The Danish National Diabetes Register: Life lost to DM

SDC
June 2016
http://bendixcarstensen.com/DMreg/demoYLL.pdf
Version 1.4

Compiled Monday 27th June, 2016, 11:22
from: /home/bendix/sdc/DMreg/NDR-demo/2012/demoYLL.tex

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Contents

Chapter 1

Analysis based on original DM definition

1.1 Life lost to diabetes

```
> library( Epi )
> load( file="./data/FU-o.Rda" )
> lls()
```

```
  name mode class            size
1 Agd  list data.frame       348066 7
2 Lx   list Lexis data.frame 469793 23
3 TT   list data.frame       6732 9
```

The dataset TT contains deaths and person-years for persons with and without diabetes:

```
> head( TT )
  sex A    P U     Y.nD      Y.DM D.DM D.nD X
1   F 0 1995 0 17025.50 0.0000000    0  137 0
2   F 0 1995 1 17100.54 0.1300479    0   16 2
3   F 0 1996 0 16468.06 1.4401095    0  134 4
4   F 0 1996 1 17067.30 1.8617385    0   23 4
5   F 0 1997 0 16434.00 0.0000000    0  152 0
6   F 0 1997 1 16499.84 1.9890486    0   14 2
```

In order to compute the years of life lost to diabetes and how this has changed over time, we fit models for the mortality of both groups (and of course, separately for men and women). The models we use will be age-period-cohort models providing estimated mortality rates for ages 0–99 and dates 1.1.1995-1.1.2012.

```
> TT <- transform( TT,
+                  A=A+(1+U)/3,
+                  P=P+(2-U)/3 )
```

```
> dd <- cbind( subset( TT, select=c(sex,A,P,D.DM,Y.DM) ), tp="DM" )
> nn <- cbind( subset( TT, select=c(sex,A,P,D.nD,Y.nD) ), tp="nD" )
> names( dd )[4:5] <-
+ names( nn )[4:5] <- c("D","Y")
> head( dd )
```

```
  sex         A        P D          Y tp
1   F 0.3333333 1995.667 0 0.0000000 DM
2   F 0.6666667 1995.333 0 0.1300479 DM
3   F 0.3333333 1996.667 0 1.4401095 DM
4   F 0.6666667 1996.333 0 1.8617385 DM
5   F 0.3333333 1997.667 0 0.0000000 DM
6   F 0.6666667 1997.333 0 1.9890486 DM
```

```
> head( nn )
```

```
  sex         A        P   D        Y tp
1   F 0.3333333 1995.667 137 17025.50 nD
2   F 0.6666667 1995.333  16 17100.54 nD
3   F 0.3333333 1996.667 134 16468.06 nD
4   F 0.6666667 1996.333  23 17067.30 nD
5   F 0.3333333 1997.667 152 16434.00 nD
6   F 0.6666667 1997.333  14 16499.84 nD
```

```
> LL <- transform( subset( rbind( dd, nn ), Y>0 ),
+                  D = pmax( 0, D ) )
> str( LL )
```

```
'data.frame':        13446 obs. of  6 variables:
 $ sex: Factor w/ 2 levels "M","F": 2 2 2 2 2 2 2 2 2 2 ...
 $ A  : num  0.667 0.333 0.667 0.667 0.667 ...
 $ P  : num  1995 1997 1996 1997 1999 ...
 $ D  : num  0 0 0 0 0 0 0 0 0 0 ...
 $ Y  : num  0.13 1.44 1.862 1.989 0.504 ...
 $ tp : Factor w/ 2 levels "DM","nD": 1 1 1 1 1 1 1 1 1 1 ...
```

With the correct age and period coding in the Lexis triangles, we fit models for the mortality. However, to stabilize the estimates we fit a model with basic age, period and cohort models and a simple linear effect of age-RR and period-RR:

```
> ( a.kn <- seq(20,95,,6) )
[1] 20 35 50 65 80 95
> ( p.kn <- seq(1996,2010,,4) )
[1] 1996.000 2000.667 2005.333 2010.000
> ( c.kn <- seq(1910,1995,,6) )
[1] 1910 1927 1944 1961 1978 1995
> mm <- glm( D ~ -1 +
+                Ns(A  ,knots=a.kn,int=TRUE) +
+                Ns(  P,knots=p.kn,ref=2005) +
+                Ns(P-A,knots=c.kn,ref=1950) +
+                tp + I(A-  50):tp + I(P-2005):tp,
+            offset = log(Y),
+            family = poisson,
+              data = subset( LL, sex=="M" & A>15 ) )
> ww <- update( mm,
+              data = subset( LL, sex=="F" & A>15 ) )
```

We briefly show the annula change in RR by age and period:

```
> round( cbind( ci.exp( mm, subset="tpDM" ),
+                ci.exp( ww, subset="tpDM" ) ), 3 )
                 exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
tpDM                 3.272 3.216 3.330     3.247 3.177 3.319
tpDM:I(A - 50)       0.978 0.977 0.978     0.979 0.978 0.980
tpDM:I(P - 2005)     0.988 0.986 0.989     0.985 0.983 0.986
```

```
> RR <- cbind( ci.exp( mm, subset="tpDM:I" ),
+              ci.exp( ww, subset="tpDM:I" ) )
> rownames(RR) <- c("% per year age","% per cal-year")
> colnames(RR)[c(1,4)] <- c("Men","Women")
> # Annual %-change in RR
> round( (RR-1)*100, 1 )
                Men 2.5% 97.5% Women 2.5% 97.5%
% per year age -2.2 -2.3  -2.2  -2.1 -2.2  -2.0
% per cal-year -1.2 -1.4  -1.1  -1.5 -1.7  -1.4
```

Graphically we can show the RR by age as in 2005, as well as the ratio of RRs by calendar year relative to 2005:

```
> a.pt <- seq(15,90,,100)
> p.pt <- seq(1995,2012,,100)
> Am <- ci.exp( mm, subset="tpDM", ctr.mat=cbind(1,a.pt-50,0) )
> Pm <- ci.exp( mm, subset="tpDM", ctr.mat=cbind(0,0,p.pt-2005) )
> Aw <- ci.exp( ww, subset="tpDM", ctr.mat=cbind(1,a.pt-50,0) )
> Pw <- ci.exp( ww, subset="tpDM", ctr.mat=cbind(0,0,p.pt-2005) )
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.pt, cbind( Am,Aw ),
+          lty=1, type="l", lwd=c(3,1,1), col=rep(c("blue","red"),each=3),
+          xlab="Age", ylab="DM / no DM mortality rate-ratio (2005)", log="y", ylim=c(1/2,1
> abline( h=1 )
> matplot( p.pt, cbind( Pm,Pw ),
+          lty=1, type="l", lwd=c(3,1,1), col=rep(c("blue","red"),each=3),
+          xlab="Date", ylab="DM / no DM mortality rate-ratio (age 50)", log="y", ylim=c(1/
> abline( h=1 )
```

1.2 Residual life time and years lost to DM

We now compute mortality rates *cross-sectionally* for DM patients and non-DM persons for the dates 1 January 1995–2012, in ages 30–100, in steps of 0.2 years — note that we predict for Y equal 0.2, since we are going to integrate the mortalities:

```
> intl <- 0.2
> a.pt <- seq(30,100,intl)
> a.lg <- length( a.pt )
> p.pt <- 1995:2012
> Mort <- NArray( list( A = a.pt,
+                       P = p.pt,
+                      tp = levels(LL$tp),
+                     sex = levels(LL$sex) ) )
> for( it in levels(LL$tp) )
+ for( ip in p.pt )
+    {
+    nd <- data.frame( A = a.pt, P = ip, tp = it, Y = intl )
+    Mort[,paste(ip),it,"M"] <- predict( mm, newdata=nd, type="response" )
+    Mort[,paste(ip),it,"F"] <- predict( ww, newdata=nd, type="response" )
+    }
```

We can then compute the expected residual life time from each age as the integral of the (conditional) survival from that age to 100. First we make an array of the conditional survival function given survival till age 30 (because that is where our array starts):

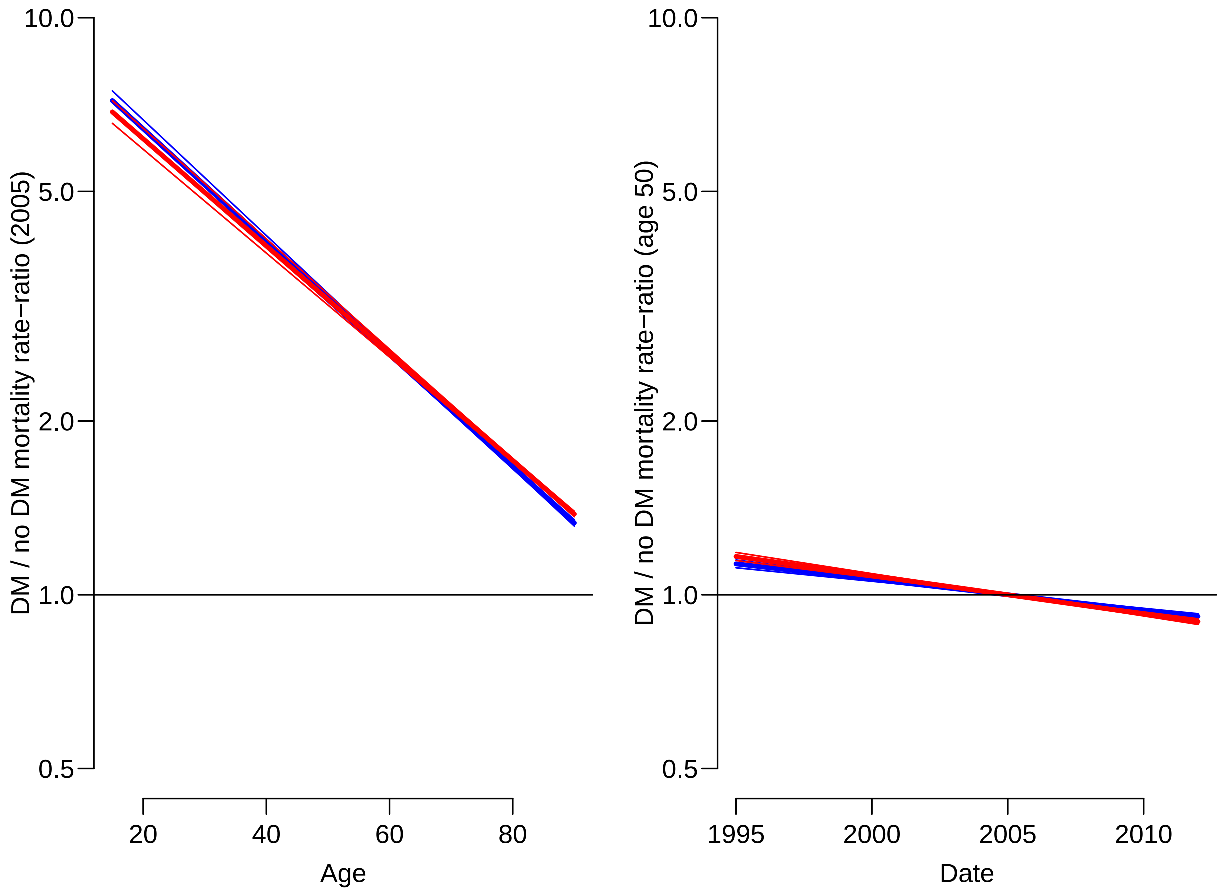

Figure 1.1: *Mortality rate-ratio, between DM and non-DM persons by age and calendar time. Blue curves are men, red women.*

```
> Surv <- exp( -apply( Mort, 2:4, cumsum ) )
> str( Surv )
 num [1:351, 1:18, 1:2, 1:2] 0.999 0.997 0.996 0.994 0.993 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"
```

From this we can show the *conditional* survival curve given that a person has reached age 30, for men and women, respectively:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> a.pt <- as.numeric( dimnames(Surv)[[1]] )
> matplot( a.pt, cbind( Surv[,"2005","nD",], Surv[,"2005","DM",] ),
+          lwd=5, type="l", col=c("blue","red"), lty=rep(1:2,each=2),
+          ylim=0:1, xlab="Age", ylab="Survival probability", yaxs="i" )
```

Now if we want the expected residual life time from age a, say, we must integrate the survival function from a to infinity (in this case 100 years); however it should be the *conditional* survival function. But what we need is just the cumulative sum (recall we now must multiply by the interval length now when we integrate) from the end, and then subsequently divide by the survival function:

```
> musmuc <- function(x) rev(cumsum(rev(x)))
> Erl <- apply( Surv, 2:4, musmuc ) * intl / Surv
> Yll <- Erl[,,"nD",] - Erl[,,"DM",]
> str( Mort )
 num [1:351, 1:18, 1:2, 1:2] 0.00139 0.00139 0.0014 0.0014 0.00141 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"

> str( Surv )

 num [1:351, 1:18, 1:2, 1:2] 0.999 0.997 0.996 0.994 0.993 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"

> str( Erl )

 num [1:351, 1:18, 1:2, 1:2] 32.6 32.4 32.3 32.1 32 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"

> str( Yll )

 num [1:351, 1:18, 1:2] 12.1 12 12 12 11.9 ...
 - attr(*, "dimnames")=List of 3
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ sex: chr [1:2] "M" "F"

> round( ftable( Erl[c(1,101,201),,,], row.vars=2 ), 1 )

     A     30                      50                      70
     tp    DM          nD          DM          nD          DM          nD
     sex    M     F     M     F     M     F     M     F     M     F     M     F
P
1995     32.6 37.7 44.6 49.2 17.8 21.5 26.3 30.3  7.5  9.9 11.5 14.4
1996     33.1 38.3 45.0 49.4 18.3 21.9 26.6 30.6  7.7 10.1 11.7 14.6
1997     33.7 38.9 45.3 49.7 18.7 22.4 26.9 30.8  7.9 10.3 11.8 14.7
1998     34.3 39.5 45.7 50.0 19.2 22.8 27.2 31.0  8.1 10.5 12.0 14.8
1999     34.8 40.0 46.0 50.2 19.6 23.3 27.5 31.2  8.3 10.7 12.1 14.9
2000     35.4 40.6 46.3 50.4 20.0 23.7 27.8 31.4  8.6 11.0 12.3 15.0
2001     35.9 41.1 46.6 50.7 20.5 24.1 28.0 31.6  8.8 11.2 12.4 15.1
2002     36.4 41.6 46.8 50.9 20.8 24.5 28.3 31.8  9.0 11.4 12.6 15.2
2003     36.8 42.1 47.0 51.1 21.2 24.9 28.5 32.0  9.2 11.6 12.7 15.3
2004     37.3 42.5 47.3 51.3 21.5 25.3 28.7 32.1  9.4 11.8 12.9 15.4
2005     37.7 43.0 47.5 51.5 21.9 25.6 28.9 32.3  9.7 12.0 13.0 15.5
2006     38.2 43.5 47.8 51.7 22.2 26.0 29.1 32.5  9.9 12.3 13.2 15.7
2007     38.7 44.0 48.0 51.9 22.6 26.4 29.4 32.7 10.2 12.5 13.3 15.8
2008     39.2 44.5 48.3 52.1 23.0 26.8 29.6 32.9 10.4 12.8 13.5 15.9
2009     39.7 45.0 48.6 52.4 23.4 27.3 29.9 33.1 10.7 13.0 13.7 16.1
2010     40.2 45.6 48.9 52.6 23.8 27.7 30.1 33.3 11.0 13.3 14.0 16.2
2011     40.8 46.1 49.2 52.9 24.2 28.1 30.4 33.5 11.3 13.6 14.2 16.4
2012     41.3 46.6 49.5 53.1 24.6 28.6 30.6 33.8 11.6 13.9 14.4 16.6

> round( ftable( Yll[c(1,101,201),,], row.vars=2 ), 1 )
```

```
     A     30          50          70
     sex     M     F     M     F     M     F
P
1995      12.1 11.4  8.5  8.8  4.0  4.6
1996      11.8 11.1  8.3  8.6  4.0  4.5
1997      11.6 10.8  8.2  8.4  3.9  4.4
1998      11.4 10.5  8.0  8.2  3.9  4.3
1999      11.1 10.2  7.9  7.9  3.8  4.2
2000      10.9  9.9  7.7  7.7  3.7  4.1
2001      10.7  9.6  7.6  7.5  3.7  4.0
2002      10.5  9.3  7.4  7.3  3.6  3.9
2003      10.2  9.0  7.3  7.1  3.5  3.7
2004      10.0  8.7  7.2  6.9  3.4  3.6
2005       9.8  8.4  7.0  6.7  3.3  3.5
2006       9.6  8.2  6.9  6.5  3.3  3.4
2007       9.4  7.9  6.7  6.3  3.2  3.3
2008       9.1  7.6  6.6  6.0  3.1  3.2
2009       8.9  7.3  6.5  5.8  3.0  3.0
2010       8.7  7.0  6.3  5.6  2.9  2.9
2011       8.4  6.8  6.2  5.4  2.8  2.8
2012       8.2  6.5  6.0  5.2  2.8  2.7
```

We can then plot the years of life lost to diabetes in different ages, and how this has evolved over time, separately for men and women:

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.pt, Yll[,,"M"],
+          type="l", lty=1, col="blue", lwd=1:2,
+          ylim=c(0,12), xlab="Age", ylab="Years lost to DM", yaxs="i" )
> abline(v=50,h=1:10,col=gray(0.7))
> matplot( a.pt, Yll[,,"F"],
+          type="l", lty=1, col="red", lwd=1:2,
+          ylim=c(0,12), xlab="Age", ylab="Years lost to DM", yaxs="i" )
> abline(v=50,h=1:10,col=gray(0.7))
```

From figure 1.2 we see that for men aged 50 the years lost to diabetes has decreased from a bit over 8 to a bit less than 6 years, and for women from 8.5 to 5 years; so a greater improvement for women.

It is illustrative to see the lines in the same plot:

```
> par( mfrow=c(1,1), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.pt, cbind(Yll[,,"M"],Yll[,,"F"]),
+          type="l", lty=1, col=rep(c("blue","red"),each=18), lwd=1:2,
+          ylim=c(0,12), xlab="Age", ylab="Years lost to DM", yaxs="i" )
> abline(v=50,h=1:10,col=gray(0.7))
```

From figure 1.2 we see that the improvement has been larger for women than for men, but it should be remembered that women have a longer life expectancy then men.

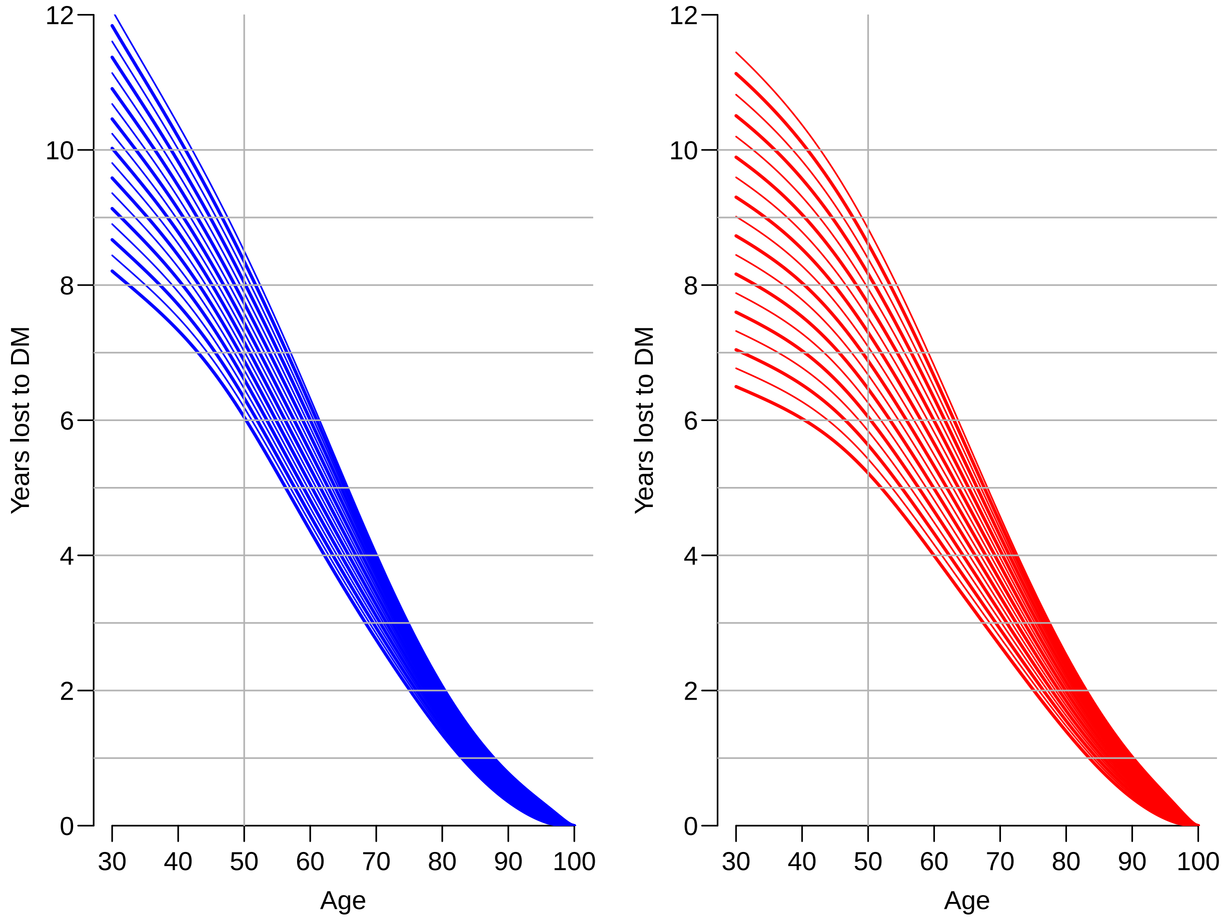

Figure 1.2: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes. The lines refer to date of evaluation; the top lines refer to 1.1.1995 the bottom ones to 1.1.2012. Blue curves are men, red women.*

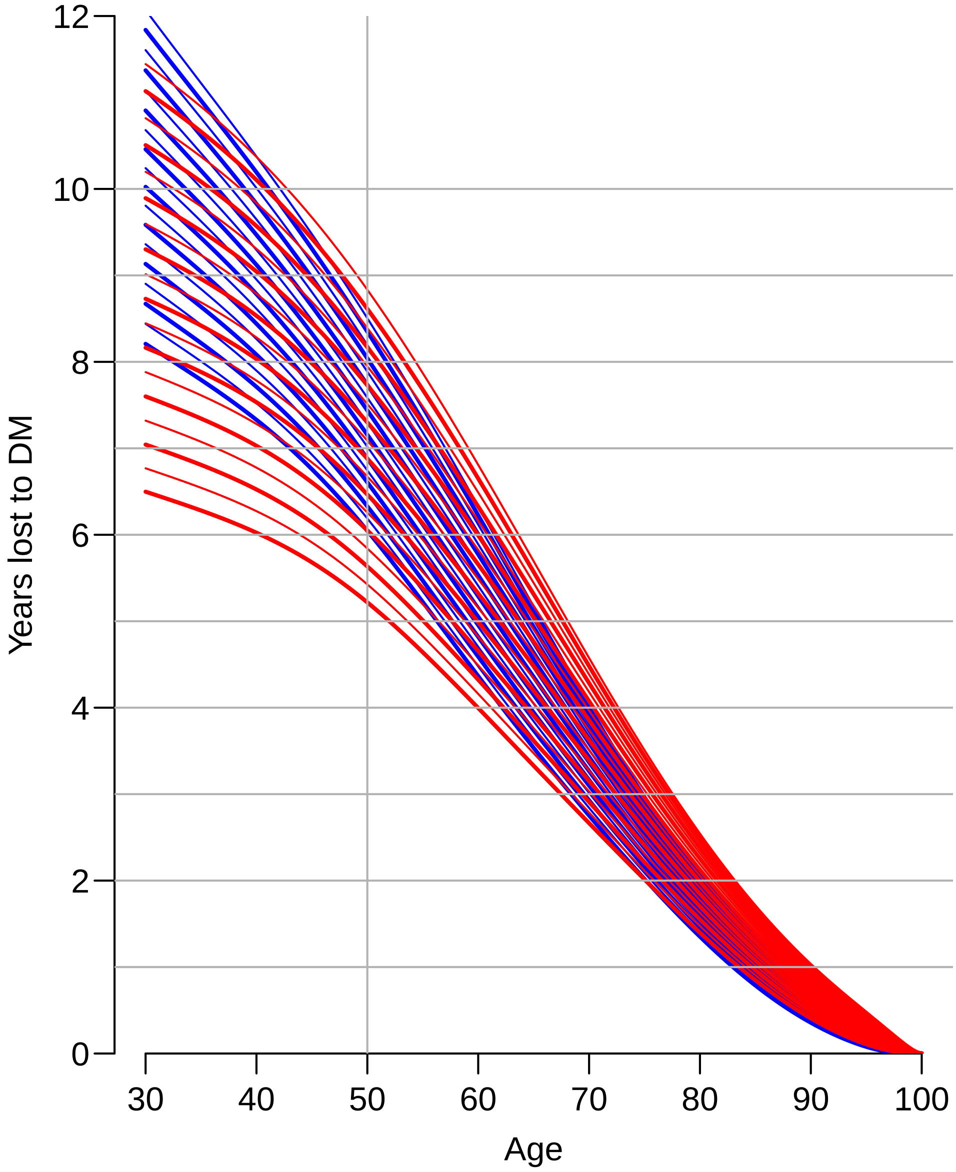

Figure 1.3: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes. The lines refer to date of evaluation; the top lines refer to 1.1.1995 the bottom ones to 1.1.2012. Blue curves are men, red women.*

Chapter 2

Analysis based on modified DM definition

2.1 Life lost to diabetes

```
> library( Epi )
> clear()
> load( file="./data/FU-m.Rda" )
> lls()
  name mode class             size
1 Lx   list Lexis data.frame 382873 23
2 TT   list data.frame       6732 9
```

The dataset TT contains deaths and person-years for persons with and without diabetes:

```
> head( TT )
  sex A    P U     Y.nD      Y.DM D.DM D.nD X
1   F 0 1995 0 17025.50 0.0000000    0  137 0
2   F 0 1995 1 17100.54 0.1300479    0   16 2
3   F 0 1996 0 16468.06 1.4401095    0  134 4
4   F 0 1996 1 17067.30 1.8617385    0   23 4
5   F 0 1997 0 16434.00 0.0000000    0  152 0
6   F 0 1997 1 16499.84 1.9890486    0   14 2
```

In order to compute the years of life lost to diabetes and how this has changed over time, we fit models for the mortality of both groups (and of course, separately for men and women). The models we use will be age-period-cohort models providing estimated mortality rates for ages 0–99 and dates 1.1.1995-1.1.2012.

```
> TT <- transform( TT,
+                  A=A+(1+U)/3,
+                  P=P+(2-U)/3 )
> summary(TT)
 sex            A                  P               U              Y.nD
 M:3366   Min.   : 0.3333   Min.   :1995   Min.   :0.0   Min.   :   46.38
 F:3366   1st Qu.:24.6667   1st Qu.:1999   1st Qu.:0.0   1st Qu.: 8607.75
          Median :49.5000   Median :2004   Median :0.5   Median :15972.72
          Mean   :49.5000   Mean   :2004   Mean   :0.5   Mean   :13235.67
          3rd Qu.:74.3333   3rd Qu.:2008   3rd Qu.:1.0   3rd Qu.:18011.50
          Max.   :98.6667   Max.   :2012   Max.   :1.0   Max.   :22944.81
      Y.DM               D.DM              D.nD              X
```

```
 Min.   :   0.00   Min.   :  0.00   Min.   : -1.0   Min.   :  0.00
 1st Qu.:  66.54   1st Qu.:  0.00   1st Qu.:  8.0   1st Qu.:  7.00
 Median : 243.43   Median :  5.00   Median : 56.0   Median : 26.00
 Mean   : 387.91   Mean   : 20.27   Mean   :122.9   Mean   : 44.27
 3rd Qu.: 610.31   3rd Qu.: 36.00   3rd Qu.:206.0   3rd Qu.: 74.00
 Max.   :2499.02   Max.   :117.00   Max.   :582.0   Max.   :319.00
```

We then stack the observations from persons with and without diabetes in order to fit a joint model — essentially two APC-models.

```
> dd <- cbind( subset( TT, select=c(sex,A,P,D.DM,Y.DM) ), tp="DM" )
> nn <- cbind( subset( TT, select=c(sex,A,P,D.nD,Y.nD) ), tp="nD" )
> cbind( names(dd), names(nn) )
     [,1]   [,2]  
[1,] "sex"  "sex" 
[2,] "A"    "A"   
[3,] "P"    "P"   
[4,] "D.DM" "D.nD"
[5,] "Y.DM" "Y.nD"
[6,] "tp"   "tp"  
> names( dd )[4:5] <-
+ names( nn )[4:5] <- c("D","Y")
> head( dd )
  sex         A        P D         Y tp
1   F 0.3333333 1995.667 0 0.0000000 DM
2   F 0.6666667 1995.333 0 0.1300479 DM
3   F 0.3333333 1996.667 0 1.4401095 DM
4   F 0.6666667 1996.333 0 1.8617385 DM
5   F 0.3333333 1997.667 0 0.0000000 DM
6   F 0.6666667 1997.333 0 1.9890486 DM
> head( nn )
  sex         A        P   D        Y tp
1   F 0.3333333 1995.667 137 17025.50 nD
2   F 0.6666667 1995.333  16 17100.54 nD
3   F 0.3333333 1996.667 134 16468.06 nD
4   F 0.6666667 1996.333  23 17067.30 nD
5   F 0.3333333 1997.667 152 16434.00 nD
6   F 0.6666667 1997.333  14 16499.84 nD
> LL <- transform( subset( rbind( dd, nn ), Y>0 ),
+                  D = pmax( 0, D ) )
> str( LL )
'data.frame':        13446 obs. of  6 variables:
 $ sex: Factor w/ 2 levels "M","F": 2 2 2 2 2 2 2 2 2 2 ...
 $ A  : num  0.667 0.333 0.667 0.667 0.667 ...
 $ P  : num  1995 1997 1996 1997 1999 ...
 $ D  : num  0 0 0 0 0 0 0 0 0 0 ...
 $ Y  : num  0.13 1.44 1.862 1.989 0.504 ...
 $ tp : Factor w/ 2 levels "DM","nD": 1 1 1 1 1 1 1 1 1 1 ...
```

With the correct age and period coding in the Lexis triangles, we fit models for the mortality. However, to stabilize the estimates we fit a model with basic age, period and cohort models and a simple linear effect of age-RR and period-RR for the DM to non-DM RRs:

```
> ( a.kn <- seq(20,95,,6) )
[1] 20 35 50 65 80 95
```

```
> ( p.kn <- seq(1996,2010,,4) )

[1] 1996.000 2000.667 2005.333 2010.000

> ( c.kn <- seq(1910,1995,,6) )

[1] 1910 1927 1944 1961 1978 1995

> mm <- glm( D ~ -1 +
+                 Ns(A   ,knots=a.kn,int=TRUE) +
+                 Ns(  P,knots=p.kn,ref=2005) +
+                 Ns(P-A,knots=c.kn,ref=1950) +
+                 tp + I(A-  50):tp + I(P-2005):tp,
+             offset = log(Y),
+             family = poisson,
+               data = subset( LL, sex=="M" & A>15 ) )
> ww <- update( mm,
+               data = subset( LL, sex=="F" & A>15 ) )
```

We briefly show the annula change in RR by age and period:

```
> round( cbind( ci.exp( mm, subset="tpDM" ),
+               ci.exp( ww, subset="tpDM" ) ), 3 )

                 exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
tpDM                 3.470 3.408 3.533     3.656 3.572 3.741
tpDM:I(A - 50)       0.978 0.977 0.978     0.978 0.977 0.978
tpDM:I(P - 2005)     0.990 0.988 0.991     0.987 0.985 0.988

> RR <- cbind( ci.exp( mm, subset="tpDM:I" ),
+              ci.exp( ww, subset="tpDM:I" ) )
> rownames(RR) <- c("% per year age","% per cal-year")
> colnames(RR)[c(1,4)] <- c("Men","Women")
> # Annual %-change in RR
> round( (RR-1)*100, 1 )

                Men 2.5% 97.5% Women 2.5% 97.5%
% per year age -2.2 -2.3  -2.2  -2.2 -2.3  -2.2
% per cal-year -1.0 -1.2  -0.9  -1.3 -1.5  -1.2
```

Graphically we can show the RR by age as in 2005, as well as the ratio of RRs by calendar year relative to 2005:

```
> a.pt <- seq(15,90,,100)
> p.pt <- seq(1995,2012,,100)
> Am <- ci.exp( mm, subset="tpDM", ctr.mat=cbind(1,a.pt-50,0) )
> Pm <- ci.exp( mm, subset="tpDM", ctr.mat=cbind(0,0,p.pt-2005) )
> Aw <- ci.exp( ww, subset="tpDM", ctr.mat=cbind(1,a.pt-50,0) )
> Pw <- ci.exp( ww, subset="tpDM", ctr.mat=cbind(0,0,p.pt-2005) )
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.pt, cbind( Am,Aw ),
+          lty=1, type="l", lwd=c(3,1,1), col=rep(c("blue","red"),each=3),
+          xlab="Age", ylab="DM / no DM mortality rate-ratio (2005)", log="y", ylim=c(1/2,1
> abline( h=1 )
> matplot( p.pt, cbind( Pm,Pw ),
+          lty=1, type="l", lwd=c(3,1,1), col=rep(c("blue","red"),each=3),
+          xlab="Date", ylab="DM / no DM mortality rate-ratio (age 50)", log="y", ylim=c(1/
> abline( h=1 )
```

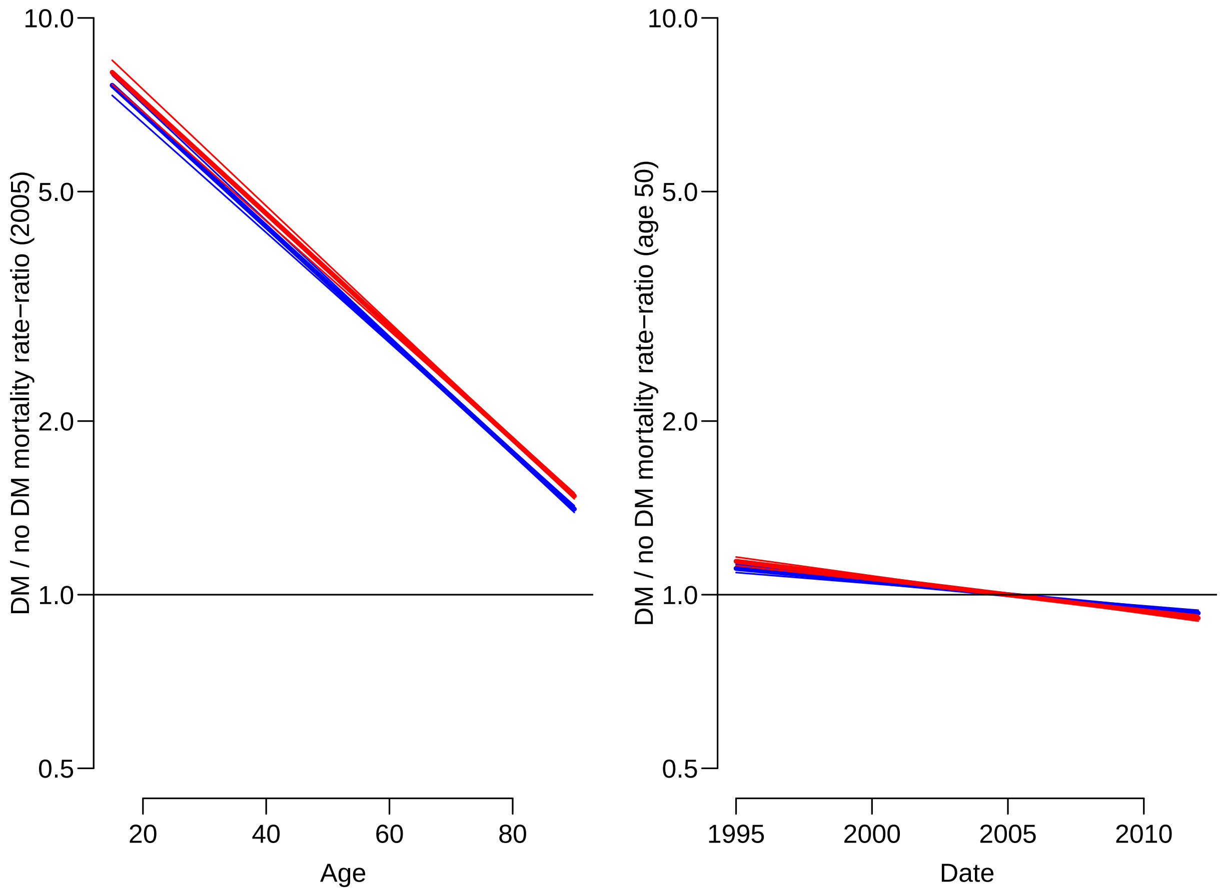

Figure 2.1: *Mortality rate-ratio, between DM and non-DM persons by age and calendar time. Blue curves are men, red women.*

2.2 Residual life time and years lost to DM

We now compute mortality rates *cross-sectionally* for DM patients and non-DM persons for the dates 1 January 1995–2012, in ages 30–100, in steps of 0.2 years — note that we predict for Y equal 0.2, since we are going to integrate the mortalities:

```
> intl <- 0.2
> a.pt <- seq(30,100,intl)
> a.lg <- length( a.pt )
> p.pt <- 1995:2012
> Mort <- NArray( list( A = a.pt,
+                       P = p.pt,
+                      tp = levels(LL$tp),
+                     sex = levels(LL$sex) ) )
> for( it in levels(LL$tp) )
+ for( ip in p.pt )
+    {
+    nd <- data.frame( A = a.pt, P = ip, tp = it, Y = intl )
+    Mort[,paste(ip),it,"M"] <- predict( mm, newdata=nd, type="response" )
+    Mort[,paste(ip),it,"F"] <- predict( ww, newdata=nd, type="response" )
+    }
```

We can then compute the expected residual life time from each age as the integral of the (conditional) survival from that age to 100. First we make an array of the conditional survival function given survival till age 30 (because that is where our array starts):

```
> Surv <- exp( -apply( Mort, 2:4, cumsum ) )
```

Now if we want the expected residual life time from age a, say, we must integrate the survival function form a to infinity (in this case 100 years); however the *conditional* survival function. But what we need is just the cumulative sum (recall we now must multiply by the interval length now when we integrate) from the end, and then subsequently divide by the survival function:

```
> musmuc <- function(x) rev(cumsum(rev(x)))
> Erl <- apply( Surv, 2:4, musmuc ) * intl / Surv
> Yll <- Erl[,,"nD",] - Erl[,,"DM",]
> str( Mort )
 num [1:351, 1:18, 1:2, 1:2] 0.00145 0.00145 0.00146 0.00147 0.00147 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"
> str( Surv )
 num [1:351, 1:18, 1:2, 1:2] 0.999 0.997 0.996 0.994 0.993 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"
> str( Erl )
 num [1:351, 1:18, 1:2, 1:2] 32 31.9 31.7 31.6 31.4 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"
> str( Yll )
 num [1:351, 1:18, 1:2] 12.5 12.5 12.5 12.4 12.4 ...
 - attr(*, "dimnames")=List of 3
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ sex: chr [1:2] "M" "F"
> round( ftable( Erl[c(1,101,201),,,], row.vars=2 ), 1 )
     A     30                      50                      70
     tp    DM          nD          DM          nD          DM          nD
     sex    M     F     M     F     M     F     M     F     M     F     M     F
P
1995     32.0  36.6  44.6  49.2  17.4  20.7  26.2  30.3   7.2   9.5  11.5  14.4
1996     32.6  37.2  44.9  49.4  17.8  21.1  26.6  30.5   7.4   9.6  11.6  14.5
1997     33.1  37.7  45.3  49.7  18.3  21.5  26.9  30.8   7.6   9.8  11.8  14.7
1998     33.7  38.3  45.6  49.9  18.7  22.0  27.2  31.0   7.8  10.0  11.9  14.8
1999     34.2  38.8  45.9  50.2  19.1  22.4  27.5  31.2   8.1  10.3  12.1  14.9
2000     34.7  39.3  46.2  50.4  19.5  22.8  27.7  31.4   8.3  10.5  12.3  15.0
2001     35.2  39.9  46.5  50.6  19.9  23.2  28.0  31.6   8.5  10.7  12.4  15.1
2002     35.7  40.3  46.8  50.8  20.3  23.5  28.2  31.8   8.7  10.8  12.5  15.2
```

```
2003     36.1 40.8 47.0 51.0 20.6 23.9 28.4 31.9  8.9 11.0 12.7 15.3
2004     36.5 41.3 47.2 51.2 20.9 24.3 28.6 32.1  9.1 11.2 12.8 15.4
2005     36.9 41.7 47.5 51.4 21.3 24.6 28.8 32.3  9.3 11.4 13.0 15.5
2006     37.4 42.2 47.7 51.6 21.6 25.0 29.1 32.4  9.5 11.7 13.1 15.6
2007     37.9 42.7 48.0 51.8 21.9 25.4 29.3 32.6  9.8 11.9 13.3 15.8
2008     38.3 43.2 48.3 52.1 22.3 25.8 29.5 32.8 10.0 12.1 13.5 15.9
2009     38.8 43.7 48.5 52.3 22.7 26.2 29.8 33.1 10.3 12.4 13.7 16.0
2010     39.3 44.2 48.8 52.6 23.0 26.6 30.0 33.3 10.6 12.7 13.9 16.2
2011     39.9 44.7 49.1 52.8 23.4 27.0 30.3 33.5 10.9 12.9 14.1 16.4
2012     40.4 45.2 49.4 53.1 23.8 27.4 30.6 33.7 11.2 13.2 14.3 16.5
> round( ftable( Yll[c(1,101,201),,], row.vars=2 ), 1 )
     A     30        50        70
     sex    M    F    M    F    M    F
P
1995     12.5 12.5  8.9  9.6  4.2  5.0
1996     12.3 12.2  8.7  9.4  4.2  4.9
1997     12.1 11.9  8.6  9.2  4.1  4.8
1998     11.9 11.6  8.4  9.0  4.1  4.7
1999     11.7 11.3  8.3  8.8  4.1  4.6
2000     11.5 11.1  8.2  8.6  4.0  4.6
2001     11.3 10.8  8.1  8.4  3.9  4.5
2002     11.1 10.5  7.9  8.2  3.9  4.4
2003     10.9 10.2  7.8  8.0  3.8  4.3
2004     10.7 10.0  7.7  7.8  3.7  4.2
2005     10.5  9.7  7.6  7.6  3.7  4.1
2006     10.3  9.4  7.5  7.5  3.6  4.0
2007     10.1  9.1  7.3  7.3  3.5  3.9
2008      9.9  8.9  7.2  7.1  3.5  3.8
2009      9.7  8.6  7.1  6.9  3.4  3.6
2010      9.5  8.3  7.0  6.7  3.3  3.5
2011      9.3  8.1  6.9  6.5  3.3  3.4
2012      9.1  7.8  6.8  6.3  3.2  3.3
```

We can then plot the years of life lost to diabetes in different ages, and how this has evolved over time, separately for men and women:

```
> plyll <- function(){
+ par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
+ matplot( a.pt, Yll[,,"M"],
+          type="l", lty=1, col="blue", lwd=1:2,
+          ylim=c(0,12), xlab="Age",
+          ylab="Years lost to DM", yaxs="i" )
+ abline(v=50,h=1:10,col=gray(0.7))
+ text( 90, 11, "Men", col="blue" )
+ text( 40, Yll["40","1995","M"], "1995", adj=c(0,0), col="blue" )
+ text( 43, Yll["44","2012","M"], "2012", adj=c(1,1), col="blue" )
+ matplot( a.pt, Yll[,,"F"],
+          type="l", lty=1, col="red", lwd=1:2,
+          ylim=c(0,12), xlab="Age",
+          ylab="Years lost to DM", yaxs="i" )
+ abline(v=50,h=1:10,col=gray(0.7))
+ text( 90, 11, "Women", col="red" )
+ text( 40, Yll["40","1995","F"], "1995", adj=c(0,0), col="red" )
+ text( 46, Yll["47","2012","F"], "2012", adj=c(1,1), col="red" )
+ }
> plyll()
> jpeg(filename = "./graph/yll-m.jpg", width=10, height=5, units="in",
+      res=300, quality=100, pointsize=14 )
```

```
> plyll()
> dev.off()
pdf
  2
```

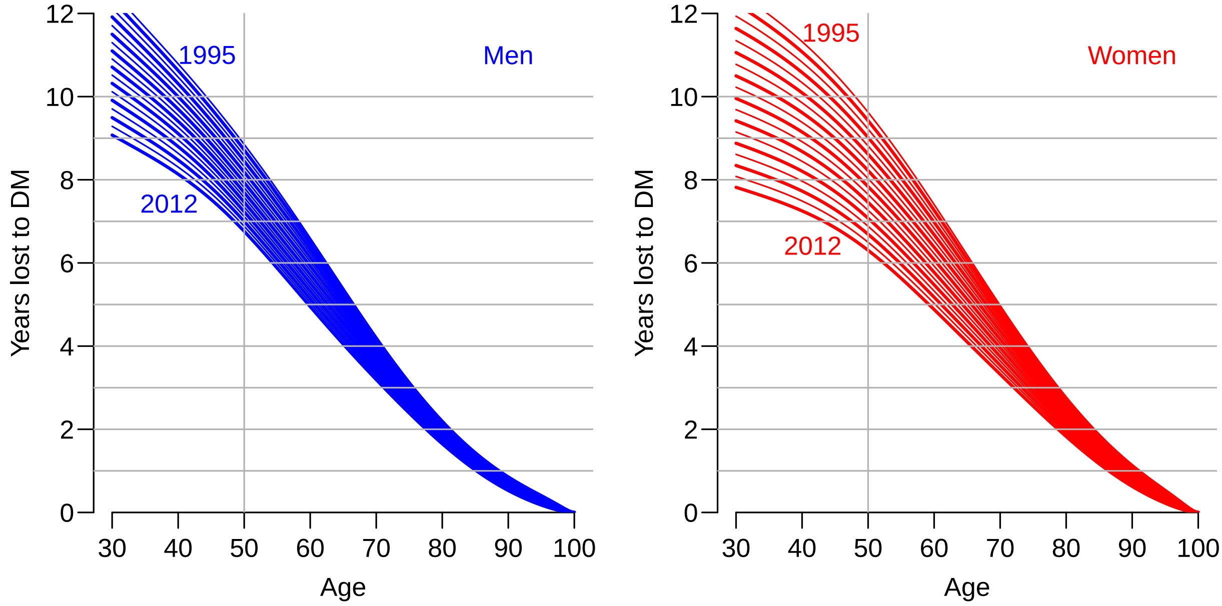

Figure 2.2: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes. The lines refer to date of evaluation; the top lines refer to 1.1.1995 the bottom ones to 1.1.2012. Blue curves are men, red women.*

From figure 1.2 we see that for men aged 50 the years lost to diabetes has decreased from a bit over 8 to a bit less than 6 years, and for women from 8.5 to 5 years; so a greater improvement for women.

It is illustrative to see the lines for men and women overlaid in the same plot:

```
> par( mfrow=c(1,1), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.pt, cbind(Yll[,,"M"],Yll[,,"F"]),
+          type="l", lty=1, col=rep(c("blue","red"),each=18), lwd=1:2,
+          ylim=c(0,12), xlab="Age", ylab="Years lost to DM", yaxs="i" )
> abline(v=50,h=1:10,col=gray(0.7))
```

From figure 2.3 we see that the improvement has been larger for women than for men, but it should be remembered that women have a longer life expectancy then men.

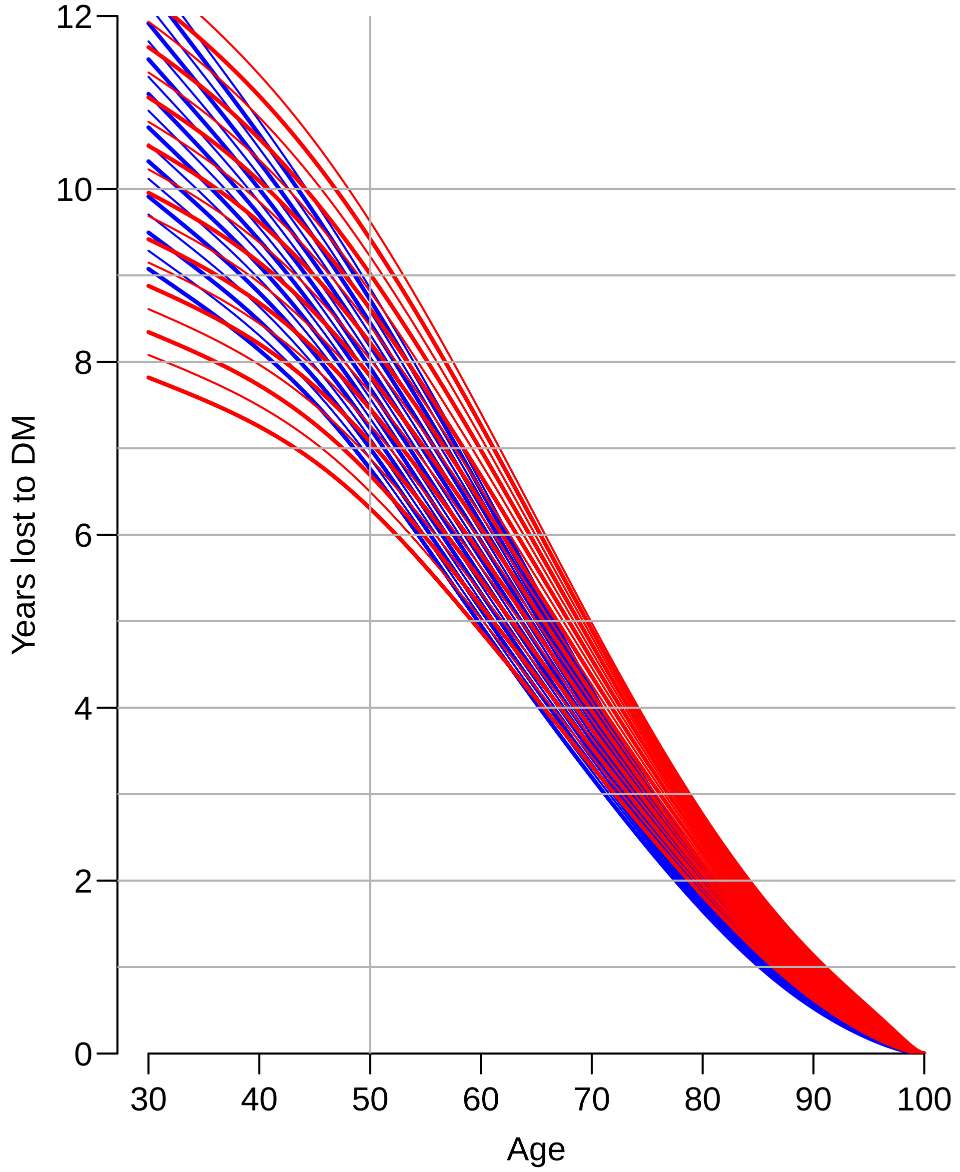

Figure 2.3: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes. The lines refer to date of evaluation; the top lines refer to 1.1.1995 the bottom ones to 1.1.2012. Blue curves are men, red women.*

2.3 Life gained by Statin treatment

Kristensen *et al.* [1] estimated the postponement of death in the course of trials of statins. The figures are however largely nonsense since they relate to trial populations of specific age-compositions, and as we shall see the effects claimed by the statin trials in terms of RR yields dramatically different results as measured by life gained in different ages.

What we do here is to use the mortality among diabetes patients as defined from the National Diabetes Register (NDR) (*minus* the blood glucose criteria) — that is persons that are classified as diabetes patients on the basis of a diagnosis in the NPR, NHSR or RMPS.

We have the mortality of these in the array `Mort`:

```
> str( Mort )
 num [1:351, 1:18, 1:2, 1:2] 0.00145 0.00145 0.00146 0.00147 0.00147 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:2] "DM" "nD"
  ..$ sex: chr [1:2] "M" "F"
```

Instead of having DM and nD persons in the array, we expand the array on this dimension with hypothetical treatments of statins, as seen in the paper namely with RRs in the range 1–0.7, we use the values 1, 0.95, . . . , 0.7, covering the range of RRs reported in the papers by Kristensen *et al.*

```
> Mx <- Mort[,,rep(1,7),]
> dimnames( Mx )[[3]] <- seq(1,0.7,-0.05)
> str( Mx )
 num [1:351, 1:18, 1:7, 1:2] 0.00145 0.00145 0.00146 0.00147 0.00147 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:7] "1" "0.95" "0.9" "0.85" ...
  ..$ sex: chr [1:2] "M" "F"
> for( i in 2:7 ) Mx[,,i,] <- Mx[,,1,]*as.numeric(dimnames(Mx)[[3]][i])
```

With these hypothetical mortalities among diabetes patients we can compute the survival functions, expected residual life etc.; just as above:

```
> Sx <- exp( -apply( Mx, 2:4, cumsum ) )
> Elx <- apply( Sx, 2:4, musmuc ) * intl / Sx
> Ylx <- Elx[,,-1,] * 0
> str( Elx )
 num [1:351, 1:18, 1:7, 1:2] 32 31.9 31.7 31.6 31.4 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:7] "1" "0.95" "0.9" "0.85" ...
  ..$ sex: chr [1:2] "M" "F"
> str( Ylx )
 num [1:351, 1:18, 1:6, 1:2] 0 0 0 0 0 0 0 0 0 0 ...
 - attr(*, "dimnames")=List of 4
  ..$ A  : chr [1:351] "30" "30.2" "30.4" "30.6" ...
  ..$ P  : chr [1:18] "1995" "1996" "1997" "1998" ...
  ..$ tp : chr [1:6] "0.95" "0.9" "0.85" "0.8" ...
  ..$ sex: chr [1:2] "M" "F"
```

```
> for( i in 2:7 ) Ylx[,,i-1,] <- Elx[,,i,] - Elx[,,1,]
```

So now we have for different combinations of sex and RR (and calendar time of evaluation) the years of life gained — and we can show a select subset of these:

```
> round( ftable( Ylx[paste(3:9*10),c("1995","2000","2005","2010","2012"),"0.9",], col.vars=
   P    1995      2000      2005      2010      2012
   sex     M    F    M    F    M    F    M    F    M    F
A
30      1.25 1.29 1.27 1.27 1.28 1.24 1.28 1.21 1.28 1.20
40      1.11 1.18 1.14 1.18 1.17 1.17 1.19 1.15 1.19 1.14
50      0.94 1.04 0.98 1.05 1.01 1.05 1.05 1.05 1.06 1.05
60      0.75 0.85 0.79 0.87 0.82 0.88 0.86 0.89 0.87 0.89
70      0.55 0.64 0.59 0.67 0.62 0.69 0.66 0.70 0.67 0.71
80      0.37 0.43 0.40 0.46 0.42 0.48 0.45 0.49 0.46 0.50
90      0.22 0.24 0.24 0.26 0.25 0.27 0.26 0.28 0.27 0.28
```

We plot the years of life gained by statins (or for that matter any other treatment associated with RRs of 0.95,. . . ,0.70):

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> a.pt <- as.numeric(dimnames(Ylx)[[1]])
> for( i in 1:2 )
+ {
+ matplot( a.pt, Ylx[,"2012",,i],
+          type="l", lwd=c(3,6,3,3,3,3), lty=1, col=c("blue","red")[i],
+          yaxs="i", ylim=c(0,4.5),
+          ylab="Years gained", xlab="Age (years)" )
+ text( rep(30,6), Ylx[1,"2012",,i]+0.02, dimnames(Ylx)[[3]], adj=c(0,0) )
+ abline(h=seq(0.5,5,0.5),v=3:9*10,col=gray(0.8))
+ }
```

Alternatively we could compute the percentage prolongation of residual life time by treatment that is the years of life gained as a percentage of expected residual life time with no treatment:

```
> Plx <- Elx[,,-1,] * 0
> for( i in 2:7 ) Plx[,,i-1,] <- 100*(Elx[,,i,]-Elx[,,1,])/Elx[,,1,]
```

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> a.pt <- as.numeric(dimnames(Ylx)[[1]])
> for( i in 1:2 )
+ {
+ matplot( a.pt, Plx[,"2012",,i],
+          type="l", lwd=c(3,6,3,3,3,3), lty=1, col=c("blue","red")[i],
+          yaxs="i", ylim=c(0,30),
+          ylab="Percent life prolongation", xlab="Age (years)" )
+ text( rep(30,6), Plx[1,"2012",,i]-0.02, dimnames(Plx)[[3]], adj=c(0,1) )
+ abline(h=seq(5,30,5),v=3:9*10,col=gray(0.8))
+ }
```

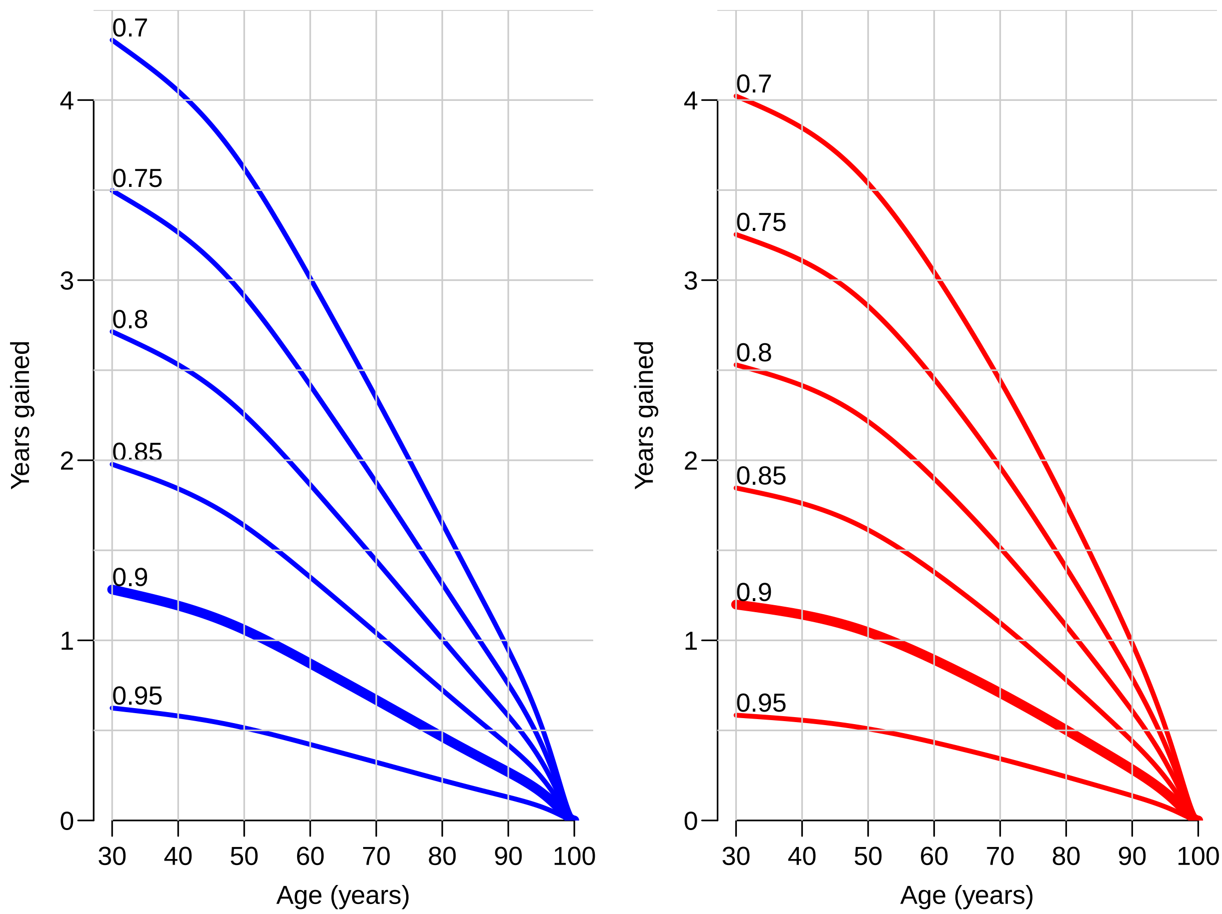

Figure 2.4: *Years of life gained by treatment reducing mortality by different RRs. The meta analysis result for the statin trials produced estimates of 0.89 and 0.91, so the thick line seems to be the most credible effect obtained with life-long treatment by statins starting at different ages.*

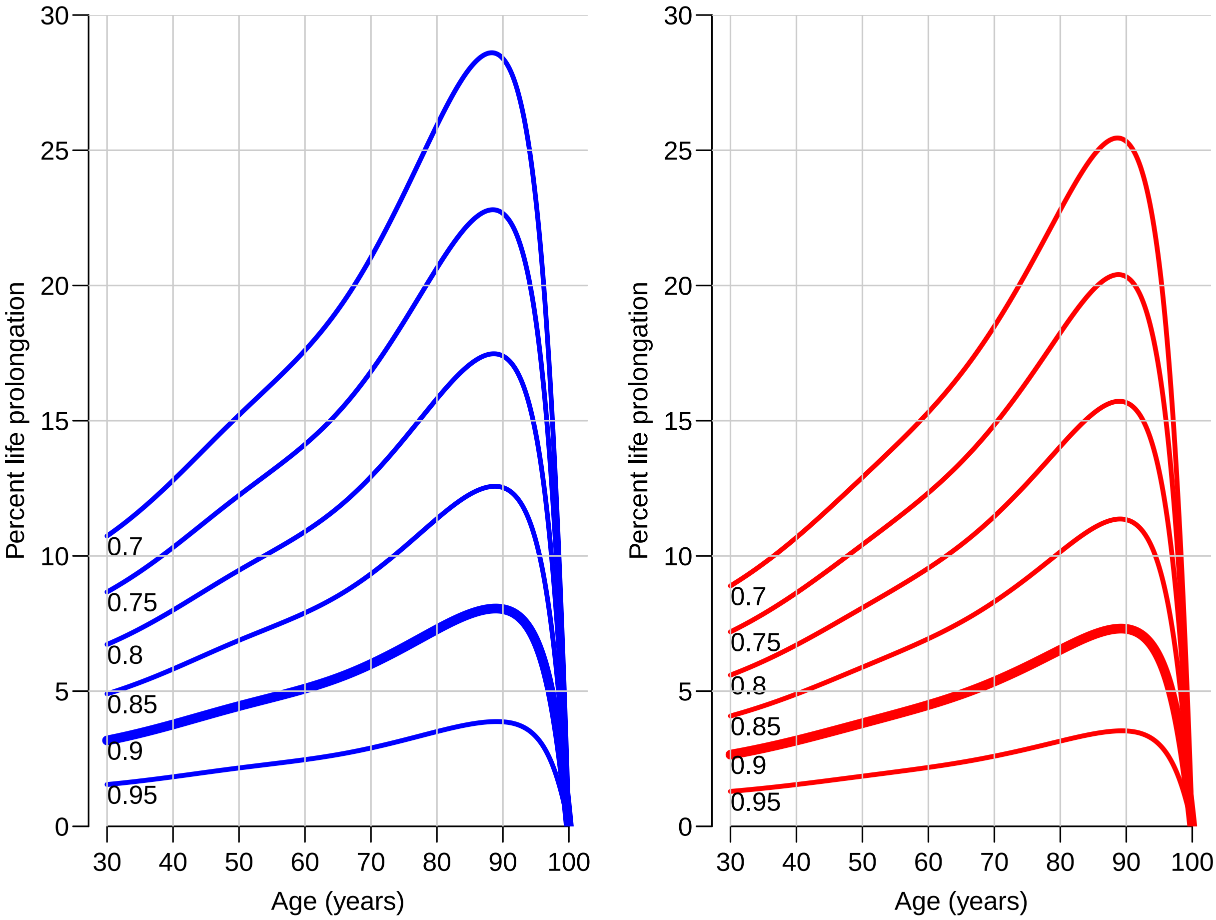

Figure 2.5: *Percentage life prolongation (death postponement) by treatment reducing mortality by different RRs. The meta analysis result for the statin trials produced an estimate of 0.89, so the thick line seems to be the most credible effect obtained with life-long treatment by statins starting at different ages.*

Bibliography

[1] M. L. Kristensen, P. M. Christensen, and J. Hallas. The effect of statins on average survival in randomised trials, an analysis of end point postponement. *BMJ Open*, 5(9):e007118, 2015.