Demography of Diabetes in Denmark or: How to put real probabilities in your transition matrix and use them

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http://BendixCarstensen.com/DMreg

Demography of diabetes in DK

- How does diabetes spread in the population?

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- Life time risk of DM

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- ...and complications

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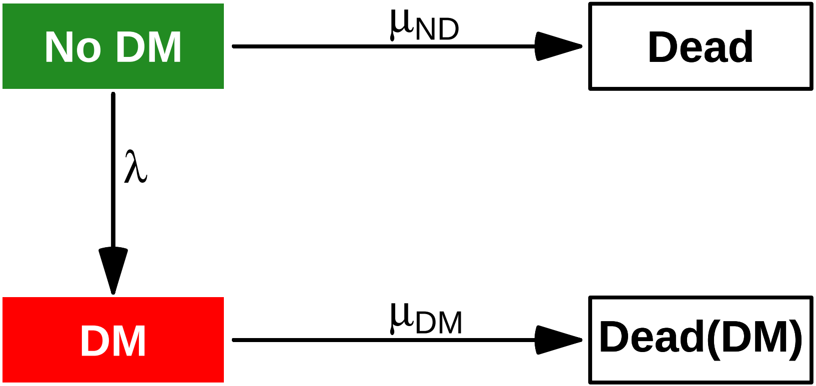
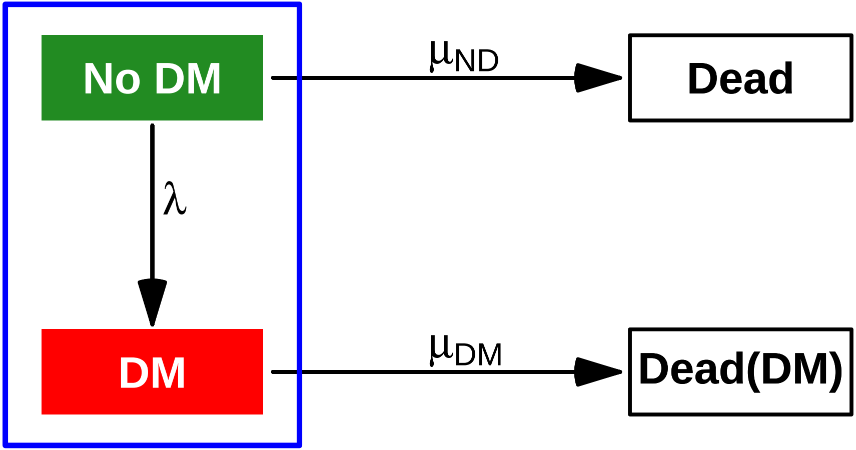
- Incidence rates have been **in**creasing (4% / year)
- Mortality rates have been **de**creasing (2% / year)
- What is the relative contribution of each?

Demographic scenario



Demographic scenario



Cancer among diabetes patients

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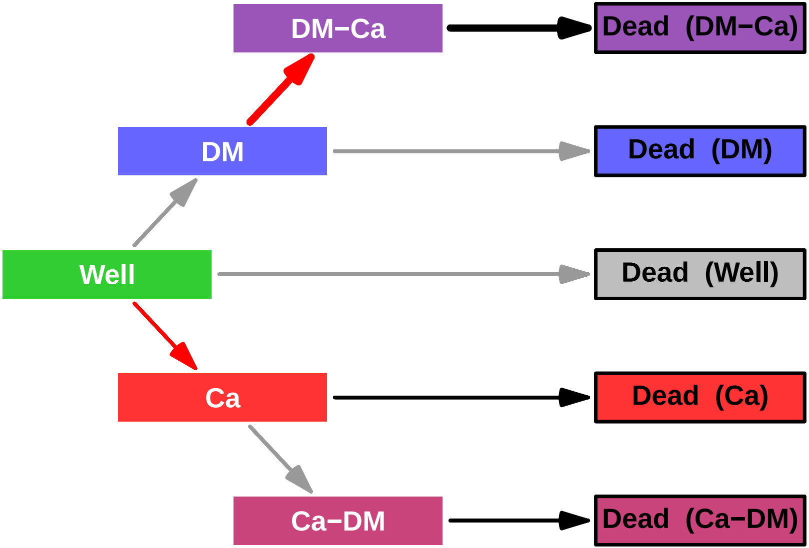
  - Changes in these 1995–2012
  - Impact of the DM vs noDM cancer incidence RR

Demographic scenario



Multistate models

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- **Age**-specific transition rates
- . . . as continuous functions of age
- . . . and possibly other time scales

Prevalence of DM — updating

Transition rates between states as function of a and p:

$$\lambda(a,p), \qquad \mu_{\mathsf{ND}}(a,p), \qquad \mu_{\mathsf{DM}}(a,p)$$

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Transition probabilities for an interval of length ℓ:

$P\left\{\text{No DM at } (a+\ell, p+\ell) \mid \text{No DM at } (a,p)\right\} = P_{\text{ND,ND}}(\ell)$:

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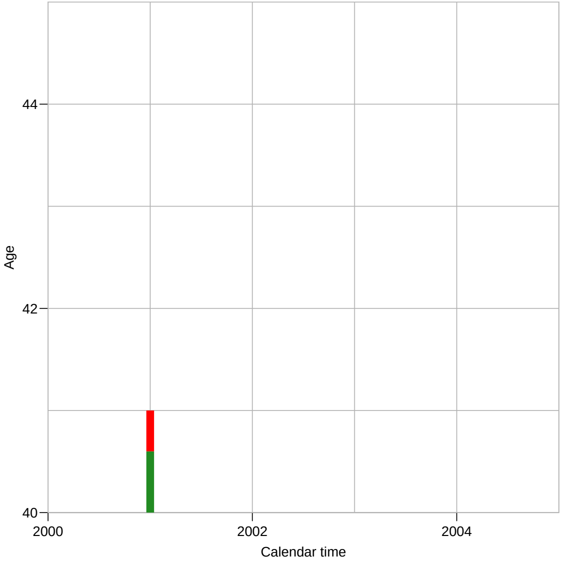
$$P_{\text{ND,ND}}(\ell) = \exp\big(-(\lambda+\mu_{\text{ND}})\ell\big)$$

$$P_{\text{ND,Dead}}(\ell) = \frac{\mu_{\text{ND}}}{\lambda+\mu_{\text{ND}}}\Big(1-\exp\big(-(\lambda+\mu_{\text{ND}})\ell\big)\Big)$$

$$P_{\text{ND,DM}}(\ell) = \frac{\lambda}{\lambda+\mu_{\text{ND}}}\Big(1-\exp\big(-(\lambda+\mu_{\text{ND}})\ell\big)\Big)$$

$$P_{\text{DM,Dead}}(\ell) = 1-\exp(-\mu_{\text{DM}}\ell)$$

Prevalence of DM — updating



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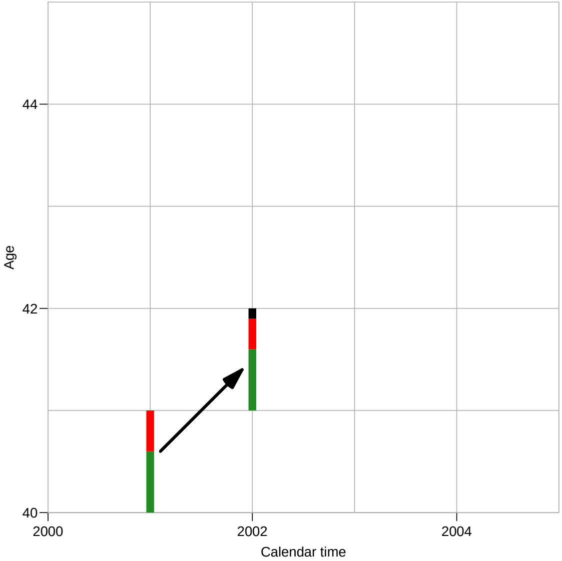

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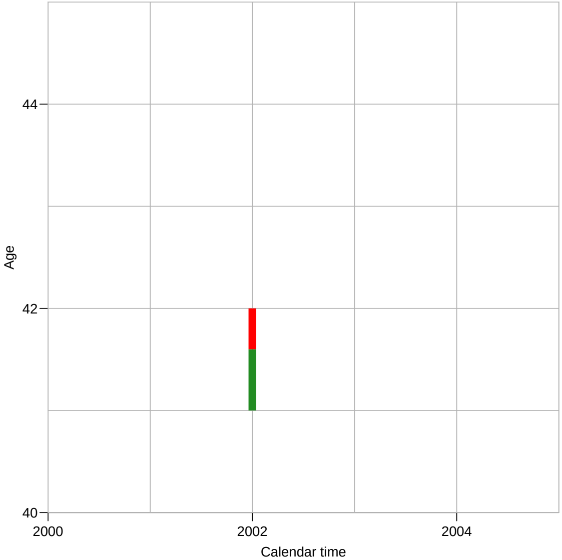

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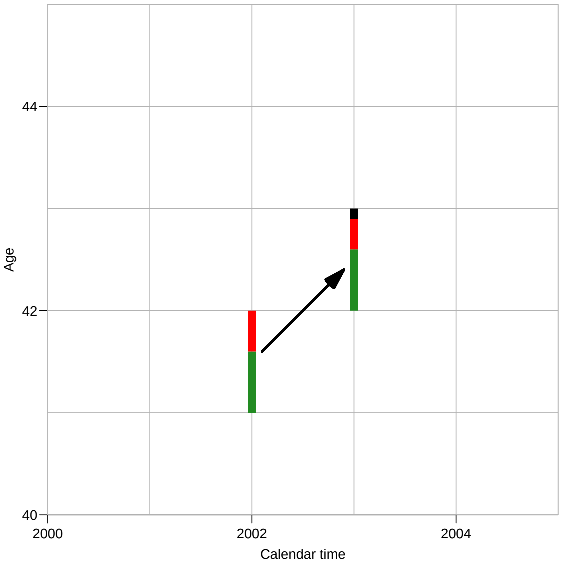

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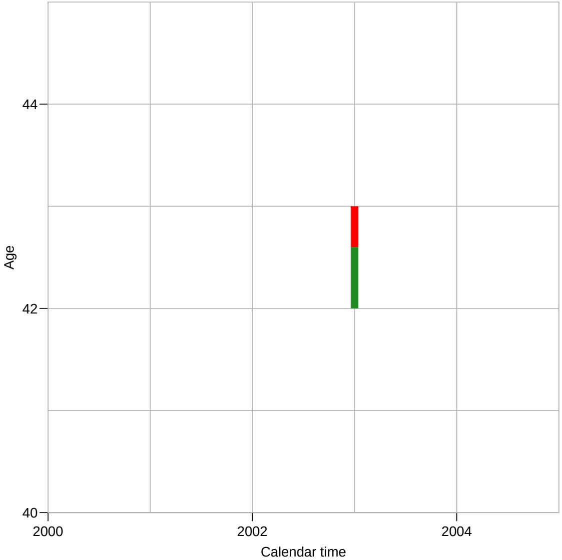

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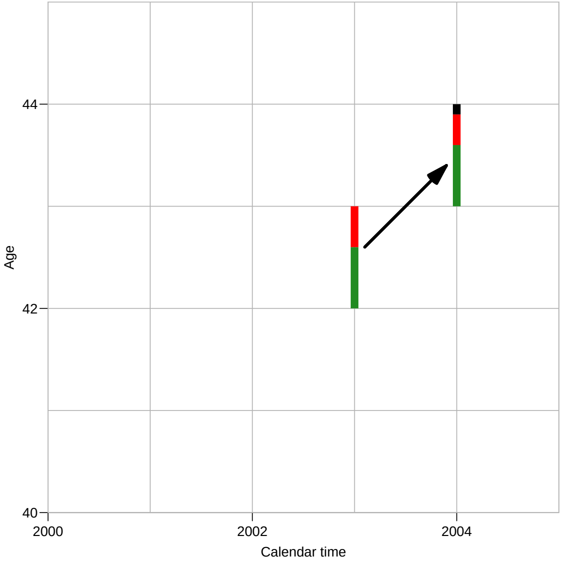

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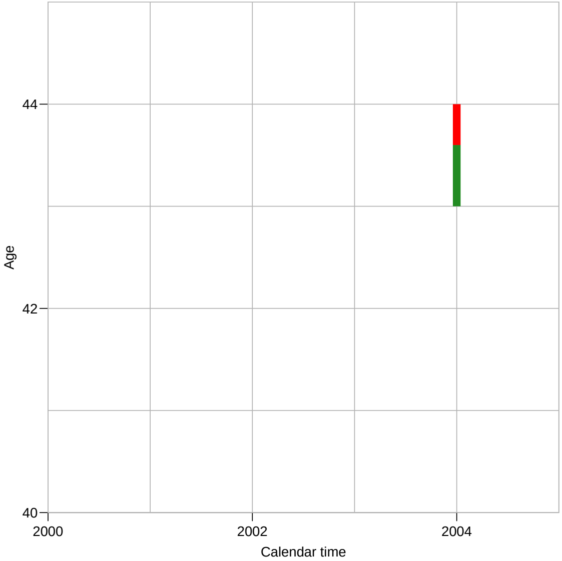

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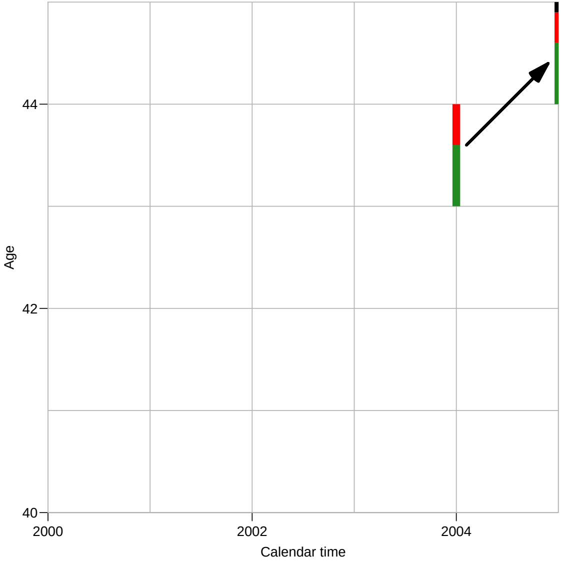

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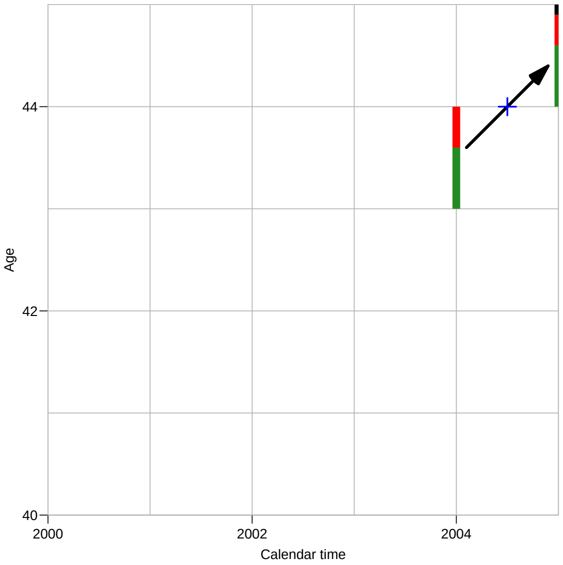

But where do we get the rates from?

Data base (both studies)

- National Diabetes Register, 1995–2011

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Incidence and mortality rates: Data

Example: state **No DM**

- Time at risk:

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- Events (transitions)

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Example: state **No DM**

- Time at risk:
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- Events (transitions)
  - **DM**

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  - **DM**
  - **Dead**

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  - **DM**
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  -

Incidence and mortality rates: Data

Example: state **No DM**

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  - **to** date of **DM** or **Dead** (or end of study)
- Events (transitions)
  - **DM**
  - **Dead**
  -
- Classification of follow-up (time and events) by age (0–100), calendar time (1995-2011) and date of birth (1-year classes) (Lexis triangles)

Incidence and mortality rates: Data

Example: state **No DM**

- Time at risk:
  - **from** date of birth or start of study
  - **to** date of **DM** or **Dead** or **Ca** (or end of study)
- Events (transitions)
  - **DM**
  - **Dead**
  - **Ca**
- Classification of follow-up (time and events) by age (0–100), calendar time (1995-2011) and date of birth (1-year classes) (Lexis triangles)
- Similary for the study with cancer states

Incidence and mortality rates: Models

- Incident cases / deaths from each state

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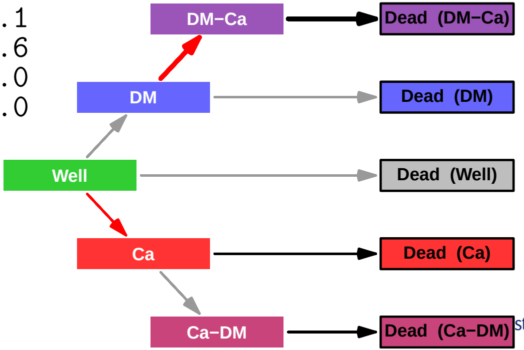
- Incident cases / deaths from each state
- Person-years in each state
- Classifed by age / date / birth in 1-year classes
- Age-Period-Cohort Poisson-model with smooth effects of A, P & C
- Note: Only use the predictions from the models

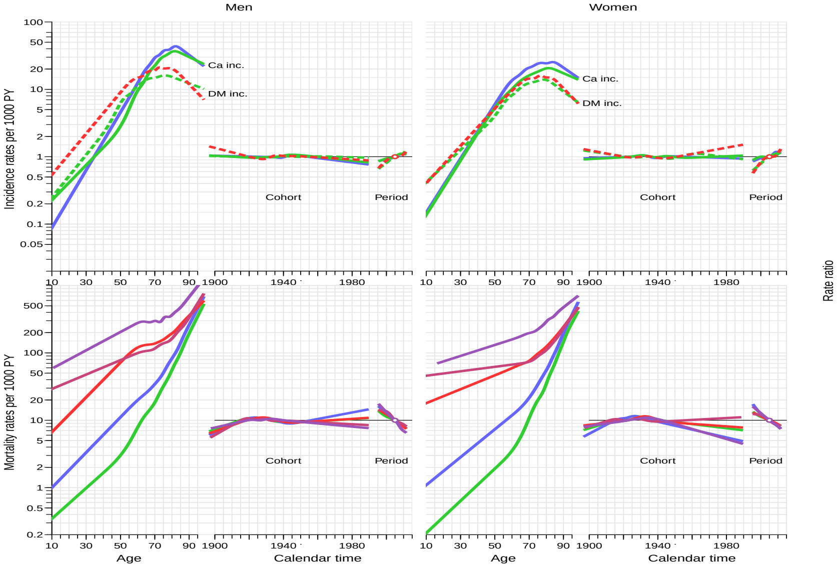
Events and risk time

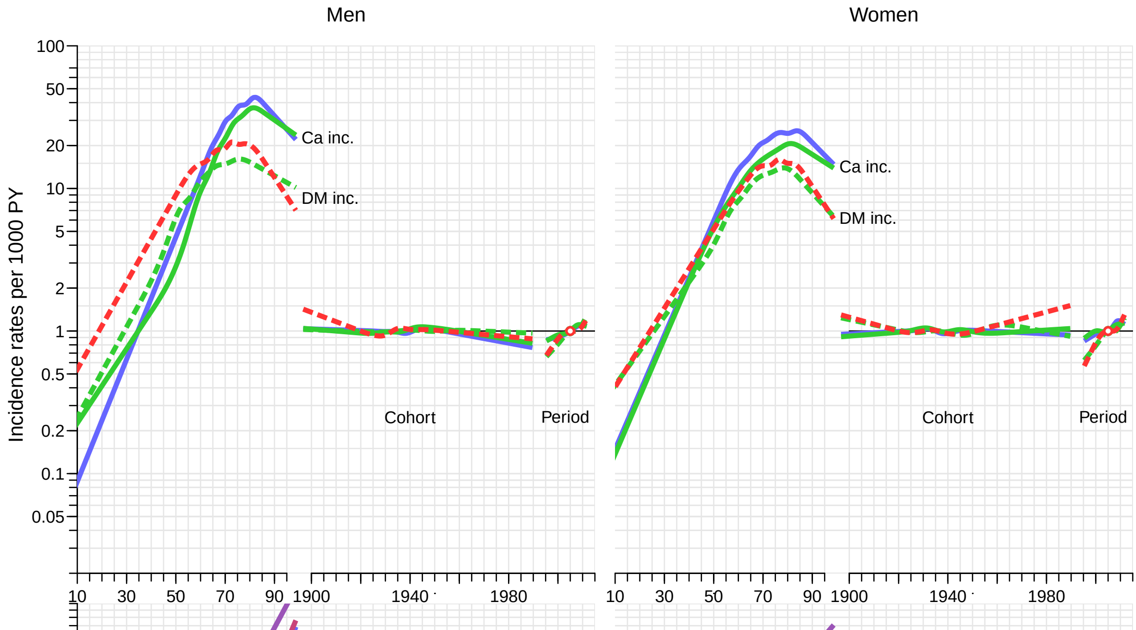
```
> cbind(
+ xtabs( cbind( D.ca, D.dm, D.dd ) ~ state, data=dcd ), round(
+ xtabs( Y/1000 ~ state, data=dcd ), 1 ) )
```

```
        D.ca   D.dm   D.dd       Y
Well  447419 345400 628705 87502.9
DM     35145      0  73480  2031.3
DM-Ca      0      0  24153    89.1
Ca         0  23508 222966  1973.6
Ca-DM      0      0  14703   117.0
Dead       0      0      0     0.0
```

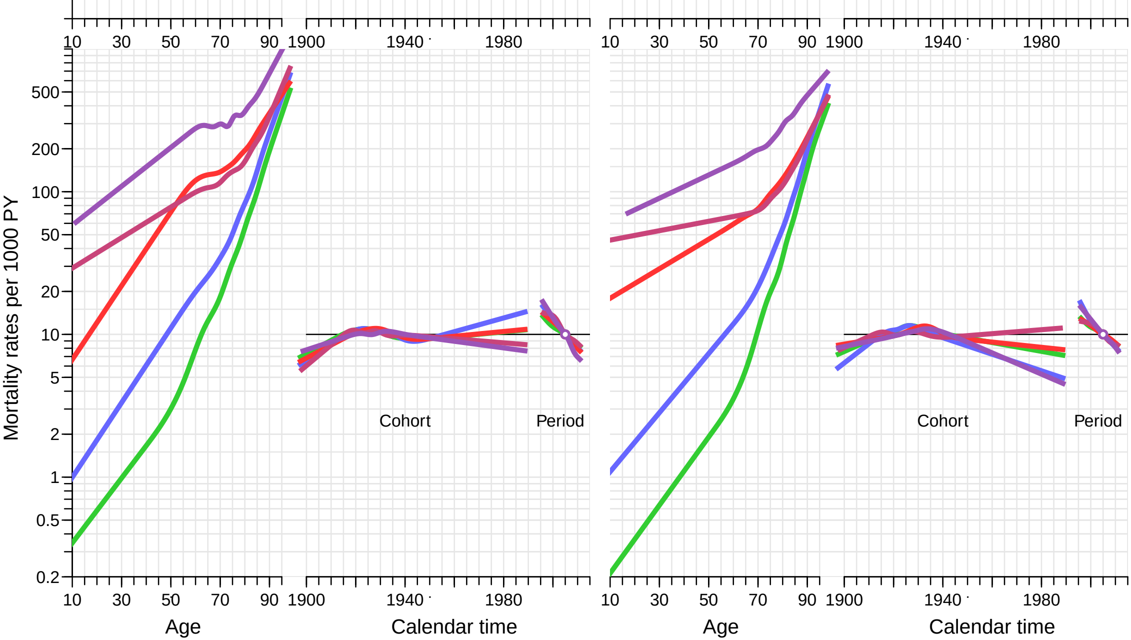


Incidence and mortality rates





Men
Women
Incidence rates per 1000 PY
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
Ca inc.
DM inc.
Cohort
Period
10
30
50
70
90
1900
1940
1980



Mortality rates per 1000 PY
500
200
100
50
20
10
5
2
1
0.5
0.2
10
30
50
70
90
1900
1940
1980
Cohort
Period
Age
Calendar time

Transition rates

```
> int <- 1/12
> a.pt <- seq(int,102,int) - int/2

> system.time(
+ for( yy in dimnames(PR)[[4]] )
+ {
+ nd <- data.frame( A=a.pt, P=as.numeric(yy), Y=int )
+
+ PR["Well" ,"DM"    ,,yy,"M"] <- ci.pred( M.w2dm$model , newdata=nd )[,1]
+ PR["Well" ,"Ca"    ,,yy,"M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" ,"D-W"   ,,yy,"M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM"   ,"DM-Ca",,yy,"M"] <- ci.pred( M.dm2ca$model, newdata=nd )[,1]
+ PR["DM"   ,"D-DM" ,,yy,"M"] <- ci.pred( M.dm2dd$model, newdata=nd )[,1]
+ PR["Ca"   ,"Ca-DM",,yy,"M"] <- ci.pred( M.ca2dm$model, newdata=nd )[,1]
+ PR["Ca"   ,"D-Ca" ,,yy,"M"] <- ci.pred( M.ca2dd$model, newdata=nd )[,1]
+ PR["DM-Ca","D-DC" ,,yy,"M"] <- ci.pred( M.dc2dd$model, newdata=nd )[,1]
+ PR["Ca-DM","D-CD" ,,yy,"M"] <- ci.pred( M.cd2dd$model, newdata=nd )[,1]
```

Transition matrices

Use the rates to generate the transition **probabilities**:

```
> print.table( round( addmargins( ci2pr( PR[,,800,1,1] )*10^4,
+                                 margin=2 ) ),
+              zero.print="." )

        to
from      Well    DM DM-Ca    Ca Ca-DM   D-W  D-DM  D-Ca  D-DC  D-CD   Sum
  Well    9963     8     .    12     .    17     .     .     .     . 10000
  DM         .  9943    16     .     .     .    40     .     .     . 10000
  DM-Ca      .     .  9578     .     .     .     .     .   422     . 10000
  Ca         .     .     .  9815     9     .     .   175     .     . 10000
  Ca-DM      .     .     .     .  9865     .     .     .     .   135 10000
  D-W        .     .     .     .     . 10000     .     .     .     . 10000
  D-DM       .     .     .     .     .     . 10000     .     .     . 10000
  D-Ca       .     .     .     .     .     .     . 10000     .     . 10000
  D-DC       .     .     .     .     .     .     .     . 10000     . 10000
  D-CD       .     .     .     .     .     .     .     .     . 10000 10000
```

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State occupancy probabilites

```
> PV <- PR[1,,,,]*0

> for( sc in dimnames(PRp)[["per"]] )
+ for( sx in dimnames(PRp)[["sex"]] )
+    {
+    # Initialize to all well at age 0:
+    PV[,1,sc,sx] <- c(1,rep(0,9))
+    # Compute distribution at endpoint of each age-interval
+    for( ag in 1:dim(PRp)[3] ) PV[,ag,sc,sx] <- PV[ ,max(ag-1,1),sc,sx] %*%
+                                                 PRp[,,    ag     ,sc,sx]
+    }
```

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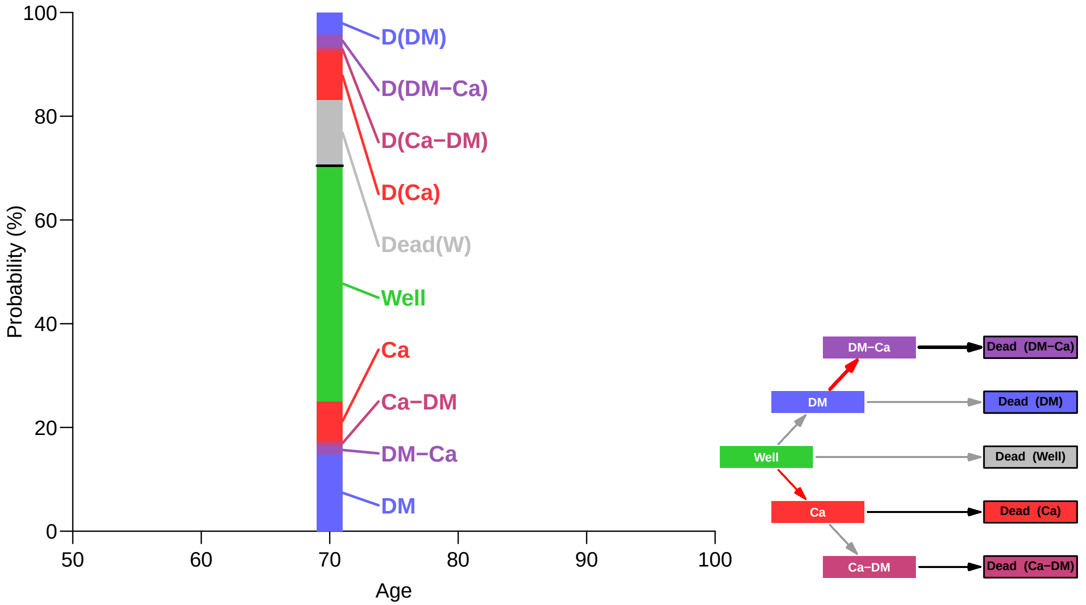
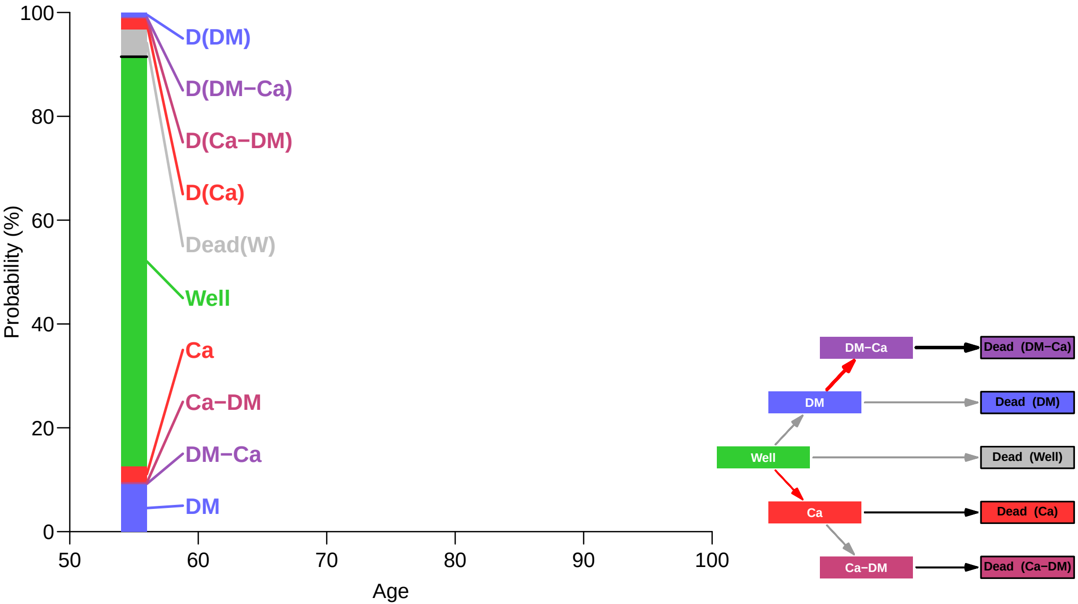
- Compute fraction in each state at each age
- Different scenarios using
  estimated (cross-sectional) rates
  at 1 January 1995, 1996, . . . , 2012


100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)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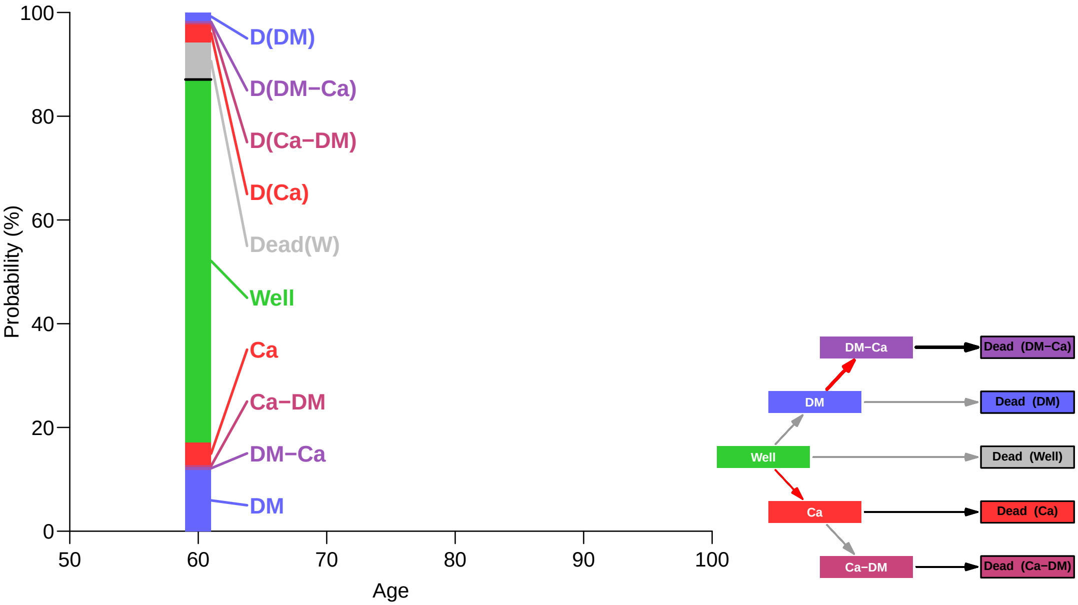
Dead (Well)
Dead (Ca)
Dead (Ca−DM)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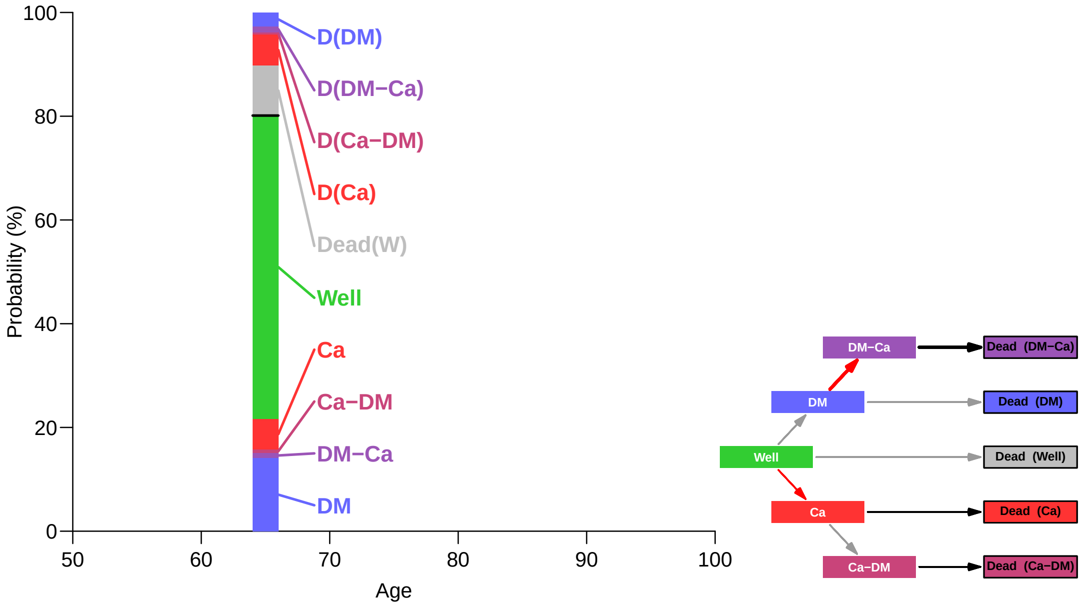

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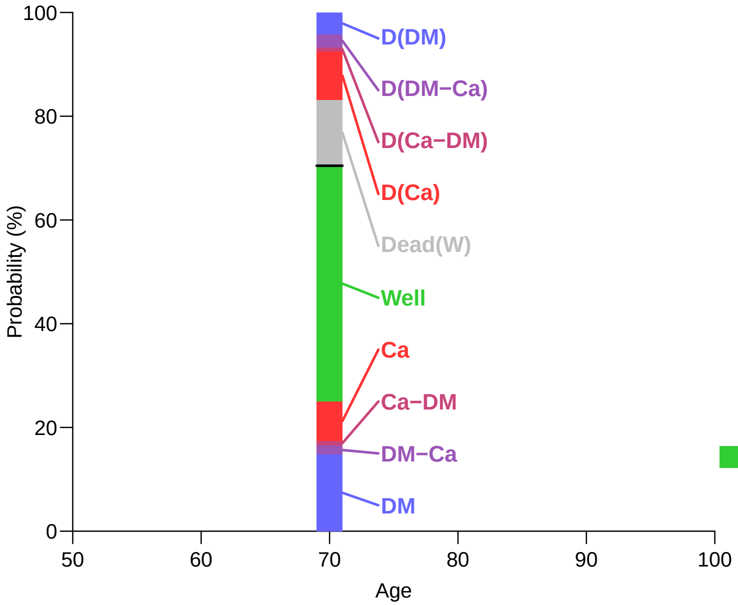
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DM−Ca
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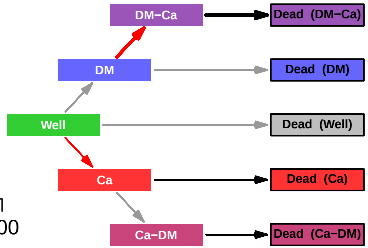
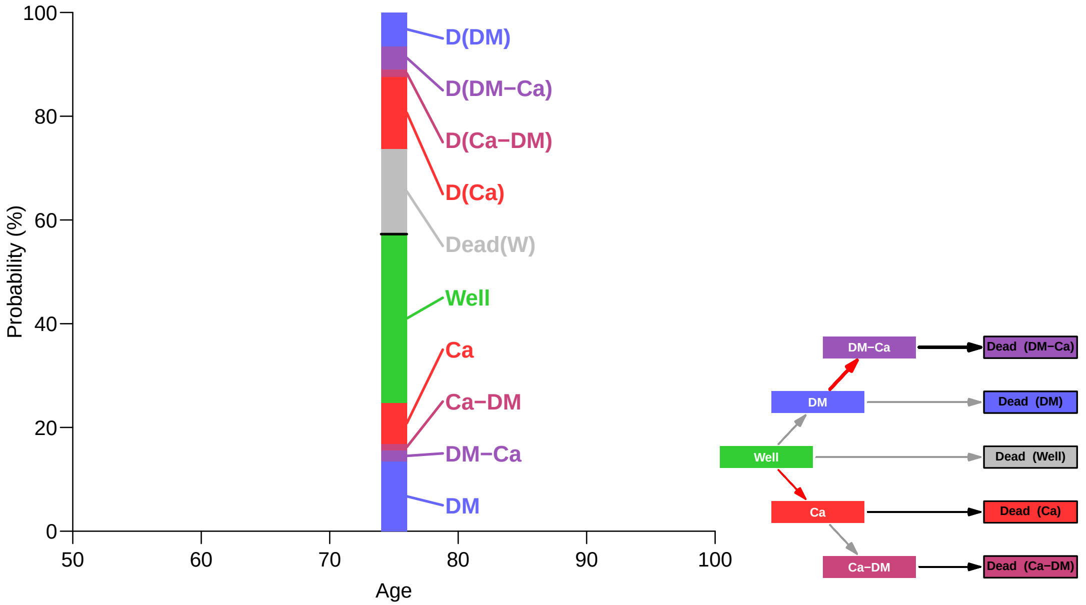

DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)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Ca−DM
DM−Ca
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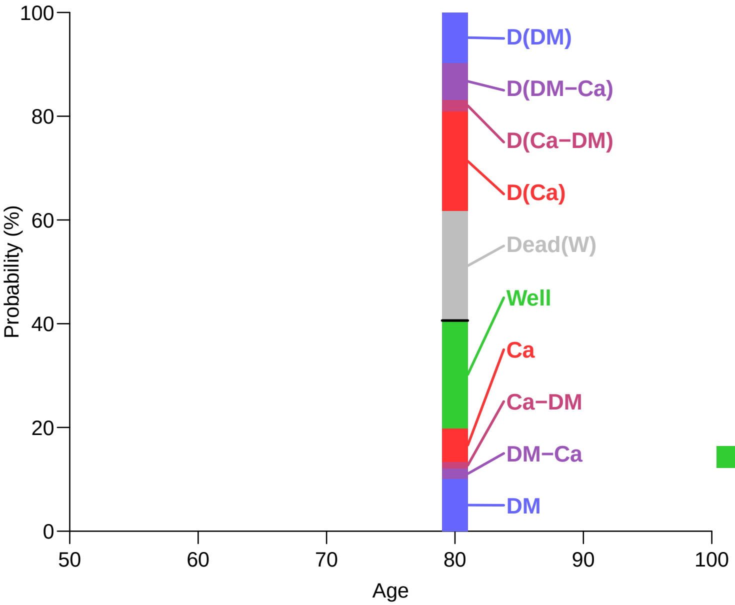
Well
Ca
Ca−DM
Dead (DM−Ca)
Dead (DM)
Dead (Well)
Dead (Ca)
Dead (Ca−DM)



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Ca
Ca−DM
DM−Ca
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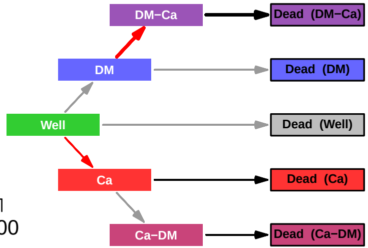
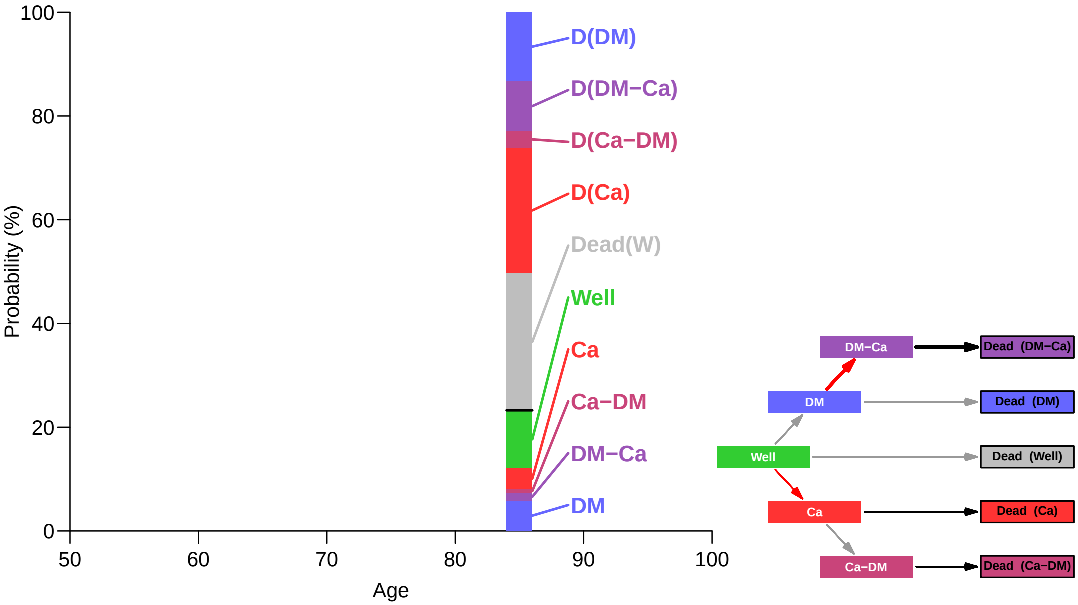
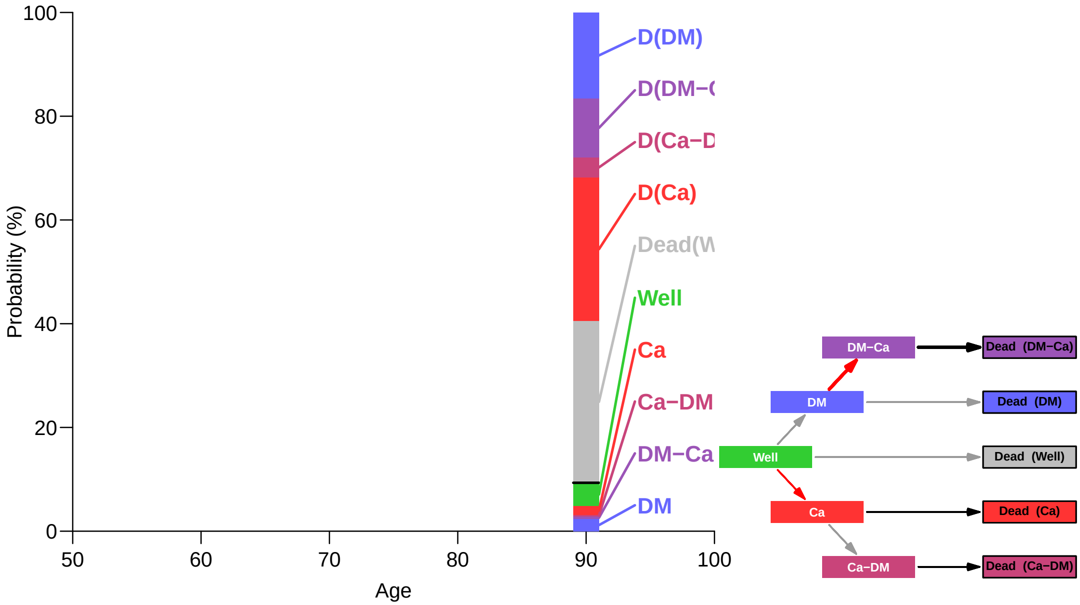


DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

steno



100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)



100
80
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Probability (%)
50
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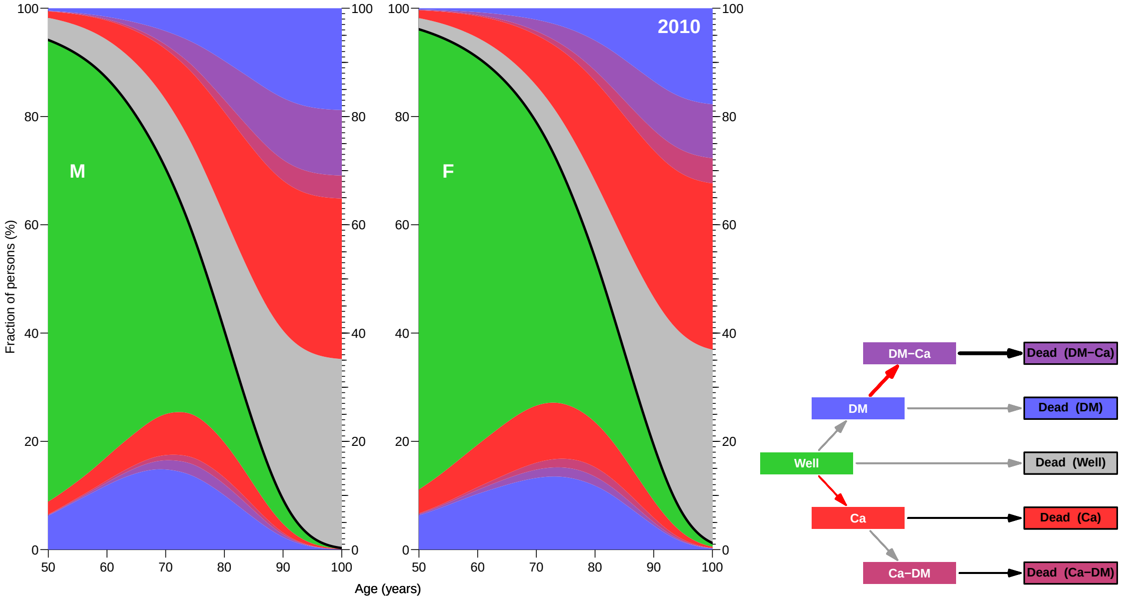
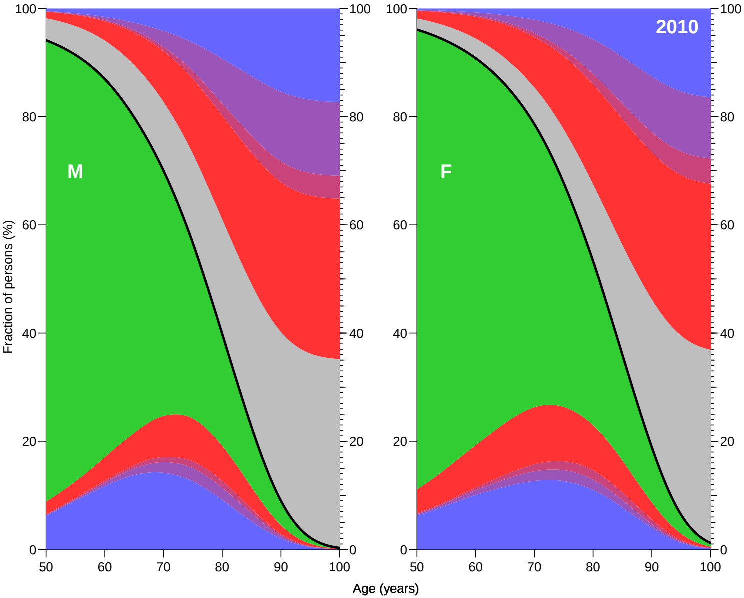
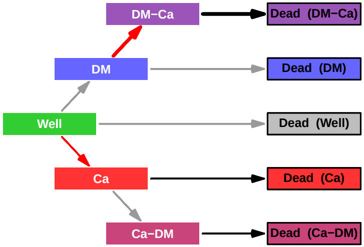
90
100
Age
D(DM)
D(DM−(
D(Ca−D
D(Ca)
Dead(W
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

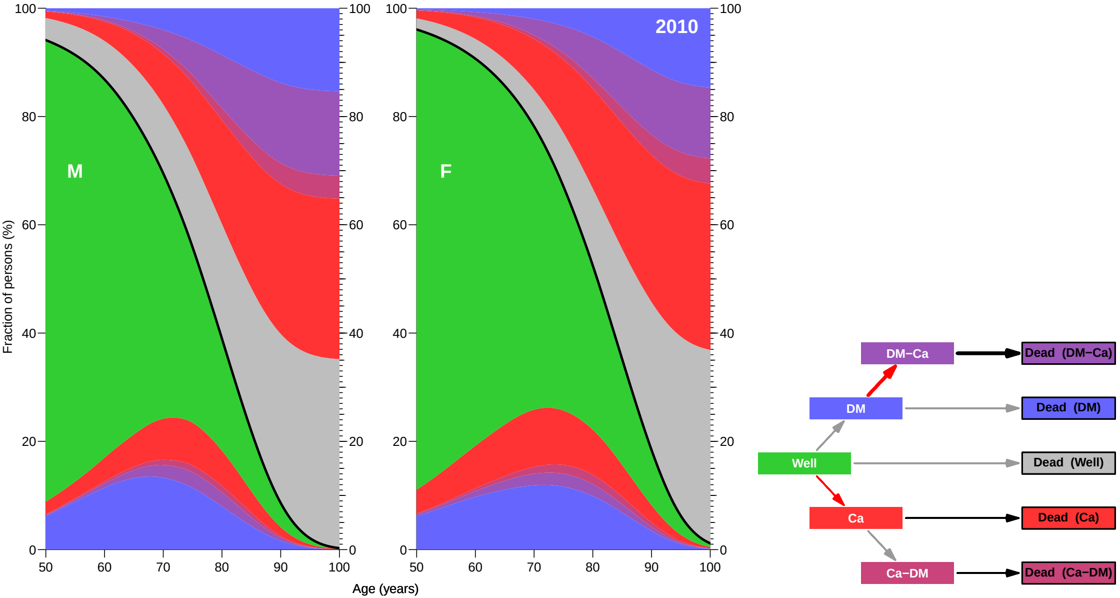
steno


2010
M
F
Fraction of persons (%)
Age (years)
100
80
60
40
20
0
50
60
70
80
90
100
DM−Ca
DM
Well
Ca
Ca−DM
Dead (DM−Ca)
Dead (DM)
Dead (Well)
Dead (Ca)
Dead (Ca−DM)





Cancer rates among DM-ptt inflated 20%



Cancer rates among DM-ptt inflated 50%

Transition rates

```
> int <- 1/12
> a.pt <- seq(int,102,int) - int/2

> system.time(
+ for( yy in dimnames(PR)[[4]] )
+ {
+ nd <- data.frame( A=a.pt, P=as.numeric(yy), Y=int )
+
+ PR["Well" ,"DM"    ,,yy,"M"] <- ci.pred( M.w2dm$model , newdata=nd )[,1]
+ PR["Well" ,"Ca"    ,,yy,"M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" ,"D-W"   ,,yy,"M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM"   ,"DM-Ca",,yy,"M"] <- ci.pred( M.dm2ca$model, newdata=nd )[,1]
+ PR["DM"   ,"D-DM" ,,yy,"M"] <- ci.pred( M.dm2dd$model, newdata=nd )[,1]
+ PR["Ca"   ,"Ca-DM",,yy,"M"] <- ci.pred( M.ca2dm$model, newdata=nd )[,1]
+ PR["Ca"   ,"D-Ca" ,,yy,"M"] <- ci.pred( M.ca2dd$model, newdata=nd )[,1]
+ PR["DM-Ca","D-DC" ,,yy,"M"] <- ci.pred( M.dc2dd$model, newdata=nd )[,1]
+ PR["Ca-DM","D-CD" ,,yy,"M"] <- ci.pred( M.cd2dd$model, newdata=nd )[,1]
```

Transition rates

```
> int <- 1/12
> a.pt <- seq(int,102,int) - int/2

> system.time(
+ for( yy in dimnames(PR)[[4]] )
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+
+ PR["Well" ,"DM"    ,,yy,"M"] <- ci.pred( M.w2dm$model , newdata=nd )[,1]
+ PR["Well" ,"Ca"    ,,yy,"M"] <- ci.pred( M.w2ca$model , newdata=nd )[,1]
+ PR["Well" ,"D-W"   ,,yy,"M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM"   ,"DM-Ca",,yy,"M"] <- ci.pred( M.dm2ca$model, newdata=nd )[,1] * 1.5
+ PR["DM"   ,"D-DM" ,,yy,"M"] <- ci.pred( M.dm2dd$model, newdata=nd )[,1]
+ PR["Ca"   ,"Ca-DM",,yy,"M"] <- ci.pred( M.ca2dm$model, newdata=nd )[,1]
+ PR["Ca"   ,"D-Ca" ,,yy,"M"] <- ci.pred( M.ca2dd$model, newdata=nd )[,1]
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```
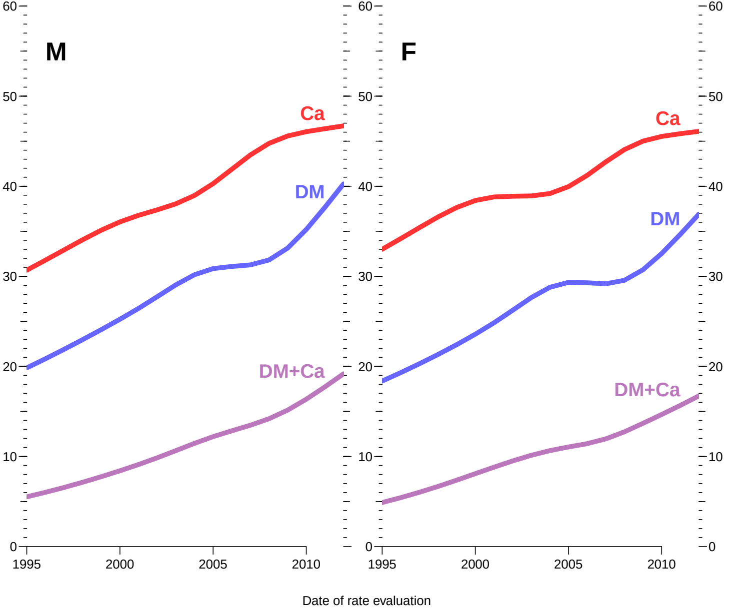
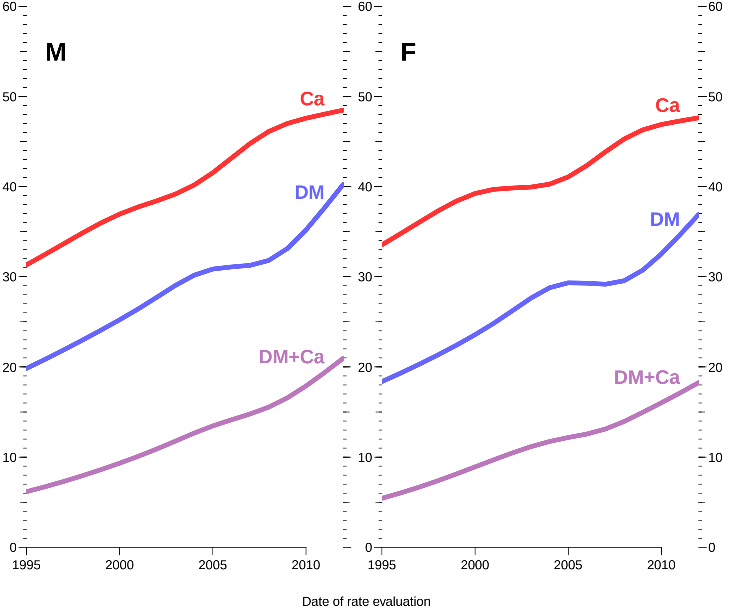

Lifetime risks



Lifetime risks - RR inflated 20%



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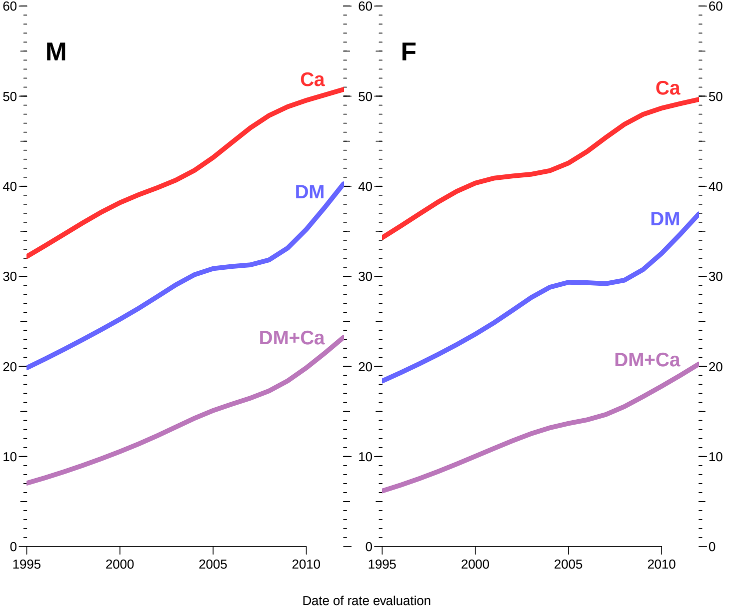
Lifetime risks - RR inflated 50%



Demographic changes in DM & Cancer 1995–2012

- Changing **rates** in period 1995–2012:

Diabetes incidence	**4%**/year
Cancer incidence	**2%**/year
Mortality	**–4%**/year

Demographic changes in DM & Cancer 1995–2012

- Changing **rates** in period 1995–2012:

Diabetes incidence	**4%**/year
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- Changing **life-time risk** 1995–2012:

		+20% Ca | DM	+50% Ca | DM
Diabetes	**19%** to **38%**	19% to 38%	19% to 38%
Cancer	**32%** to **46%**	33% to 48%	34% to 50%
DM + Ca	**6%** to **18%**	6% to 20%	7% to 22%

Conclusion — DM & Cancer

- Increasing incidence rates of DM and Cancer
  is what matters for (changes in) lifetime risk. . .

Conclusion — DM & Cancer

- Increasing incidence rates of DM and Cancer is what matters for (changes in) lifetime risk...
- **not** the (slightly) elevated risk of Cancer among DM paitents.

Prevalence of DM — updating

- Start with age-specific prevalences 1995

Prevalence of DM — updating

- Start with age-specific prevalences 1995
- Use fitted models for incidence and mortality - as function of ge and calendar time — to predict prevalences 2012

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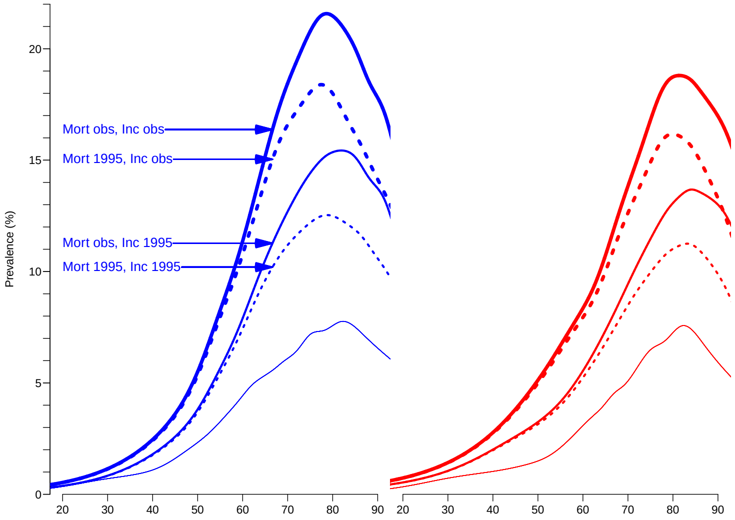
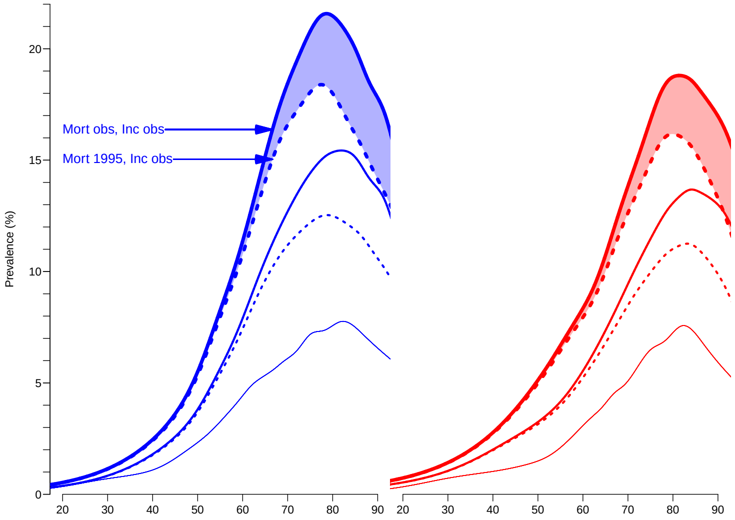
Prevalence of DM — updating

- Start with age-specific prevalences 1995
- Use fitted models for incidence and mortality - as function of ge and calendar time — to predict prevalences 2012
- Assume:
  - Incidence rates had remained at 1995 level
  - Mortality rates had remained at 1995 level
  - Both had remained at 1995 level
- Differences between predicted prevalences gives the contribution from incidence rate changes, mortality rate changes and 1995 disequilibrium.

Prevalence of DM — updating



Prevalence of DM — updating



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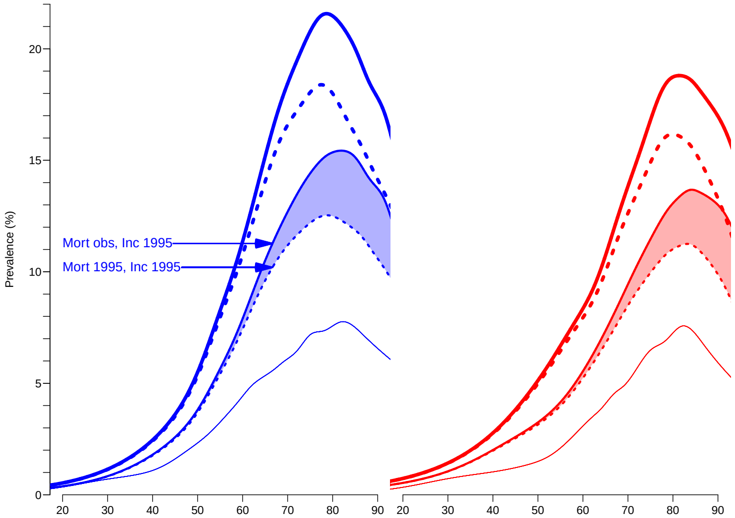
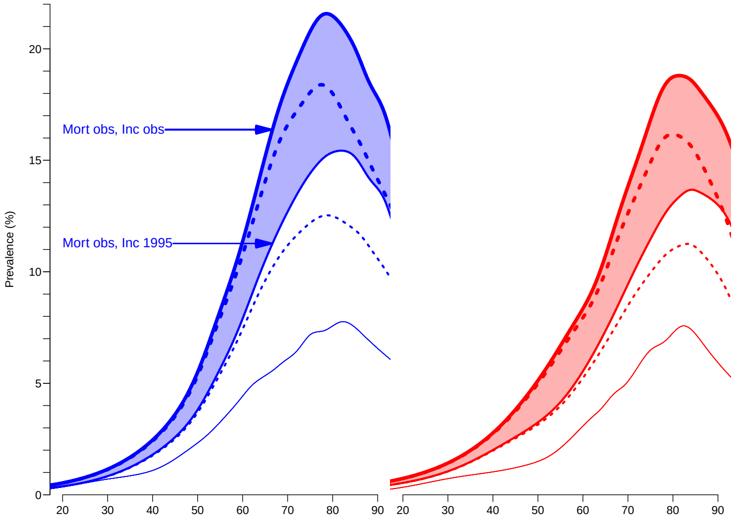
Prevalence of DM — updating



Prevalence of DM — updating



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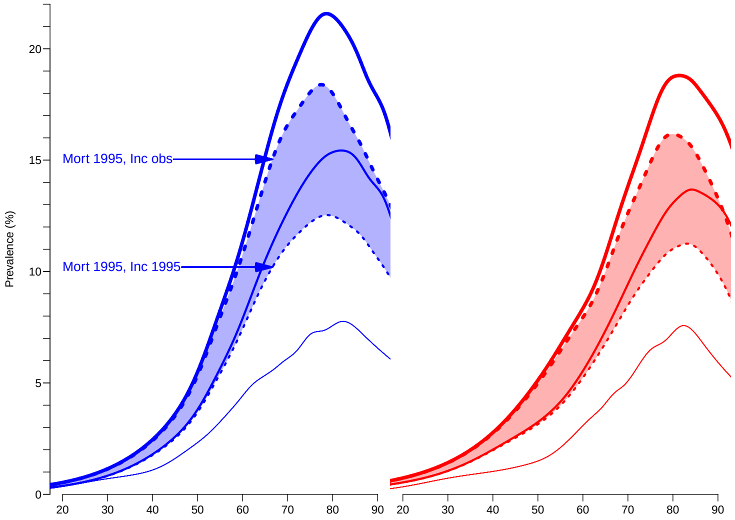
Prevalence of DM — updating



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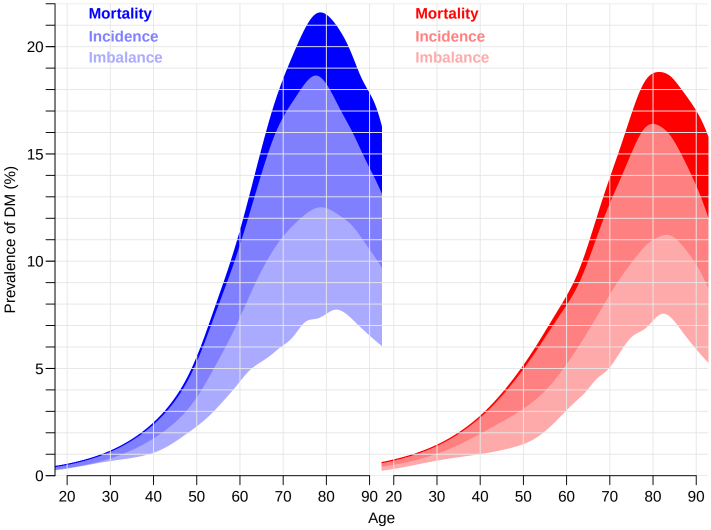
Componets of prevalent cases



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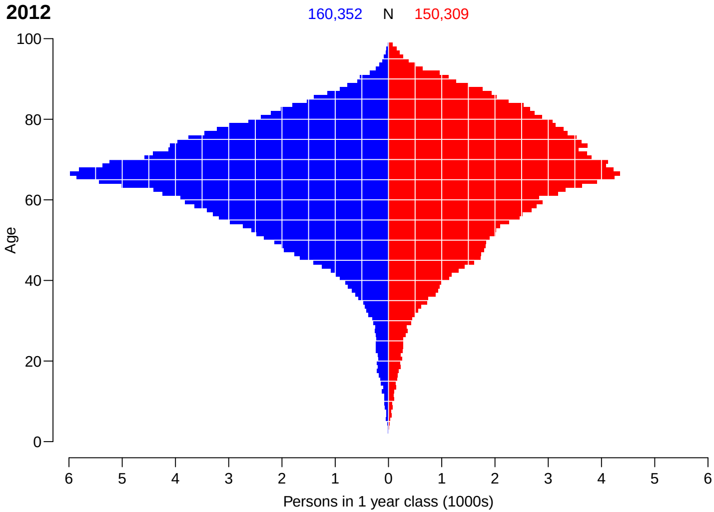
Prevalent cases



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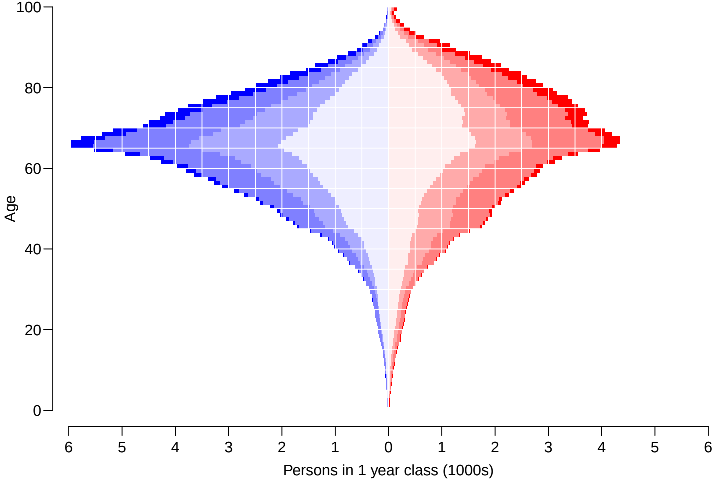
Components of prevalent cases

2012	Mort	Inc	Imbal	Org	All		All	Org	Imbal	Inc	Mort
	12,273	47,282	40,568	61,510	161,632	N	152,001	55,939	38,232	46,486	11,344
	7.6	29.3	25.1	38.1		%		36.8	25.2	30.6	7.5



Thanks for your attention