T1 diabetes incidence in Europe: APC-models for trends

SDC
August 2015
http://bendixcarstensen.com/SDC/T1APC
Version 1.1

Compiled Tuesday 25th August, 2015, 17:40
from: /home/bendix/sdc/proj/T1APC/r/t1apc

Bendix Carstensen
Steno Diabetes Center, Gentofte, Denmark
& Department of Biostatistics, University of Copenhagen
bxc@steno.dk
http://BendixCarstensen.com

Contents

Chapter 1

Reading data

1.1 Case data

The data are given by date of birth and date of diagnosis for different countries:

```
> library( Epi )
> ca <- read.csv( "../data/cases.csv", header=TRUE )
> names( ca ) <- tolower( names(ca) )
> ( tt <- table( ca$cen ) )
  A1   B1   K1   L1   S1   U1   W3   X1   Y1
4571  610 1862  312 3363 2652 2361 2704  949
> cn <- names( tt )
> co <- c("Austria",
+         "Belgium (Antwerp)",
+         "Lithuania",
+         "Luxembourg",
+         "Spain (Catalonia)",
+         "UK (N.Ireland)",
+         "Poland (Katowice)",
+         "Sweden (Stockholm)",
+         "Slovenia")
> data.frame( co, cn, tt )
                  co cn Var1 Freq
1            Austria A1   A1 4571
2  Belgium (Antwerp) B1   B1  610
3          Lithuania K1   K1 1862
4         Luxembourg L1   L1  312
5  Spain (Catalonia) S1   S1 3363
6     UK (N.Ireland) U1   U1 2652
7  Poland (Katowice) W3   W3 2361
8 Sweden (Stockholm) X1   X1 2704
9           Slovenia Y1   Y1  949
> ca <- transform( ca, cen = factor( cen, levels=cn, labels=co ),
+                      sex = factor( sex, levels=1:2, labels=c("M","F") ),
+                      bda = cal.yr( as.Date(bda,format="%m/%d/%Y") ),
+                      ida = cal.yr( as.Date(ida,format="%m/%d/%Y") ) )
> ca <- transform( ca, A = as.numeric(floor(ida-bda)),
+                      P = as.numeric(floor(ida)),
+                      C = as.numeric(floor(bda)) )
> str( ca )
'data.frame':       19384 obs. of  9 variables:
 $ cen: Factor w/ 9 levels "Austria","Belgium (Antwerp)",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ cid: int  1 2 3 4 5 6 7 8 9 10 ...
 $ bda:Classes 'cal.yr', 'numeric'  num [1:19384] 1979 1976 1978 1984 1985 ...
 $ sex: Factor w/ 2 levels "M","F": 1 2 1 2 1 2 2 2 2 1 ...
 $ ida:Classes 'cal.yr', 'numeric'  num [1:19384] 1989 1989 1989 1989 1989 ...
```

```
 $ age: int  9 13 10 4 3 7 6 3 8 11 ...
 $ A  : num  9 13 10 4 3 7 6 3 8 11 ...
 $ P  : num  1989 1989 1989 1989 1989 ...
 $ C  : num  1979 1975 1978 1984 1985 ...
```

```
> head( ca )
```

```
      cen cid      bda sex      ida age  A    P    C
1 Austria   1 1979.150   M 1989.031   9  9 1989 1979
2 Austria   2 1975.960   F 1989.025  13 13 1989 1975
3 Austria   3 1978.260   M 1989.072  10 10 1989 1978
4 Austria   4 1984.174   F 1989.099   4  4 1989 1984
5 Austria   5 1985.414   M 1989.187   3  3 1989 1985
6 Austria   6 1981.745   F 1989.244   7  7 1989 1981
```

With this groomed database we can now make a table of cases by sex, age and date of follow-up and date of birth and center:

```
> cl <- aggregate( rep(1,nrow(ca)), by=ca[,c("sex","A","P","C","cen")], FUN=sum )
> with( cl, table(P-A-C) )
> names( cl )[match("x",names(cl))] <- "D"
> str( cl )
```

Thus `cl` now have one entry for each Lexis triangle with at least one case of T1D for the ages 0–15, dates 1989–2013 subdivided by year of birth. Well, for each sex and centre.

1.1.1 C-sets of cases

```
> cl <- aggregate( rep(1,nrow(ca)), by=ca[,c("sex","A","P","cen")], FUN=sum )
> names( cl )[match("x",names(cl))] <- "D"
> str( cl )
```

```
'data.frame':        5213 obs. of  5 variables:
 $ sex: Factor w/ 2 levels "M","F": 2 1 2 1 2 1 2 1 2 1 ...
 $ A  : num  0 1 1 2 2 3 3 4 4 5 ...
 $ P  : num  1989 1989 1989 1989 1989 ...
 $ cen: Factor w/ 9 levels "Austria","Belgium (Antwerp)",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ D  : num  1 3 3 5 1 5 3 3 4 1 ...
```

Thus `cl` now have one entry for each Lexis C-set with at least one case of T1D for the ages 0–15 and dates 1989–2013; so-called sets of the Lexis diagram. Well, for each sex and centre.

1.2 Population data

We now read the population data, assuming that we have them as person-years for each combination of age and period:

```
> pop <- read.table( "../data/popdat.txt", header=TRUE, sep="\t" )
> head( pop )
```

```
  Year Age   A1M   A1F  B1M  B1F  L1M  L1F   K1M   K1F   S1M   S1F   U1M   U1F   W3M   W3F   X1M
1 1989   0 45319 42625 5290 5134 2365 2330 29004 27772 28631 26925 13617 12731 26659 24932 12099
2 1989   1 44428 42305 5479 5290 2218 2172 30155 29069 29241 27498 13873 13247 28689 27260 11568
3 1989   2 44913 42771 5522 5215 2338 2215 31362 29595 30329 28521 14065 13197 30619 29002 10632
4 1989   3 45474 42769 5257 5096 2150 1986 30125 29483 31915 30012 13820 13063 32331 30569 10215
5 1989   4 45997 44011 5438 5151 2222 2037 29971 28839 32715 30765 13697 12814 34368 33312  9563
6 1989   5 46395 44195 5614 5232 2158 2135 30055 28522 33255 31458 13542 12891 35944 33525  9229
    X1F   Y1M   Y1F
1 11574 12337 11570
2 11010 13185 12514
```

```
3 10154 12994 12514
4  9729 12778 12171
5  9256 13528 13051
6  8681 13817 13039
```

```
> dim( pop )
```

```
[1] 375  20
```

```
> yl <- reshape( pop, varying = 3:20,
+                     v.names = "Y",
+                     timevar = "gr",
+                       times = names(pop)[3:20],
+                   direction = "long" )
> head( yl )
```

```
      Year Age  gr     Y id
1.A1M 1989   0 A1M 45319  1
2.A1M 1989   1 A1M 44428  2
3.A1M 1989   2 A1M 44913  3
4.A1M 1989   3 A1M 45474  4
5.A1M 1989   4 A1M 45997  5
6.A1M 1989   5 A1M 46395  6
```

```
> unique( yl$gr )
```

```
 [1] "A1M" "A1F" "B1M" "B1F" "L1M" "L1F" "K1M" "K1F" "S1M" "S1F" "U1M" "U1F" "W3M" "W3F" "X1M" "X1F"
[17] "Y1M" "Y1F"
```

```
> table( substr( yl$gr, 1, 1 ) )
```

```
  A   B   K   L   S   U   W   X   Y
750 750 750 750 750 750 750 750 750
```

```
> table( substr( yl$gr, 3, 3 ) )
```

```
   F    M
3375 3375
```

```
> ( tt <- table( substr( yl$gr, 1, 1 ) ) )
```

```
  A   B   K   L   S   U   W   X   Y
750 750 750 750 750 750 750 750 750
```

```
> cn <- names( tt )
> cbind( cn, co )
```

```
      cn  co
 [1,] "A" "Austria"
 [2,] "B" "Belgium (Antwerp)"
 [3,] "K" "Lithuania"
 [4,] "L" "Luxembourg"
 [5,] "S" "Spain (Catalonia)"
 [6,] "U" "UK (N.Ireland)"
 [7,] "W" "Poland (Katowice)"
 [8,] "X" "Sweden (Stockholm)"
 [9,] "Y" "Slovenia"
```

```
> yl <- transform( yl, sex = factor( substr( gr, 3, 3 ),
+                                    levels=c("M","F") ),
+                      cen = factor( substr( gr, 1, 1 ),
+                                    levels = cn,
+                                    labels = co ) )[,
+                  c("sex","Age","Year","cen","Y")]
> names( yl ) <- c("sex","A","P","cen","Y")
> head( yl )
```

```
      sex A    P     cen     Y
1.A1M   M 0 1989 Austria 45319
2.A1M   M 1 1989 Austria 44428
3.A1M   M 2 1989 Austria 44913
4.A1M   M 3 1989 Austria 45474
5.A1M   M 4 1989 Austria 45997
6.A1M   M 5 1989 Austria 46395
```

1.2.1 Population data in Lexis triangles

The data in `pl` is population risk time in C-sets (classified by age and date) of the Lexis diagram, but we would like to have the data in Lexis triangles, now we have the T1D cases in these.

(...)

1.3 Merging population and case data

First a brief overview of the two data sets

```
> str( cl )
'data.frame':        5213 obs. of  5 variables:
 $ sex: Factor w/ 2 levels "M","F": 2 1 2 1 2 1 2 1 2 1 ...
 $ A  : num  0 1 1 2 2 3 3 4 4 5 ...
 $ P  : num  1989 1989 1989 1989 1989 ...
 $ cen: Factor w/ 9 levels "Austria","Belgium (Antwerp)",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ D  : num  1 3 3 5 1 5 3 3 4 1 ...
> str( yl )
'data.frame':        6750 obs. of  5 variables:
 $ sex: Factor w/ 2 levels "M","F": 1 1 1 1 1 1 1 1 1 1 ...
 $ A  : int  0 1 2 3 4 5 6 7 8 9 ...
 $ P  : int  1989 1989 1989 1989 1989 1989 1989 1989 1989 1989 ...
 $ cen: Factor w/ 9 levels "Austria","Belgium (Antwerp)",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ Y  : num  45319 44428 44913 45474 45997 ...
> aa <- merge( cl, yl, all=T )
> dim( aa )
[1] 6750    6
> table( is.na(aa$D) )
FALSE  TRUE
 5213  1537
> aa$D[is.na(aa$D)] <- 0
> # code A and P as the midpoints
> aa <- transform( aa, A = A+0.5,
+                      P = P+0.5 )
> summary( aa )
 sex          A               P                      cen              D                Y
 M:3375   Min.   : 0.5   Min.   :1990   Austria          : 750   Min.   : 0.000   Min.   : 1957
 F:3375   1st Qu.: 3.5   1st Qu.:1996   Belgium (Antwerp): 750   1st Qu.: 1.000   1st Qu.: 9080
          Median : 7.5   Median :2002   Lithuania        : 750   Median : 2.000   Median :13145
          Mean   : 7.5   Mean   :2002   Luxembourg       : 750   Mean   : 2.872   Mean   :18756
          3rd Qu.:11.5   3rd Qu.:2008   Spain (Catalonia): 750   3rd Qu.: 4.000   3rd Qu.:28470
          Max.   :14.5   Max.   :2014   UK (N.Ireland)   : 750   Max.   :22.000   Max.   :52431
                                        (Other)          :2250
```

We now have the dataset to be used for analysis, first an overview of the number of cases per center and sex:

```
> addmargins( xtabs( D ~ cen + sex, data=aa ) )
                     sex
cen                      M    F  Sum
  Austria             2474 2097 4571
  Belgium (Antwerp)    318  292  610
  Lithuania            927  935 1862
  Luxembourg           159  153  312
  Spain (Catalonia)   1753 1610 3363
  UK (N.Ireland)      1382 1270 2652
```

```
  Poland (Katowice)   1219  1142  2361
  Sweden (Stockholm)  1438  1266  2704
  Slovenia             446   503   949
  Sum                10116  9268 19384
```

```
> addmargins( xtabs( D ~   P + sex, data=aa ) )
```

```
        sex
P            M     F   Sum
  1989.5   288   246   534
  1990.5   293   275   568
  1991.5   314   292   606
  1992.5   307   289   596
  1993.5   322   317   639
  1994.5   317   286   603
  1995.5   336   304   640
  1996.5   334   310   644
  1997.5   340   345   685
  1998.5   330   323   653
  1999.5   356   339   695
  2000.5   406   362   768
  2001.5   403   333   736
  2002.5   426   427   853
  2003.5   475   382   857
  2004.5   456   443   899
  2005.5   428   385   813
  2006.5   438   436   874
  2007.5   482   396   878
  2008.5   475   415   890
  2009.5   488   426   914
  2010.5   471   462   933
  2011.5   526   468   994
  2012.5   553   488  1041
  2013.5   552   519  1071
  Sum    10116  9268 19384
```

```
> addmargins( xtabs( D ~   A + sex, data=aa ) )
```

```
      sex
A          M     F   Sum
  0.5    100    72   172
  1.5    438   360   798
  2.5    557   439   996
  3.5    563   501  1064
  4.5    523   555  1078
  5.5    543   570  1113
  6.5    600   608  1208
  7.5    682   681  1363
  8.5    708   730  1438
  9.5    758   843  1601
  10.5   858   930  1788
  11.5   931   903  1834
  12.5   957   865  1822
  13.5  1033   708  1741
  14.5   865   503  1368
  Sum  10116  9268 19384
```

```
> round( addmargins( xtabs( D ~ cen + sex, data=aa ) ) /
+        addmargins( xtabs( Y ~ cen + sex, data=aa ) )*10^5, 1 )
```

```
                    sex
cen                     M    F  Sum
  Austria            14.5 12.9 13.7
  Belgium (Antwerp)  15.2 14.6 14.9
  Lithuania          11.0 11.6 11.3
  Luxembourg         15.4 15.6 15.5
  Spain (Catalonia)  13.5 13.2 13.4
  UK (N.Ireland)     29.0 28.0 28.5
  Poland (Katowice)  12.2 12.0 12.1
```

```
  Sweden (Stockholm) 33.2 30.7 32.0
  Slovenia           10.6 12.6 11.5
  Sum                15.6 15.0 15.3
```

```
> round( addmargins( xtabs( D ~   P + sex, data=aa ) ) /
+        addmargins( xtabs( Y ~   P + sex, data=aa ) )*10^5, 1 )
```

```
        sex
P           M    F  Sum
  1989.5 10.0  9.0  9.5
  1990.5 10.3 10.2 10.2
  1991.5 11.1 10.9 11.0
  1992.5 10.9 10.8 10.9
  1993.5 11.5 12.0 11.8
  1994.5 11.5 10.9 11.2
  1995.5 12.4 11.8 12.1
  1996.5 12.6 12.2 12.4
  1997.5 13.0 13.8 13.4
  1998.5 12.3 12.7 12.5
  1999.5 13.5 13.6 13.6
  2000.5 15.7 14.7 15.2
  2001.5 15.8 13.7 14.8
  2002.5 16.9 17.8 17.4
  2003.5 19.0 16.1 17.6
  2004.5 18.4 18.8 18.6
  2005.5 17.4 16.5 16.9
  2006.5 17.9 18.8 18.3
  2007.5 19.8 17.1 18.5
  2008.5 19.5 17.9 18.7
  2009.5 20.0 18.4 19.2
  2010.5 19.2 19.9 19.5
  2011.5 21.3 20.0 20.7
  2012.5 22.4 20.9 21.7
  2013.5 22.4 22.2 22.3
  Sum    15.6 15.0 15.3
```

```
> round( addmargins( xtabs( D ~   A + sex, data=aa ) ) /
+        addmargins( xtabs( Y ~   A + sex, data=aa ) )*10^5, 1 )
```

```
      sex
A         M    F  Sum
  0.5   2.5  1.9  2.2
  1.5  10.7  9.3 10.0
  2.5  13.5 11.2 12.4
  3.5  13.5 12.7 13.1
  4.5  12.5 14.0 13.2
  5.5  12.9 14.2 13.5
  6.5  14.1 15.1 14.6
  7.5  15.9 16.7 16.3
  8.5  16.3 17.7 17.0
  9.5  17.3 20.2 18.7
  10.5 19.3 22.0 20.6
  11.5 20.7 21.1 20.9
  12.5 21.0 19.9 20.5
  13.5 22.3 16.1 19.3
  14.5 18.5 11.3 15.0
  Sum  15.6 15.0 15.3
```

Chapter 2

APC-analysis

2.1 Separate models

First we make an APC-analysis of each of the countries and plot the results in a panel for each. We choose a parametrization with a flat calendar time effect in order to show the birth-cohort effects. First we define the knots to be used, we use 5 knots for each effect (3-non-linear parameters), except for age where we use 6.

```
> a.kn <- with( aa, quantile( rep(  A,D), probs=(1:6-0.5)/6 ) )
> p.kn <- with( aa, quantile( rep(P  ,D), probs=(1:5-0.5)/5 ) )
> c.kn <- with( aa, quantile( rep(P-A,D), probs=(1:5-0.5)/5 ) )
```

For the purpose of plotting we devise a function to extract and write the annual drift as a character variable, and also devise two arrays to hold the tests for non-linearity of cohort and period effects, as well as the deviance of d.f. for the APC-model fitted:

```
> drf <-
+ function( oo )
+ {
+ paste( formatC( (oo$Drift[1,1]-1)*100, format="f", digits=1 ), " (",
+        formatC( (oo$Drift[1,2]-1)*100, format="f", digits=1 ), ";",
+        formatC( (oo$Drift[1,3]-1)*100, format="f", digits=1 ), ")" )
+ }
> dev <- NArray( list( cen=levels(aa$cen),
+                      sex=levels(aa$sex),
+                      mod=c("Sep","Joint"),
+                      typ=c("deviance","df") ) )
> tst <- NArray( list( cen=levels(aa$cen),
+                      sex=levels(aa$sex),
+                      eff=c("Per","Coh"),
+                      ref=c("APC","Ad") ) )
```

With these prerequisites we can now fit an APC-model separately for each sex and center:

```
> par( mfrow=c(3,3), mar=c(0,0,0,0), oma=c(3,4,4,4), mgp=c(3,1,0)/1.6 )
> for( i in 1:nlevels(aa$cen) )
+ {
+ side <- NULL
+ if( i > 6       ) side <- c(side,1)
+ if( i%%3 == 1 )   side <- c(side,2)
+ if( i < 4       ) side <- c(side,3)
+ if( i%%3 == 0 )   side <- c(side,4)
+ cn <- levels(aa$cen)[i]
+ cat( "\n......", cn, ".............\n")
+ cat( "        Boys\n")
+ mc <- apc.fit( data = subset( aa, cen==cn & sex=="M" ),
```

```
+                 parm = "ACP",
+                ref.c = 1993,
+                scale = 10^5,
+                 npar = list(A=a.kn,P=p.kn,C=c.kn) )
+ cat( "         Girls\n")
+ fc <- apc.fit( data = subset( aa, cen==cn & sex=="F" ),
+                 parm = "ACP",
+                ref.c = 1993,
+                scale = 10^5,
+                 npar = list(A=a.kn,P=p.kn,C=c.kn) )
+ dev[cn,"M","Sep",] <- c( mc$Model$deviance, mc$Model$df.residual )
+ dev[cn,"F","Sep",] <- c( fc$Model$deviance, fc$Model$df.residual )
+ tst[cn,"M",,] <- mc$Anova[c(4,5,6,3),5]
+ tst[cn,"F",,] <- fc$Anova[c(4,5,6,3),5]
+ apc.frame( a.lab = seq(0,15,5),
+          # a.tic = 0:15,
+           cp.lab = seq(1980,2010,10),
+           cp.tic = seq(1975,2015,5),
+            r.lab = c( c(2,5), c(1,2,5)*10 ),
+            r.tic = c( c(2:9), c(1:7)*10 ),
+           rr.ref = 10,
+             side = side )
+ apc.lines( mc, ci=TRUE, lwd=c(4,1,1), lty=c(1,0,1), col="blue" )
+ apc.lines( fc, ci=TRUE, lwd=c(4,1,1), lty=c(1,0,1), col="red" )
+ pc.matlines( mc$Per[,1], mc$Per[,-1], ci=TRUE, lwd=c(4,1,1), lty="11", col="blue" )
+ pc.matlines( fc$Per[,1], fc$Per[,-1], ci=TRUE, lwd=c(4,1,1), lty="11", col="red" )
+ text( 50, 55, paste( cn, ", annual drift (%):", sep="" ), cex=1.2, font=2, adj=1 )
+ text( 50, 55/ 1.17      , drf(mc), col="blue", cex=1.2, font=2, adj=1 )
+ text( 50, 55/(1.17*1.13), drf(fc), col="red" , cex=1.2, font=2, adj=1 )
+ }
```

```
...... Austria .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     716.25
Age-drift               368     478.50  1  237.747   <2e-16
Age-Cohort              365     472.97  3    5.527   0.1370
Age-Period-Cohort       362     466.77  3    6.203   0.1021
Age-Period              365     472.37 -3   -5.598   0.1329
Age-drift               368     478.50 -3   -6.133   0.1053
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     369     636.52
Age-drift               368     469.15  1  167.374 < 2.2e-16
Age-Cohort              365     463.59  3    5.562  0.134955
Age-Period-Cohort       362     448.90  3   14.683  0.002108
Age-Period              365     463.08 -3  -14.174  0.002678
Age-drift               368     469.15 -3   -6.072  0.108172

...... Belgium (Antwerp) .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     369     419.99
Age-drift               368     406.88  1  13.1062 0.0002943
Age-Cohort              365     404.54  3   2.3396 0.5049809
```

```
Age-Period-Cohort       362     401.50  3   3.0436 0.3849499
Age-Period              365     401.89 -3  -0.3941 0.9414676
Age-drift               368     406.88 -3  -4.9891 0.1725945
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     395.24
Age-drift               368     390.32  1   4.9137  0.02664
Age-Cohort              365     388.33  3   1.9901  0.57446
Age-Period-Cohort       362     387.65  3   0.6831  0.87717
Age-Period              365     390.00 -3  -2.3560  0.50188
Age-drift               368     390.32 -3  -0.3172  0.95675

...... Lithuania .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     369     556.95
Age-drift               368     434.07  1  122.887 < 2.2e-16
Age-Cohort              365     424.17  3    9.891  0.019512
Age-Period-Cohort       362     418.87  3    5.300  0.151105
Age-Period              365     420.92 -3   -2.048  0.562436
Age-drift               368     434.07 -3  -13.143  0.004337
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     541.61
Age-drift               368     409.05  1  132.553  < 2e-16
Age-Cohort              365     398.25  3   10.802  0.01285
Age-Period-Cohort       362     398.09  3    0.158  0.98408
Age-Period              365     405.21 -3   -7.116  0.06830
Age-drift               368     409.05 -3   -3.844  0.27882

...... Luxembourg .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     333.87
Age-drift               368     322.48  1  11.3836 0.000741
Age-Cohort              365     321.71  3   0.7750 0.855429
Age-Period-Cohort       362     321.10  3   0.6105 0.894017
Age-Period              365     322.06 -3  -0.9590 0.811174
Age-drift               368     322.48 -3  -0.4266 0.934699
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     332.21
Age-drift               368     330.57  1  1.64350   0.1998
Age-Cohort              365     329.12  3  1.44957   0.6940
Age-Period-Cohort       362     328.86  3  0.25935   0.9675
Age-Period              365     330.29 -3 -1.42761   0.6991
```

```
Age-drift               368     330.57 -3 -0.28131   0.9635

...... Spain (Catalonia) .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     511.72
Age-drift               368     509.37  1   2.3486  0.12539
Age-Cohort              365     503.23  3   6.1393  0.10503
Age-Period-Cohort       362     496.55  3   6.6806  0.08280
Age-Period              365     506.26 -3  -9.7117  0.02118
Age-drift               368     509.37 -3  -3.1082  0.37525
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     492.63
Age-drift               368     490.89  1   1.7345  0.18783
Age-Cohort              365     480.41  3  10.4798  0.01490
Age-Period-Cohort       362     471.96  3   8.4478  0.03761
Age-Period              365     481.81 -3  -9.8492  0.01989
Age-drift               368     490.89 -3  -9.0784  0.02827

...... UK (N.Ireland) .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     369     527.03
Age-drift               368     472.79  1   54.237 1.777e-13
Age-Cohort              365     464.07  3    8.716   0.03332
Age-Period-Cohort       362     461.22  3    2.858   0.41408
Age-Period              365     469.37 -3   -8.153   0.04295
Age-drift               368     472.79 -3   -3.420   0.33125
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                     369     493.17
Age-drift               368     440.54  1   52.624 4.04e-13
Age-Cohort              365     434.69  3    5.851  0.11910
Age-Period-Cohort       362     431.70  3    2.998  0.39196
Age-Period              365     434.01 -3   -2.309  0.51071
Age-drift               368     440.54 -3   -6.539  0.08813

...... Poland (Katowice) .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     369     714.30
Age-drift               368     474.84  1  239.453 < 2.2e-16
Age-Cohort              365     473.89  3    0.956 0.8118581
Age-Period-Cohort       362     453.29  3   20.592 0.0001279
Age-Period              365     462.37 -3   -9.076 0.0282940
```

```
Age-drift                368     474.84 -3  -12.472 0.0059289
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                      369     721.09
Age-drift                368     469.52  1  251.570 < 2.2e-16
Age-Cohort               365     466.28  3    3.245 0.3553741
Age-Period-Cohort        362     419.28  3   46.996 3.482e-10
Age-Period               365     453.14 -3  -33.862 2.118e-07
Age-drift                368     469.52 -3  -16.379 0.0009481

...... Sweden (Stockholm) .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                      369     489.51
Age-drift                368     452.72  1   36.792 1.315e-09
Age-Cohort               365     447.39  3    5.327   0.14937
Age-Period-Cohort        362     441.78  3    5.612   0.13207
Age-Period               365     445.73 -3   -3.953   0.26661
Age-drift                368     452.72 -3   -6.986   0.07233
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                      369     469.42
Age-drift                368     434.52  1   34.897 3.476e-09
Age-Cohort               365     434.24  3    0.286   0.96261
Age-Period-Cohort        362     426.14  3    8.097   0.04405
Age-Period               365     427.82 -3   -1.683   0.64077
Age-drift                368     434.52 -3   -6.701   0.08208

...... Slovenia .............
        Boys
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                      369     464.93
Age-drift                368     427.00  1   37.931 7.331e-10
Age-Cohort               365     421.22  3    5.780   0.12280
Age-Period-Cohort        362     417.11  3    4.110   0.24987
Age-Period               365     424.10 -3   -6.983   0.07244
Age-drift                368     427.00 -3   -2.907   0.40621
        Girls
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

                  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                      369     495.20
Age-drift                368     457.74  1   37.452 9.37e-10
Age-Cohort               365     454.43  3    3.312  0.34593
Age-Period-Cohort        362     447.98  3    6.455  0.09146
Age-Period               365     453.92 -3   -5.943  0.11440
Age-drift                368     457.74 -3   -3.824  0.28113
```

We also collected the residual deviances as well as the tests for linearity of period / cohort effects

```
> round( ftable( addmargins( dev[,,"Sep",], 1 ), row.vars=1 ), 1 )
                   sex        M                F
                   typ deviance     df deviance     df
cen
Austria                   466.8  362.0    448.9  362.0
Belgium (Antwerp)         401.5  362.0    387.6  362.0
Lithuania                 418.9  362.0    398.1  362.0
Luxembourg                321.1  362.0    328.9  362.0
Spain (Catalonia)         496.6  362.0    472.0  362.0
UK (N.Ireland)            461.2  362.0    431.7  362.0
Poland (Katowice)         453.3  362.0    419.3  362.0
Sweden (Stockholm)        441.8  362.0    426.1  362.0
Slovenia                  417.1  362.0    448.0  362.0
Sum                      3878.2 3258.0   3760.6 3258.0
```

The test for the non-linearity of period or cohort can either be as removal of a non-linear effect from the APC-model or addition of a non-linear effect to the Age-drift model. To get a quick overview of the tests for linearity of period / cohort effects we collected these p-values in a handy form, and they are (in %):

```
> round( ftable( tst*100, col.vars=c(3,2,4) ), 1 )
                   eff  Per                 Coh
                   sex    M         F         M         F
                   ref  APC   Ad  APC   Ad  APC   Ad  APC   Ad
cen
Austria                10.2 10.5  0.2 10.8 13.3 13.7  0.3 13.5
Belgium (Antwerp)      38.5 17.3 87.7 95.7 94.1 50.5 50.2 57.4
Lithuania              15.1  0.4 98.4 27.9 56.2  2.0  6.8  1.3
Luxembourg             89.4 93.5 96.7 96.4 81.1 85.5 69.9 69.4
Spain (Catalonia)       8.3 37.5  3.8  2.8  2.1 10.5  2.0  1.5
UK (N.Ireland)         41.4 33.1 39.2  8.8  4.3  3.3 51.1 11.9
Poland (Katowice)       0.0  0.6  0.0  0.1  2.8 81.2  0.0 35.5
Sweden (Stockholm)     13.2  7.2  4.4  8.2 26.7 14.9 64.1 96.3
Slovenia               25.0 40.6  9.1 28.1  7.2 12.3 11.4 34.6
```

From these p-values we see that only Poland exhibit strong evidence for non-linearity of the period effect; from the graph it is seen that this can be attributed to a similar pattern among boys and girls with a peak period-effect around 2000. Since this is the de-trended period-effects, we can only say on this basis is that there seem to be some sort of calendar time change at this point in Poland.

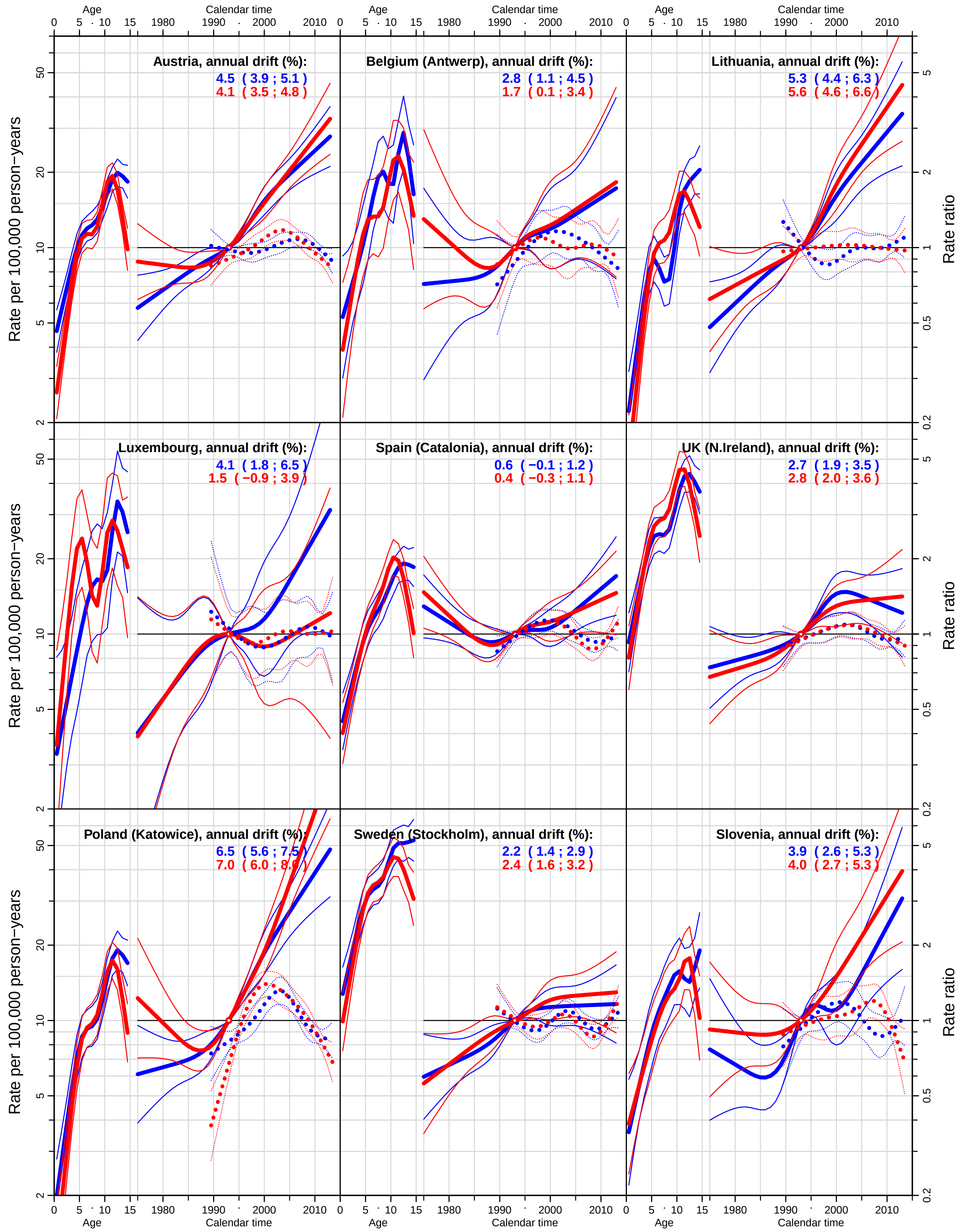

Figure 2.1: *Age-Period-Cohort models for the centers separately, and separately for boys (blue) and girls (red), with period effects (dotted) constrained to be horizontal and 1 on average, and cohort-effects to be 1 at 1993; that is the age-specific incidence rates shown refer to the 1993 generation of children.*

Chapter 3

Joint models

3.1 Intermediate models

Despite the observation of a formally statistically significant non-linearity of period-effects in some centres, we fit a joint model for all countries with separate cohort effects but common age effects, ignoring (the non-linear component of) the period effects.

```
> Mm <- glm( D ~ Ns( A, kn=a.kn ) +
+                cen +
+                cen:Ns( P-A, kn=c.kn ),
+             offset = log(Y),
+             family = poisson,
+               data = subset(aa,sex=="M") )
> Fm <- update( Mm, data = subset(aa,sex=="F") )
```

If we want to compare with separate models we need to fit the corresponding interaction models; one with all three effects separately and one with only age and cohort effects:

```
> Mi <- glm( D ~ cen:( Ns(   A, kn=a.kn, i=T ) +
+                      Ns( P   , kn=p.kn, ref=2000 ) +
+                      Ns( P-A, kn=c.kn, ref=1993 ) ) - 1,
+             offset = log(Y),
+             family = poisson,
+               data = subset(aa,sex=="M") )
> Fi <- update( Mi, data = subset(aa,sex=="F") )
> Mc <- glm( D ~ cen:( Ns(   A, kn=a.kn, i=T ) +
+                      Ns( P-A, kn=c.kn, ref=1993 ) ) - 1,
+             offset = log(Y),
+             family = poisson,
+               data = subset(aa,sex=="M") )
> Fc <- update( Mc, data = subset(aa,sex=="F") )
```

In order to compare these models we compute the deviance residuals, so that we can compute the likelihood-ratio statistics as well as the contribution from each centre to these:

```
> Dev <- NArray( list( cen=levels(aa$cen),
+                      sex=levels(aa$sex),
+                      mod=c("APC:c","AC:c","A+C:c","no Per","same Age") ) )
> Dev[,"M","APC:c"] <- tapply( residuals(Mi)^2, aa[aa$sex=="M","cen"], sum )
> Dev[,"M","AC:c" ] <- tapply( residuals(Mc)^2, aa[aa$sex=="M","cen"], sum )
> Dev[,"M","A+C:c"] <- tapply( residuals(Mm)^2, aa[aa$sex=="M","cen"], sum )
> Dev[,"F","APC:c"] <- tapply( residuals(Fi)^2, aa[aa$sex=="F","cen"], sum )
> Dev[,"F","AC:c" ] <- tapply( residuals(Fc)^2, aa[aa$sex=="F","cen"], sum )
> Dev[,"F","A+C:c"] <- tapply( residuals(Fm)^2, aa[aa$sex=="F","cen"], sum )
> Dev[,,"no Per"]   <- Dev[,,"AC:c" ] - Dev[,,"APC:c"]
```

```
> Dev[,,"same Age"] <- Dev[,,"A+C:c"] - Dev[,,"AC:c" ]
> round( ftable( addmargins(Dev,1), col.vars=c(2,3) ), 1 )
                    sex      M                                       F
                    mod  APC:c   AC:c  A+C:c no Per same Age  APC:c   AC:c  A+C:c no Per same Age
cen
Austria                  466.8  473.0  477.5    6.2      4.5  448.9  463.6  466.1   14.7      2.5
Belgium (Antwerp)        401.5  404.5  412.9    3.0      8.3  387.6  388.3  389.0    0.7      0.7
Lithuania                418.9  424.2  449.8    5.3     25.6  398.1  398.3  413.4    0.2     15.2
Luxembourg               321.1  321.7  327.4    0.6      5.7  328.9  329.1  337.7    0.3      8.6
Spain (Catalonia)        496.6  503.2  505.6    6.7      2.4  472.0  480.4  489.9    8.4      9.5
UK (N.Ireland)           461.2  464.1  467.2    2.9      3.1  431.7  434.7  436.6    3.0      1.9
Poland (Katowice)        453.3  473.9  487.5   20.6     13.6  419.3  466.3  481.5   47.0     15.2
Sweden (Stockholm)       441.8  447.4  451.0    5.6      3.6  426.1  434.2  443.6    8.1      9.4
Slovenia                 417.1  421.2  428.0    4.1      6.8  448.0  454.4  462.0    6.5      7.5
Sum                     3878.2 3933.2 4006.9   55.0     73.7 3760.6 3849.3 3919.9   88.8     70.5
> round( c( Mi$deviance,
+           Mc$deviance,
+           Mm$deviance,
+           Fi$deviance,
+           Fc$deviance,
+           Fm$deviance ), 1 )
[1] 3878.2 3933.2 4006.9 3760.6 3849.3 3919.9
> df <- diff( c( sum(!is.na(coef(Mm))),
+                sum(!is.na(coef(Mc))),
+                sum(!is.na(coef(Mi))) ) ) / 9
> round( cbind( df, Q=qchisq( p=0.95, df=df ) ), 1 )
      df    Q
[1,] 4.4 10.2
[2,] 3.0  7.8
> pval <- addmargins(Dev,1)[,,4:5]
> fmat <- pval[-10,-10,]
> fmat[,,1] <- df[2]
> fmat[,,2] <- df[1]
> fmat <- addmargins(fmat,1)
> pval <- 1-pchisq(pval,fmat)
> round( ftable(pval*100,col.vars=3:2), 1 )
                    mod no Per      same Age
                    sex      M    F        M    F
cen
Austria                   10.2  0.2     40.4 71.0
Belgium (Antwerp)         38.5 87.7     10.5 97.0
Lithuania                 15.1 98.4      0.0  0.6
Luxembourg                89.4 96.7     26.9  9.4
Spain (Catalonia)          8.3  3.8     72.4  6.5
UK (N.Ireland)            41.4 39.2     61.0 80.6
Poland (Katowice)          0.0  0.0      1.2  0.6
Sweden (Stockholm)        13.2  4.4     53.0  6.9
Slovenia                  25.0  9.1     18.3 14.1
Sum                        0.1  0.0      0.1  0.2
```

The number of d.f. per center is quite small (3 and 4.4), and 1 and 3 centers respectively contribute significantly to the test for linearity of the period effect for men (Poland) and women (Poland, Spain, Austria), whereas only two centres (Poland, Lithuania) contribute significantly to the test for common age-effects across centers.

3.2 Joint model

We shall therefore further reduce the model to one where we assume a common cohort effect for the two sexes for each center. This will be a model for the entire dataset where we will have separate age-effects for boys and girls, common for all centres, but cohort effects common for both sexes but separately for each centre.

As a first approximation we fit a model with separate age-effects for boys and girls but common cohort effect, separately for each center. In order to extract the effects we set up the contrast matrices for age and for the cohort-effects with reference 1993.

```
> clr <- rainbow(9)
> a.pt <- seq(0,15,,100)
> c.pt <- seq(1975,2013,,100)
> Ca <- Ns( a.pt, knots=a.kn, i=T )
> Cc <- Ns( c.pt, knots=c.kn, ref=1993 )
> par( mfrow=c(3,3), mar=c(0,0,0,0), oma=c(3,4,4,4), mgp=c(3,1,0)/1.6 )
> for( i in 1:nlevels(aa$cen) )
+ {
+ side <- NULL
+ if( i > 6       ) side <- c(side,1)
+ if( i%%3 == 1 )   side <- c(side,2)
+ if( i < 4       ) side <- c(side,3)
+ if( i%%3 == 0 )   side <- c(side,4)
+ cn <- levels(aa$cen)[i]
+ Mc <- glm( D ~ sex:( Ns(   A, kn=a.kn, i=T ) ) +
+                      Ns( P-A, kn=c.kn, ref=1993 ) - 1,
+            family = poisson,
+            offset = log( Y ),
+              data = subset(aa,cen==cn) )
+ Ma <- ci.exp( Mc, subset="xM", ctr.mat=Ca ) * 10^5
+ Fa <- ci.exp( Mc, subset="xF", ctr.mat=Ca ) * 10^5
+ nM <- data.frame( A=a.pt, P=1993+a.pt, sex="M", Y=10^5 )
+ nF <- data.frame( A=a.pt, P=1993+a.pt, sex="F", Y=10^5 )
+ Mp <- ci.pred( Mc, newdata=nM )
+ Fp <- ci.pred( Mc, newdata=nF )
+ Ra <- ci.exp( Mc, subset=c("xM","xF"), ctr.mat=cbind(Ca,-Ca) )
+ Rc <- ci.exp( Mc, subset="P", ctr.mat=Cc )
+ apc.frame( a.lab = seq(0,15,5),
+          # a.tic = 0:15,
+           cp.lab = seq(1980,2010,10),
+           cp.tic = seq(1975,2015,5),
+            r.lab = c( c(1,2,5), c(1,2,5)*10 ),
+            r.tic = c( c(2:9), c(1:7)*10 ),
+           rr.ref = 10,
+             side = side )
+    matlines( a.pt, cbind(Ma,Fa,Ra*10),
+              lwd=c(3,1,1), lty=1, col=rep(c("blue","red","gray"),each=3) )
+ pc.matlines( c.pt, Rc,
+              lwd=c(3,1,1), lty=1, col=clr[i] )
+ text( 50, 55, cn, cex=1.2, font=2, adj=1, col=clr[i] )
+ }
```

From figure 3.1 we see that the general look of the age-curves are quite similar with a peak among girls around 10–12 and among boys a bit later. Also pretty consistently is the M/F RR which is below 1 in the range 5–11 (where girls have higher incidence than boys), and quite steeply increasing toward the end of the covered age-range.

3.3 Final model

Therefore it is obvious to summarize the entire dataset in a model with separate age-effects for the two sexes (but common across centres) and separate cohort-effects for each centre (but common for the two sexes). The rationale for this is that the age-dependence of incidence of T1D is then taken as an aging phenomenon that is thought to be universal, whereas the level of the intensity of the process is subject to temporal and geographical influence.

```
> MJ <- glm( D ~ Ns(   A, kn=a.kn, intercept=TRUE ):sex +
+           cen + Ns( P-A, kn=c.kn, ref=1993       ):cen,
+             family = poisson,
+             offset = log( Y ),
+               data = aa )
> round( ci.exp( MJ ), 3 )
```

```
                                                       exp(Est.)  2.5% 97.5%
(Intercept)                                                0.085 0.046 0.157
cenBelgium (Antwerp)                                       1.236 1.046 1.460
cenLithuania                                               0.794 0.711 0.886
cenLuxembourg                                              1.292 1.034 1.613
cenSpain (Catalonia)                                       1.016 0.925 1.117
cenUK (N.Ireland)                                          2.283 2.075 2.513
cenPoland (Katowice)                                       0.942 0.852 1.042
cenSweden (Stockholm)                                      2.629 2.394 2.886
cenSlovenia                                                0.935 0.809 1.081
Ns(A, kn = a.kn, intercept = TRUE)1:sexM                   0.005 0.003 0.009
Ns(A, kn = a.kn, intercept = TRUE)2:sexM                   0.001 0.001 0.002
Ns(A, kn = a.kn, intercept = TRUE)3:sexM                   0.002 0.001 0.004
Ns(A, kn = a.kn, intercept = TRUE)4:sexM                   0.020 0.013 0.031
Ns(A, kn = a.kn, intercept = TRUE)5:sexM                   0.000 0.000 0.000
Ns(A, kn = a.kn, intercept = TRUE)6:sexM                   1.282 1.185 1.387
Ns(A, kn = a.kn, intercept = TRUE)1:sexF                   0.006 0.003 0.010
Ns(A, kn = a.kn, intercept = TRUE)2:sexF                   0.001 0.001 0.002
Ns(A, kn = a.kn, intercept = TRUE)3:sexF                   0.003 0.001 0.005
Ns(A, kn = a.kn, intercept = TRUE)4:sexF                   0.020 0.013 0.029
Ns(A, kn = a.kn, intercept = TRUE)5:sexF                   0.000 0.000 0.000
Ns(A, kn = a.kn, intercept = TRUE)6:sexF                   1.000 1.000 1.000
cenAustria:Ns(P - A, kn = c.kn, ref = 1993)1               1.543 1.352 1.760
cenBelgium (Antwerp):Ns(P - A, kn = c.kn, ref = 1993)1     1.537 1.081 2.185
cenLithuania:Ns(P - A, kn = c.kn, ref = 1993)1             1.343 1.096 1.647
cenLuxembourg:Ns(P - A, kn = c.kn, ref = 1993)1            1.548 0.940 2.551
cenSpain (Catalonia):Ns(P - A, kn = c.kn, ref = 1993)1     1.049 0.897 1.227
cenUK (N.Ireland):Ns(P - A, kn = c.kn, ref = 1993)1        1.513 1.277 1.794
cenPoland (Katowice):Ns(P - A, kn = c.kn, ref = 1993)1     2.103 1.751 2.525
cenSweden (Stockholm):Ns(P - A, kn = c.kn, ref = 1993)1    1.520 1.280 1.805
cenSlovenia:Ns(P - A, kn = c.kn, ref = 1993)1              1.819 1.365 2.424
cenAustria:Ns(P - A, kn = c.kn, ref = 1993)2               1.995 1.808 2.200
cenBelgium (Antwerp):Ns(P - A, kn = c.kn, ref = 1993)2     1.493 1.138 1.961
cenLithuania:Ns(P - A, kn = c.kn, ref = 1993)2             2.221 1.901 2.595
cenLuxembourg:Ns(P - A, kn = c.kn, ref = 1993)2            1.309 0.896 1.914
cenSpain (Catalonia):Ns(P - A, kn = c.kn, ref = 1993)2     1.012 0.898 1.139
cenUK (N.Ireland):Ns(P - A, kn = c.kn, ref = 1993)2        1.841 1.616 2.098
cenPoland (Katowice):Ns(P - A, kn = c.kn, ref = 1993)2     2.559 2.231 2.936
cenSweden (Stockholm):Ns(P - A, kn = c.kn, ref = 1993)2    1.542 1.355 1.756
cenSlovenia:Ns(P - A, kn = c.kn, ref = 1993)2              1.659 1.332 2.065
cenAustria:Ns(P - A, kn = c.kn, ref = 1993)3               2.767 2.351 3.256
cenBelgium (Antwerp):Ns(P - A, kn = c.kn, ref = 1993)3     1.709 1.131 2.581
cenLithuania:Ns(P - A, kn = c.kn, ref = 1993)3             2.792 2.220 3.511
cenLuxembourg:Ns(P - A, kn = c.kn, ref = 1993)3            2.110 1.095 4.067
cenSpain (Catalonia):Ns(P - A, kn = c.kn, ref = 1993)3     1.043 0.904 1.203
cenUK (N.Ireland):Ns(P - A, kn = c.kn, ref = 1993)3        2.273 1.852 2.790
cenPoland (Katowice):Ns(P - A, kn = c.kn, ref = 1993)3     4.228 3.368 5.308
cenSweden (Stockholm):Ns(P - A, kn = c.kn, ref = 1993)3    2.051 1.647 2.556
cenSlovenia:Ns(P - A, kn = c.kn, ref = 1993)3              2.170 1.602 2.939
cenAustria:Ns(P - A, kn = c.kn, ref = 1993)4               2.448 2.247 2.667
cenBelgium (Antwerp):Ns(P - A, kn = c.kn, ref = 1993)4     1.655 1.314 2.085
cenLithuania:Ns(P - A, kn = c.kn, ref = 1993)4             2.715 2.383 3.094
cenLuxembourg:Ns(P - A, kn = c.kn, ref = 1993)4            1.571 1.140 2.165
cenSpain (Catalonia):Ns(P - A, kn = c.kn, ref = 1993)4     1.261 1.143 1.392
cenUK (N.Ireland):Ns(P - A, kn = c.kn, ref = 1993)4        1.705 1.522 1.910
cenPoland (Katowice):Ns(P - A, kn = c.kn, ref = 1993)4     3.109 2.774 3.485
cenSweden (Stockholm):Ns(P - A, kn = c.kn, ref = 1993)4    1.661 1.489 1.852
```

```
cenSlovenia:Ns(P - A, kn = c.kn, ref = 1993)4            2.451 2.053 2.925
```

```
> Ma <- ci.exp( MJ, subset=c("Int","xM"), ctr.mat=cbind(1,Ca) ) * 10^5
> Fa <- ci.exp( MJ, subset=c("Int","xF"), ctr.mat=cbind(1,Ca) ) * 10^5
> Ra <- ci.exp( MJ, subset=c( "xM","xF"), ctr.mat=cbind(Ca,-Ca) )
> Ce <- ci.exp( MJ, subset= levels(aa$cen)[1], ctr.mat=Cc )
> # The gsub(...) is necessary because "(" has a special status in regexp
> for( cn in levels(aa$cen)[-1] )
+ Ce <- cbind( Ce, ci.exp( MJ, subset=gsub("\\(","\\\\(",cn), ctr.mat=cbind(1,Cc) ) )
```

Once we fitted the model and extracted the results we can plot the results as age-specific rates referring to the

```
> fmod <- function( ci.A=TRUE, ci.C=TRUE )
+ {
+ par( mar=c(3,4,1,4), mgp=c(3,1,0)/1.6, las=1 )
+ apc.frame( a.lab = seq(0,15,5),
+           cp.lab = seq(1980,2010,10),
+           cp.tic = c(seq(1975,2010,5),2028),
+           cp.txt = "Date of birth",
+            r.lab = c( c(2,5), c(1,2)*10 ),
+            r.tic = c( c(2:9), c(1:2)*10, 25 ),
+           rr.ref = 5 )
+ fp <- options()[["apc.frame.par"]]
+ abline( h=fp[2] )
+    matlines( a.pt, cbind(Ma,Fa,Ra*5),
+              lwd=c(4,1,1), lty=1, col=rep(c("blue","red",gray(0.5)),each=3) )
+ pc.matlines( c.pt, Ce, lwd=c(4,1,1), lty=if(ci.C) 1 else c(1,0,0), col=rep(clr,each=3) )
+ pc.points( 1993, 1, pch=16, cex=1.5, col=clr[1] )
+ last <- Ce[100,0:8*3+1] # last points on the cohort curves
+ perm <- order( last )   # the order in which they are
+ nl <- nlevels(aa$cen)
+ ln <-  levels(aa$cen)
+ text( rep(2014.1,nl)-fp[1], ty <- fp[2]*1.2*1.15^(1:nl),
+       ln[perm], col=clr[perm], font=2, adj=0, cex=1.2 )
+ segments( rep(2013,nl)-fp[1], last[perm]*fp[2],
+           rep(2014,nl)-fp[1], ty, col=clr[perm] )
+ }
> fmod()
```

```
> fmod( ci.C=FALSE )
```

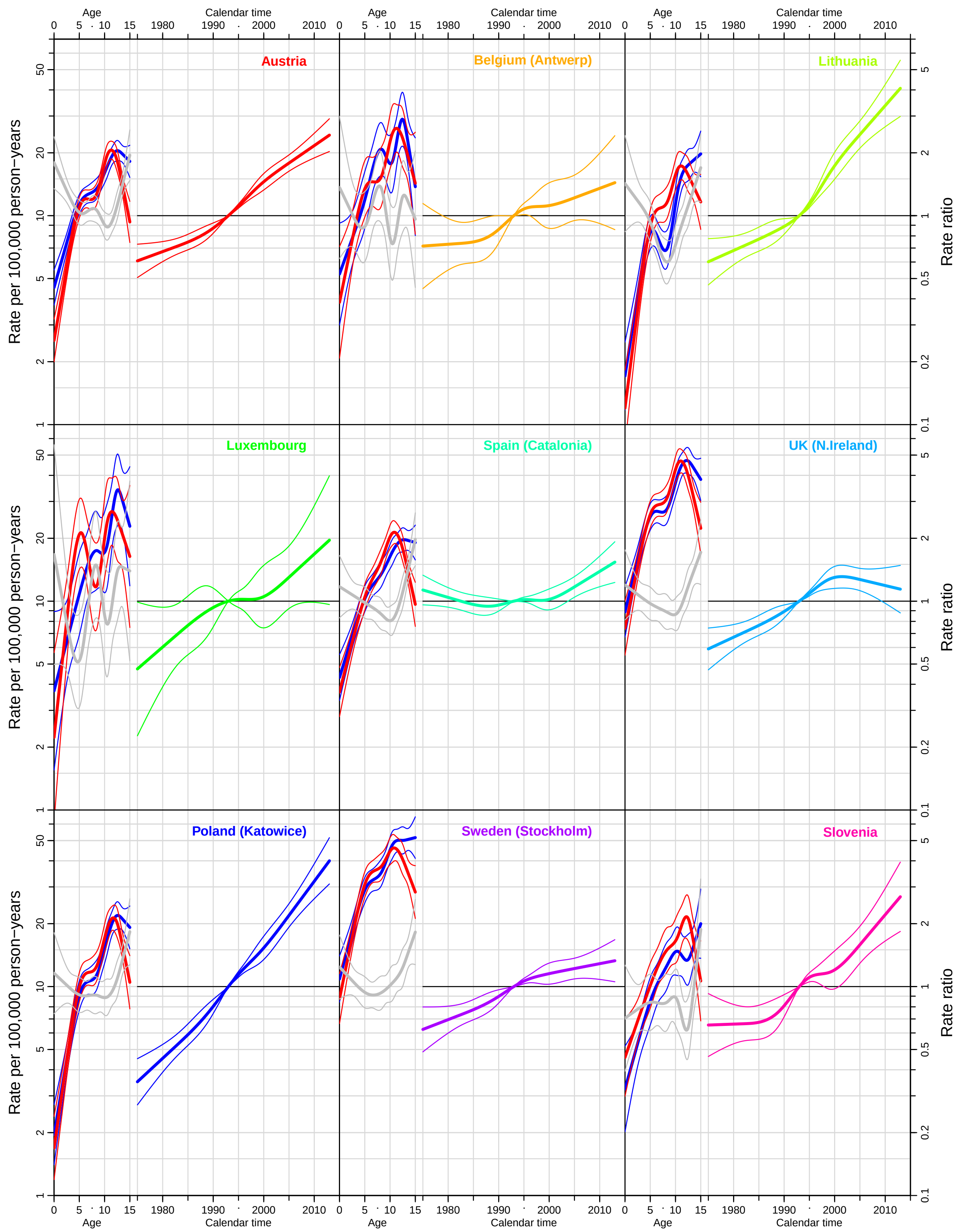

Figure 3.1: *Separate models for each center with age-effects separate for each sex, but common cohort-effect. The gray curve in the age-range is the M/F RR.*

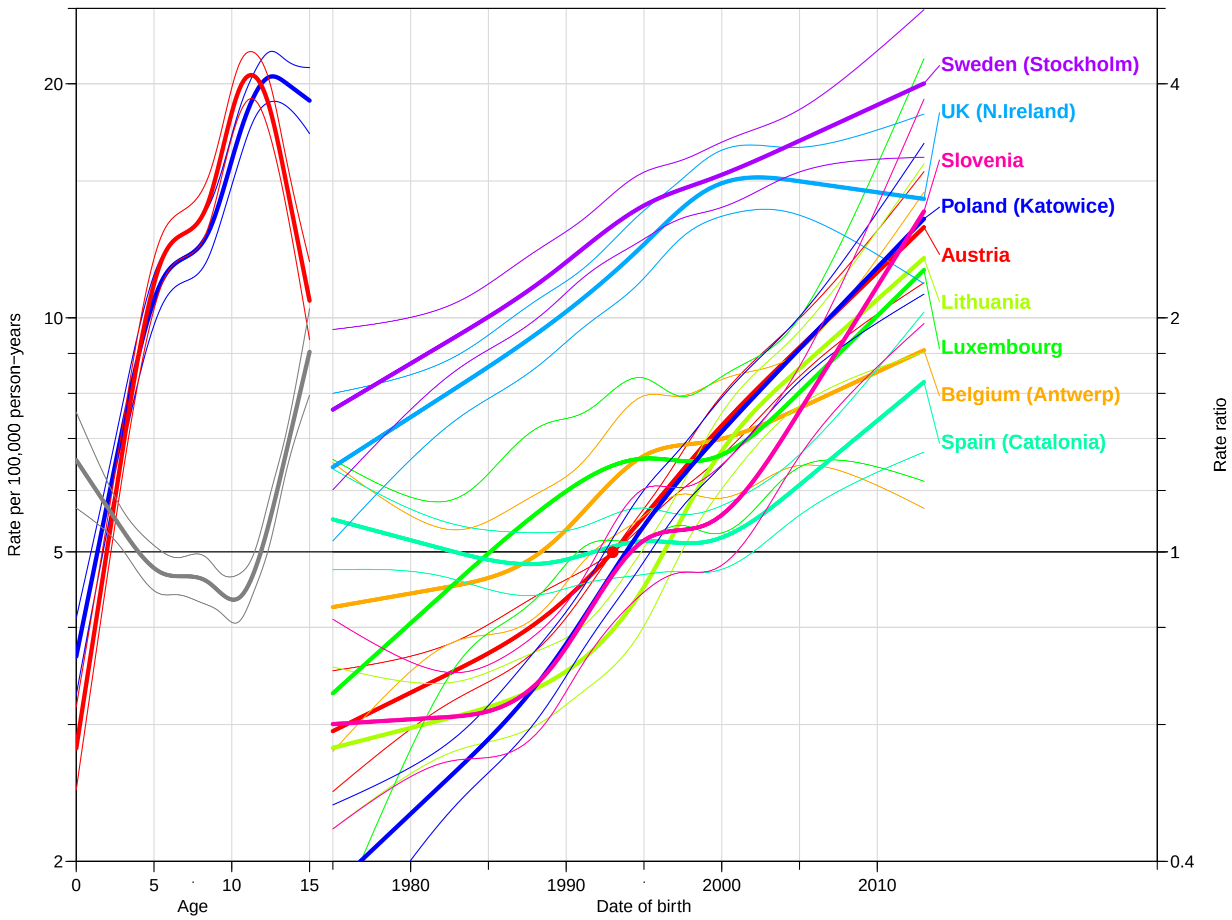

Figure 3.2: *Age-specific cohort (longitudinal) incidence rates of T1D (blue—boys; red—girls) and their ratio (gray), referring to the 1993 birth cohort in Austria. In the right hand side of the panel are the cohort RRs relative to the 1993 birth cohort in Austria. Thin lines indicate 95% confidence limits.*

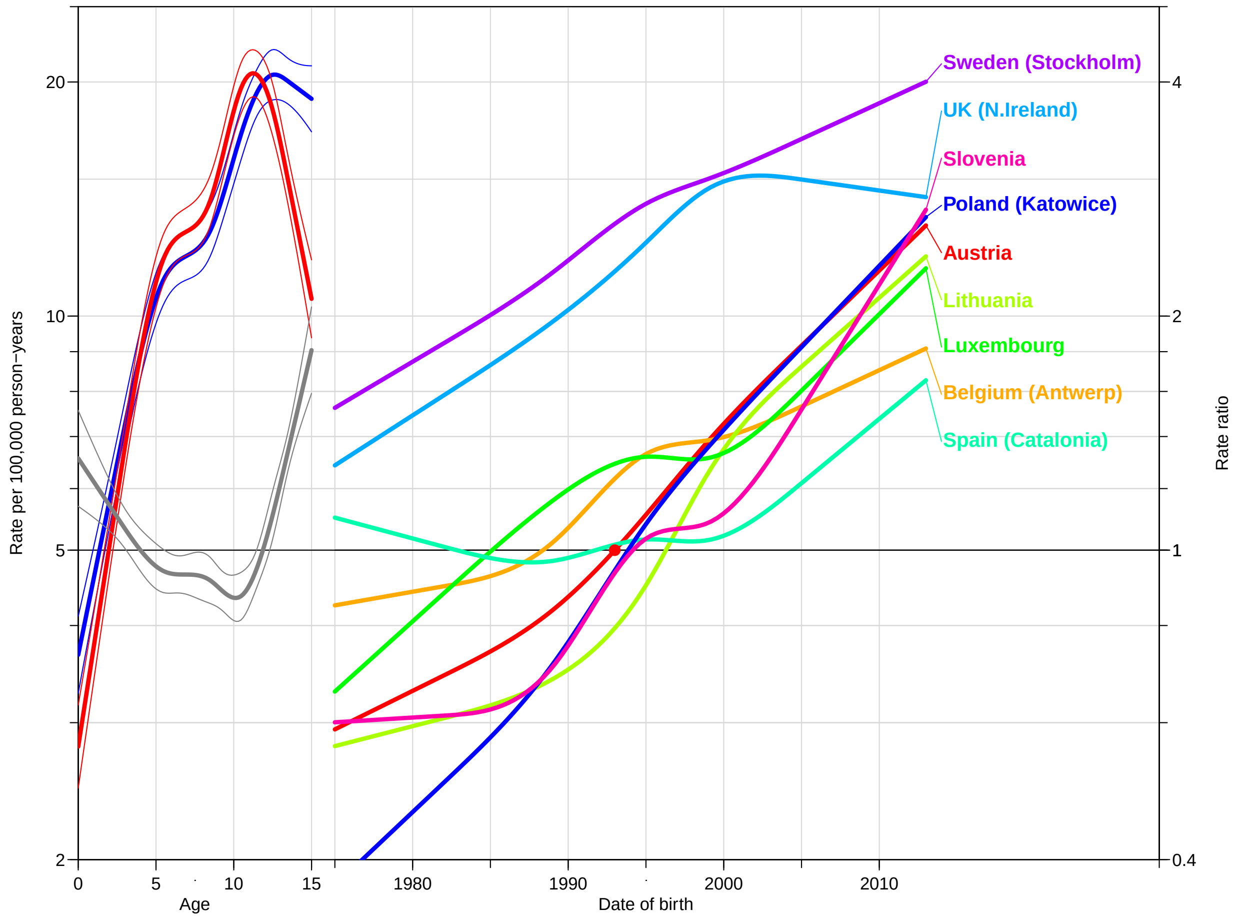

Figure 3.3: *Age-specific cohort (longitudinal) incidence rates of T1D (blue—boys; red—girls) and their ratio (gray), referring to the 1993 birth cohort in Austria. In the right hand side of the panel are the cohort RRs relative to the 1993 birth cohort in Austria. Thin lines indicate 95% confidence limits; confidence limits for the cohort effects are omitted for clarity of exposition.*

3.4 Conclusion

The incidence of T1D is increasing throughput Europe, the average annual rate increase is broadly between 2 and 5%; Catalonia with a slower increase (0.5%/year) and Poland with a higher (7%/year) (figure reffig:APC).

There is no clear pattern in the relationship between the magnitude of incidence rates and change in incidence rates; some centres show a tendency to a flattening of the increase across birth cohorts (Sweden, Poland, Belgium), others an upward increase (Spain, Slovenia) — figure 3.3.

The age-specific rates peak at age 11–12 for girls and 12–13 for boys, at roughly the same level. In the reference cohort (Austria, 1993) this is around 20 per 100,000 PY, but Swedish and Polish rates are more than twice as high for this birth cohort; and later birth cohorts (around 2010) exhibit also twice as high incidence rates — figure 3.3.

We also observed a consistent pattern throughout with higher incidence rates among girls in the range 4–12 years and higher among boys before and after this — figure 3.3.