

# The Danish National Diabetes Register: Life lost to DM

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# Chapter 1

## Theory and technicalities

### 1.1 Defining years of life lost (YLL)

to diabetes or any other disease for that matter.

The general concept in calculation of “years lost to...” is the comparison of the expected lifetime between two groups of persons; one with and one without disease (DM). The expected lifetime is the area under the survival curve, so basically the exercise requires two survival curves deemed relevant be available.

The years of life lost is really the area between the survival curves for those “Well”,  $S_W(t)$ , and for those “Diseased”,  $S_D(t)$ :

$$\text{YLL} = \int_0^{\infty} S_W(t) - S_D(t) dt$$

The time called  $t$  could of course be age, but it could also be “time after age 50” and the survival curves compared would then be survival curves *conditional* on survival till age 50.

### 1.2 Constructing the survival curves

YLL can be computed in two different ways, depending on the way the expected lifetime of a person *without* diabetes is computed:

- Assume that the person is *immune* to diabetes — use the non-DM mortality rates throughout for calculation of expected life time.
- Assume that the person *can* get diabetes and thereby see an increased mortality.

The former gives a higher YLL because the comparison is to persons assumed immune to DM (and yet with the same mortality as non-immune prior to diagnosis), the latter gives a realistic picture of the comparison of group of persons with and without diabetes at a given age that can be interpreted in the real world.

The differences can be illustrated by figure 1.1; the immune approach corresponds to an assumption of  $\lambda(t) = 0$  in the calculation of the survival curve for a person in the “Well” state.

Calculation of the survival of a diseased person already in the “DM” state is unaffected by assumptions about  $\lambda$ .

```

> zz$Arrowtext <- c(
+ expression(lambda),
+ expression(mu[W]),
+ expression(mu[D][M]) )
> boxes( zz )

```

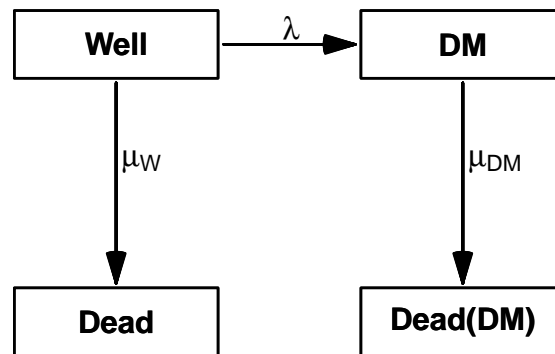


Figure 1.1: *Illness-death model describing diabetes incidence and -mortality.*

### 1.2.1 Computing integrals

The practical calculations of survival curves and YLL involves calculation of (cumulative) integrals of rates and functions of these. This is easy if we have a closed form expression of the function at any time point — as will be the case if we model rates by smooth parametric functions:

- Compute the value of the function (that is the rates) at the midpoints of a sequence of narrow intervals — for example one-month intervals of age, say.
- Take the cumulative sum of these values — they will be a very close approximation to the integrals evaluated at the end of the interval.
- If the intervals are really small (like 1/100 year), the distinction between the value at the middle and at the end of each interval becomes irrelevant.
- Still with, say, 10,000 intervals over the age-range 0–100 years, there will be no calculation inaccuracies from the actual computing.

Note that in the above it is assumed that the rates are given in units corresponding to the interval length — or more precisely, as the cumulative rates over the interval.

In the functions devised below, the length of the intervals and unit of rates is separated out in order to be able to recover the actual age scale properly.

## 1.2.2 Immune approach

In this case both survival functions are the usual simple transformation of the cumulative rates:

$$S_W(a) = \exp\left(-\int_0^a \mu_W(u) du\right), \quad S_D(a) = \exp\left(-\int_0^a \mu_D(u) du\right)$$

### 1.2.2.1 Conditional survival functions

If we want the *conditional* survival functions given survival to age  $A$ , say, they are just:

$$S_W(a|A) = S_W(a)/S_W(A), \quad S_D(a|A) = S_D(a)/S_D(A)$$

## 1.2.3 Non-immune approach

The survival function for a person without disease (at age 0) is:

$$S(a) = P\{\text{Well}\}(a) + P\{\text{DM}\}(a)$$

In the appendix of the paper [1] is an indication of how to compute the probability of being in any of the four states shown in figure 1.1, which I shall repeat here:

In terms of the rates, the probability of being in the “Well” box is simply the probability of escaping both death (at a rate of  $\mu_W(a)$ ) and diabetes (at a rate of  $\lambda(a)$ ):

$$P\{\text{Well}\}(a) = \exp\left(-\int_0^a \mu_W(u) + \lambda(u) du\right)$$

The probability of being alive with diabetes at age  $a$ , is computed given that diabetes occurred at age  $s < a$  and then integrated over  $s$  from 0 to  $a$ :

$$\begin{aligned} P\{\text{DM}\}(a) &= \int_0^a P\{\text{survive to } s, \text{ DM diagnosed at } s\} \\ &\quad \times P\{\text{survive with DM from } s \text{ to } a\} ds \\ &= \int_0^a \lambda(s) \exp\left(-\int_0^s \lambda(u) + \mu_W(u) du\right) \\ &\quad \times \exp\left(-\int_s^a \mu_D(u) du\right) ds \end{aligned}$$

Sometimes we will use a version where the mortality among diabetes patients depend both on age  $a$  and duration of diabetes  $d$ ,  $\mu_D(a, d)$ , in which case we get:

$$\begin{aligned} P\{\text{DM}\}(a) &= \int_0^a \lambda(s) \exp\left(-\int_0^s \lambda(u) + \mu_W(u) du\right) \\ &\quad \times \exp\left(-\int_s^a \mu_D(u, u-s) du\right) ds \end{aligned}$$

because the integration variable  $u$  is the age-scale and the second integral refers to mortality among persons diagnosed at age  $s$ , that is, with duration  $u - s$  at age  $u$ .

### 1.2.3.1 Conditional survival functions

Unlike the immune approach, the conditional survival function in the more realistic case is not just a ratio of the unconditional to the value at the conditioning age,  $A$ , say. This would amount to conditioning on being merely *alive* at age  $A$ , but what we want is to condition on being in the “Well” state at age  $A$ .

The formulae for the conditional probabilities of being either in “Well” or “DM”, given being in “Well” at age  $A$  are basically replicates of the unconditional, albeit with changes in integration limits:

$$P \{ \text{Well} | \text{Well at } A \} (a) = \exp \left( \int_A^a -\mu_W(u) - \lambda(u) \right) du$$

$$P \{ \text{DM} | \text{Well at } A \} (a) = \int_A^a \lambda(s) \exp \left( - \int_A^s \lambda(u) + \mu_W(u) du \right) \\ \times \exp \left( - \int_s^a \mu_D(u, u-s) du \right) ds$$

## 1.3 Implementation

We devise a function that wraps these formulæ up for practical use. We shall assume that the functions  $\mu_W$ ,  $\mu_D$  and  $\lambda$  are given as vectors corresponding to equidistantly (tightly) spaced ages from 0 to  $K$  where  $K$  is the age where everyone can safely be assumed dead.

Thus we can define the function with these three arguments and the interval length of course. However, first we define a simple function that computes the survival function from a vector of mortality rates, and optionally the conditional survival given being alive at prespecified ages:

```
> options( keep.source=TRUE )
> source( "yll.R" )
> surv1
function( int, mu, A=0, age.in=0 )
{
# Computes the survival function from age A till the end, assuming
# that mu is a vector of mortalities in intervals of length int.
# int and mu should be in compatible units that is T and T^-1 for
# some unit T (months, years, ...)

# age-class boundaries
age <- 0:length(mu)*int + age.in

# cumulative rates and survival at the boundaries
Mu <- c( 0, cumsum( mu )*int )
Sv <- exp( -Mu )
surv <- data.frame( age=age, surv=Sv )

# if a vector of conditioning ages A is given
if( length(A)>1 )
{
j <- 2
for( ia in A )
{
```

```

    j <- j+1
    cA <- which( diff(age>ia)==1 )
    surv <- cbind( surv, pmin( 1, surv$surv/(surv$surv[cA]) ) )
    colnames( surv )[j] <- paste( "S(a)|A=", ia, sep="" )
  }
}
return( surv )
}

```

We also define a function that computes the survival function for a non-diseased person that may become diseased with rate  $\lambda$  and after that die at a rate of  $\mu_D$  (corresponding to the formulae above):

```

> surv2
function( int, muW, muD, lam, A=0, age.in=0 )
{
# check the vectors
if( length(muW) != length(muD) |
    length(muD) != length(lam) )
  stop( "Vectors with rates must have same length:\n",
        "length(muW)=", length(muW),
        ", length(muD)=", length(muD),
        ", length(lam)=", length(lam) )

# First the workhorse that computes the survival function for a
# person in Well assuming that the mortality rate from this state is
# muW, disease incidence is in lam, and mortality in the diseased
# state is muD, and that all refer to constant rates intervals of
# length int starting from age.in, conditional on survival to A
wsurv2 <-
function( int, muW, muD, lam, A=0, age.in=0 )
{
# age-class boundaries - note one longer that rate vectors refers to
# boundaries of intervals not midpoints
age <- 0:length(muW)*int + age.in

# cumulative rates at the boundaries, given survival to A
MuW <- cumsum( c( 0, muW ) * ( age > A ) ) * int
MuD <- cumsum( c( 0, muD ) * ( age > A ) ) * int
Lam <- cumsum( c( 0, lam ) * ( age > A ) ) * int

# probability of being well
pW <- exp( -( Lam + MuW ) )

# probability of diagnosis at s --- first term in the integral for
# P(DM at a). Note that we explicitly add a 0 at the start so we get a
# probability of 0 of transition at the first age point
Dis <- c(0,lam) * ( age > A ) * exp( -(Lam+MuW) ) * int

# for each age (age[ia]) we compute the integral over the range
# [0,age] of the product of the probability of diagnosis and the
# probability of surviving from diagnosis till age ia
pDM <- Dis * 0
for( ia in 1:length(age) )
  pDM[ia] <- sum( Dis[1:ia] * exp( -(MuD[ia]-MuD[1:ia]) ) )
                # 1st term as function of s (1:ia)
                # 2nd term integral range s:age
                # upper integration limit is age (ia) and the lower

```

```

        # limit is the intermediate age (at DM) (1:ia)
# Finally, we add the probabilities of being in Well resp. DM to get
# the overall survival:
surv <- data.frame( age = age, surv = pDM + pW )
return( surv )
}

# survival from start
surv <- wsurv2( int, muW, muD, lam, A=0, age.in=age.in )

# add columns for conditioning ages
if( A[1] != 0 | length(A) > 1 )
{
for( j in 1:length(A) )
{
surv <- cbind( surv,
              wsurv2( int, muW, muD, lam, A=A[j], age.in=age.in )[,2] )
colnames( surv )[2+j] <- paste( "S(a|", A[j], ")", sep="" )
}
}

# done!
return( surv )
}

```

Finally we devised a function using these to compute the years of life lost to diabetes:

```

> yll
function( int,
         muW,
         muD,
         lam = NULL,
         A = 0,
         age.in = 0,
         immune = is.null(lam) )
{
# Computes years of life lost under different scenarios
if( !immune & is.null(lam) ) stop( "'lam' is required when immune=FALSE\n" )
      sD <- surv1( int=int,      muD,      A = A, age.in = age.in )
if( immune ) sW <- surv1( int=int, muW,      A = A, age.in = age.in )
else      sW <- surv2( int=int, muW, muD, lam, A = A, age.in = age.in )
apply( (sW-sD)[,-1], 2, sum ) * int
}

```

# Chapter 2

## Analyses based on modified DM definition

As noted above the calculations of YLL requires access to (age-specific) rates of incidence of DM and mortality for persons with and without DM.

### 2.1 Modeling mortality and incidence data

We read in the dataset of DM and population mortality and incidence, TT:

```
> 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
```

For each combination of sex, age, period and date of birth in 1 year age groups, we have the person-years in the “Well” (Y.nD) and the “DM” (Y.DM) states, as well as the number of deaths from these (D.nD, D.DM) and the number of incident diabetes cases from the “Well” state (X).

In order to compute the years of life lost to diabetes and how this has changed over time, we fit models for the mortality and incidence 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.

First we transform the age and period variables to reflect the mean age and period in each of the Lexis triangles. Moreover we restrict the dataset to age over 30:

```

> TT <- transform( TT,
+                 A=A+(1+U)/3,
+                 P=P+(2-U)/3 )
> TT <- subset( TT, A>30 )
> head(TT)
  sex      A      P U      Y.nD      Y.DM D.DM D.nD  X
817  F 30.33333 1995.667 0 20917.25 130.2464  0  7 21
818  F 30.66667 1995.333 1 20301.18 114.6509  1  8 22
819  F 30.33333 1996.667 0 21728.44 138.3943  1  7 15
820  F 30.66667 1996.333 1 21000.00 132.9959  0  6 12
821  F 30.33333 1997.667 0 20302.66 138.5038  0  8 13
822  F 30.66667 1997.333 1 21755.12 142.7118  1 12 15

```

With the correct age and period coding in the Lexis triangles, we fit models for the mortalities and incidences.

```

> # Knots used in all models
> ( a.kn <- seq(20,95,,6) )
[1] 20 35 50 65 80 95
> ( p.kn <- seq(1996,2011,,4) )
[1] 1996 2001 2006 2011
> ( c.kn <- seq(1910,1980,,6) )
[1] 1910 1924 1938 1952 1966 1980
> mW.m <- glm( D.nD ~ -1 + Ns(A ,knots=a.kn,int=TRUE) +
+             Ns( P,knots=p.kn,ref=2005) +
+             Ns(P-A,knots=c.kn,ref=1950),
+             offset = log(Y.nD),
+             family = poisson,
+             data = subset( TT, sex=="M" ) )
> mD.m <- update( mW.m, D.DM ~ . , offset=log(Y.DM) )
> lW.m <- update( mW.m, X ~ . )
> # Model for women
> mW.f <- update( mW.m, data = subset( TT, sex=="F" ) )
> mD.f <- update( mD.m, data = subset( TT, sex=="F" ) )
> lW.f <- update( lW.m, data = subset( TT, sex=="F" ) )

```

A brief overview of fitted models:

```

> summary( mW.m )
Call:
glm(formula = D.nD ~ -1 + Ns(A, knots = a.kn, int = TRUE) + Ns(P,
  knots = p.kn, ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950),
  family = poisson, data = subset(TT, sex == "M"), offset = log(Y.nD))

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-4.6106  -0.7956  -0.0260   0.7856   4.0744

```

```

Coefficients: (1 not defined because of singularities)
              Estimate Std. Error z value Pr(>|z|)
Ns(A, knots = a.kn, int = TRUE)1  -5.874756  0.052687 -111.503 < 2e-16
Ns(A, knots = a.kn, int = TRUE)2  -5.504688  0.013646 -403.381 < 2e-16
Ns(A, knots = a.kn, int = TRUE)3  -4.088264  0.015119 -270.397 < 2e-16
Ns(A, knots = a.kn, int = TRUE)4   0.401564  0.031838  12.613 < 2e-16
Ns(A, knots = a.kn, int = TRUE)5 -10.383934  0.101896 -101.907 < 2e-16
Ns(A, knots = a.kn, int = TRUE)6   5.191821  0.061174  84.870 < 2e-16

```

```

Ns(P, knots = p.kn, ref = 2005)1      -0.271900    0.009576   -28.393 < 2e-16
Ns(P, knots = p.kn, ref = 2005)2      -0.626226    0.017191   -36.429 < 2e-16
Ns(P, knots = p.kn, ref = 2005)3      -0.391096    0.010608   -36.867 < 2e-16
Ns(P - A, knots = c.kn, ref = 1950)1   0.129823    0.026342    4.928 8.29e-07
Ns(P - A, knots = c.kn, ref = 1950)2   0.359271    0.035737   10.053 < 2e-16
Ns(P - A, knots = c.kn, ref = 1950)3   0.388545    0.052632    7.382 1.56e-13
Ns(P - A, knots = c.kn, ref = 1950)4   0.591133    0.034024   17.374 < 2e-16
Ns(P - A, knots = c.kn, ref = 1950)5           NA           NA           NA           NA

```

(Dispersion parameter for poisson family taken to be 1)

```

Null deviance: 50379227.5 on 2346 degrees of freedom
Residual deviance: 3225.3 on 2333 degrees of freedom
AIC: 18644

```

Number of Fisher Scoring iterations: 4

```
> summary( mD.m )
```

Call:

```

glm(formula = D.DM ~ Ns(A, knots = a.kn, int = TRUE) + Ns(P,
  knots = p.kn, ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950) -
  1, family = poisson, data = subset(TT, sex == "M"), offset = log(Y.DM))

```

Deviance Residuals:

```

      Min       1Q   Median       3Q      Max
-3.6726 -0.7862 -0.0350  0.6565  3.5854

```

Coefficients: (1 not defined because of singularities)

```

              Estimate Std. Error z value Pr(>|z|)
Ns(A, knots = a.kn, int = TRUE)1  -3.91676    0.18578  -21.083 < 2e-16
Ns(A, knots = a.kn, int = TRUE)2  -4.25080    0.03835 -110.852 < 2e-16
Ns(A, knots = a.kn, int = TRUE)3  -3.32148    0.04228  -78.561 < 2e-16
Ns(A, knots = a.kn, int = TRUE)4    0.23310    0.12268   1.900 0.05742
Ns(A, knots = a.kn, int = TRUE)5  -8.83861    0.42360  -20.865 < 2e-16
Ns(A, knots = a.kn, int = TRUE)6   4.24223    0.24130  17.581 < 2e-16
Ns(P, knots = p.kn, ref = 2005)1  -0.34199    0.03031  -11.284 < 2e-16
Ns(P, knots = p.kn, ref = 2005)2  -0.68440    0.05960  -11.483 < 2e-16
Ns(P, knots = p.kn, ref = 2005)3  -0.44970    0.03803  -11.824 < 2e-16
Ns(P - A, knots = c.kn, ref = 1950)1  0.03760    0.09124   0.412 0.68024
Ns(P - A, knots = c.kn, ref = 1950)2  0.03009    0.12951   0.232 0.81625
Ns(P - A, knots = c.kn, ref = 1950)3 -0.01333    0.18957  -0.070 0.94396
Ns(P - A, knots = c.kn, ref = 1950)4  0.34329    0.12127   2.831 0.00464
Ns(P - A, knots = c.kn, ref = 1950)5           NA           NA           NA           NA

```

(Dispersion parameter for poisson family taken to be 1)

```

Null deviance: 2168369.3 on 2346 degrees of freedom
Residual deviance: 2505.2 on 2333 degrees of freedom
AIC: 13077

```

Number of Fisher Scoring iterations: 5

```
> summary( lW.m )
```

Call:

```

glm(formula = X ~ Ns(A, knots = a.kn, int = TRUE) + Ns(P, knots = p.kn,
  ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950) - 1, family = poisson,
  data = subset(TT, sex == "M"), offset = log(Y.nD))

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-3.5697	-0.9055	-0.1018	0.7188	4.7695

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z )
Ns(A, knots = a.kn, int = TRUE)1	-5.35537	0.05394	-99.280	< 2e-16
Ns(A, knots = a.kn, int = TRUE)2	-5.21078	0.01571	-331.731	< 2e-16
Ns(A, knots = a.kn, int = TRUE)3	-4.40972	0.01769	-249.338	< 2e-16
Ns(A, knots = a.kn, int = TRUE)4	-0.92822	0.03435	-27.020	< 2e-16
Ns(A, knots = a.kn, int = TRUE)5	-14.48496	0.11201	-129.314	< 2e-16
Ns(A, knots = a.kn, int = TRUE)6	1.61428	0.07267	22.214	< 2e-16
Ns(P, knots = p.kn, ref = 2005)1	0.15510	0.01184	13.096	< 2e-16
Ns(P, knots = p.kn, ref = 2005)2	0.70554	0.02188	32.249	< 2e-16
Ns(P, knots = p.kn, ref = 2005)3	0.41807	0.01019	41.038	< 2e-16
Ns(P - A, knots = c.kn, ref = 1950)1	-0.15646	0.03334	-4.693	2.70e-06
Ns(P - A, knots = c.kn, ref = 1950)2	-0.15984	0.03974	-4.023	5.75e-05
Ns(P - A, knots = c.kn, ref = 1950)3	0.02831	0.04880	0.580	0.562
Ns(P - A, knots = c.kn, ref = 1950)4	-0.41270	0.05467	-7.549	4.40e-14
Ns(P - A, knots = c.kn, ref = 1950)5	NA	NA	NA	NA

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 51827886.8 on 2346 degrees of freedom  
Residual deviance: 3437.5 on 2333 degrees of freedom  
AIC: 16313

Number of Fisher Scoring iterations: 4

&gt; summary(mW.f)

Call:

```
glm(formula = D.nD ~ -1 + Ns(A, knots = a.kn, int = TRUE) + Ns(P,
  knots = p.kn, ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950),
  family = poisson, data = subset(TT, sex == "F"), offset = log(Y.nD))
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-5.6388	-0.8786	-0.0531	0.8244	4.4918

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z )
Ns(A, knots = a.kn, int = TRUE)1	-6.15121	0.07166	-85.842	< 2e-16
Ns(A, knots = a.kn, int = TRUE)2	-5.88659	0.01672	-352.092	< 2e-16
Ns(A, knots = a.kn, int = TRUE)3	-4.59063	0.01873	-245.036	< 2e-16
Ns(A, knots = a.kn, int = TRUE)4	0.53981	0.04598	11.740	< 2e-16
Ns(A, knots = a.kn, int = TRUE)5	-12.10048	0.14717	-82.221	< 2e-16
Ns(A, knots = a.kn, int = TRUE)6	6.14339	0.08799	69.818	< 2e-16
Ns(P, knots = p.kn, ref = 2005)1	-0.28596	0.01208	-23.678	< 2e-16
Ns(P, knots = p.kn, ref = 2005)2	-0.62624	0.02298	-27.249	< 2e-16
Ns(P, knots = p.kn, ref = 2005)3	-0.41693	0.01499	-27.812	< 2e-16
Ns(P - A, knots = c.kn, ref = 1950)1	0.46986	0.03640	12.907	< 2e-16
Ns(P - A, knots = c.kn, ref = 1950)2	0.42634	0.05025	8.485	< 2e-16
Ns(P - A, knots = c.kn, ref = 1950)3	0.58089	0.07562	7.681	1.57e-14
Ns(P - A, knots = c.kn, ref = 1950)4	0.65908	0.04683	14.075	< 2e-16
Ns(P - A, knots = c.kn, ref = 1950)5	NA	NA	NA	NA

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 53928882.4 on 2346 degrees of freedom  
Residual deviance: 3756.9 on 2333 degrees of freedom

AIC: 18854

Number of Fisher Scoring iterations: 4

> `summary( mD.f )`

Call:

```
glm(formula = D.DM ~ Ns(A, knots = a.kn, int = TRUE) + Ns(P,
  knots = p.kn, ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950) -
  1, family = poisson, data = subset(TT, sex == "F"), offset = log(Y.DM))
```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-3.6212	-0.8634	-0.0347	0.6446	3.5400

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z )
Ns(A, knots = a.kn, int = TRUE)1	-4.95179	0.26173	-18.920	< 2e-16
Ns(A, knots = a.kn, int = TRUE)2	-4.49632	0.05345	-84.127	< 2e-16
Ns(A, knots = a.kn, int = TRUE)3	-3.78809	0.05821	-65.077	< 2e-16
Ns(A, knots = a.kn, int = TRUE)4	-0.28424	0.16795	-1.692	0.0906
Ns(A, knots = a.kn, int = TRUE)5	-9.01373	0.57962	-15.551	< 2e-16
Ns(A, knots = a.kn, int = TRUE)6	3.83692	0.32642	11.754	< 2e-16
Ns(P, knots = p.kn, ref = 2005)1	-0.33168	0.04063	-8.164	3.23e-16
Ns(P, knots = p.kn, ref = 2005)2	-0.73643	0.08060	-9.137	< 2e-16
Ns(P, knots = p.kn, ref = 2005)3	-0.41871	0.05334	-7.850	4.17e-15
Ns(P - A, knots = c.kn, ref = 1950)1	0.11242	0.12639	0.889	0.3738
Ns(P - A, knots = c.kn, ref = 1950)2	-0.08348	0.18169	-0.459	0.6459
Ns(P - A, knots = c.kn, ref = 1950)3	-0.13046	0.26564	-0.491	0.6234
Ns(P - A, knots = c.kn, ref = 1950)4	0.27266	0.16588	1.644	0.1002
Ns(P - A, knots = c.kn, ref = 1950)5	NA	NA	NA	NA

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 1903561 on 2346 degrees of freedom  
 Residual deviance: 2435 on 2333 degrees of freedom  
 AIC: 12249

Number of Fisher Scoring iterations: 5

> `summary( lW.f )`

Call:

```
glm(formula = X ~ Ns(A, knots = a.kn, int = TRUE) + Ns(P, knots = p.kn,
  ref = 2005) + Ns(P - A, knots = c.kn, ref = 1950) - 1, family = poisson,
  data = subset(TT, sex == "F"), offset = log(Y.nD))
```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-4.4643	-0.9514	-0.1813	0.6851	10.5994

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z )
Ns(A, knots = a.kn, int = TRUE)1	-5.86371	0.06092	-96.255	< 2e-16
Ns(A, knots = a.kn, int = TRUE)2	-5.76902	0.01838	-313.904	< 2e-16
Ns(A, knots = a.kn, int = TRUE)3	-4.82916	0.02021	-238.972	< 2e-16
Ns(A, knots = a.kn, int = TRUE)4	-1.21470	0.03677	-33.031	< 2e-16
Ns(A, knots = a.kn, int = TRUE)5	-14.49467	0.11813	-122.704	< 2e-16
Ns(A, knots = a.kn, int = TRUE)6	1.21315	0.07346	16.515	< 2e-16
Ns(P, knots = p.kn, ref = 2005)1	0.11364	0.01316	8.633	< 2e-16
Ns(P, knots = p.kn, ref = 2005)2	0.72039	0.02415	29.835	< 2e-16

```

Ns(P, knots = p.kn, ref = 2005)3      0.37585      0.01118      33.630 < 2e-16
Ns(P - A, knots = c.kn, ref = 1950)1 -0.11591      0.03323      -3.488 0.000487
Ns(P - A, knots = c.kn, ref = 1950)2 -0.20183      0.04094      -4.930 8.21e-07
Ns(P - A, knots = c.kn, ref = 1950)3  0.38937      0.05357       7.269 3.63e-13
Ns(P - A, knots = c.kn, ref = 1950)4 -0.20239      0.04934      -4.102 4.10e-05
Ns(P - A, knots = c.kn, ref = 1950)5      NA          NA          NA          NA

```

(Dispersion parameter for poisson family taken to be 1)

```

Null deviance: 55755779.6 on 2346 degrees of freedom
Residual deviance: 4641.7 on 2333 degrees of freedom
AIC: 17548

```

Number of Fisher Scoring iterations: 4

We can make an overview plot of the estimated mortality and incidence effects:

## 2.2 Residual life time and years lost to DM

We now collect the estimated years of life lost classified by method (immune assumption or not), sex, age and calendar time:

```

> source( "y11.R" )
> a.ref <- 30:90
> p.ref <- 1995:2012
> aYLL <- NArray( list( type = c("Imm","Sus","Dif","Ex%"),
+                          sex = levels( TT$sex ),
+                          age = a.ref,
+                          date = p.ref ) )
> str( aYLL )
logi [1:4, 1:2, 1:61, 1:18] NA NA NA NA NA NA ...
- attr(*, "dimnames")=List of 4
..$ type: chr [1:4] "Imm" "Sus" "Dif" "Ex%"
..$ sex : chr [1:2] "M" "F"
..$ age : chr [1:61] "30" "31" "32" "33" ...
..$ date: chr [1:18] "1995" "1996" "1997" "1998" ...

> system.time(
+ for( ip in p.ref )
+ {
+   nd <- data.frame( A = seq(30,90,0.2)+0.1,
+                     P = ip,
+                     Y.nD = 1,
+                     Y.DM = 1 )
+   muW.m <- ci.pred( mW.m, nd )[,1]
+   muD.m <- ci.pred( mD.m, nd )[,1]
+   lam.m <- ci.pred( lW.m, nd )[,1]
+   muW.f <- ci.pred( mW.f, nd )[,1]
+   muD.f <- ci.pred( mD.f, nd )[,1]
+   lam.f <- ci.pred( lW.f, nd )[,1]
+   aYLL["Imm","M",,paste(ip)] <- yll( int=0.2, muW.m, muD.m, lam=NULL, A=a.ref, age.in=3
+   aYLL["Imm","F",,paste(ip)] <- yll( int=0.2, muW.f, muD.f, lam=NULL, A=a.ref, age.in=3
+   aYLL["Sus","M",,paste(ip)] <- yll( int=0.2, muW.m, muD.m, lam=lam.m, A=a.ref, age.in=3
+   aYLL["Sus","F",,paste(ip)] <- yll( int=0.2, muW.f, muD.f, lam=lam.f, A=a.ref, age.in=3
+ } )

user system elapsed
11.297 0.028 11.324

```

```

> aYLL[3,,] <- aYLL[1,,] - aYLL[2,,]
> aYLL[4,,] <- (aYLL[1,,] - aYLL[2,,]) / aYLL[2,,] * 100
> round( ftable( aYLL[, , seq(1,61,10)], col.vars=c(3,2) ), 1 )

```

	age	30		40		50		60		70		80		90	
	sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
type	date														
Imm	1995	12.8	12.4	11.0	11.2	8.7	9.6	6.2	7.1	3.8	4.4	1.7	1.9	0.0	0.0
	1996	12.6	12.0	10.9	10.8	8.6	9.2	6.2	6.9	3.7	4.3	1.6	1.8	0.0	0.0
	1997	12.4	11.5	10.7	10.4	8.5	8.8	6.1	6.6	3.7	4.1	1.6	1.8	0.0	0.0
	1998	12.2	11.1	10.5	10.0	8.4	8.5	6.0	6.4	3.7	4.0	1.6	1.7	0.0	0.0
	1999	12.0	10.7	10.4	9.6	8.2	8.2	6.0	6.1	3.6	3.8	1.6	1.6	0.0	0.0
	2000	11.8	10.3	10.2	9.2	8.1	7.8	5.9	5.9	3.6	3.7	1.6	1.6	0.0	0.0
	2001	11.6	9.9	10.0	8.9	7.9	7.6	5.7	5.7	3.5	3.5	1.5	1.5	0.0	0.0
	2002	11.3	9.6	9.7	8.6	7.7	7.3	5.6	5.5	3.4	3.4	1.5	1.5	0.0	0.0
	2003	11.0	9.4	9.5	8.4	7.5	7.1	5.5	5.3	3.3	3.3	1.4	1.4	0.0	0.0
	2004	10.8	9.1	9.2	8.1	7.3	6.9	5.3	5.1	3.3	3.2	1.4	1.4	0.0	0.0
	2005	10.5	8.9	9.0	7.9	7.1	6.7	5.2	5.0	3.2	3.1	1.3	1.3	0.0	0.0
	2006	10.3	8.7	8.8	7.7	6.9	6.5	5.0	4.9	3.1	3.1	1.3	1.3	0.0	0.0
	2007	10.1	8.5	8.6	7.5	6.8	6.3	4.9	4.7	3.0	3.0	1.3	1.3	0.0	0.0
2008	9.9	8.4	8.5	7.4	6.7	6.2	4.8	4.6	3.0	2.9	1.2	1.2	0.0	0.0	
2009	9.8	8.2	8.3	7.2	6.5	6.0	4.7	4.5	2.9	2.8	1.2	1.2	0.0	0.0	
2010	9.6	8.0	8.2	7.0	6.4	5.8	4.7	4.3	2.9	2.7	1.2	1.2	0.0	0.0	
2011	9.5	7.9	8.1	6.9	6.3	5.7	4.6	4.2	2.8	2.6	1.2	1.1	0.0	0.0	
2012	9.4	7.7	8.0	6.7	6.2	5.5	4.5	4.1	2.8	2.5	1.2	1.1	0.0	0.0	
Sus	1995	11.8	11.6	10.1	10.5	8.0	8.9	5.8	6.7	3.5	4.2	1.6	1.9	0.0	0.0
	1996	11.6	11.1	9.9	10.1	7.8	8.6	5.7	6.4	3.5	4.1	1.6	1.8	0.0	0.0
	1997	11.3	10.6	9.7	9.6	7.7	8.2	5.6	6.2	3.5	3.9	1.6	1.7	0.0	0.0
	1998	11.1	10.2	9.5	9.2	7.5	7.8	5.5	5.9	3.4	3.8	1.6	1.6	0.0	0.0
	1999	10.8	9.8	9.3	8.8	7.3	7.5	5.4	5.6	3.4	3.6	1.5	1.6	0.0	0.0
	2000	10.6	9.4	9.1	8.4	7.2	7.2	5.3	5.4	3.3	3.5	1.5	1.5	0.0	0.0
	2001	10.3	9.0	8.8	8.1	7.0	6.9	5.1	5.2	3.3	3.3	1.5	1.5	0.0	0.0
	2002	10.1	8.7	8.6	7.8	6.8	6.6	5.0	5.0	3.2	3.2	1.4	1.4	0.0	0.0
	2003	9.8	8.5	8.4	7.6	6.6	6.4	4.9	4.8	3.1	3.1	1.4	1.4	0.0	0.0
	2004	9.6	8.3	8.1	7.4	6.4	6.2	4.7	4.7	3.0	3.0	1.3	1.3	0.0	0.0
	2005	9.3	8.1	7.9	7.2	6.2	6.1	4.6	4.6	2.9	2.9	1.3	1.3	0.0	0.0
	2006	9.1	7.9	7.7	7.0	6.0	5.9	4.5	4.4	2.8	2.8	1.2	1.3	0.0	0.0
	2007	8.9	7.7	7.5	6.8	5.9	5.7	4.3	4.3	2.8	2.8	1.2	1.2	0.0	0.0
2008	8.7	7.5	7.3	6.6	5.7	5.5	4.2	4.1	2.7	2.7	1.2	1.2	0.0	0.0	
2009	8.5	7.3	7.1	6.4	5.6	5.3	4.1	4.0	2.6	2.6	1.2	1.2	0.0	0.0	
2010	8.3	7.1	6.9	6.2	5.4	5.1	4.0	3.9	2.6	2.5	1.2	1.1	0.0	0.0	
2011	8.1	6.9	6.8	6.0	5.2	5.0	3.9	3.7	2.5	2.4	1.1	1.1	0.0	0.0	
2012	7.9	6.7	6.6	5.8	5.1	4.8	3.8	3.6	2.5	2.3	1.1	1.0	0.0	0.0	
Dif	1995	1.0	0.8	0.9	0.7	0.7	0.6	0.5	0.4	0.2	0.2	0.1	0.0	0.0	0.0
	1996	1.0	0.8	1.0	0.8	0.8	0.6	0.5	0.4	0.2	0.2	0.1	0.0	0.0	0.0
	1997	1.1	0.9	1.0	0.8	0.8	0.7	0.5	0.5	0.2	0.2	0.1	0.0	0.0	0.0
	1998	1.1	0.9	1.0	0.8	0.9	0.7	0.5	0.5	0.2	0.2	0.1	0.0	0.0	0.0
	1999	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.5	0.2	0.2	0.1	0.0	0.0	0.0
	2000	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.5	0.3	0.2	0.1	0.0	0.0	0.0
	2001	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.5	0.3	0.2	0.1	0.0	0.0	0.0
	2002	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.5	0.3	0.2	0.1	0.0	0.0	0.0
	2003	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.5	0.3	0.2	0.1	0.0	0.0	0.0
	2004	1.2	0.9	1.1	0.8	0.9	0.6	0.6	0.4	0.2	0.2	0.0	0.0	0.0	0.0
	2005	1.2	0.8	1.1	0.8	0.9	0.6	0.6	0.4	0.2	0.2	0.0	0.0	0.0	0.0
	2006	1.2	0.8	1.1	0.8	0.9	0.6	0.6	0.4	0.2	0.2	0.0	0.0	0.0	0.0
	2007	1.2	0.9	1.1	0.8	0.9	0.6	0.6	0.4	0.3	0.2	0.0	0.0	0.0	0.0
2008	1.2	0.9	1.1	0.8	0.9	0.7	0.6	0.4	0.3	0.2	0.0	0.0	0.0	0.0	
2009	1.3	0.9	1.2	0.8	1.0	0.7	0.6	0.5	0.3	0.2	0.1	0.0	0.0	0.0	
2010	1.4	0.9	1.3	0.9	1.0	0.7	0.7	0.5	0.3	0.2	0.1	0.0	0.0	0.0	

	2011	1.4	1.0	1.3	0.9	1.1	0.7	0.7	0.5	0.3	0.2	0.1	0.0	0.0	0.0
	2012	1.5	1.0	1.4	0.9	1.1	0.8	0.7	0.5	0.3	0.2	0.1	0.0	0.0	0.0
Ex%	1995	8.3	7.0	9.0	7.1	9.2	7.0	8.0	6.4	5.9	5.0	3.1	2.6	0.0	0.0
	1996	8.9	7.5	9.6	7.6	9.9	7.5	8.6	6.9	6.2	5.3	3.2	2.7	0.0	0.0
	1997	9.6	8.1	10.3	8.2	10.6	8.0	9.2	7.4	6.5	5.6	3.4	2.8	0.0	0.0
	1998	10.3	8.7	11.0	8.8	11.4	8.6	9.9	7.9	6.9	5.9	3.5	3.0	0.0	0.0
	1999	10.9	9.2	11.7	9.3	12.1	9.1	10.5	8.4	7.3	6.2	3.6	3.1	0.0	0.0
	2000	11.5	9.7	12.4	9.8	12.8	9.6	11.1	8.8	7.6	6.5	3.7	3.2	0.0	0.0
	2001	11.9	10.1	12.9	10.2	13.3	10.0	11.6	9.1	7.8	6.7	3.7	3.2	0.0	0.0
	2002	12.2	10.3	13.2	10.4	13.6	10.2	11.9	9.3	8.0	6.8	3.7	3.2	0.0	0.0
	2003	12.4	10.3	13.4	10.5	13.9	10.2	12.1	9.4	8.1	6.9	3.7	3.2	0.0	0.0
	2004	12.5	10.4	13.6	10.6	14.1	10.3	12.4	9.4	8.3	6.9	3.7	3.2	0.0	0.0
	2005	12.7	10.5	13.8	10.8	14.4	10.4	12.6	9.5	8.4	7.0	3.7	3.2	0.0	0.0
	2006	13.0	10.7	14.2	11.0	14.8	10.7	13.0	9.7	8.7	7.1	3.8	3.2	0.0	0.0
	2007	13.6	11.1	14.9	11.5	15.5	11.1	13.7	10.1	9.2	7.4	3.9	3.3	0.0	0.0
	2008	14.3	11.6	15.7	12.2	16.5	11.8	14.5	10.7	9.8	7.9	4.1	3.5	0.0	0.0
	2009	15.3	12.4	16.8	13.0	17.7	12.6	15.6	11.4	10.5	8.4	4.4	3.7	0.0	0.0
	2010	16.4	13.3	18.1	14.0	19.1	13.7	16.9	12.3	11.4	9.1	4.7	4.0	0.0	0.0
	2011	17.6	14.2	19.5	15.2	20.7	14.9	18.4	13.3	12.4	9.8	5.1	4.3	0.0	0.0
	2012	18.9	15.3	21.1	16.4	22.4	16.2	19.9	14.4	13.5	10.6	5.5	4.7	0.0	0.0

We now have the relevant points for the graph showing YLL to diabetes for men and women by age, and calendar year, both under the immunity and susceptibility models for the calculation of YLL.

```
> plyll <- function(wh){
+ par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
+ matplot( a.ref, aYLL[wh,"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", adj=1 )
+ text( 40, aYLL[wh,"M","40","1995"], "1995", adj=c(0,0), col="blue" )
+ text( 43, aYLL[wh,"M","44","2012"], "2012", adj=c(1,1), col="blue" )
+
+ matplot( a.ref, aYLL[wh,"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", adj=1 )
+ text( 40, aYLL[wh,"F","40","1995"], "1995", adj=c(0,0), col="red" )
+ text( 43, aYLL[wh,"F","44","2012"], "2012", adj=c(1,1), col="red" )
+ }
> plyll("Imm")

> plyll("Sus")
```

From figure ?? 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 — here side by side for the two different approaches to computation of YLL:

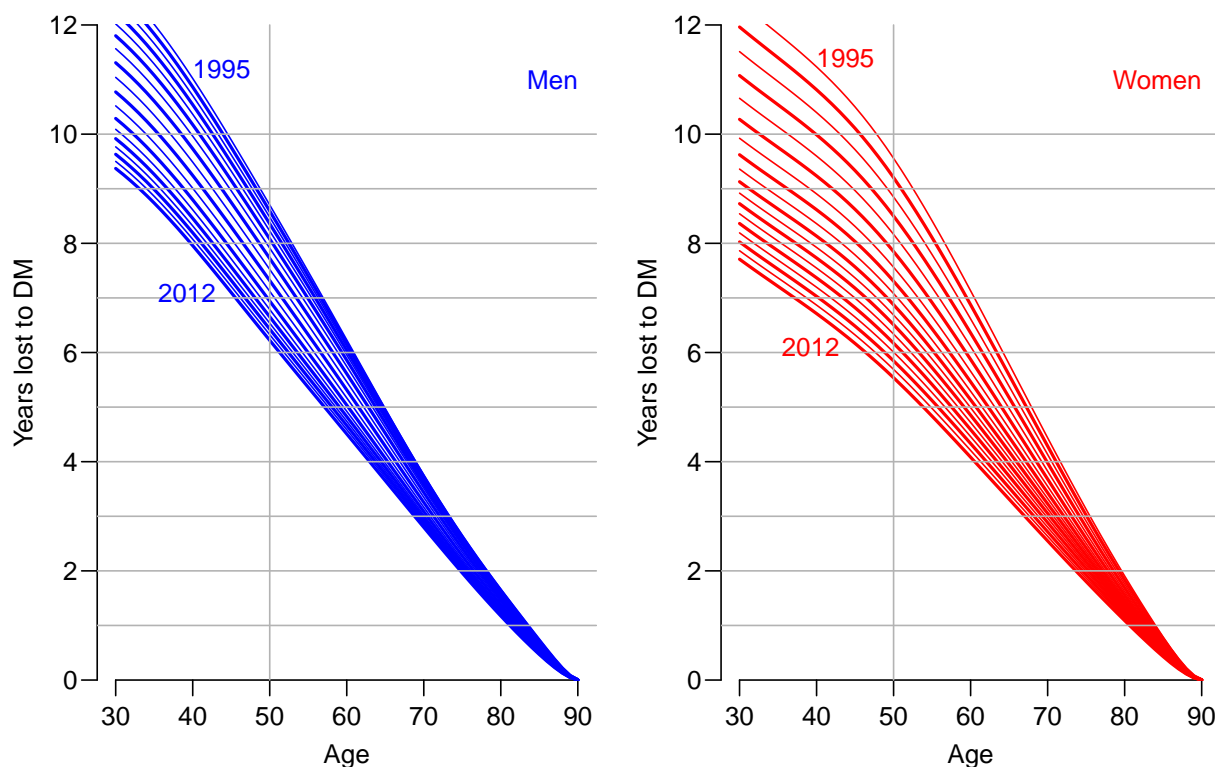


Figure 2.1: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes, assuming the persons without diabetes at a given age remain free from diabetes (immunity assumption). The lines refer to date of evaluation; the top lines refer to 1.1.1995 the bottom ones to 1.1.2012. Blue curves are men, red women.*

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matplot( a.ref, cbind(aYLL["Imm","M",,],aYLL["Imm","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))
> text( 40, aYLL["Imm","F","40","1995"], "1995", adj=c(0,0) )
> text( 43, aYLL["Imm","F","44","2012"], "2012", adj=c(1,1) )
> mtext( "Immunity to DM", side=3 )
> matplot( a.ref, cbind(aYLL["Sus","M",,],aYLL["Sus","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))
> text( 40, aYLL["Sus","F","40","1995"], "1995", adj=c(0,0) )
> text( 43, aYLL["Sus","F","44","2012"], "2012", adj=c(1,1) )
> mtext( "Susceptible to DM", side=3 )
```

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 than men. Under the (unrealistic) assumption of immunity the improvement in years of life lost to DM for 50-year old women were from 9.6 to 5.5 years and for men from 8.7 to 6.2 years. Under the more realistic assumption that the non-diseased comparison group is allowed to acquire

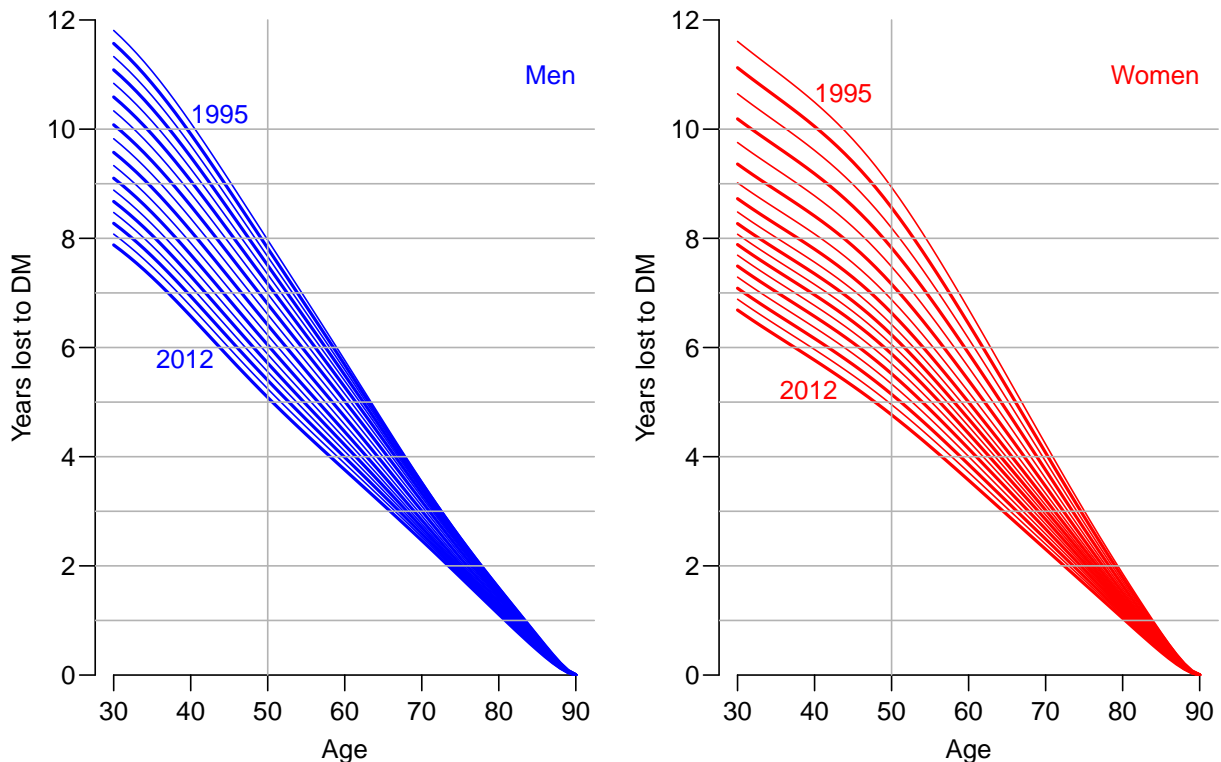


Figure 2.2: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes, allowing the persons without diabetes at a given to contract diabetes and thus be subject to higher mortality. The lines refer to date of evaluation; the top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

diabetes after the conditioning age, the drop in YLL for women were from 8.9 to 4.8 and for men from 8 to 5.1 years.

Also from the tables above we see that the general pattern in the difference between the naive (Immune) and the more realistic (Susceptible) is an overestimation of the years of life lost by about 1 year, or some 5–10%. That is not dramatic, but certainly neither negligible.

### 2.2.1 For the poster

For the poster we devise 3 separate plots of the YLL:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> matplot( a.ref, aYLL["Sus","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", adj=1 )
> text( 40, aYLL["Sus","M","40","1995"], "1995", adj=c(0,0), col="blue" )
> text( 43, aYLL["Sus","M","44","2012"], "2012", adj=c(1,1), col="blue" )
```

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> matplot( a.ref, aYLL["Sus","F",,],
```

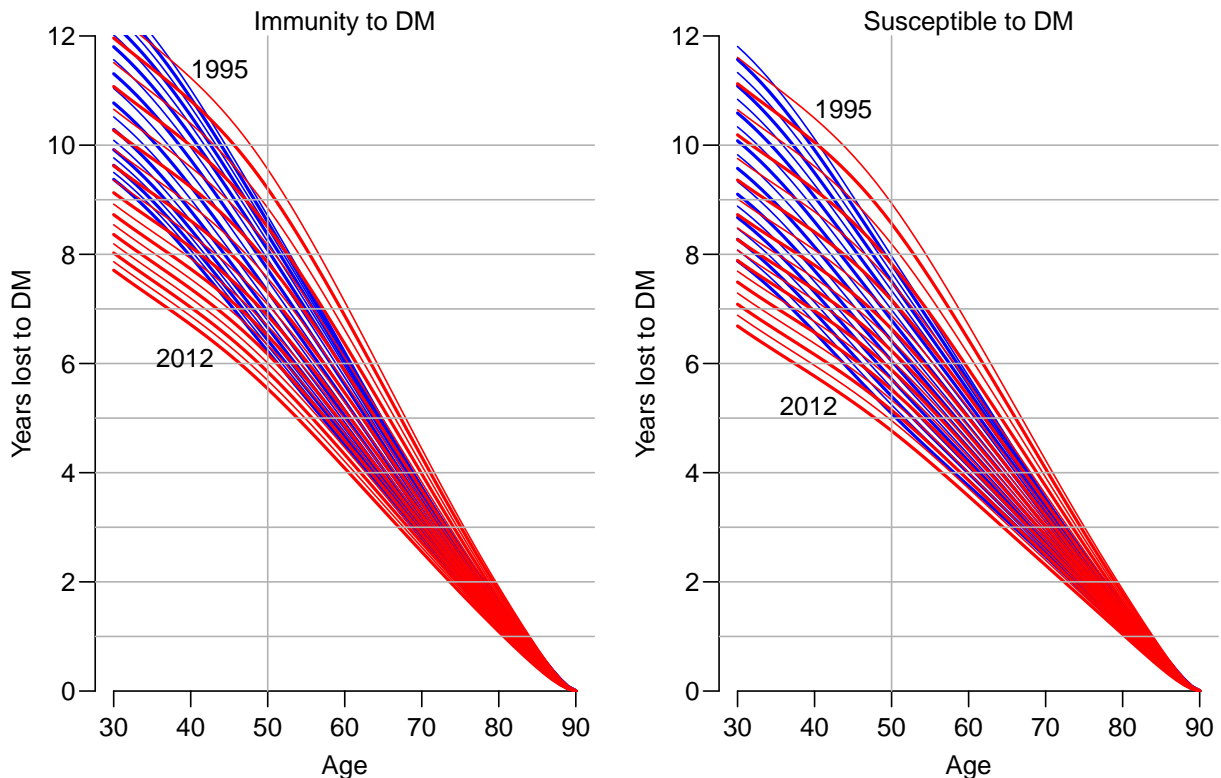


Figure 2.3: *Years of life lost to DM: the difference in expected residual life time at different ages between persons with and without diabetes. The left panel is based on an assumption that persons without DM at a given age will not contract DM; the right panel is based on a model where persons at a given age can contract diabetes and thus transfer to a state with higher mortality. 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.*

```

+       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", adj=1 )
> text( 40, aYLL["Sus","F","40","1995"], "1995", adj=c(0,0), col="red" )
> text( 43, aYLL["Sus","F","44","2012"], "2012", adj=c(1,1), col="red" )

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> matplot( a.ref, cbind(aYLL["Sus","M",,],aYLL["Sus","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))
> text( 40, aYLL["Sus","F","40","1995"], "1995", adj=c(0,0), col=gray(0.5) )
> text( 43, aYLL["Sus","F","44","2012"], "2012", adj=c(1,1), col=gray(0.5) )

```

# Bibliography

- [1] B. Carstensen, J.K. Kristensen, P. Ottosen, and K. Borch-Johnsen. The Danish National Diabetes Register: Trends in incidence, prevalence and mortality. *Diabetologia*, 51:2187–2196, 2008.