restore.par=FALSE )
> axis( side=2, at=c(9,7,3),
+       labels=c( expression( "Body mass index (kg/*m^2*)" ),
+                 expression( "GFR (-10 ml/min/1.73*m^2*)" ),
+                 expression( HbA[1][c]*"%" ) ),
+       las=1, tick=FALSE )
> et <- pmax( ee, 0.4 )
> linesEst( et[-1,1:3], y=11:1-0.15, lwd=3, cex=1.1, col=clr[2])
> et <- pmax( eed, 0.4 )
> linesEst( et[-1,1:3], y=11:1 , lwd=3, cex=1.1, col=clr[4])
> mtext( "RR of pre-ESRD death" , side=1, line=par("mgp")[1] , at=sqrt(10)*0.4, col=clr[1])
> mtext( "RR of ESRD" , side=1, line=par("mgp")[1]+2, at=sqrt(10)*0.4, col=clr[2])
> mtext( "RR of post-ESRD death", side=1, line=par("mgp")[1]+1, at=sqrt(10)*0.4, col=clr[4])
```

From figures 1.4 and 1.5 it is clear that the major risk factors for death are CVD, GFR and smoking, whereas the significant risk factors for ESRD are blood pressure, GFR, albuminuria, HbA_{1c} and low hemoglobin. Interestingly it seems that prior CVD decreases the risk of ESRD, though not significant.

1.1.4 Baseline effects

These RR estimates are all conditional on the baseline hazard which depends on time since entry (*tfn*), duration of diabetes (*dur*) and current age (*age*).

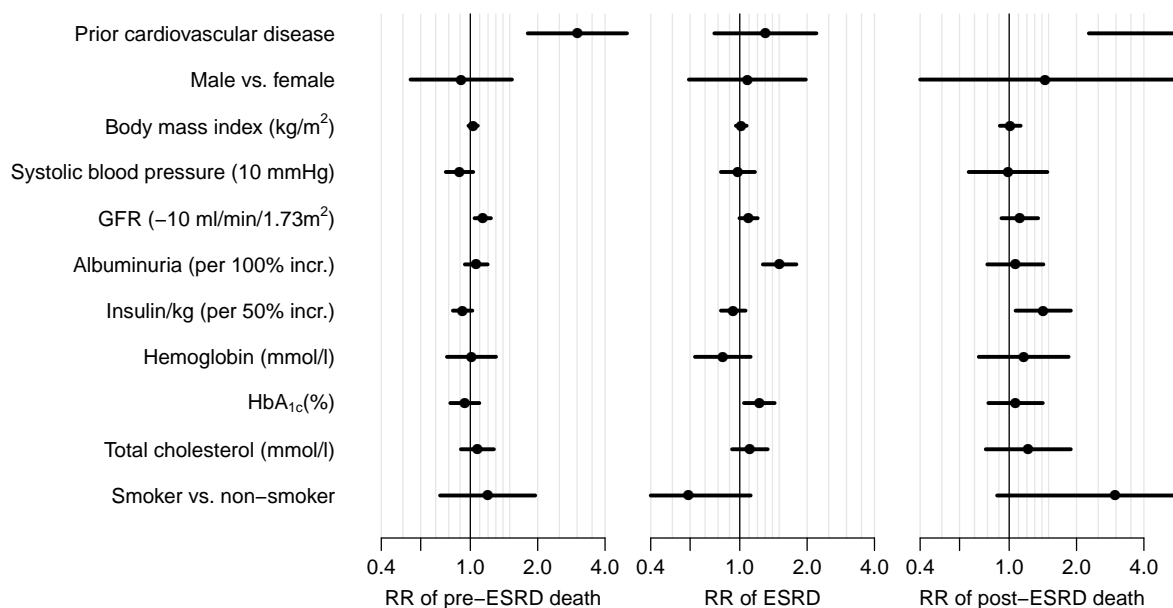


Figure 1.4: *RRs associated with the different risk factors for the transitions from DN and CVD, to either death or ESRD or from ESRD to death (see figure 1.2).*

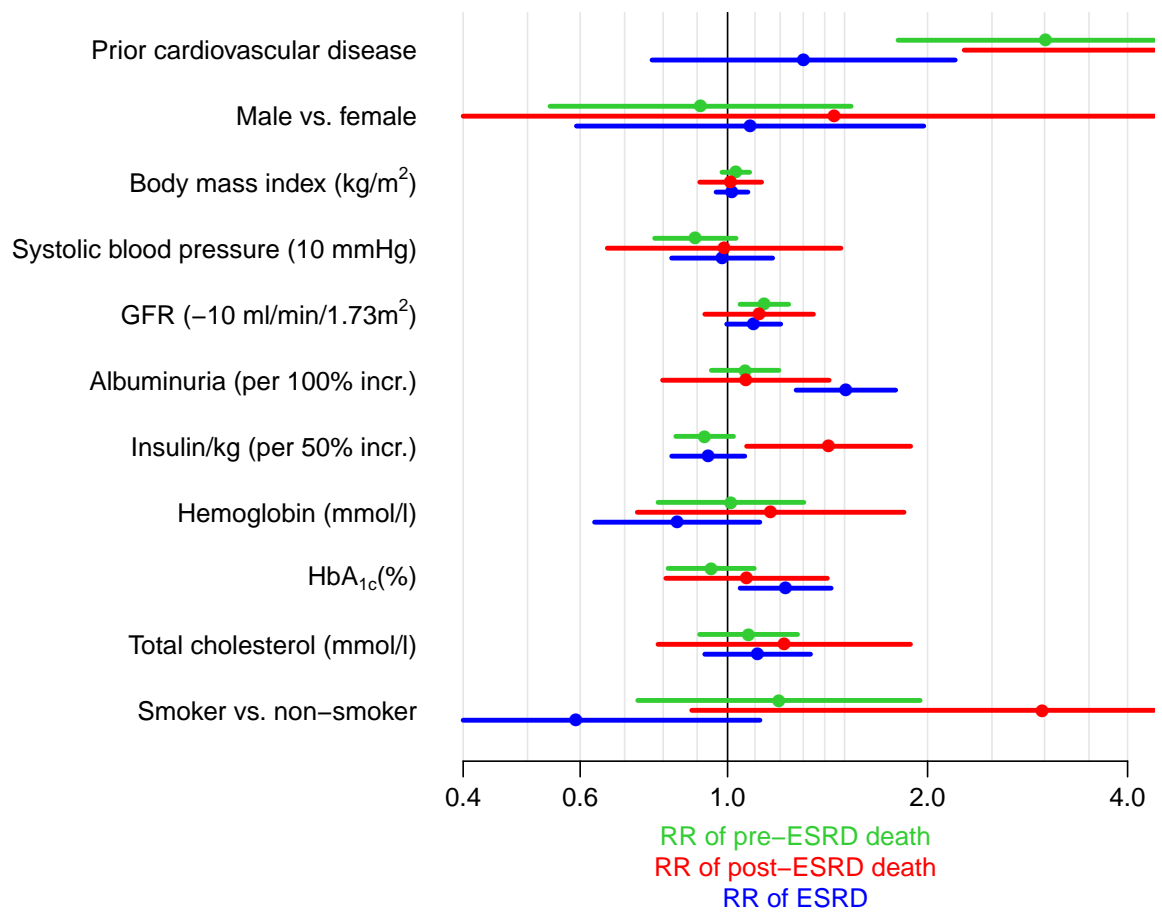


Figure 1.5: *RRs associated with the different risk factors for the transitions from DN and CVD, to either death or ESRD or from ESRD to death (see figure 1.2).*

```
> quantile( L1$lex.dur, probs=0:4/4 )
      0%      25%      50%      75%     100%
0.02464066 3.32101300 5.72484600 8.77207392 10.98699521
> pairs( L1[,c("age","tfn","dur")], gap=0, pch=16 )
```

We want to show the mortality rates as a function of time since DN for times from 0 to 10 years. Since the mortality also depends on DM duration and current age, we need to take these into account too, so draw mortality curves for different combinations of age and duration at entry. Moreover, we will of course also need to fix the values of the other covariates, so we just get an overview of the distribution of the covariates as measured at baseline:

```
> wh <- c("bmi","sys.bt","gfr","alb","ins.kg","hmgb","hba1c","tchol")
> mm <- t( apply( as.matrix(L1[,wh]),
+               2,
+               quantile,
+               probs=0:4/4,
+               na.rm=TRUE ) )
```

We use the following rounded values for the covariates when computing the rates, here shown together with the quantiles of the variables in the data:

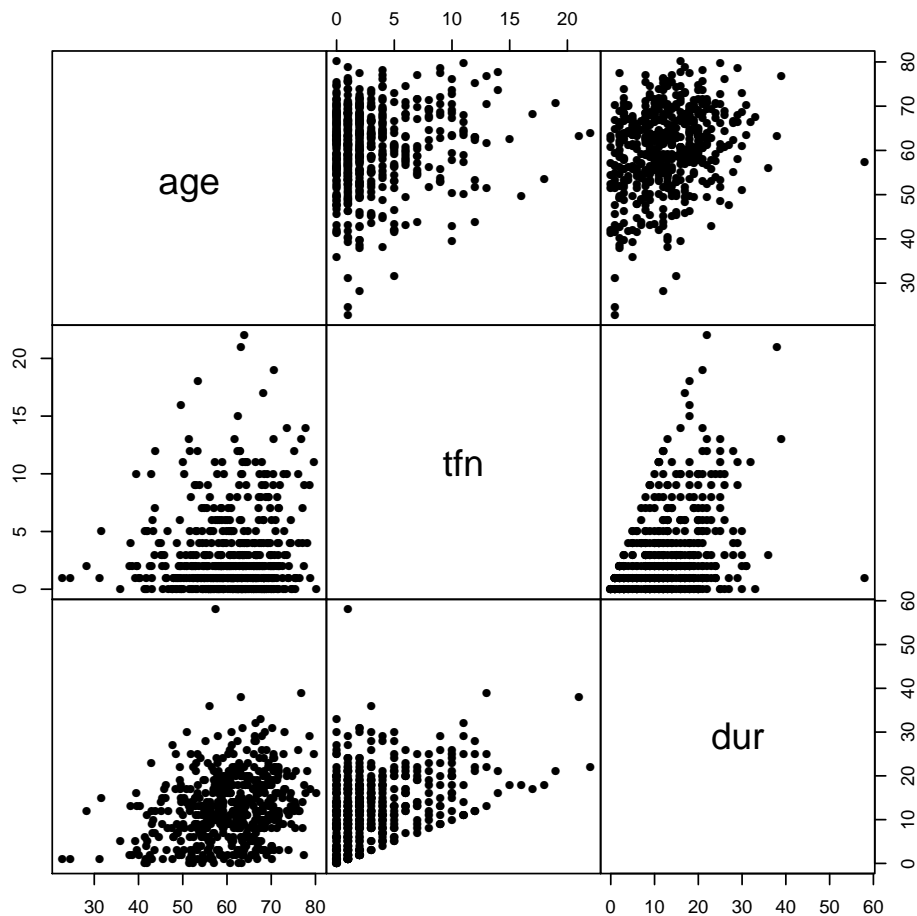


Figure 1.6: Pairs plot of the entry times on the 3 time-scales in the models.

```
> round( cbind( mm, c(21,150,70,500,0.7,8,9,5) ), 2 )
      0%    25%    50%    75%   100%
bmi    13.74  23.64  26.73  30.20  50.35  21.0
sys.bt 110.00 137.25 148.00 160.00 233.00 150.0
gfr    10.00  50.00  71.00  95.00 175.00  70.0
alb     6.00 257.00 485.00 937.00 7380.00 500.0
ins.kg  0.00  0.44  0.78  1.34  14.39  0.7
hmgb   4.70  7.60  8.40  9.00  12.30  8.0
hba1c  5.20  7.20  8.30  9.40  15.20  9.0
tchol  2.30  3.80  4.60  5.40  11.10  5.0
```

So we set up a prediction frame using these covariate values. The data frame `pr1` will have one line per follow-up time, repeated over 4 ages and 3 DM durations at start.

```
> np <- 200
> pr.tnf <- c(seq(0,10,,np-1),NA)
> # ages at entry
> a1 <- c(45,55,65,75)
> na <- length(a1)
> # DM duration at entry
> d1 <- c(5,10,20)
> nd <- length(d1)
> # Common covariate values:
> pr0 <- data.frame( sex = factor( 1, levels=2:1, labels=c("F","M") ),
+                   bmi = 25,
+                   gfr = 70.0,
+                   sys.bt = 150.0,
+                   alb = 500.0,
+                   ins.kg = 0.7,
+                   hmgb = 8.0,
+                   hba1c = 9.0,
+                   tchol = 5.0,
+                   smoke = factor(1,levels=1:2,labels=levels(S7d$smoke)),
+                   lex.dur = 100,
+                   lex.Cst = factor(1,levels=1:5,labels=levels(S7d$lex.Cst)),
+                   tfn = rep(pr.tnf,na*nd) )
> pr1 <- data.frame( age = rep(a1,each=nd*np) + pr0$tfn,
+                   ain = rep(a1,each=nd*np),
+                   dur = rep(d1,na,each=np) + pr0$tfn,
+                   din = rep(d1,na,each=np),
+                   pr0 )
```

Note that we only need to give the values of the variables, the transformation of them is made in the model object. Also note that we set `lex.dur`, the risk time variable, to 100, which means that we get the rates in cases per 100 years or % per year.

With this data frame in place we can now plot the mortality rates and the ESRD rates for these 3 types of T2 patients:

```
> get.rates <-
+ function( obj, nd )
+ {
+ ff <- predict.glm( obj, newdata = nd, se.fit=TRUE )
+ dfr <-
+ data.frame( tfn=nd$tfn, a=factor(nd$ain), d=factor(nd$din),
+             exp( cbind( ff$fit, ff$se.fit ) %*% ci.mat() ) )
+ names( dfr )[4:6] <- c("r","l","h")
+ dfr
+ }
> pr.Bd <- get.rates( Bd, pr1 )
> str( pr.Bd )
'data.frame':      2400 obs. of  6 variables:
 $ tfn: num  0 0.0505 0.101 0.1515 0.202 ...
 $ a  : Factor w/ 4 levels "45","55","65",...: 1 1 1 1 1 1 1 1 1 1 ...
```

```

$ d : Factor w/ 3 levels "5","10","20": 1 1 1 1 1 1 1 1 1 1 ...
$ r : num 0.905 0.911 0.916 0.922 0.927 ...
$ l : num 0.353 0.357 0.361 0.365 0.369 ...
$ h : num 2.32 2.32 2.33 2.33 2.33 ...

> pr.Be <- get.rates( Be, pr1 )
> pr.Ed <- get.rates( Bd, pr1 )
> pr.Ee <- get.rates( Ee, pr1 )

```

We can now plot the resulting estimates, using a convenience function as wrapper:

```

> plr <-
+ function( mr, er, tit, wh=1:3 )
+ {
+ matplot( mr$tfn, cbind(mr[,3+wh],er[,3+wh]), type="n",
+ log="y", xaxt="n", yaxt="n", ylab="", xlab="" )
+ for( ia in 1:na )
+ for( id in 1:nd )
+ with( subset(mr, a==levels(a)[ia] &
+ d==levels(d)[id] ),
+ matlines( tfn, cbind(r,l,h)[,wh],
+ lty=(1:nd)[id], lwd=c(3,1,1),
+ col=gray((1:na/(na+1))[ia]) ) )
+ }

```

With this function in place it straight-forward to plot the estimates of Death and ESRD rates for T2 patients, both adjusted and not adjusted for the covariates of interest:

```

> par( mfrow=c(2,2), oma=c(0,2,2,0)+c(3,3,1,1), mar=c(0,0,0,0), las=1 )
> plr( pr.Bd, pr.Be, "" ) ; axis(side=2)
> plr( pr.Ed, pr.Ee, "" )
> plr( pr.Be, pr.Bd, "" ) ; axis(side=1) ; axis(side=2)
> plr( pr.Ee, pr.Ed, "" ) ; axis(side=1)
> mtext( "Time since DN", side=1, line=2, las=0, outer=TRUE )
> mtext( "Mortality rates (% per year)", side=2, line=3.5, at=0.75, las=0, outer=TRUE )
> mtext( "ESRD rates (% per year)", side=2, line=3.5, at=0.25, las=0, outer=TRUE )
> mtext( "Undadjusted", side=3, line=1, at=0.25, las=0, outer=TRUE )
> mtext( "Adjusted to median", side=3, line=1, at=0.75, las=0, outer=TRUE )
> mtext( "T2", side=3, line=1, at=-0.1, adj=0, las=0, outer=TRUE )

> par( mfrow=c(2,2), oma=c(0,2,2,0)+c(3,3,1,1), mar=c(0,0,0,0), las=1 )
> plr( pr.Bd, pr.Be, "", wh=1 ) ; axis(side=2)
> plr( pr.Ed, pr.Ee, "", wh=1 )
> plr( pr.Be, pr.Bd, "", wh=1 ) ; axis(side=1) ; axis(side=2)
> plr( pr.Ee, pr.Ed, "", wh=1 ) ; axis(side=1)
> mtext( "Time since DN", side=1, line=2, las=0, outer=TRUE )
> mtext( "Mortality rates (% per year)", side=2, line=3.5, at=0.75, las=0, outer=TRUE )
> mtext( "ESRD rates (% per year)", side=2, line=3.5, at=0.25, las=0, outer=TRUE )
> mtext( "Undadjusted", side=3, line=1, at=0.25, las=0, outer=TRUE )
> mtext( "Adjusted to median", side=3, line=1, at=0.75, las=0, outer=TRUE )
> mtext( "T2", side=3, line=1, at=-0.1, adj=0, las=0, outer=TRUE )

> save( Ed, Ee, a.kn, d.kn, n.kn, clr, clx, file="./data/T2E-models.Rda" )

```

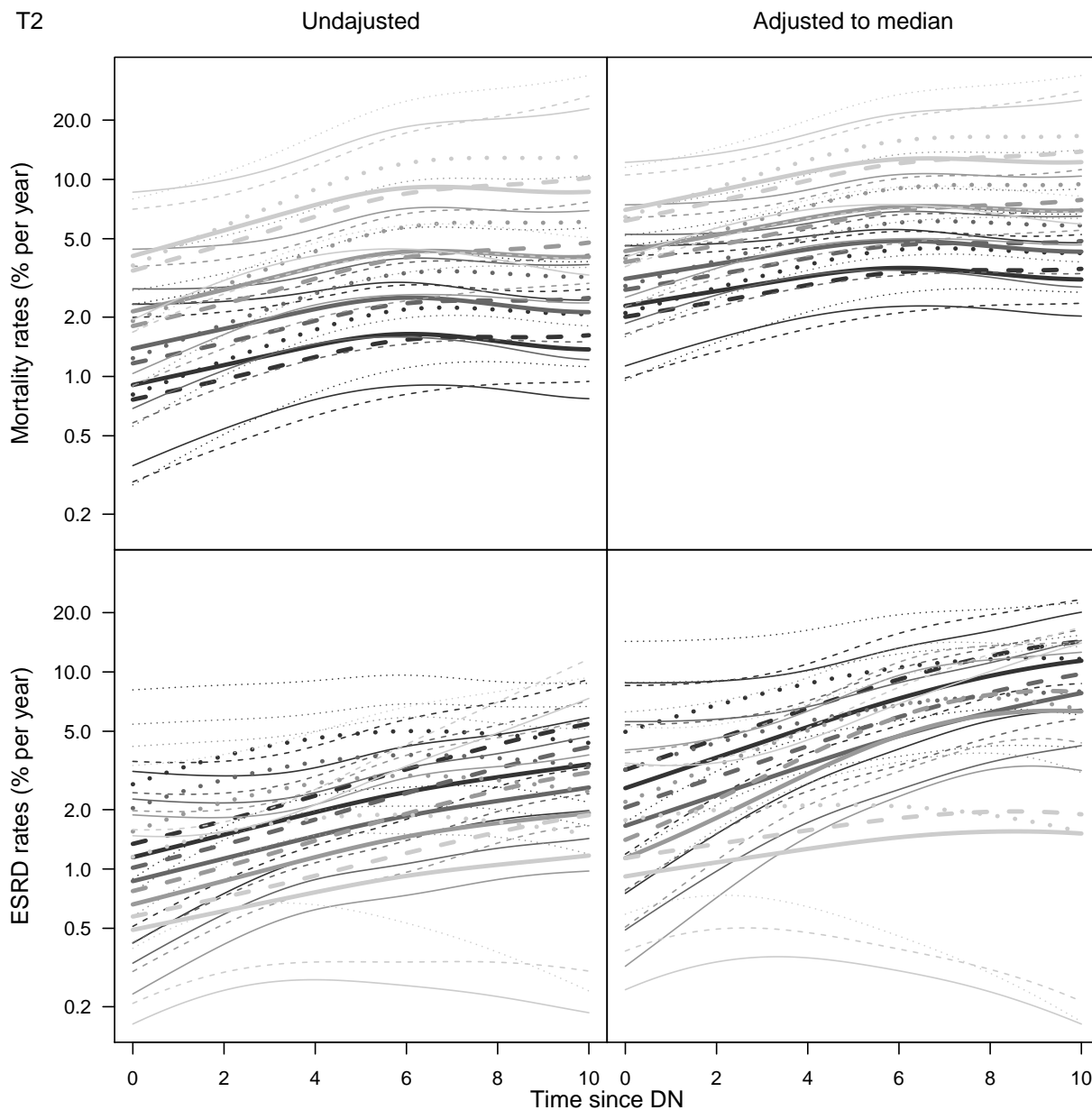


Figure 1.7: Mortality and ESRD rates for T2 patients with 95% c.i., as a function of time since entry into the study. Rates are for persons without CVD, for ages at entry 45, 55, 65, 75 (dark to light color), and duration of diabetes at entry 5, 10, 20 (full, dashed and dotted lines).

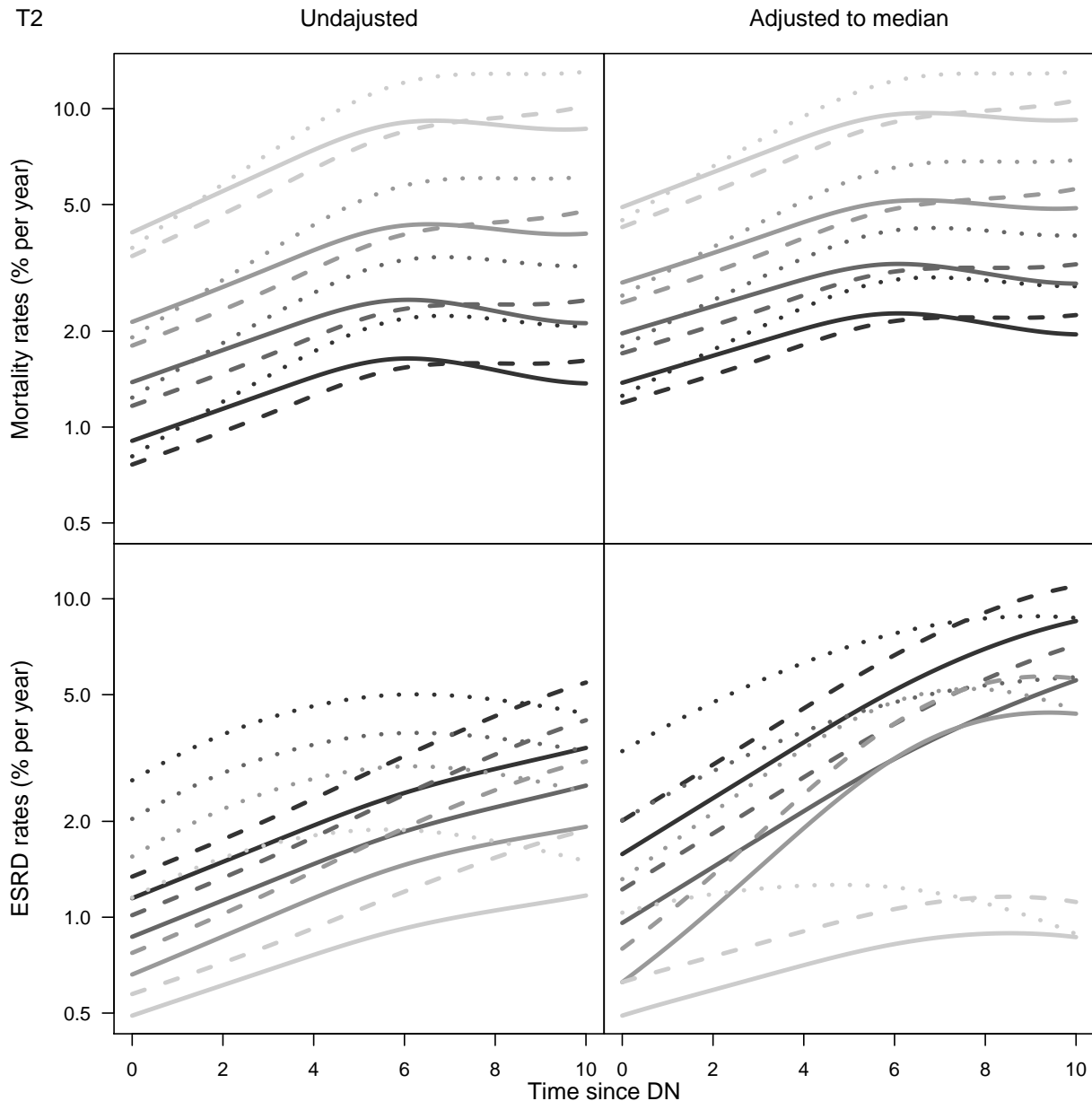


Figure 1.8: *Mortality and ESRD rates for T2 patients, as a function of time since entry into the study. Rates are for persons without CVD, for ages at entry 45, 55, 65, 75 (dark to light color), and duration of diabetes at entry 5, 10, 20 (full, dashed and dotted lines). It is seen that age and diabetes duration at entry has a more pronounced effect on mortality rates than on ESRD rates. For both sets of rates it is also clear that rates do not increase so much by time for those with the longest diabetes duration (over 25 years), which is presumably a selection phenomenon.*

1.1.5 Time trends

We would like to see if there are any time-trends in mortality, so we would introduce an effect of either current calendar time (follow-up date) or date of diagnosis of DN. However, `tfn`, time since diagnosis of DN is already in the model, so those two would have the same coefficient, hence including current calendar time, `per`, is sufficient:

```
> Bed <- update( Be, . ~ . + per )
> Bdd <- update( Bd, . ~ . + per )
> Eed <- update( Ee, . ~ . + per )
> Edd <- update( Ed, . ~ . + per )
> per.eff <- cbind(
+   rbind( ci.exp( Bed, subset="per" ),
+         ci.exp( Bdd, subset="per" ) ),
+   rbind( ci.exp( Eed, subset="per" ),
+         ci.exp( Edd, subset="per" ) ) )
> rownames( per.eff ) <- c( "ESRD", "Dead" )
> round( per.eff, 2 )
      exp(Est.) 2.5% 97.5% exp(Est.) 2.5% 97.5%
ESRD      1.01 0.94  1.08      1.16 1.06  1.27
Dead      0.99 0.94  1.05      1.05 0.97  1.13
```

The leftmost 3 columns of this are the annual increases in mortality/ESRD rates by calendar time when using a model with no covariates, showing basically no change in mortality but slight increase in ESRD by time, whereas the estimates in the rightmost shows a stronger increase in both mortality ESRD rates when controlling for the covariates.

This indicates that there is a change in covariates to the better, because the latter time-estimates are estimates for a *given* set of covariates. Hence, if the covariates are changing to the better, then mortality when measured *with* control for covariates should exhibit an increase relative to that measured *without*.

So the conclusion of this is that we should *not* take the time trend into account when reporting the effect of covariates, that is that we should only look at the model *without* the time-trend in order to evaluate covariate effects, and a model without covariates if we really want to evaluate the time trends.

```
> save( S7, file="./data/T2S7.Rda" )
```

1.2 Prediction of life course

We have so far fitted models for the mortality rates for patients without ESRD, incorporating CVD, these are in the models `Ed` for death as outcome and `Ee` for ESRD as outcome for type 2 patients. These models all contain CVD as a time-dependent variable, that is the transition rates are considered proportional (and we checked that).

If we want to model how different covariates influence the risk ever having ESRD and dying from the different states we must have a model for *all* transitions in the observed network.

```
> options( width=90 )
> library( Epi )
> library( splines )

> load( file="./data/T2S7.Rda" )
> load( file="./data/T2E-models.Rda" )
```


So far we only have models for 6 of the transitions, we also want models for the remaining two transitions, namely the occurrence of CVD among DN patients and ESRD patients, respectively.

For a start we model the CVD occurrence the same way as we modeled mortality and occurrence of ESRD, however since there are only 16 CVD events after ESRD, a very simple model for this transition:

```
> log1.5 <- function(x) log(x)/log(1.5)
> Ec <- update( Ed, (lex.Xst=="CVD") ~ . - I(lex.Cst=="CVD"),
+             data = subset( S7, lex.Cst=="DN" ) )
> Ece <- update( Ed, (lex.Xst=="ESRD+CVD") ~ sex +
+             tfn +
+             age +
+             tfESRD,
+             data = subset( S7, lex.Cst=="ESRD" ) )
> round( ci.exp( Ec ), 3 )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.182	0.004	9.342
Ns(age, kn = a.kn)1	1.382	0.463	4.128
Ns(age, kn = a.kn)2	1.929	0.878	4.240
Ns(age, kn = a.kn)3	1.621	0.701	3.745
Ns(dur, kn = d.kn)1	1.649	0.647	4.203
Ns(dur, kn = d.kn)2	0.991	0.350	2.805
Ns(dur, kn = d.kn)3	1.196	0.540	2.650
Ns(tfn, kn = n.kn)1	1.401	0.467	4.205
Ns(tfn, kn = n.kn)2	0.959	0.418	2.204
Ns(tfn, kn = n.kn)3	1.948	0.831	4.569
sexM	1.258	0.640	2.472
bmi	1.007	0.953	1.063
I(sys.bt/10)	0.940	0.782	1.130
I(-gfr/10)	0.891	0.800	0.993
log2(alb)	1.185	0.994	1.412
log1.5(pmax(ins.kg, 0.03))	1.042	0.904	1.202
hmgb	0.745	0.544	1.019
hba1c	0.980	0.817	1.176
tchol	0.974	0.747	1.269
smoke4-20+20+	1.091	0.620	1.920

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

	exp(Est.)	2.5%	97.5%
(Intercept)	0.432	0.015	12.420
sexM	0.948	0.349	2.571
tfn	1.055	0.909	1.224
age	0.969	0.915	1.026
tfESRD	1.309	0.954	1.798

Because of the overfitting of the model for mortality after ESRD (which has 39 events, out of which only 1 event among ESRD patients without CVD), we fit a simpler model with only 6 parameters, not using CVD status, sex, DN duration, age and a quadratic in time since ESRD:

```
> En <- update( Ed, (substr(lex.Xst,1,4)=="Dead") ~ sex +
+             tfn +
+             age +
+             pmin(tfESRD, tfCE, na.rm=TRUE) +
+             I(pmin(tfESRD, tfCE, na.rm=TRUE)^2),
+             data = subset( S7, substr(lex.Cst,1,4)=="ESRD" ) )
> ci.exp( En )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.0005962757	3.390918e-05	0.01048521
sexM	1.2491201741	6.225946e-01	2.50612705
tfn	1.0199427314	9.627810e-01	1.08049822

```

age                1.0790953528 1.034329e+00 1.12579963
pmin(tfESRD, tfCE, na.rm = TRUE) 0.9714342804 6.331516e-01 1.49045591
I(pmin(tfESRD, tfCE, na.rm = TRUE)^2) 1.0147501072 9.554774e-01 1.07769974

```

Once we have these models we can set up a transition object for use in simulation of probabilities:

```

> Tr <- list( "DN" = list( "Dead(DN)" = Ed,
+                          "CVD"      = Ec,
+                          "ESRD"     = Ee ),
+            "CVD" = list( "Dead(CVD)" = Ed,
+                          "ESRD+CVD" = Ee ),
+            "ESRD" = list( "ESRD+CVD" = Ece,
+                          "Dead(ESRD)" = En ),
+            "ESRD+CVD" = list( "Dead(ESRD+CVD)" = En ) )

```

We can actually derive the induced transition matrix from this:

```

> st <- union( names(Tr), unlist(lapply( Tr, names )))
> dn <- list( from=st, to=st )
> tm <- array( NA, dim=sapply(dn,length), dimnames=dn )
> for( i in names(Tr) ) for( j in names(Tr[[i]]) ) tm[i,j] <- 1
> tm[c(1,2,4,3,5,6,8,7),c(1,2,4,3,5,6,8,7)]

```

from	to							
	DN	CVD	ESRD+CVD	ESRD	Dead(DN)	Dead(CVD)	Dead(ESRD+CVD)	Dead(ESRD)
DN	NA	1	NA	1	1	NA	NA	NA
CVD	NA	NA	1	NA	NA	1	NA	NA
ESRD+CVD	NA	NA	NA	NA	NA	NA	1	NA
ESRD	NA	NA	1	NA	NA	NA	NA	1
Dead(DN)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(CVD)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(ESRD+CVD)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(ESRD)	NA	NA	NA	NA	NA	NA	NA	NA

```

> tmat( S7 )

```

	DN	CVD	ESRD+CVD	ESRD	Dead(DN)	Dead(CVD)	Dead(ESRD+CVD)	Dead(ESRD)
DN	NA	107	NA	38	37	NA	NA	NA
CVD	NA	NA	63	NA	NA	120	NA	NA
ESRD+CVD	NA	NA	NA	NA	NA	NA	43	NA
ESRD	NA	NA	16	NA	NA	NA	NA	1
Dead(DN)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(CVD)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(ESRD+CVD)	NA	NA	NA	NA	NA	NA	NA	NA
Dead(ESRD)	NA	NA	NA	NA	NA	NA	NA	NA

We now set up an initial state data frame as input for simulation by `simLexis`. In order to get timescales and attributes right, specifically the `time.scales` and the `time.since` attributes, we must use `subset` since the “[” operator purges attributes when selecting columns:

```

> init <- subset( S7, FALSE ,
+               select=c(timeScales(S7), "lex.Cst",
+                       "sex", "hba1c", "sys.bt", "tchol", "alb",
+                       "smoke", "bmi", "gfr", "hmgb", "ins.kg") )
> str( init )
Classes 'Lexis' and 'data.frame':    0 obs. of  19 variables:
 $ age      : num
 $ per      : num
 $ tfi      : num
 $ tfn      : num
 $ dur      : num
 $ tfCVD    : num
 $ tfESRD   : num

```

```

$ tfCE : num
$ lex.Cst: Factor w/ 8 levels "DN","CVD","ESRD+CVD",...:
$ sex : Factor w/ 2 levels "F","M":
$ hba1c : num
$ sys.bt : num
$ tchol : num
$ alb : num
$ smoke : Factor w/ 2 levels "never+<3","4-20+20+":
$ bmi : num
$ gfr : num
$ hmgb : num
$ ins.kg : num
- attr(*, "breaks")=List of 8
..$ age : NULL
..$ per : NULL
..$ tfi : NULL
..$ tfn : num 0 0.167 0.333 0.5 0.667 ...
..$ dur : NULL
..$ tfCVD : NULL
..$ tfESRD: NULL
..$ tfCE : NULL
- attr(*, "time.scales")= chr "age" "per" "tfi" "tfn" ...
- attr(*, "time.since")= chr "" "" "" "" ...
> cbind( attr(init,"time.scales"),
+ attr(init,"time.since") )
      [,1] [,2]
[1,] "age" ""
[2,] "per" ""
[3,] "tfi" ""
[4,] "tfn" ""
[5,] "dur" ""
[6,] "tfCVD" "CVD"
[7,] "tfESRD" "ESRD"
[8,] "tfCE" "ESRD+CVD"

```

Then we must devise values for all covariates that are to enter in the estimation of state probabilities. They are also shown in table 1.1.

```

> init[1:2,"sex"] <- rep(levels(init$sex)[2],2)
> init[1:2,"age"] <- c(55,55)
> init[1:2,"tfn"] <- rep(5,2)
> init[1:2,"dur"] <- c(10,10)
> init[1:2,"lex.Cst"]<- rep("DN",2)
> init[1:2,"hba1c"] <- c(7.5,9)
> init[1:2,"sys.bt"] <- c(130,150)
> init[1:2,"tchol"] <- c(4.5,5.5)
> init[1:2,"alb"] <- c(3,10)*100
> init[1:2,"smoke"] <- levels(init$smoke)[c(1,2)]
> init[1:2,"bmi"] <- c(25,30)
> init[1:2,"gfr"] <- 70
> init[1:2,"hmgb"] <- 8
> init[1:2,"ins.kg"] <- 0.75
> init$regl <- factor(c("Fair","Poor"))
> init
      age per tfi tfn dur tfCVD tfESRD tfCE lex.Cst sex hba1c sys.bt tchol alb  smoke bmi
1  55 NA NA  5 10  NA  NA  NA  DN  M  7.5  130  4.5  300 never+<3 25
2  55 NA NA  5 10  NA  NA  NA  DN  M  9.0  150  5.5 1000 4-20+20+ 30
      gfr hmgb ins.kg regl
1  70  8  0.75 Fair
2  70  8  0.75 Poor

```

A quick glance at figure 1.2 shows that a substantial part of the patients enter the study *after* CVD, and it is therefore of interest to see how these fare. Hence we make a duplicate

Table 1.1: Starting values for estimation of probabilities

Regulation	Good	Bad
Sex	Man	Man
Age	55/65	55/65
Time since DN	5	5
Diabetes duration	10	10
Sex	M	M
HbA< 1c	7.5	9.0
Systolic blood pr.	130	150
Total cholesterol	4.5	5.5
Albumin	300	1000
Smoking	never, < 3	4-20, 20+
BMI	25	30
GFR	70	70
Hemoglobin	8	8
Insulin dose per kg	0.75	0.75

version of the `init` data set where the persons are assumed to start in the CVD state. Based on the distribution of age at entry into the study we also do the calculation for a person aged 45, resp. 55. Thus we will simulate probabilities for $8 = 2^3$ different combinations:

- age: 55/65, DN dur: 10/20, DM dur: 5/15
- regulation: Fair/Poor
- state: DN/CVD

Note we do not have to specify CVD duration as this is not included in any of the models. DN duration will still exist as a time scale in the Lexis object but it will just be updated as NA during the iteration, and it has no effect since the variable is never used in any model for transitions subsequent to CVD.

```
> i.cvd <- transform( init, lex.Cst=factor("CVD",levels=levels(lex.Cst)) )
> i.old <- transform( init, age=age+10,
+                   tfn=tfn+10,
+                   dur=dur+10 )
> i.ocv <- transform( init, age=age+10,
+                   tfn=tfn+10,
+                   dur=dur+10,
+                   lex.Cst=factor("CVD",levels=levels(lex.Cst)) )
> init <- rbind( init, i.cvd, i.old, i.ocv )
> init$i.state <- init$lex.Cst
> init$i.age <- init$age
> init
```

	age	per	tfi	tfn	dur	tfCVD	tfESRD	tfCE	lex.Cst	sex	hba1c	sys.bt	tchol	alb	smoke	bmi
1	55	NA	NA	5	10	NA	NA	NA	DN	M	7.5	130	4.5	300	never+<3	25
2	55	NA	NA	5	10	NA	NA	NA	DN	M	9.0	150	5.5	1000	4-20+20+	30
3	55	NA	NA	5	10	NA	NA	NA	CVD	M	7.5	130	4.5	300	never+<3	25
4	55	NA	NA	5	10	NA	NA	NA	CVD	M	9.0	150	5.5	1000	4-20+20+	30
5	65	NA	NA	15	20	NA	NA	NA	DN	M	7.5	130	4.5	300	never+<3	25

```

6 65 NA NA 15 20 NA NA NA DN M 9.0 150 5.5 1000 4-20+20+ 30
7 65 NA NA 15 20 NA NA NA CVD M 7.5 130 4.5 300 never+<3 25
8 65 NA NA 15 20 NA NA NA CVD M 9.0 150 5.5 1000 4-20+20+ 30
  gfr hmgb ins.kg regl i.state i.age
1 70 8 0.75 Fair DN 55
2 70 8 0.75 Poor DN 55
3 70 8 0.75 Fair CVD 55
4 70 8 0.75 Poor CVD 55
5 70 8 0.75 Fair DN 65
6 70 8 0.75 Poor DN 65
7 70 8 0.75 Fair CVD 65
8 70 8 0.75 Poor CVD 65

```

Now we can simulate transitions through the defined model for a specified number of patients with these patterns of initial values. Since simulation of 10,000 patients in one go would be too much, we simulate in chunks of 500 replicates of each type of patient:

```

> NN <- 500
> system.time(
+ simL <- simLexis( Tr, init,
+                  time.pts=seq(0,15,0.2), N=NN )
+                )
  user system elapsed
29.22  2.26  32.15
> summary( simL )
Transitions:
  To
From      DN  CVD  ESRD+CVD  ESRD  Dead(DN)  Dead(CVD)  Dead(ESRD+CVD)  Dead(ESRD)  Records:
DN         53 1288         0  428      231         0             0             0             2000
CVD         0  494      1172   0         0      1622         0             0             3288
ESRD+CVD    0   0         201   0         0         0      1216         0             1417
ESRD         0   0         245  17         0         0         0        166             428
Sum         53 1782      1618  445      231      1622      1216        166             7133

Transitions:
  To
From      Events: Risk time:  Persons:
DN         1947   9327.61    2000
CVD         2794  18612.06    3288
ESRD+CVD    1216   5294.65    1417
ESRD         411   1059.49     428
Sum         6368  34293.81    4000

```

We can then simulate another 19,000 to get a sample of 20,000 simulated patients for each of the 8 types of initial persons:

```

> system.time(
+ for( i in 1:19 )
+ {
+ simL <- rbind( simL, simLexis( Tr, init,
+                               time.pts=seq(0,15,0.2), N=NN,
+                               lex.id=i*(NN*nrow(init))+1:(NN*nrow(init)) ) )
+ cat( "Iter ", i, "at", strftime(Sys.time(), "%Y-%m-%d, %H:%M:%S"), "\n" )
+ flush.console()
+ } )
Iter 1 at 2013-12-24, 15:55:52
Iter 2 at 2013-12-24, 15:56:27
Iter 3 at 2013-12-24, 15:56:59
Iter 4 at 2013-12-24, 15:57:31
Iter 5 at 2013-12-24, 15:58:03
Iter 6 at 2013-12-24, 15:58:36
Iter 7 at 2013-12-24, 15:59:11
Iter 8 at 2013-12-24, 15:59:44

```

```

Iter 9 at 2013-12-24, 16:00:17
Iter 10 at 2013-12-24, 16:00:50
Iter 11 at 2013-12-24, 16:01:24
Iter 12 at 2013-12-24, 16:01:57
Iter 13 at 2013-12-24, 16:02:31
Iter 14 at 2013-12-24, 16:03:05
Iter 15 at 2013-12-24, 16:03:40
Iter 16 at 2013-12-24, 16:04:14
Iter 17 at 2013-12-24, 16:04:50
Iter 18 at 2013-12-24, 16:05:26
Iter 19 at 2013-12-24, 16:06:02
      user system elapsed
621.83    8.62   642.80

```

We then save the simulated data for possible future use:

```

> save( simL, file="./data/simL2.Rda" )
> load( file="./data/simL2.Rda" )

```

We now have a data frame (a Lexis-object) with the lifecourse of 80,000 persons — 10,000 for each combination of variables, and thus with somewhat more records:

```

> dim( simL )
[1] 142394    26

> summary( simL )

Transitions:
  To
From   DN    CVD  ESRD+CVD  ESRD  Dead(DN)  Dead(CVD)  Dead(ESRD+CVD)  Dead(ESRD)  Records:
DN      899 26069      0 8319    4713      0      0      0      40000
CVD      0 10389   23274  0      0      32406     0      0      66069
ESRD+CVD 0  0      4048  0      0      0      23958     0      28006
ESRD      0  0      4732  231     0      0      0      3356     8319
Sum      899 36458   32054 8550   4713   32406   23958   3356   142394

Transitions:
  To
From   Events: Risk time: Persons:
DN      39101 185168.46  40000
CVD      55680 375573.70  66069
ESRD+CVD 23958 104117.43  28006
ESRD      8088  21147.31  8319
Sum      126827 686006.90  80000

> with( simL, ftable(regl,i.age,i.state) )

      i.state   DN    CVD  ESRD+CVD  ESRD  Dead(DN)  Dead(CVD)  Dead(ESRD+CVD)  Dead(ESRD)
regl i.age
Fair 55      20573 12991      0    0      0      0      0      0
     65      21599 13122      0    0      0      0      0      0
Poor 55      22335 14199      0    0      0      0      0      0
     65      22918 14657      0    0      0      0      0      0

```

Once we have the simulated Lexis objects we can compute the state occupancy probabilities. We want to show these in different displays, so it is most convenient to collect the estimated fractions in a large array, suitably indexing the dimensions of the array:

```

> times <- seq(0,15,0.1)
> perm <- c(1:4,8:5)
> levels( simL$lex.Cst )[perm]
[1] "DN"          "CVD"          "ESRD+CVD"    "ESRD"        "Dead(ESRD)"
[6] "Dead(ESRD+CVD)" "Dead(CVD)"    "Dead(DN)"

```

```

> pArr <- NArray( list( i.age = c(55,65),
+                       regl = c("Fair","Poor"),
+                       i.state = c("DN","CVD"),
+                       times = times,
+                       state = levels( simL$lex.Cst )[perm] ) )
> dimnames( pArr )[-4]

$i.age
[1] "55" "65"

$regl
[1] "Fair" "Poor"

$i.state
[1] "DN" "CVD"

$state
[1] "DN"          "CVD"          "ESRD+CVD"    "ESRD"        "Dead(ESRD) "
[6] "Dead(ESRD+CVD)" "Dead(CVD)"    "Dead(DN)"

> for( ia in dimnames(pArr)$i.age )
+ for( ir in dimnames(pArr)$regl )
+ for( ii in dimnames(pArr)$i.state )
+ pArr[ia,ir,ii,,] <- pState( nState( subset( simL, i.age==as.numeric(ia) &
+                                           regl==ir &
+                                           i.state==ii ),
+                                           at = times,
+                                           from = as.numeric(ia),
+                                           time.scale = "age" ),
+                               perm = perm )
> save( pArr, file="./data/simP2.Rda" )

```

Now (re-)load the simulated survival curves (well, state occupancy probability curves):

```

> load( file="./data/simP2.Rda" )
> round( pArr[1,1,1,1:10,], 3 )

```

times	DN	CVD	ESRD+CVD	ESRD	Dead(ESRD)	Dead(ESRD+CVD)	Dead(CVD)	Dead(DN)
0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1
0.1	0.990	0.996	0.996	0.997	0.997	0.997	0.997	1
0.2	0.981	0.992	0.992	0.995	0.995	0.995	0.996	1
0.3	0.972	0.988	0.988	0.993	0.993	0.993	0.994	1
0.4	0.965	0.986	0.986	0.992	0.992	0.992	0.993	1
0.5	0.954	0.981	0.981	0.989	0.989	0.989	0.990	1
0.6	0.946	0.977	0.978	0.987	0.987	0.987	0.987	1
0.7	0.938	0.974	0.974	0.985	0.985	0.985	0.986	1
0.8	0.929	0.970	0.971	0.982	0.982	0.982	0.983	1
0.9	0.922	0.966	0.967	0.979	0.980	0.980	0.981	1

Once we have the tables with the simulated probabilities we can plot them, using the same colors as in the state diagram (figure 1.2).

```

> grps <- function(ia)
+ {
+   par( mfrow=c(2,2), mar=c(6,6,3,2)/2.5, mgp=c(3,1,0)/1.6, las=1, oma=c(2,2,0,0) )
+   il <- 0
+   for( ii in dimnames(pArr)$i.state )
+   for( ir in dimnames(pArr)$regl )
+   {
+     xx <- pArr[ia,ir,ii,,]
+     ai <- as.numeric( ia )
+     class( xx ) <- c("pState","matrix")
+     plot( xx, col=clx[c(1:4,8:5)], xlab="", ylab="",
+           xlim = c(0,10), xaxt="n" )
+     abline( h=1:19/20, v=1:9, col=gray(0.6), lty="13" )
+     lines( as.numeric(rownames(xx)), xx[, "ESRD"], lwd=3 )
+   }
+ }

```

```

+ axis( side=1, at=0:10, labels=rep("",11) )
+ axis( side=1, at=0:5*2, labels=seq(ai,ai+10,2) )
+ axis( side=4, at=0:20/20, tcl=-0.3, labels=FALSE )
+ axis( side=4, at=0:10/10, tcl=-0.6, labels=FALSE )
+ text( 0.5, 0.15,
+       paste( ii,"\n", ir, " control of risk factors", sep="" ),
+       col="white", font=2, adj=c(0,0) )
+ box(col="white")
+ mtext(letters[il<-il+1],line=0.2,adj=0)
+ }
+ mtext( "Probability", side=2, line=0, outer=TRUE, las=0 )
+ mtext( "Age at follow-up", side=1, line=0, outer=TRUE )
+ }

```

```
> grps("55")
```

```
> grps("65")
```

Also, we want to see the numerical size of some of the cumulative risks:

- 10-year cumulative risks of any ESRD
- 10-year cumulative risks of death
- fraction of those acquiring ESRD that are dead at 10 years

So we set up an array to hold these quantities for the 8 types of T2 patients that we are considering:

```

> times <- c(5,10,15)
> CumR <- NArray( c( dimnames( pArr )[1:3],
+                   list( when = times,
+                   what = c("cr-Death","cr-ESRD","pr-ESRDdead") ) ) )
> str( CumR )
logi [1:2, 1:2, 1:2, 1:3, 1:3] NA NA NA NA NA NA ...
- attr(*, "dimnames")=List of 5
..$ i.age : chr [1:2] "55" "65"
..$ regl : chr [1:2] "Fair" "Poor"
..$ i.state: chr [1:2] "DN" "CVD"
..$ when : chr [1:3] "5" "10" "15"
..$ what : chr [1:3] "cr-Death" "cr-ESRD" "pr-ESRDdead"
> tms <- dimnames(CumR)$when

```

— and then extract the quantities at these specified times:

```

> CumR[,,,,"cr-Death"] <- pArr[,,,tms,"ESRD"]
> CumR[,,,,"cr-ESRD"] <- pArr[,,,tms,"Dead(ESRD+CVD)"]-pArr[,,,tms,"CVD"]
> CumR[,,,,"pr-ESRDdead"] <-
+ (pArr[,,,tms,"Dead(ESRD+CVD)"]-pArr[,,,tms,"ESRD"])/
+ (pArr[,,,tms,"Dead(ESRD+CVD)"]-pArr[,,,tms,"CVD"] )

```

Finally we can show the cumulative risks in two different lay-outs:

```
> round( 100*ftable( CumR, col.vars=3:4 ), 1 )
```


i.age	regl	what	i.state when	DN			CVD		
				5	10	15	5	10	15
55	Fair	cr-Death		86.1	67.6	0.0	71.8	49.1	0.0
		cr-ESRD		10.1	23.2	39.4	11.3	22.6	30.6
		pr-ESRDdead		16.1	38.4	100.0	15.4	45.1	100.0
	Poor	cr-Death		83.4	59.0	0.0	66.7	41.4	0.0
		cr-ESRD		17.8	38.0	51.2	18.8	34.4	40.4
		pr-ESRDdead		14.7	40.3	100.0	16.6	45.4	100.0
65	Fair	cr-Death		74.6	38.8	0.0	63.0	29.3	0.0
		cr-ESRD		20.3	31.0	39.4	20.5	29.5	35.2
	pr-ESRDdead		36.5	77.9	100.0	40.6	81.2	100.0	
	Poor	cr-Death		67.5	26.4	0.0	56.5	18.7	0.0

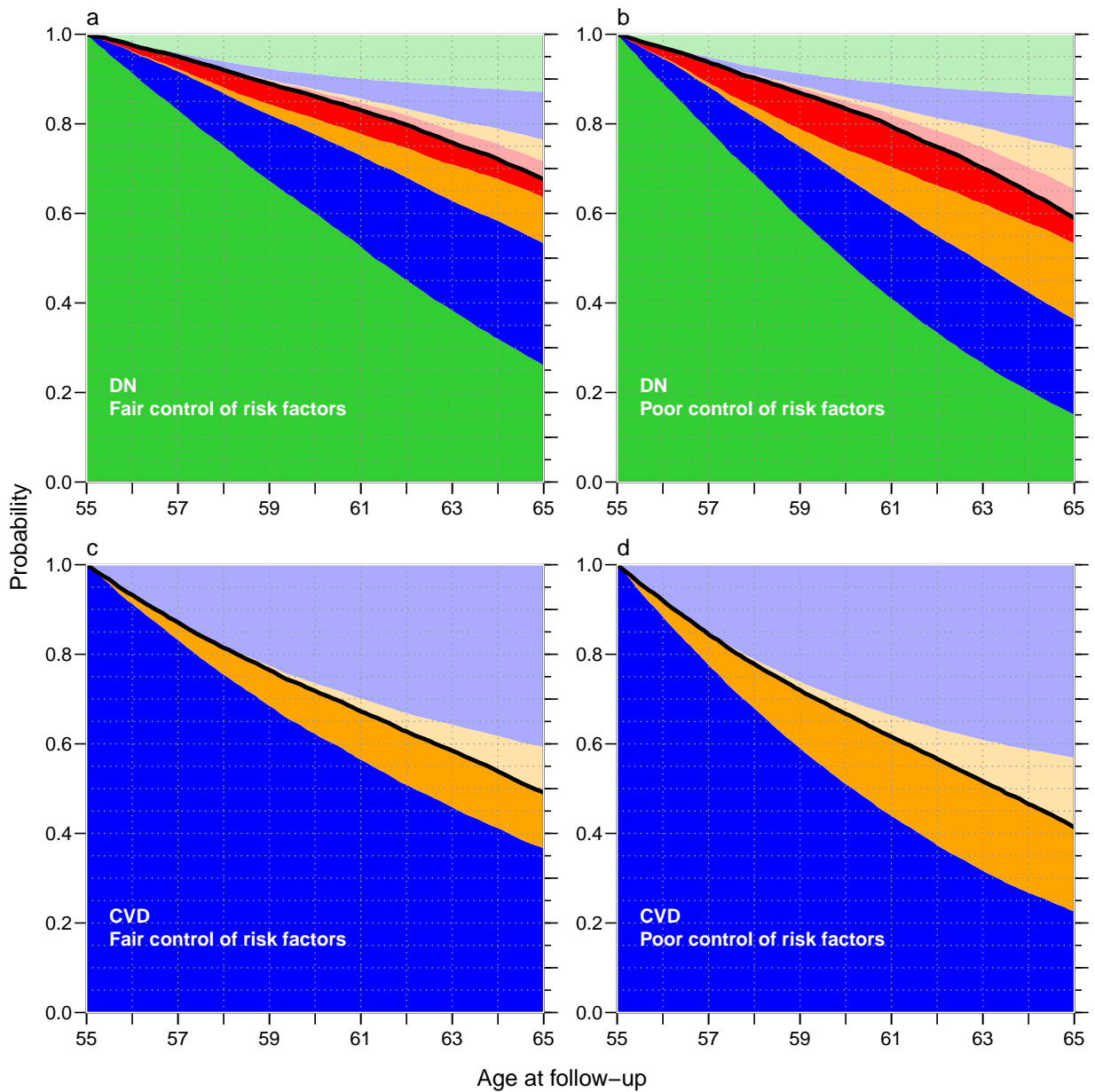


Figure 1.9: Estimated probabilities of being in different states for patients shown in table 1.1, for T2 patients entering at age 55. Coloring as in figure 1.2. The black line is the survival curve, the (pale) states above the line are the death states.

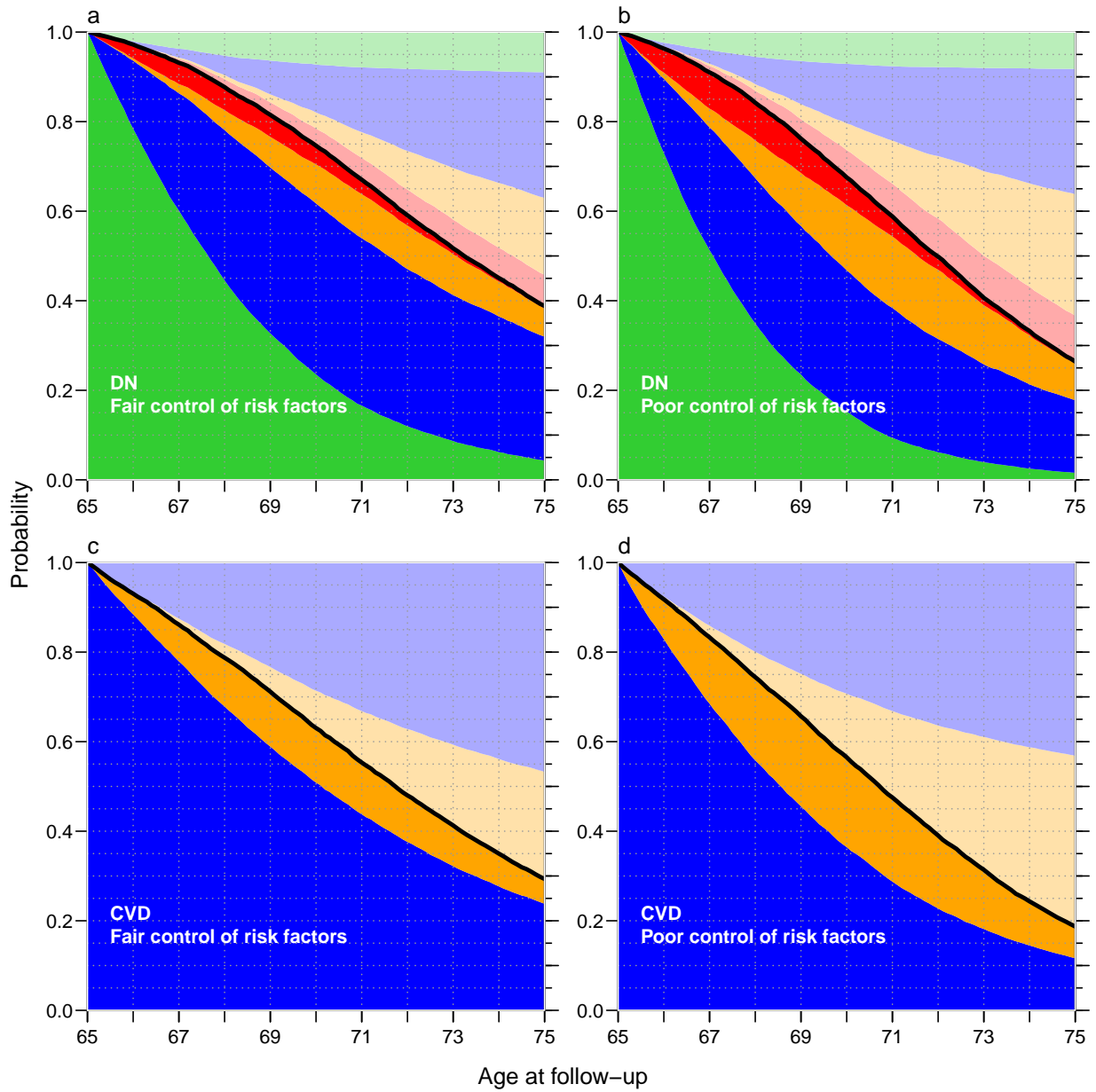


Figure 1.10: Estimated probabilities of being in different states for patients shown in table 1.1, for T2 patients enterin at age 65. Coloring as in figure 1.2. The black line is the survival curve, the (pale) states above the line are the death states.

```

cr-ESRD          32.8  46.1  52.0  34.3  45.2  48.7
pr-ESRDdead     36.8  81.2 100.0  41.5  84.4 100.0

```

```
> round( 100*ftable( CumR, col.vars=c(3,5) ), 1 )
```

i.age	regl	when	i.state			CVD			
			what	DN cr-Death	cr-ESRD	pr-ESRDdead	cr-Death	cr-ESRD	pr-ESRDdead
55	Fair	5		86.1	10.1	16.1	71.8	11.3	15.4
		10		67.6	23.2	38.4	49.1	22.6	45.1
		15		0.0	39.4	100.0	0.0	30.6	100.0
	Poor	5		83.4	17.8	14.7	66.7	18.8	16.6
		10		59.0	38.0	40.3	41.4	34.4	45.4
		15		0.0	51.2	100.0	0.0	40.4	100.0
65	Fair	5		74.6	20.3	36.5	63.0	20.5	40.6
		10		38.8	31.0	77.9	29.3	29.5	81.2
		15		0.0	39.4	100.0	0.0	35.2	100.0
	Poor	5		67.5	32.8	36.8	56.5	34.3	41.5
		10		26.4	46.1	81.2	18.7	45.2	84.4
		15		0.0	52.0	100.0	0.0	48.7	100.0

Compilation log

R 3.0.2

```
-----
Program: DN2.rnw
Folder: c:\Bendix\Steno\GbAd
Started: tirsdag 24. december 2013, 15:54:05
-----
```

Writing to file DN2.tex

Processing code chunks with options ...

```
1 : echo keep.source term hide (T2nef.rnw:5)
2 : echo keep.source term verbatim (T2nef.rnw:10)
3 : echo keep.source term verbatim (T2nef.rnw:17)
4 : echo keep.source term verbatim eps pdf (label = boxes-tp2, T2nef.rnw:92)
5 : echo keep.source term verbatim (T2nef.rnw:114)
6 : echo keep.source term verbatim (T2nef.rnw:123)
7 : echo keep.source term verbatim (label = stack, T2nef.rnw:135)
8 : echo keep.source term verbatim (label = subset-stack, T2nef.rnw:145)
9 : echo keep.source term verbatim (label = m0, T2nef.rnw:158)
10 : echo keep.source term verbatim (label = prop-tests, T2nef.rnw:181)
11 : echo keep.source term verbatim (T2nef.rnw:210)
12 : echo keep.source term verbatim (label = m1-m2-cov, T2nef.rnw:280)
13 : echo keep.source term verbatim (label = base-separate, T2nef.rnw:306)
14 : echo keep.source term verbatim eps pdf (label = base-CVD2, T2nef.rnw:342)
15 : echo keep.source term verbatim (label = RR-comp-mort2, T2nef.rnw:369)
16 : echo keep.source term verbatim (label = RR-comp-ESRD, T2nef.rnw:380)
17 : echo keep.source term verbatim eps pdf (label = xforest2, T2nef.rnw:399)
18 : echo keep.source term verbatim eps pdf (label = xforestcol2, T2nef.rnw:444)
19 : echo keep.source term verbatim eps pdf (label = pairs2, T2nef.rnw:481)
20 : echo keep.source term verbatim (label = covariaate-medians, T2nef.rnw:495)
21 : echo keep.source term verbatim (label = used-values, T2nef.rnw:506)
22 : echo keep.source term verbatim (label = pred-frames, T2nef.rnw:512)
23 : echo keep.source term verbatim (label = get-rates, T2nef.rnw:548)
24 : echo keep.source term verbatim (label = plr-def, T2nef.rnw:567)
25 : echo keep.source term verbatim eps pdf (label = crates, T2nef.rnw:585)
26 : echo keep.source term verbatim eps pdf (label = rates, T2nef.rnw:599)
27 : echo keep.source term verbatim (T2nef.rnw:630)
28 : echo keep.source term verbatim (label = per-eff, T2nef.rnw:643)
29 : echo keep.source term verbatim (T2nef.rnw:674)
30 : echo keep.source term verbatim (T2pred.rnw:15)
31 : echo keep.source term verbatim (T2pred.rnw:20)
32 : echo keep.source term verbatim (T2pred.rnw:31)
33 : echo keep.source term verbatim (T2pred.rnw:47)
34 : echo keep.source term verbatim (T2pred.rnw:58)
35 : echo keep.source term verbatim (T2pred.rnw:69)
36 : echo keep.source term verbatim (T2pred.rnw:82)
37 : echo keep.source term verbatim (T2pred.rnw:119)
38 : echo keep.source term verbatim (T2pred.rnw:155)
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45 : echo keep.source term verbatim (label = defpl, T2pred.rnw:242)
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48 : echo keep.source term verbatim (T2pred.rnw:297)
49 : echo keep.source term verbatim (T2pred.rnw:306)
50 : echo keep.source term verbatim (T2pred.rnw:314)
```

You can now run (pdf)latex on 'DN2.tex'

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Program: DN2.rnw
Folder: c:\Bendix\Steno\GbAd
Ended: tirsdag 24. december 2013, 16:07:52
Elapsed: 00:13:46
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