Mortality and morbidity among T1D DN patients

GbAd, PRo / SDC

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Contents

Chapter 1

Analysis of T1 patients' follow-up

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

Initially we load the T1D patients from the datasets with the follow-up:

```
> load( file="./data/Base-Lexis.Rda" )
> L1 <- subset( L1, dm.type=="type1" )
> L7 <- subset( L7, dm.type=="type1" )
```

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(0,40)
> pdf( "./graph/DN1-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=plsymb, cex=0.7, col=clr[L7$lex.Cst] )
> dev.off()
null device
          1
> xl <- c(0,15)+1998
> pdf( "./graph/DN1-per-Lexis.pdf",
+       height=1+diff(yl)/ypi,
+       width=1+diff(xl)/ypi )
> par( mai=c(3,3,1,1)/4, omi=c(0,0,0,0),
+      mgp=c(3,1,0)/1.6, las=1 )
> plsymb <- c(NA,16)[1+(substr(L7$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(0,30)
> X7 <- subset( L7, !is.na(tfCVD) )
> pdf( "./graph/DN1-cvd-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(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=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( 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 T1D 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)
  DN       14949   70        0   92       34         0              0
  CVD          0 4976       56    0        0        42              0
  ESRD+CVD     0    0     1458    0        0         0             45
  ESRD         0    0       35 1544        0         0              0
  Sum      14949 5046     1549 1636       34        42             45

Transitions:
     To
From       Dead(ESRD)  Records:  Events: Risk time:  Persons:
```

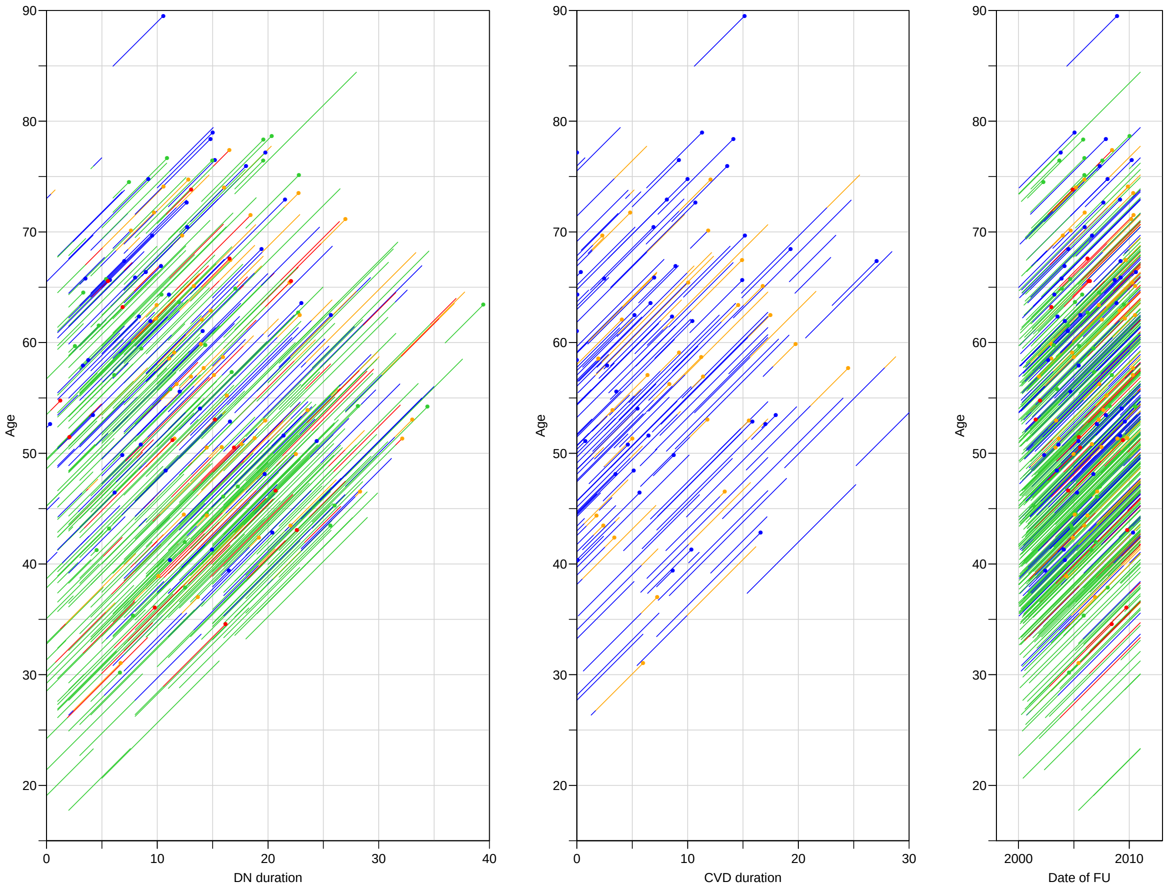

Figure 1.1: *Lexis diagrams for the follow-up of T1 patients by DN duration, CVD duration and calendar time versus age. DN state is green, CVD blue, ESRD after CVD orange and ESRD without CVD red. Dots indicate deaths.*

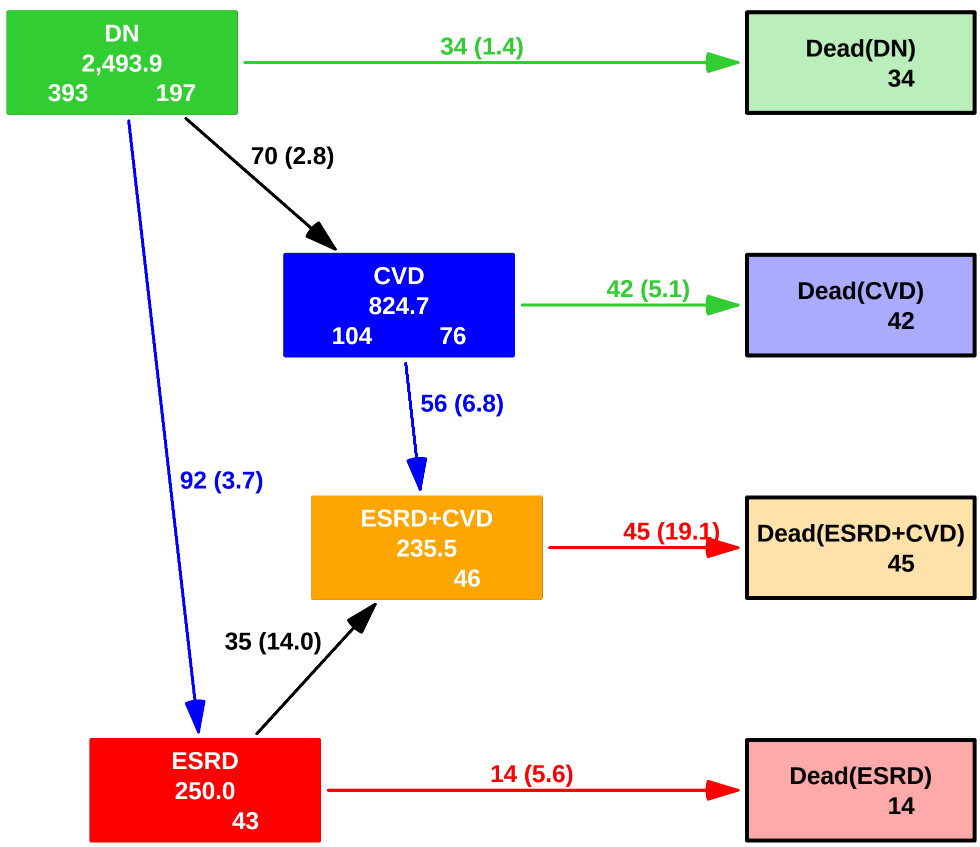

Figure 1.2: *States and transitions between them in the analysis set-up for T1D patients. Numbers in the boxes are the person-years, and the number of persons starting, respectively ending in each state. The numbers on the arrows are the number of transitions (rate per 100 PY).*
Note that some persons start their follow-up in the CVD state; these patients also suffer from DN.

```
  DN                 0     15145     196    2493.86      393
  CVD                0      5074      98     824.70      174
  ESRD+CVD           0      1503      45     235.53       91
  ESRD              14      1593      49     249.96       92
  Sum               14     23315     388    3804.05      497
```

```
> addmargins(with(L7,table(table(lex.id))))
```

```
   1   2   3 Sum
 302 137  58 497
```

```
> addmargins(with(S7,table(table(lex.id))))
```

```
   1   2   3   4   6   7   8   9  10  11  12  14  15  16  17  18  19  20  21  22
   3   2   1   3   5   4   3   9   4   6   2   4   5   3   4   2   6   6   4   4
  23  24  25  26  27  28  29  30  31  32  33  34  35  36  37  38  39  40  41  42
   1   7   2   6   7   5   6   2  10   2   4   6  14  10   5   4   2   4   3   9
  43  44  45  46  47  48  49  50  51  52  53  54  55  56  57  58  59  60  61  62
   5   4   2   5   8   2   5   3   2   5   5   7   2   5   9   7  14  11  16  21
  63  64  65  66  67  68 Sum
  25  41  30  50  22   2 497
```

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%
 6.512834 11.613963 15.953799 22.643395
```

```
> ( 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%
43.39493 53.93977 63.35524 74.02259
```

```
> ( 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%
21.22519 31.26626 39.30459 49.35164
```

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] 60272    40
```

```
> xtabs( cbind(lex.dur,lex.Fail) ~ lex.Tr, data=St7 )
```

```
lex.Tr                         lex.dur  lex.Fail
  DN->CVD                    2493.8563   70.0000
  DN->ESRD                   2493.8563   92.0000
  DN->Dead(DN)               2493.8563   34.0000
  CVD->ESRD+CVD               824.7036   56.0000
  CVD->Dead(CVD)              824.7036   42.0000
  ESRD+CVD->Dead(ESRD+CVD)    235.5291   45.0000
  ESRD->ESRD+CVD              249.9576   35.0000
  ESRD->Dead(ESRD)            249.9576   14.0000
```

We are not (initially) interested in the first and last three of these transitions, so we subset to the relevant 4 transitions; we specifically 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.Tr   DN->ESRD       DN->Dead(DN)       CVD->ESRD+CVD       CVD->Dead(CVD)
              lex.Fail    FALSE  TRUE         FALSE  TRUE          FALSE  TRUE          FALSE  TRUE
lex.Xst
DN                        14949     0         14949     0              0     0              0     0
CVD                          70     0            70     0           4976     0           4976     0
ESRD+CVD                      0     0             0     0              0    56             56     0
ESRD                          0    92            92     0              0     0              0     0
Dead(DN)                     34     0             0    34              0     0              0     0
Dead(CVD)                     0     0             0     0             42     0              0    42
Dead(ESRD+CVD)                0     0             0     0              0     0              0     0
Dead(ESRD)                    0     0             0     0              0     0              0     0
> dim( St4 )
[1] 40438    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 three 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)              0.028 0.019 0.041
  lex.TrDN->Dead(DN)       0.370 0.249 0.548
  lex.TrCVD->ESRD+CVD      1.627 1.155 2.291
  lex.TrCVD->Dead(CVD)     1.220 0.839 1.774
  sexM                     1.258 0.943 1.679
  Ns(tfn, kn = n.kn)1      0.922 0.563 1.509
  Ns(tfn, kn = n.kn)2      1.361 0.816 2.271
  Ns(tfn, kn = n.kn)3      1.110 0.741 1.663
  Ns(age, kn = a.kn)1      1.791 1.070 2.999
  Ns(age, kn = a.kn)2      2.689 1.694 4.270
  Ns(age, kn = a.kn)3      2.742 1.759 4.275
  Ns(dur, kn = d.kn)1      0.592 0.352 0.996
  Ns(dur, kn = d.kn)2      0.685 0.399 1.175
  Ns(dur, kn = d.kn)3      0.615 0.393 0.962
> 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)        0.37 0.25  0.55
  lex.TrCVD->ESRD+CVD       1.63 1.15  2.29
  lex.TrCVD->Dead(CVD)      1.22 0.84  1.77
> 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            0.37 0.25  0.55
  CVD->ESRD+CVD vs. DN->ESRD           1.63 1.15  2.29
  CVD->Dead(CVD) vs. CVD->ESRD+CVD     0.75 0.50  1.12
  CVD->Dead(CVD) vs. DN->Dead(DN)      3.30 2.08  5.23
```

This means that CVD influences the occurrence of ESRD by a factor of 1.6, whereas there is a 3.3-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   19.592    0.021
+i.tfn   9   12.453    0.189
+i.dur   9    7.146    0.622
-i.tfn  -9  -11.786    0.226
-i.dur  -9   -7.813    0.553
```

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 at 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   10.193    0.017       3      7.521      0.057
 +i.tfn      3    1.218    0.749       3      5.615      0.132
 +i.dur      3    1.072    0.784       3      0.725      0.867
 -i.tfn     -3   -1.234    0.745      -3     -6.022      0.111
 -i.dur     -3   -1.055    0.788      -3     -0.318      0.957
> round( prop[,1:6+6], 3 )
        toDeath Deviance Pr(>Chi) toESRD Deviance.1 Pr(>Chi).1
 +i.age       3    1.567    0.667      3      1.516      0.679
 +i.tfn       3    4.030    0.258      3      3.128      0.372
 +i.dur       3    1.773    0.621      3      3.420      0.331
 -i.tfn      -3   -3.339    0.342     -3     -2.381      0.497
 -i.dur      -3   -2.465    0.482     -3     -4.167      0.244
```

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 we 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 is 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)      2.770 1.720 4.460
 lex.TrCVD->ESRD+CVD       1.776 1.255 2.512
```

So there is a strong effect of CVD occurrence on the rate of Death, and a somewhat weaker 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 *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:
      To
 From     DN  CVD ESRD+CVD ESRD Dead  Records:  Events: Risk time:  Persons:
   DN  14949   70        0   92   34     15145      196    2493.86       393
   CVD     0 4976       56    0   42      5074       98     824.70       174
   Sum 14949 5046       56   92   76     20219      294    3318.56       497
```

We shall also address the mortality subsequent to ESRD, so we make a dataset for the analysis of these transitions too:

```
> 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:
      To
 From       DN CVD ESRD+CVD ESRD Dead  Records:  Events: Risk time:  Persons:
   ESRD+CVD  0   0     1458    0   45      1503       45     235.53        91
   ESRD      0   0       35 1544   14      1593       49     249.96        92
   Sum       0   0     1493 1544   59      3096       94     485.49       148
```

The naming convention is having the first uppercase letter as `B` for models without covariates or `E` for models extended with covariates, followed by a lowercase `d` for deaths without ESRD, `e` for ESRD events and `ed` for deaths subsequent to ESRD:

```
> # 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 coccurrence
> 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(0,20),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       2.770 1.720 4.460
  I(lex.Cst == "CVD")TRUE       2.578 1.554 4.277
  sexM                          1.078 0.604 1.925
  bmi                           0.942 0.863 1.028
  I(sys.bt/10)                  1.029 0.886 1.195
  I(-gfr/10)                    1.180 1.060 1.314
  log2(alb)                     0.974 0.851 1.115
```

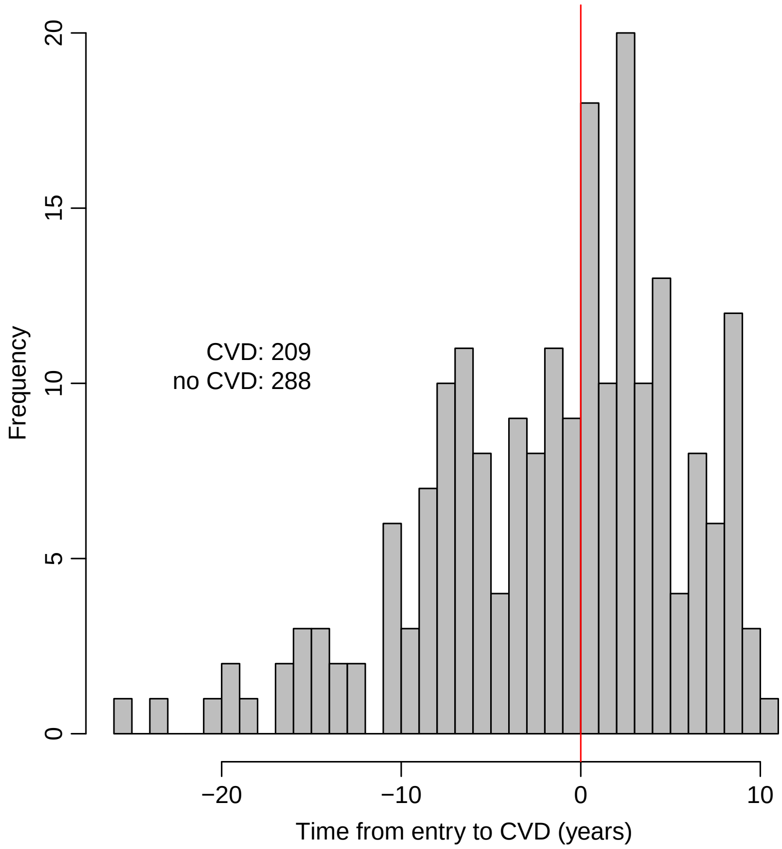

Figure 1.3: *Histogram of time from entry (date of DN) to CVD; hence, negative numbers refer to patients with CVD* prior *to entry. Note that the numbers w/o CVD here is the* total *number in the database, also those 34 who have a recorded date of CVD* after *ESRD, and who thus do not appear in figure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

```
  log1.5(pmax(ins.kg, 0.03))      0.904 0.785 1.042
  hmgb                            1.330 0.982 1.802
  hba1c                           1.077 0.895 1.297
  tchol                           0.903 0.717 1.136
  smoke4-20+20+                   2.240 1.302 3.852
```

It seems that only smoking (RR=2.2 (1.3–3.9)), presence of CVD (RR=2.6 (1.6–4.3)) and GFR (RR per 10: 1.2 (1.1–1.3)) influence the mortality significantly. There is a borderline significant effect of hemoglobin (RR per %: 1.3 (1.0–1.8)).

The same figures for the rates of ESRD and death subsequents 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         1.776 1.255 2.512
  I(lex.Cst == "CVD")TRUE         1.158 0.790 1.698
  sexM                            1.826 1.217 2.741
  bmi                             1.007 0.951 1.066
  I(sys.bt/10)                    1.170 1.041 1.315
  I(-gfr/10)                      1.232 1.138 1.333
  log2(alb)                       1.514 1.340 1.710
  log1.5(pmax(ins.kg, 0.03))      0.991 0.885 1.110
  hmgb                            0.616 0.498 0.761
  hba1c                           1.178 1.033 1.344
  tchol                           1.054 0.892 1.245
  smoke4-20+20+                   1.073 0.732 1.572
> 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      3.622 1.916 6.847
  I(lex.Cst == "ESRD+CVD")TRUE      2.945 1.463 5.928
  sexM                              0.679 0.311 1.481
  bmi                               0.985 0.909 1.066
  I(sys.bt/10)                      1.008 0.811 1.253
  I(-gfr/10)                        1.259 1.070 1.480
  log2(alb)                         0.939 0.739 1.193
  log1.5(pmax(ins.kg, 0.03))        0.801 0.676 0.948
  hmgb                              0.905 0.586 1.399
  hba1c                             1.093 0.892 1.339
  tchol                             1.051 0.801 1.379
  smoke4-20+20+                     2.055 1.017 4.156
```

The pattern of effects on rates of ESRD is very different from the effects on the mortality rates; CVD is a much weaker 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 (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-smok
> 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,

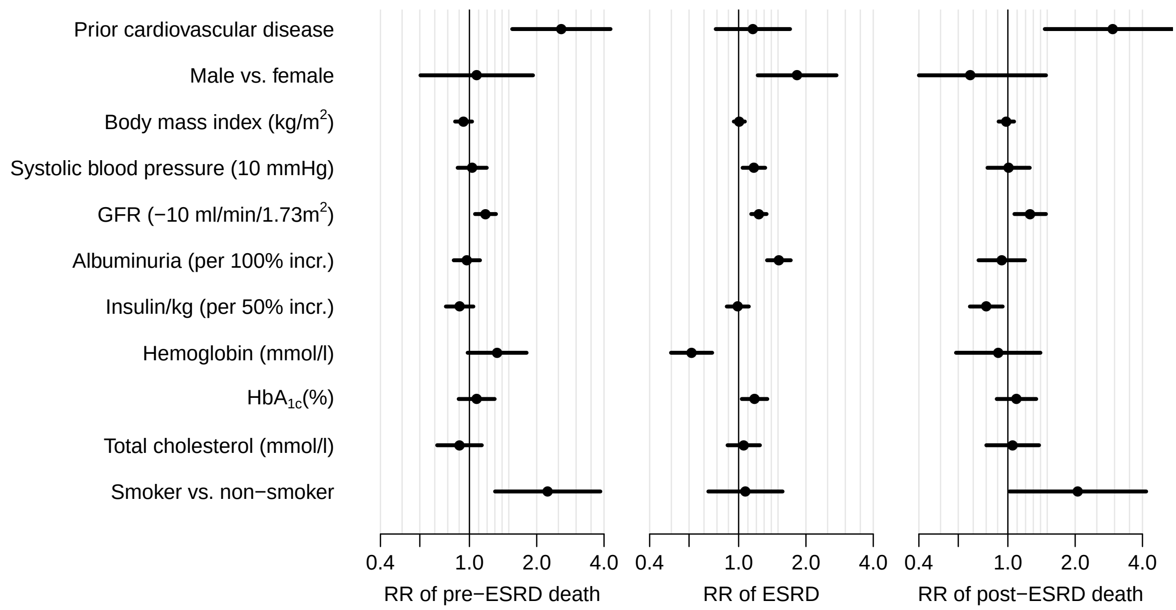

Figure 1.4: *RRs associated with the different risk factors for the transitions* from *DN and CVD,* to *either death or ESRD or from ESRD to death (see figure 1.2).*

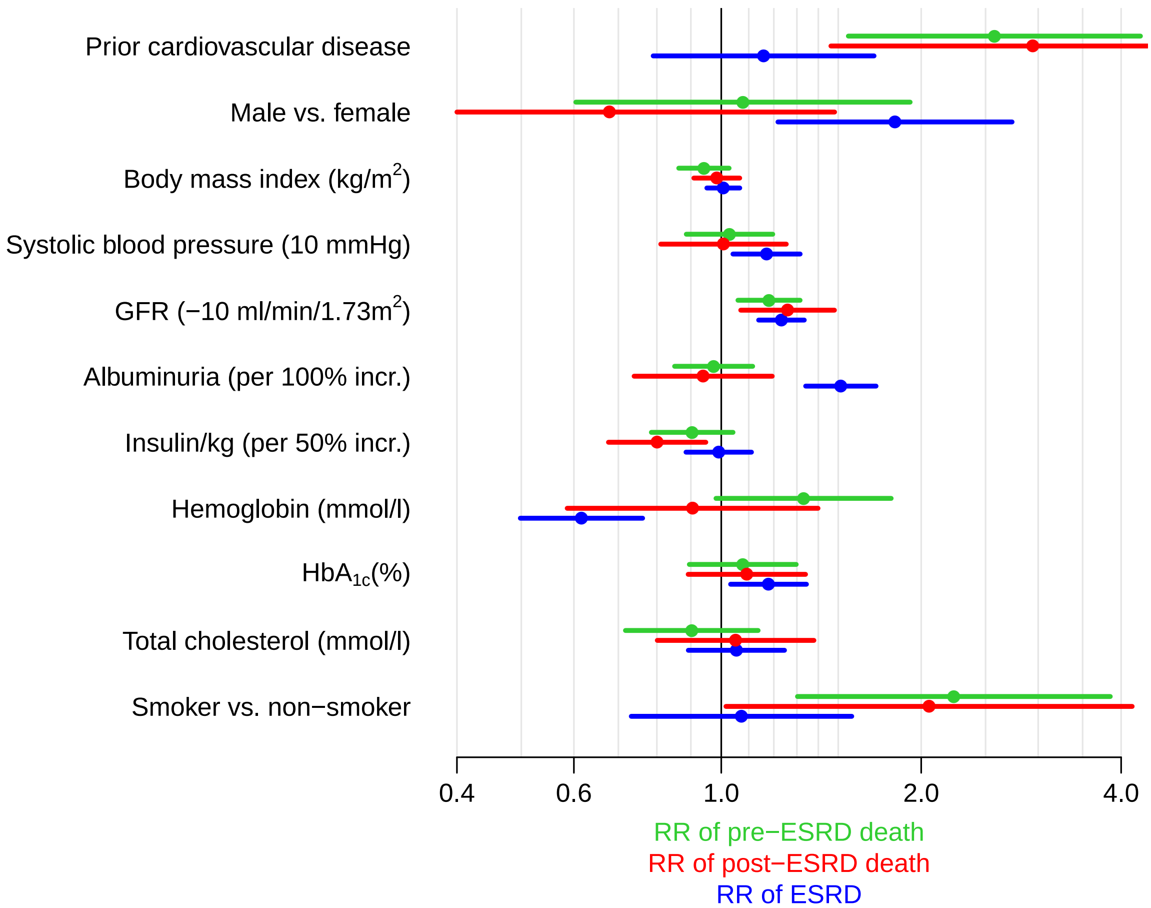

Figure 1.5: *RRs associated with the different risk factors for the transitions* from *DN and CVD,* to *either death or ESRD or from ESRD to death (see figure 1.2).*

albuminuria, HbA_{1c} and low hemoglobin.

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`).

```
> quantile( L1$lex.dur, probs=0:4/4 )
         0%         25%         50%         75%        100%
 0.02737851  5.09787817  9.13347023 10.54893908 10.98973306
> 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:

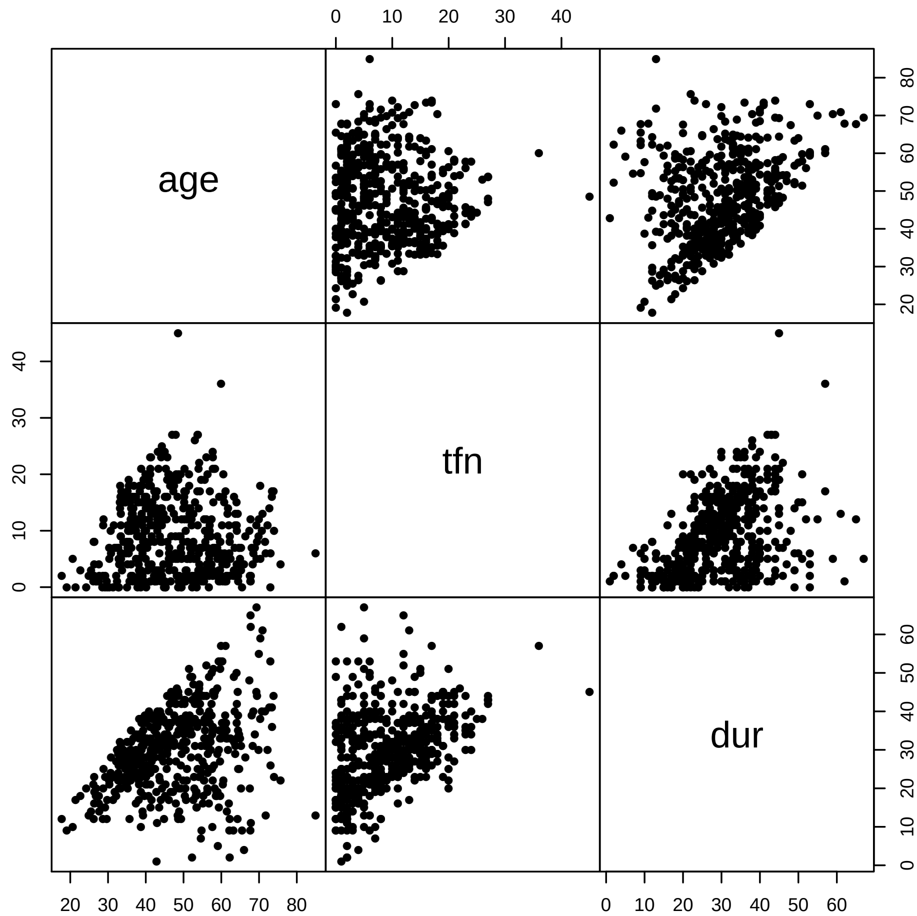

Figure 1.6: *Pairs plot of the entry times on the 3 time-scales in the models.*

```
> 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 (chosen close to the median) for the covariates when computing the rates, here shown together with the quantiles of the variables in the data:

```
> round( cbind( mm, c(21,150,70,500,0.7,8,9,5) ), 2 )
           0%    25%    50%     75%     100%
bmi     13.78  19.53  21.52   23.68    37.22  21.0
sys.bt 104.00 130.00 141.00  153.25   220.00 150.0
gfr      7.00  45.00  69.00   93.00   178.00  70.0
alb      6.00 193.25 483.00 1087.75 10962.00 500.0
ins.kg   0.00   0.51   0.68    0.93    28.78   0.7
hmgb     4.50   7.40   8.10    8.70    12.00   8.0
hba1c    5.30   8.20   9.00    9.90    16.30   9.0
tchol    1.80   4.50   5.10    5.90     9.20   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(25,35,45,55)
> na <- length(a1)
> # DM duration at entry
> d1 <- c(5,15,25)
> nd <- length(d1)
> # Common covariate values:
> pr0 <- data.frame( sex = factor( 1, levels=2:1, labels=c("F","M") ),
+                    bmi = 21,
+                    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 person-years or % per year, since the units used for `lex.dur` is years.

With this data frame in place we can now plot the mortality rates and the ESRD rates for these 3 types of T1 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 "25","35","45",..: 1 1 1 1 1 1 1 1 1 1 ...
  $ d  : Factor w/ 3 levels "5","15","25": 1 1 1 1 1 1 1 1 1 1 ...
  $ r  : num  0.336 0.337 0.338 0.339 0.34 ...
  $ l  : num  0.0476 0.0481 0.0485 0.0489 0.0494 ...
  $ h  : num  2.37 2.36 2.35 2.35 2.34 ...
> 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 T1 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( "Undajusted", 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( "T1", 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( "Undajusted", 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( "T1", 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/T1E-models.Rda" )
```

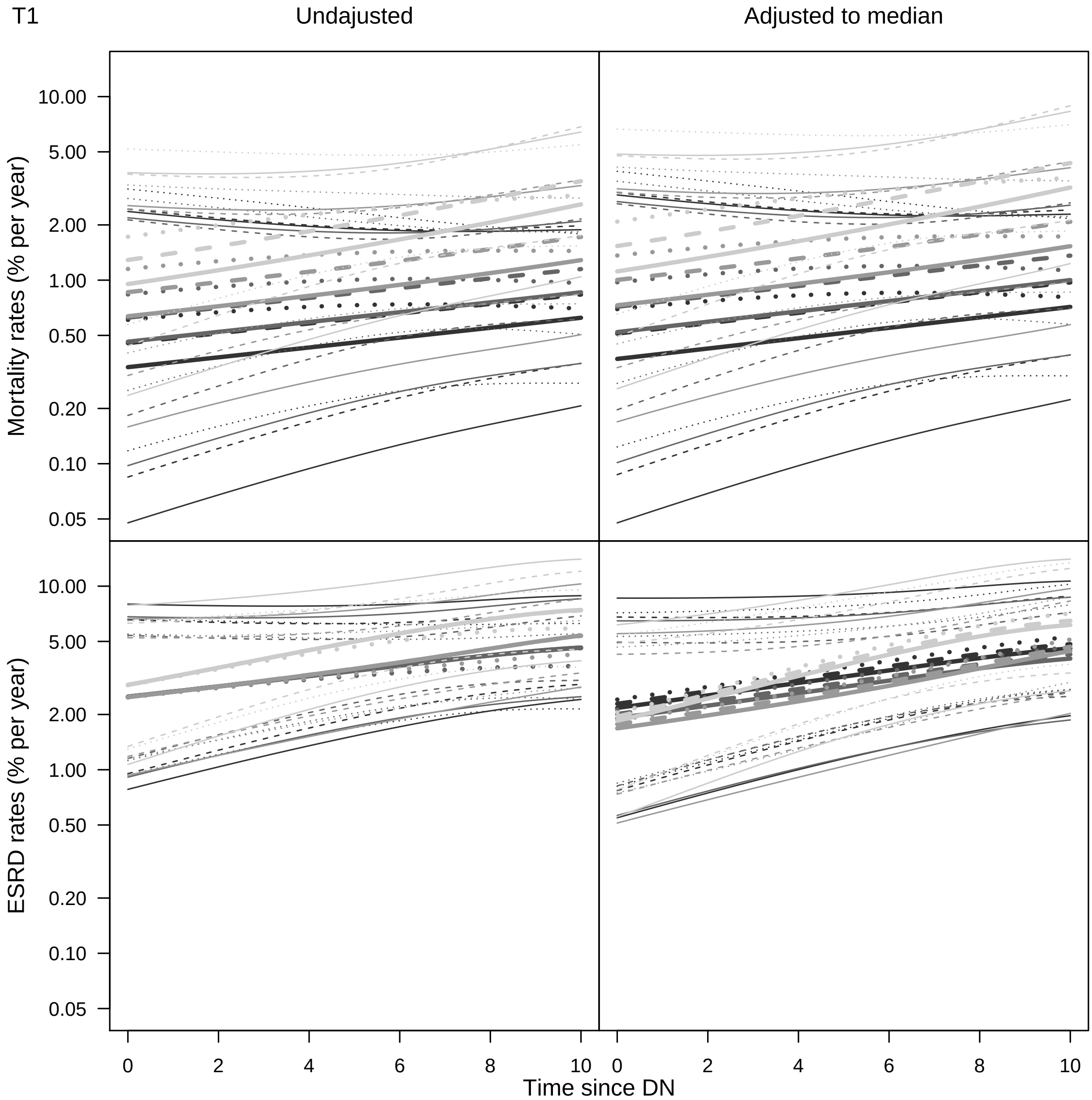

Figure 1.7: *Mortality and ESRD rates for T1 patients with 95% c.i., as a function of time since entry into the study. Rates are for persons* without *CVD, for ages at entry 25, 35, 45, 55 (dark to light color), and duration of diabetes at entry 5, 15, 25 (full, dashed and dotted lines).*

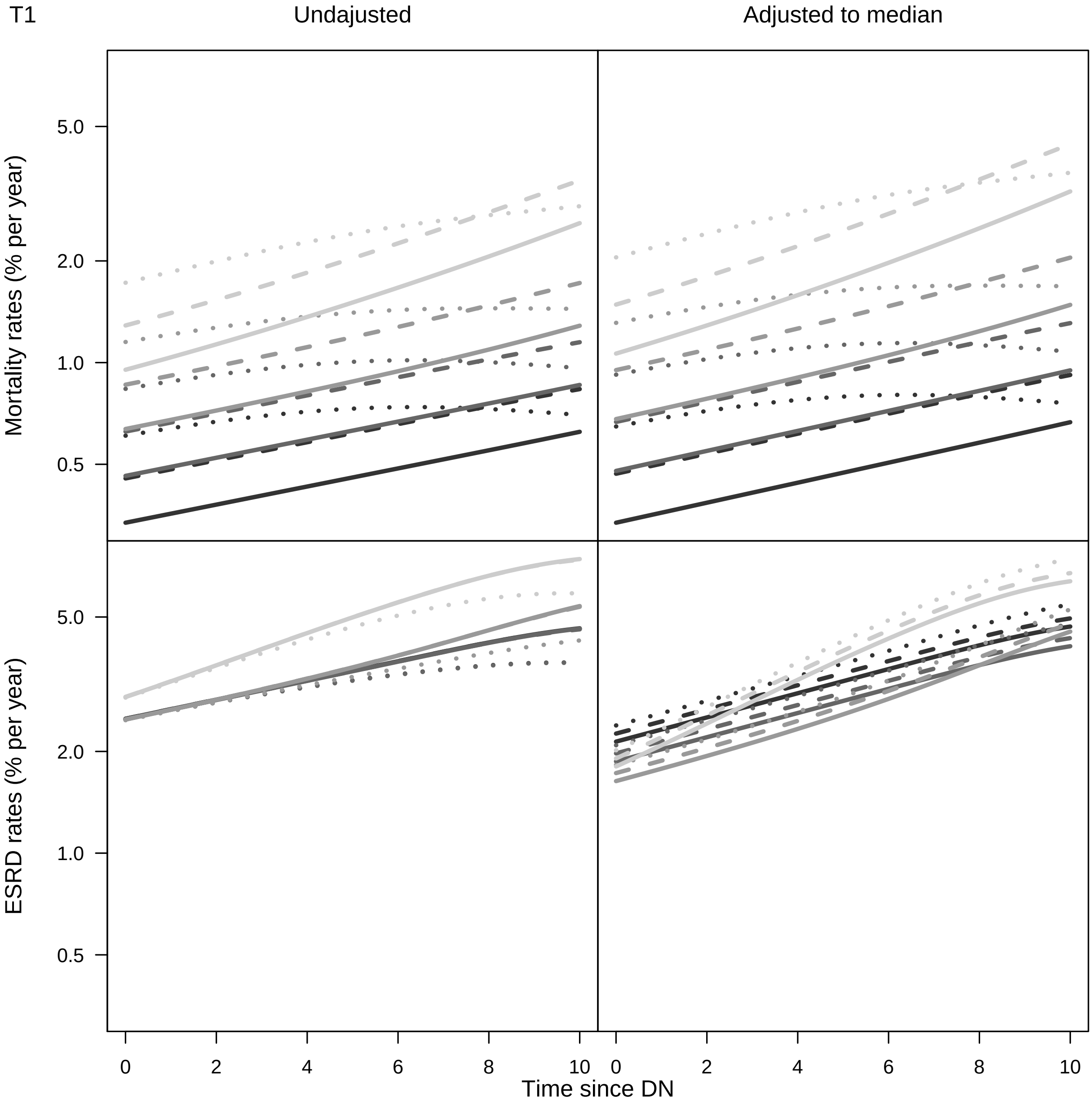

Figure 1.8: *Mortality and ESRD rates for T1 patients, as a function of time since entry into the study. Rates are for persons* without *CVD, for ages at entry 25, 35, 45, 55 (dark to light color), and duration of diabetes at entry 5, 15, 25 (full, dashed and dotted lines).*
It is seen that age and diabetes 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      1.03 0.98  1.09      1.20 1.13  1.28
Dead      1.03 0.95  1.11      1.08 0.98  1.18
```

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 and in particular 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 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.

The conclusion is therefore that there seems to be small, non-significant increase in mortality and ESRD rates overall, but a substantial improvement in the distribution of risk factors over time.

```
> save( S7, file="./data/T1S7.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 1 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 he observed network.

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

```
> load( file="./data/T1S7.Rda" )
> load( file="./data/T1E-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:

```
> 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") ~ . - I(lex.Cst=="CVD"),
+                 data = subset( S7, lex.Cst=="ESRD" ) )
> round( cbind( ci.exp( Ec ), ci.exp( Ece ) ), 3 )
                             exp(Est.)  2.5% 97.5% exp(Est.)  2.5%   97.5%
  (Intercept)                    0.003 0.000 0.247     0.105 0.000 161.278
  Ns(age, kn = a.kn)1            0.722 0.223 2.337     0.130 0.013   1.334
  Ns(age, kn = a.kn)2            1.000 0.312 3.207    14.865 2.384  92.690
  Ns(age, kn = a.kn)3            0.892 0.271 2.933    10.013 2.080  48.206
  Ns(dur, kn = d.kn)1            1.490 0.569 3.901     0.209 0.034   1.303
  Ns(dur, kn = d.kn)2            1.234 0.374 4.077     0.497 0.035   7.039
  Ns(dur, kn = d.kn)3            1.670 0.700 3.986     0.233 0.044   1.238
  Ns(tfn, kn = n.kn)1            0.445 0.164 1.208     0.822 0.169   4.001
  Ns(tfn, kn = n.kn)2            0.495 0.191 1.286     0.740 0.113   4.848
  Ns(tfn, kn = n.kn)3            0.492 0.225 1.074     1.426 0.355   5.722
  sexM                           1.577 0.833 2.984     2.706 0.933   7.848
  bmi                            1.020 0.929 1.120     0.864 0.732   1.019
  I(sys.bt/10)                   1.132 0.941 1.363     1.221 0.931   1.602
  I(-gfr/10)                     1.193 1.074 1.326     1.010 0.820   1.243
  log2(alb)                      0.811 0.700 0.940     1.222 0.815   1.833
  log1.5(pmax(ins.kg, 0.03))     1.101 0.895 1.356     1.151 0.845   1.568
  hmgb                           0.988 0.692 1.410     0.715 0.441   1.161
  hba1c                          1.205 0.988 1.470     1.161 0.784   1.720
  tchol                          1.243 0.975 1.583     0.859 0.573   1.289
  smoke4-20+20+                  1.831 1.032 3.251     1.107 0.415   2.953
```

Because of the overfitting of the model for mortality after ESRD (which has 59 events), we fit a simpler model with only 6 parameters, using only CVD, sex, DN duration, age and a quadratic in time since ESRD:

```
> En <- update( Ed, (substr(lex.Xst,1,4)=="Dead") ~ I(lex.Cst=="ESRD+CVD") +
+                                                   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)                         0.03350861 0.007786894 0.1441944
  I(lex.Cst == "ESRD+CVD")TRUE        3.44452981 1.827610681 6.4919656
  sexM                                0.58788892 0.331119880 1.0437712
  tfn                                 0.96698189 0.932286002 1.0029690
  age                                 1.02751001 1.003547924 1.0520442
  pmin(tfESRD, tfCE, na.rm = TRUE)    0.93975450 0.641123062 1.3774867
  I(pmin(tfESRD, tfCE, na.rm = TRUE)^2) 1.00540419 0.950965133 1.0629597
```

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)]
                 to
  from             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  70       NA   92       34        NA             NA         NA
    CVD            NA  NA       56   NA       NA        42             NA         NA
    ESRD+CVD       NA  NA       NA   NA       NA        NA             45         NA
    ESRD           NA  NA       35   NA       NA        NA             NA         14
    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.

Table 1.1: *Starting values for estimation of probabilities*

Regulation	Fair	Poor
Sex	Man	Man
Age	45/55	45/55
Time since DN	5	5
Diabetes duration	25	25
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	22	22
GFR	70	70
Hemoglobin	8	8
Insulin dose per kg	0.75	0.75

```
> init[1:2,"sex"] <- rep(levels(init$sex)[2],2)
> init[1:2,"age"] <- c(45,45)
> init[1:2,"tfn"] <- rep(5,2)
> init[1:2,"dur"] <- c(25,25)
> init[1:2,"lex.Cst"]<- rep("DN",2)
> init[1:2,"hba1c"]  <- c(7.5,9)
> init[1:2,"sys.bt"] <- c(130,150)
> init[1:2,"tchol"]  <- c(4.5,5.5)
> init[1:2,"alb"]    <- c(3,10)*100
> init[1:2,"smoke"]  <- levels(init$smoke)[c(1,2)]
> init[1:2,"bmi"]    <- c(22,22)
> 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  45  NA  NA   5  25    NA     NA   NA      DN   M   7.5    130   4.5  300 never+<3  22
2  45  NA  NA   5  25    NA     NA   NA      DN   M   9.0    150   5.5 1000 4-20+20+  22
  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 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 claculation for a person aged 45, resp. 55. Thus we will simulate probabilities for $8 = 2^3$ different combinations:

- age: 45/55, DN dur: 5/15, DM dur: 25/35
- 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  45  NA  NA   5  25    NA     NA   NA      DN   M   7.5    130   4.5  300 never+<3  22
2  45  NA  NA   5  25    NA     NA   NA      DN   M   9.0    150   5.5 1000 4-20+20+  22
3  45  NA  NA   5  25    NA     NA   NA     CVD   M   7.5    130   4.5  300 never+<3  22
4  45  NA  NA   5  25    NA     NA   NA     CVD   M   9.0    150   5.5 1000 4-20+20+  22
5  55  NA  NA  15  35    NA     NA   NA      DN   M   7.5    130   4.5  300 never+<3  22
6  55  NA  NA  15  35    NA     NA   NA      DN   M   9.0    150   5.5 1000 4-20+20+  22
7  55  NA  NA  15  35    NA     NA   NA     CVD   M   7.5    130   4.5  300 never+<3  22
```

```
8  55   NA   NA   15   35     NA      NA    NA     CVD    M    9.0     150    5.5 1000 4-20+20+  22
  gfr hmgb ins.kg regl i.state i.age
1  70    8   0.75 Fair      DN    45
2  70    8   0.75 Poor      DN    45
3  70    8   0.75 Fair     CVD    45
4  70    8   0.75 Poor     CVD    45
5  70    8   0.75 Fair      DN    55
6  70    8   0.75 Poor      DN    55
7  70    8   0.75 Fair     CVD    55
8  70    8   0.75 Poor     CVD    55
```

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(0,15.2,0.2), N=NN )
+            )
     user  system elapsed
    25.51    2.41   28.27
> summary( simL )
  Transitions:
       To
  From         DN  CVD ESRD+CVD ESRD Dead(DN) Dead(CVD) Dead(ESRD+CVD) Dead(ESRD)  Records:
    DN        624  428        0  723      225         0              0          0      2000
    CVD         0  772      996    0        0       660              0          0      2428
    ESRD+CVD    0    0      471    0        0         0            868          0      1339
    ESRD        0    0      343  230        0         0              0        150       723
    Sum       624 1200     1810  953      225       660            868        150      6490

  Transitions:
       To
  From         Events: Risk time:  Persons:
    DN           1376   17852.83       2000
    CVD          1656   20636.92       2428
    ESRD+CVD      868    5248.99       1339
    ESRD          493    3257.10        723
    Sum          4393   46995.84       4000
```

We can then simulate another 19 times to get a sample of 10,000 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(0,15.2,0.2), 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 2014-01-01, 21:04:04
  Iter  2 at 2014-01-01, 21:04:31
  Iter  3 at 2014-01-01, 21:04:57
  Iter  4 at 2014-01-01, 21:05:24
  Iter  5 at 2014-01-01, 21:05:50
  Iter  6 at 2014-01-01, 21:06:17
  Iter  7 at 2014-01-01, 21:06:44
  Iter  8 at 2014-01-01, 21:07:12
  Iter  9 at 2014-01-01, 21:07:40
  Iter  10 at 2014-01-01, 21:08:08
```

```
Iter  11 at 2014-01-01, 21:08:36
Iter  12 at 2014-01-01, 21:09:04
Iter  13 at 2014-01-01, 21:09:32
Iter  14 at 2014-01-01, 21:10:01
Iter  15 at 2014-01-01, 21:10:31
Iter  16 at 2014-01-01, 21:11:00
Iter  17 at 2014-01-01, 21:11:29
Iter  18 at 2014-01-01, 21:11:58
Iter  19 at 2014-01-01, 21:12:28
   user  system elapsed
 523.10    5.60  529.48
```

We then save the simulated data for possible future use:

```
> save( simL, file="./data/simL1.Rda" )
> load( file="./data/simL1.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] 129451     26
> summary( simL )
Transitions:
     To
From          DN   CVD  ESRD+CVD  ESRD  Dead(DN)  Dead(CVD)  Dead(ESRD+CVD)  Dead(ESRD)
  DN       12780  8094         0 14629      4497          0               0           0
  CVD          0 15382     19740     0         0      12972               0           0
  ESRD+CVD     0     0      9812     0         0          0           16916           0
  ESRD         0     0      6988  4515         0          0               0        3126
  Sum      12780 23476     36540 19144      4497      12972           16916        3126

Transitions:
     To
From          Records:  Events: Risk time:  Persons:
  DN             40000    27220  362432.22     40000
  CVD            48094    32712  410801.93     48094
  ESRD+CVD       26728    16916  106142.72     26728
  ESRD           14629    10114   65389.53     14629
  Sum           129451    86962  944766.39     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 45             14401 12091        0     0        0         0              0          0
     55             15096 13150        0     0        0         0              0          0
Poor 45             21011 15101        0     0        0         0              0          0
     55             22220 16381        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(0,15.2,0.1)
> perm  <- c(1:4,8:5)
> levels( simL$lex.Cst )[perm]
[1] "DN"              "CVD"             "ESRD+CVD"        "ESRD"            "Dead(ESRD)"
[6] "Dead(ESRD+CVD)" "Dead(CVD)"       "Dead(DN)"
> pArr <- NArray( list( i.age = c(45,55),
+                         regl = c("Fair","Poor"),
+                      i.state = c("DN","CVD"),
+                        times = times,
+                        state = levels( simL$lex.Cst )[perm] ) )
> dimnames( pArr )[-4]
```

```
$i.age
[1] "45" "55"

$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/simP1.Rda" )
```

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

```
> load( file="./data/simP1.Rda" )
> round( pArr[1,1,1,1:10,], 3 )
```

```
      state
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 0.996 0.998    0.998 0.999      0.999          0.999     0.999        1
  0.2 0.993 0.997    0.997 0.999      0.999          0.999     0.999        1
  0.3 0.989 0.996    0.996 0.998      0.998          0.998     0.998        1
  0.4 0.985 0.994    0.994 0.997      0.997          0.997     0.997        1
  0.5 0.982 0.992    0.992 0.997      0.997          0.997     0.997        1
  0.6 0.979 0.991    0.991 0.996      0.996          0.996     0.996        1
  0.7 0.976 0.989    0.990 0.996      0.996          0.996     0.996        1
  0.8 0.973 0.988    0.988 0.994      0.995          0.995     0.995        1
  0.9 0.969 0.986    0.986 0.994      0.994          0.994     0.994        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("45")
```

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

Also, we want to see the numerical size of some of the cumulative risks at 5, 10 and 15 years after DN, specifically:

- cumulative risks of any ESRD (red and orange areas)
- cumulative risks of death (the survival curve))
- fraction of those acquiring ESRD that are dead (pale red and orange areas relative to total red and orange areas)

So we set up an array to hold these quantities for the 8 types of T1 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] "45" "55"
    ..$ 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"] <- 1-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.state   DN              CVD
                         when        5   10   15     5   10   15
  i.age regl what
  45    Fair cr-Death              4.4 11.2 19.3 10.7 22.8 35.3
             cr-ESRD               5.8 13.2 20.5  6.3 13.6 20.6
             pr-ESRDdead          16.1 30.8 43.1 33.9 51.3 62.9
        Poor cr-Death             12.8 31.7 50.4 24.2 48.1 66.9
```

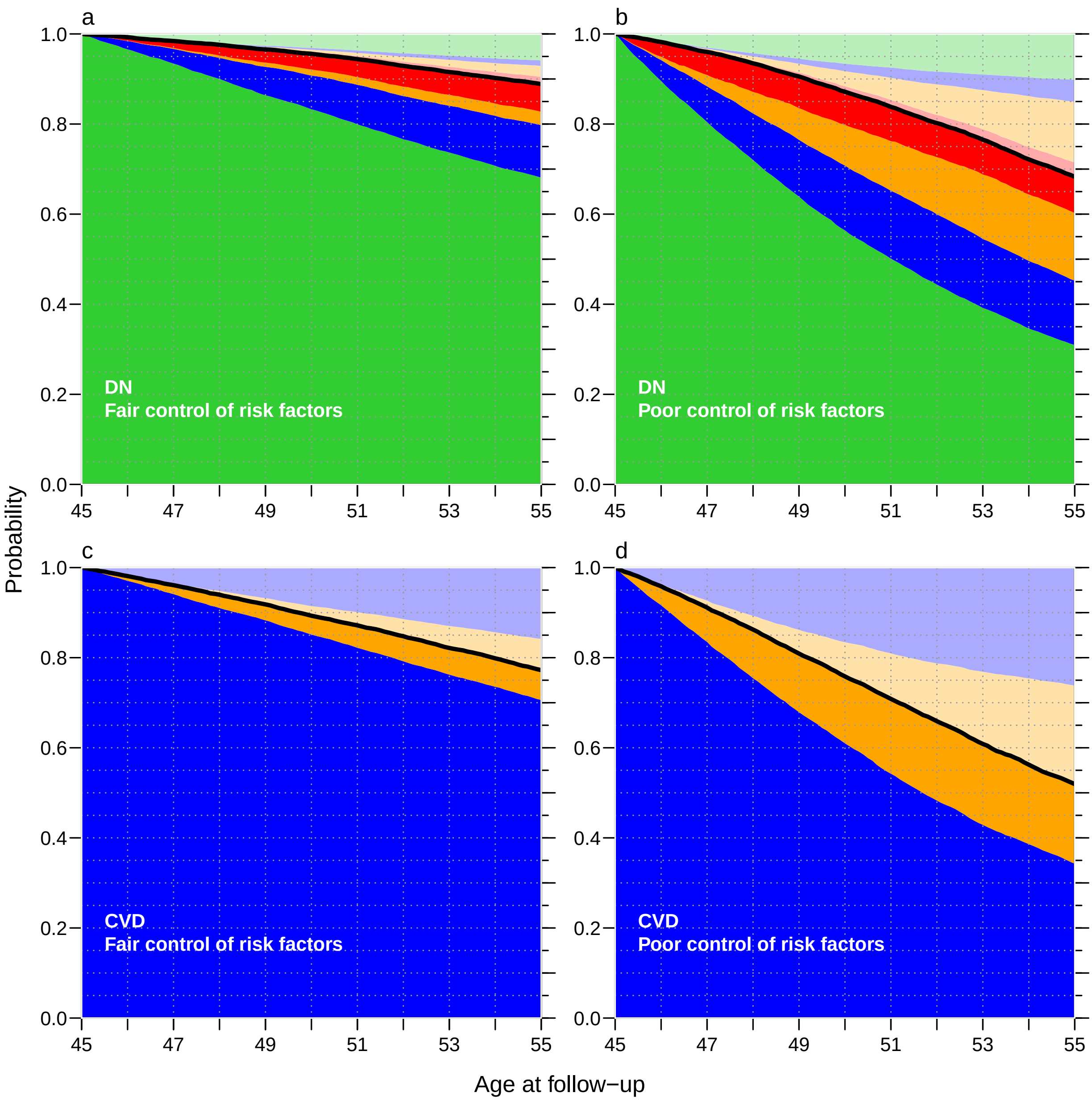

Figure 1.9: *Estimated probabilities of being in different states for patients shown in table 1.1, for T1 patients enterin at age 45. Coloring as in figure 1.2. The black line is the survival curve, the (pale) states above the line are the death states.*

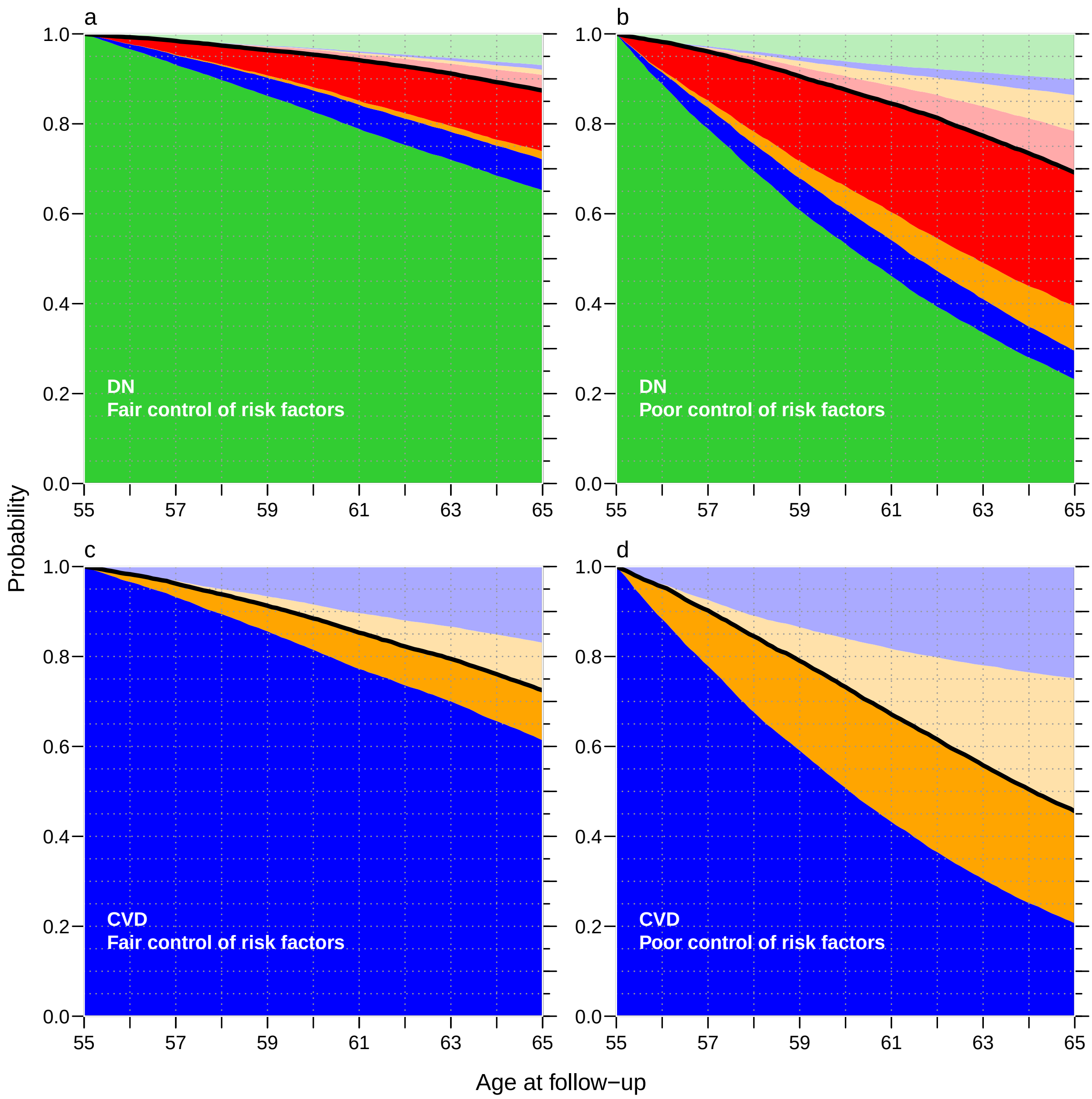

Figure 1.10: *Estimated probabilities of being in different states for patients shown in table 1.1, for T1 patients enterin at age 55. Coloring as in figure 1.2. The black line is the survival curve, the (pale) states above the line are the death states.*

```
          cr-ESRD              21.0 39.7 54.2 22.5 39.5 50.5
          pr-ESRDdead          21.8 41.9 56.0 33.9 55.3 69.1
  55   Fair cr-Death            4.6 12.6 24.5 11.6 27.5 45.6
          cr-ESRD               9.2 20.0 30.2 10.1 21.7 31.2
          pr-ESRDdead          13.3 23.2 35.3 30.9 48.8 62.1
       Poor cr-Death           12.4 30.9 52.3 26.8 54.4 75.9
          cr-ESRD              31.7 56.9 70.0 33.2 54.5 63.6
          pr-ESRDdead          15.9 30.3 48.7 32.6 54.3 72.0
```

```
> round( 100*ftable( CumR, col.vars=c(3,5) ), 1 )
               i.state       DN                                CVD
               what     cr-Death cr-ESRD pr-ESRDdead cr-Death cr-ESRD pr-ESRDdead
  i.age regl when
  45    Fair 5                4.4     5.8        16.1     10.7     6.3        33.9
             10              11.2    13.2        30.8     22.8    13.6        51.3
             15              19.3    20.5        43.1     35.3    20.6        62.9
        Poor 5               12.8    21.0        21.8     24.2    22.5        33.9
             10              31.7    39.7        41.9     48.1    39.5        55.3
             15              50.4    54.2        56.0     66.9    50.5        69.1
  55    Fair 5                4.6     9.2        13.3     11.6    10.1        30.9
             10              12.6    20.0        23.2     27.5    21.7        48.8
             15              24.5    30.2        35.3     45.6    31.2        62.1
        Poor 5               12.4    31.7        15.9     26.8    33.2        32.6
             10              30.9    56.9        30.3     54.4    54.5        54.3
             15              52.3    70.0        48.7     75.9    63.6        72.0
```

Compilation log

```
 R 3.0.2
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 Program:  DN1.rnw
  Folder:  c:\Bendix\Steno\GbAd
 Started:  onsdag 01. januar 2014, 21:02:15
 --------------------------------------------
Writing to file DN1.tex
Processing code chunks with options ...
 1 : echo keep.source term hide (T1nef.rnw:5)
 2 : echo keep.source term verbatim (T1nef.rnw:10)
 3 : echo keep.source term verbatim (T1nef.rnw:17)
 4 : echo keep.source term verbatim eps pdf  (label = boxes-tp1, T1nef.rnw:92)
 5 : echo keep.source term verbatim (T1nef.rnw:114)
 6 : echo keep.source term verbatim (T1nef.rnw:123)
 7 : echo keep.source term verbatim (label = stack, T1nef.rnw:135)
 8 : echo keep.source term verbatim (label = subset-stack, T1nef.rnw:144)
 9 : echo keep.source term verbatim (label = m0, T1nef.rnw:158)
10 : echo keep.source term verbatim (label = prop-tests, T1nef.rnw:181)
11 : echo keep.source term verbatim (T1nef.rnw:210)
12 : echo keep.source term verbatim (label = m1-m2-cov, T1nef.rnw:281)
13 : echo keep.source term verbatim (label = base-separate, T1nef.rnw:308)
14 : echo keep.source term verbatim (T1nef.rnw:315)
15 : echo keep.source term verbatim (T1nef.rnw:325)
16 : echo keep.source term verbatim eps pdf  (label = base-CVD1, T1nef.rnw:355)
17 : echo keep.source term verbatim (label = RR-comp-mort1, T1nef.rnw:382)
18 : echo keep.source term verbatim (label = RR-comp-ESRD, T1nef.rnw:393)
19 : echo keep.source term verbatim eps pdf  (label = xforest1, T1nef.rnw:411)
20 : echo keep.source term verbatim eps pdf  (label = xforestcol1, T1nef.rnw:456)
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23 : echo keep.source term verbatim (label = used-values, T1nef.rnw:517)
24 : echo keep.source term verbatim (label = pred-frames, T1nef.rnw:523)
25 : echo keep.source term verbatim (label = get-rates, T1nef.rnw:560)
26 : echo keep.source term verbatim (label = plr-def, T1nef.rnw:579)
27 : echo keep.source term verbatim eps pdf  (label = crates, T1nef.rnw:597)
28 : echo keep.source term verbatim eps pdf  (label = rates, T1nef.rnw:611)
29 : echo keep.source term verbatim (T1nef.rnw:642)
30 : echo keep.source term verbatim (label = per-eff, T1nef.rnw:655)
31 : echo keep.source term verbatim (T1nef.rnw:690)
32 : echo keep.source term verbatim (T1pred.rnw:15)
33 : echo keep.source term verbatim (T1pred.rnw:20)
34 : echo keep.source term verbatim (T1pred.rnw:30)
35 : echo keep.source term verbatim (T1pred.rnw:41)
36 : echo keep.source term verbatim (T1pred.rnw:53)
37 : echo keep.source term verbatim (T1pred.rnw:64)
38 : echo keep.source term verbatim (T1pred.rnw:77)
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51 : echo keep.source term verbatim (T1pred.rnw:303)
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You can now run (pdf)latex on 'DN1.tex'

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 Program: DN1.rnw
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   Ended: onsdag 01. januar 2014, 21:13:58
 Elapsed: 00:11:43
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