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

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16 June 2015

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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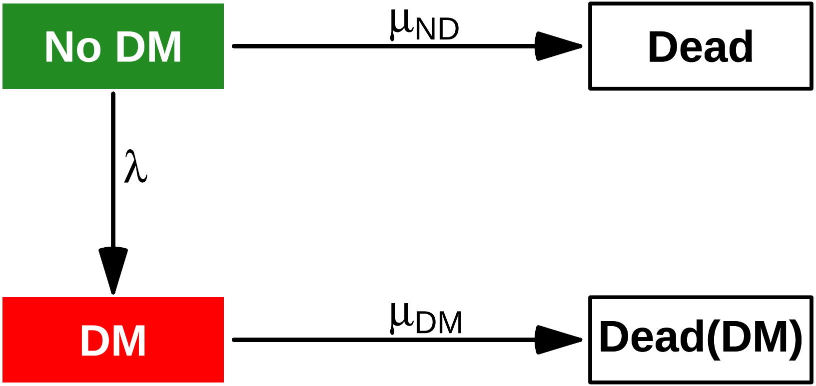
- What is the relative contribution of each?

Demographic scenario



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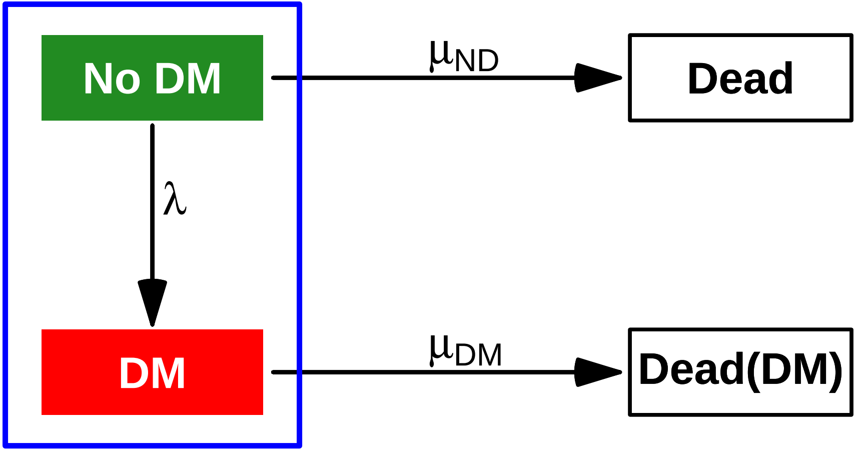

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  - Impact of the DM vs noDM cancer incidence RR

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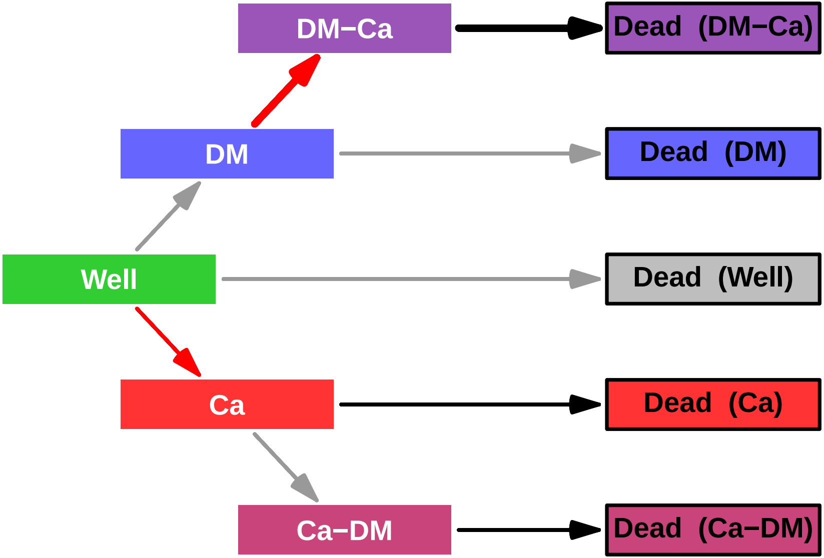

Multistate models

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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:

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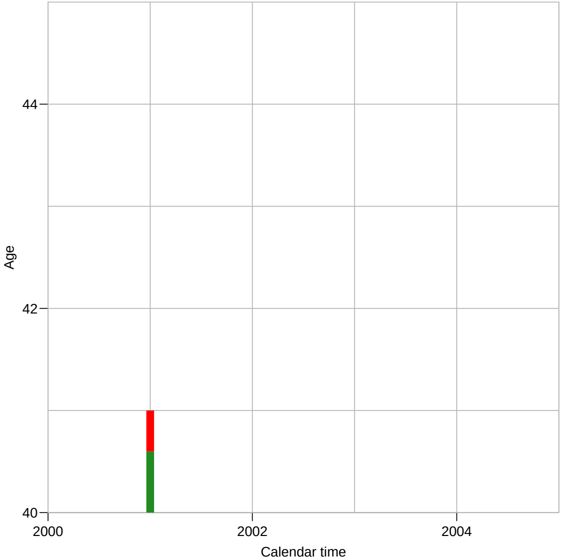

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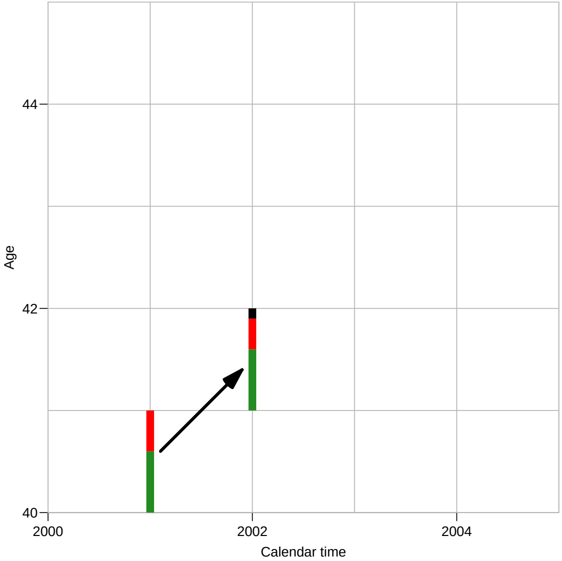

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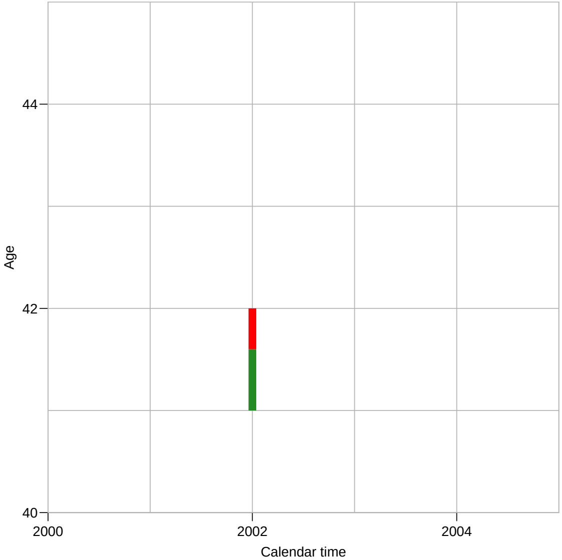

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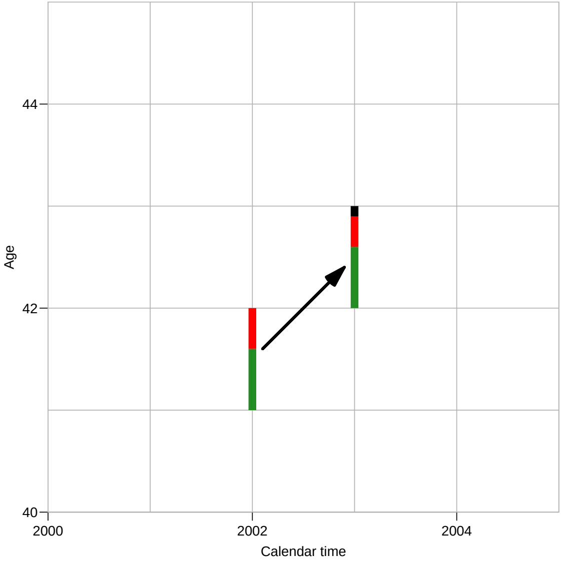

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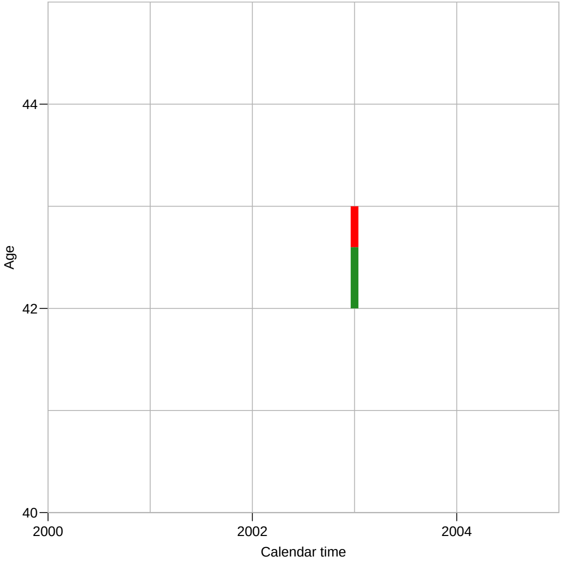

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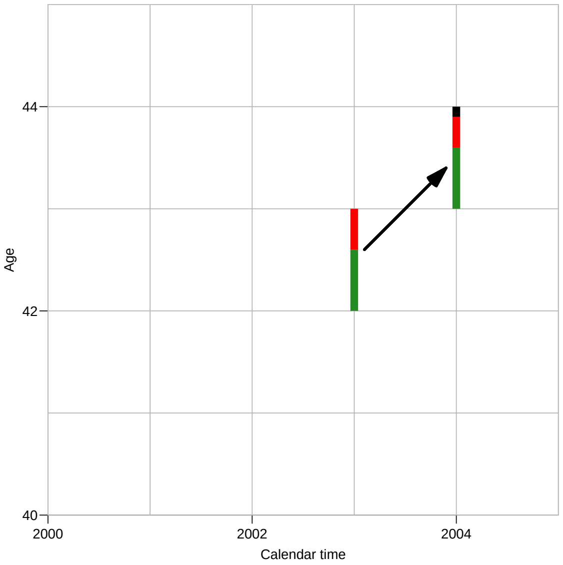

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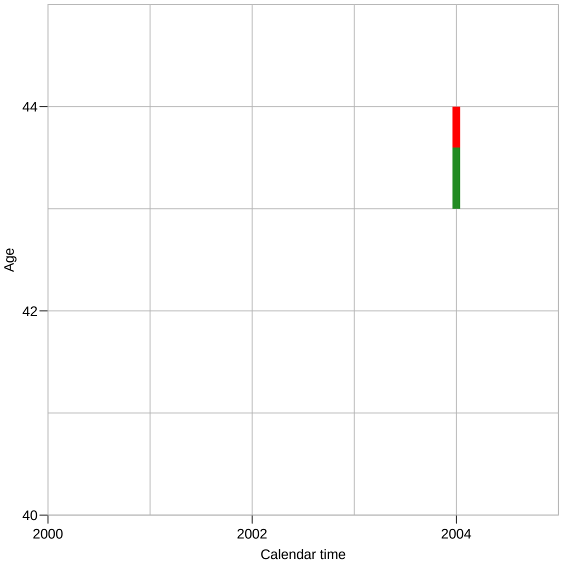

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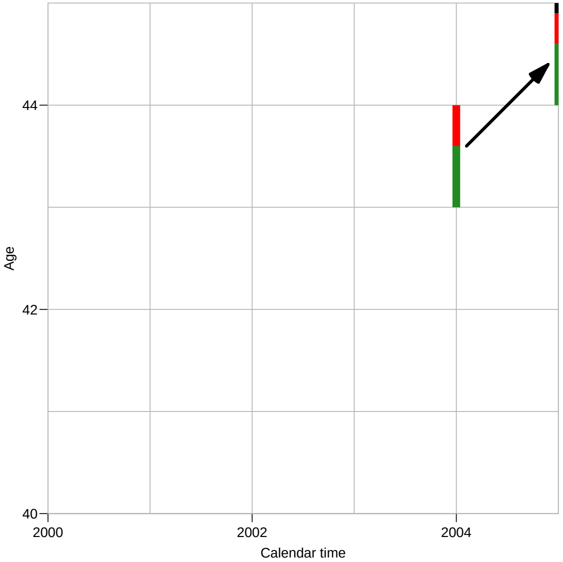

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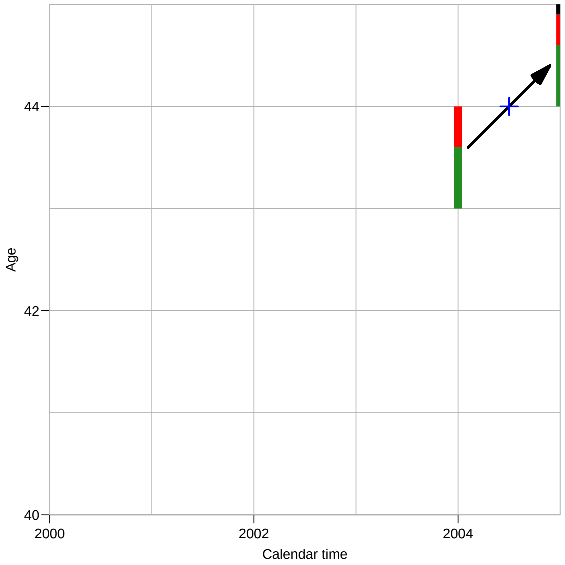

Where do we get the rates from?

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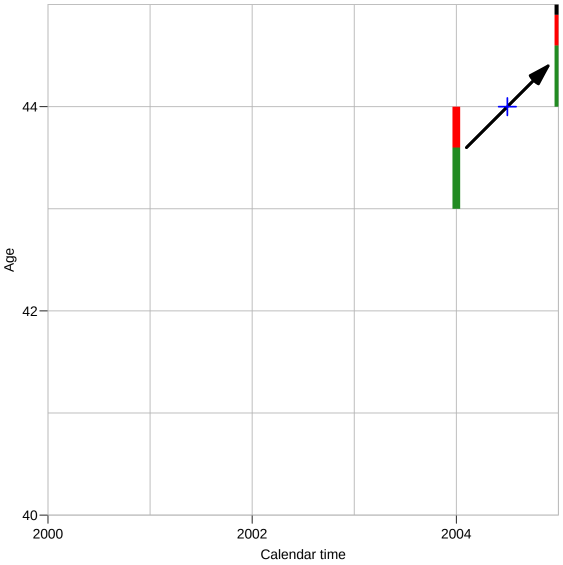

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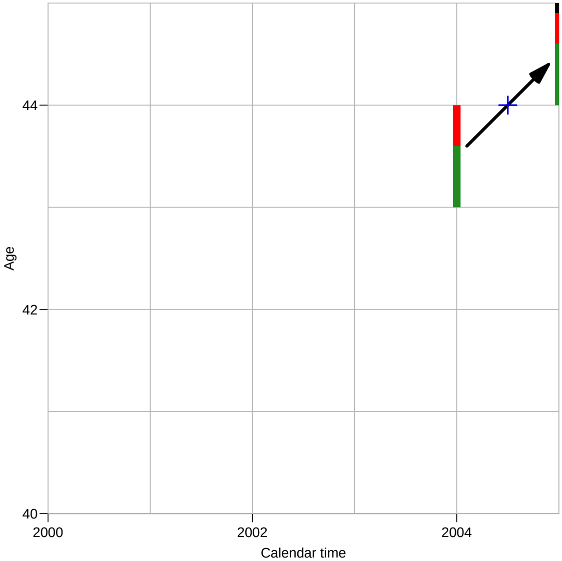

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Why are the formulae wrong?

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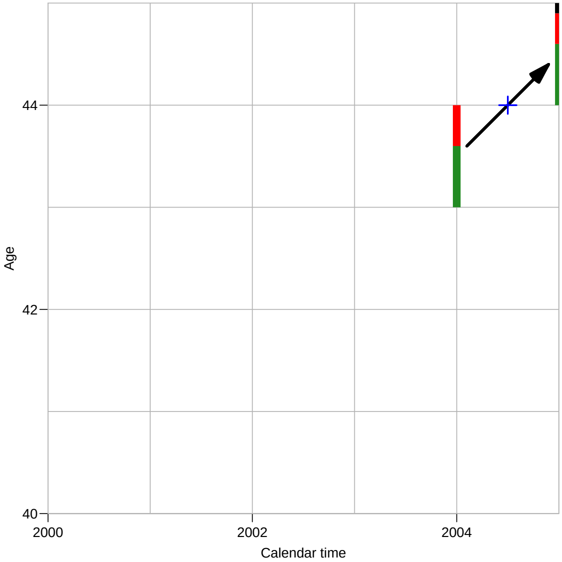

Why are the formulae wrong?
and how do we rectify that?

Transition intensities revisited — assumptions

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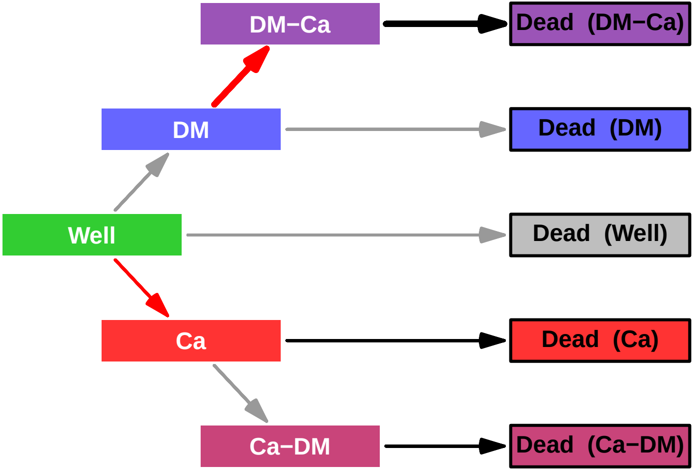
- $\Rightarrow$ 1-year intervals usually too long
- $\Rightarrow$ rates only assumed constant in intervals of length ℓ

Accuracy of multistate calculations

Transition probabilities in DM-Ca study, from age $70 \to 75$, based on 1, 3 and 6-month intervals respectively



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1: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	7306	600	33	813	42	722	67	388	20	10	10001
DM	.	6867	653	.	.	.	1783	.	697	.	10000
DM-Ca	.	.	2146	.	.	.	.	.	7854	.	10000
Ca	.	.	.	4182	463	.	.	5174	.	181	10000
Ca-DM	.	.	.	.	5242	.	.	.	.	4758	10000

3: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	7306	604	33	825	41	722	65	378	18	9	10001
DM	.	6867	670	.	.	.	1783	.	680	.	10000
DM-Ca	.	.	2146	.	.	.	.	.	7854	.	10000
Ca	.	.	.	4182	468	.	.	5174	.	176	10000
Ca-DM	.	.	.	.	5242	.	.	.	.	4758	10000

6: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	7313	610	33	841	40	718	62	360	16	8	10001
DM	.	6874	695	.	.	.	1777	.	653	.	9999
DM-Ca	.	.	2149	.	.	.	.	.	7851	.	10000
Ca	.	.	.	4187	477	.	.	5167	.	169	10000
Ca-DM	.	.	.	.	5248	.	.	.	.	4752	10000

Accuracy of multistate calculations

Differences in transition probabilities, from age $70 \to 75$: based on 3, 6 and 12-month vs. 1 month intervals:

3 vs. 1: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	.	4	.	12	.	.	-2	-11	-2	-1	.
DM	.	.	17	.	.	.	.	.	-17	.	.
DM-Ca	.	.	.	.	.	.	.	.	.	.	.
Ca	.	.	.	.	5	.	.	.	.	-5	.
Ca-DM	.	.	.	.	.	.	.	.	.	.	.

6 vs. 1: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	7	10	.	29	-1	-4	-6	-28	-4	-2	1
DM	.	7	42	.	.	.	-6	.	-44	.	-1
DM-Ca	.	.	3	.	.	.	.	.	-3	.	.
Ca	.	.	.	5	14	.	.	-6	.	-13	.
Ca-DM	.	.	.	.	6	.	.	.	.	-6	.

12 vs. 1: to

from	Well	DM	DM-Ca	Ca	Ca-DM	D-W	D-DM	D-Ca	D-DC	D-CD	Sum
Well	.	21	.	68	-3	-1	-12	-60	-9	-4	.
DM	.	1	98	.	.	.	-1	.	-97	.	1
DM-Ca	.	.	1	.	.	.	.	.	-1	.	.
Ca	.	.	.	.	29	.	.	-1	.	-29	-1
Ca-DM	.	.	.	.	1	.	.	.	.	-1	.

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- consider whether you should use a model with rates varying **continuously** (smoothly) with age, date, ...
- it **will** actually make life easier

Data base (both studies)

- National Diabetes Register, 1995–2011

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- Danish Cancer Register, 1943–2011

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Incidence and mortality rates: Data

Example: state **No DM**

- Time at risk:

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- Classification of follow-up (time and events) by age (0–100), calendar time (1995-2011) and date of birth (1-year classes) (Lexis triangles)

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- Similary for the study with cancer states

Incidence and mortality rates: Models

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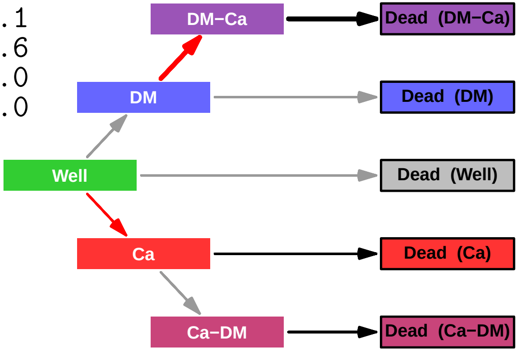
- Classifed by age / date / birth in 1-year classes
- Age-Period-Cohort Poisson-model with smooth effects of A, P & C
- Note: Only use the predictions from the models

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
```



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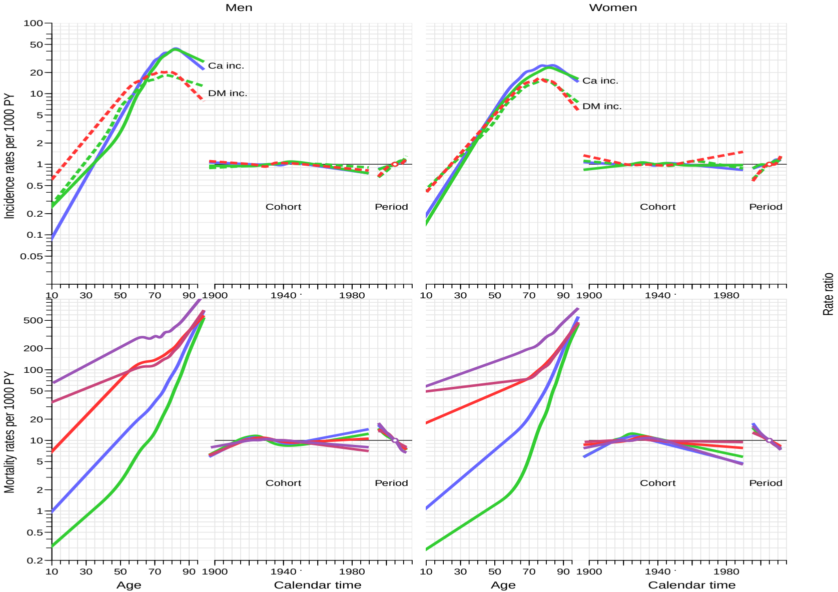
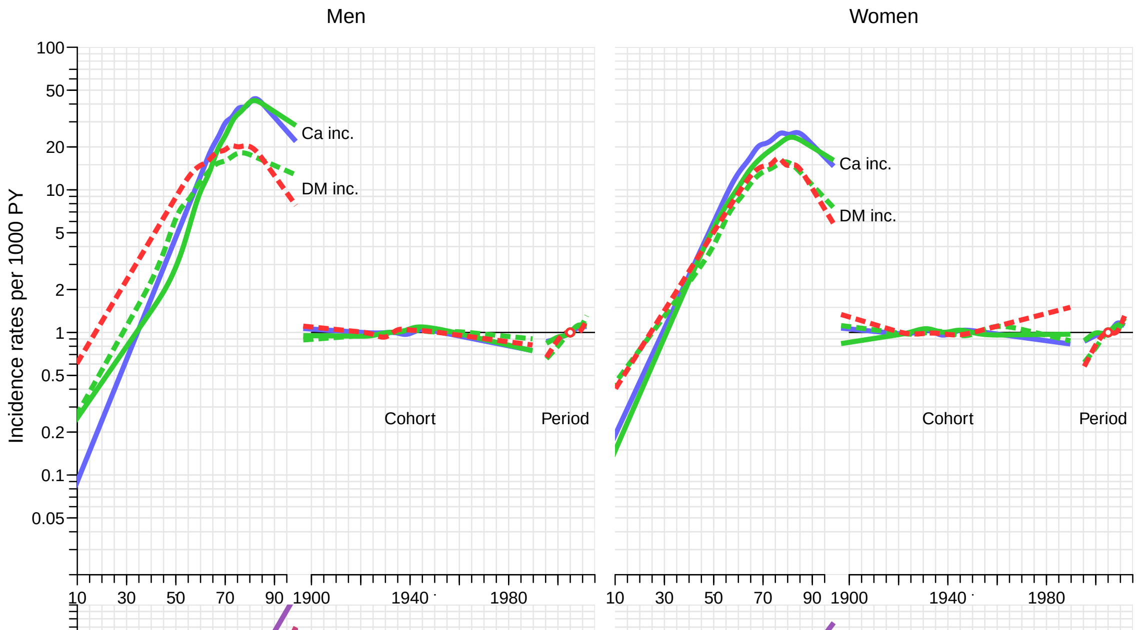
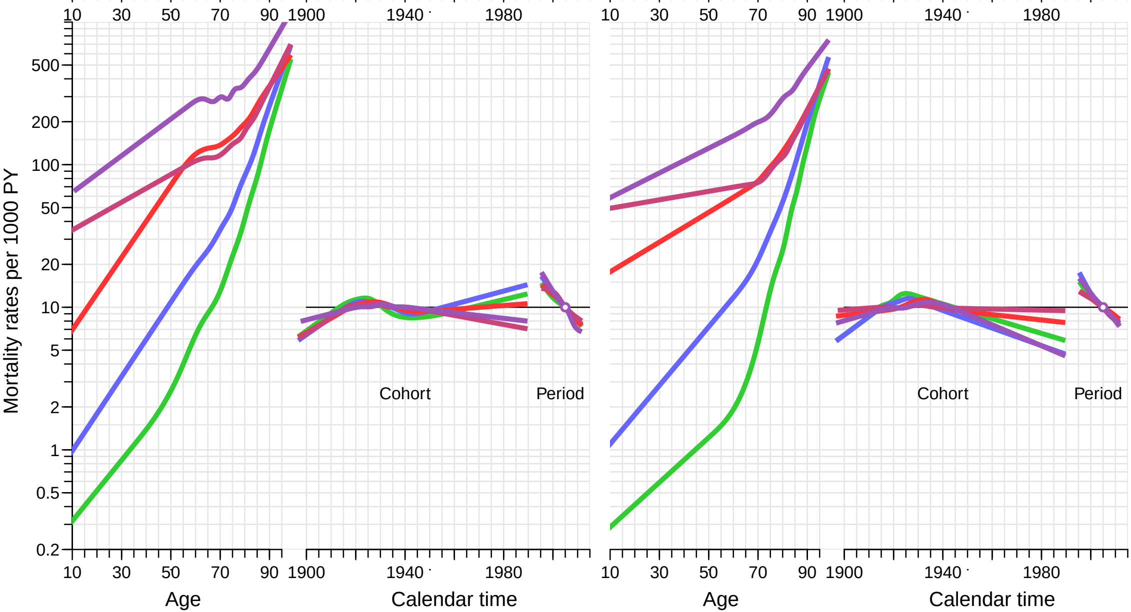




Men
Women
Incidence rates per 1000 PY
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
Ca inc.
DM inc.
Cohort
Period
10
30
50
70
90
1900
1940
1980


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
Age
Calendar time
Cohort
Period

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 **1 month** 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
```

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]
+    }
```

Prediction methods

- Start all in age 0 in state “**Well**”

Prediction methods

- Start all in age 0 in state “**Well**”
- Use rates to predict how many transfer to “**DM**”, “**Ca**”, “**Dead**” during a small interval

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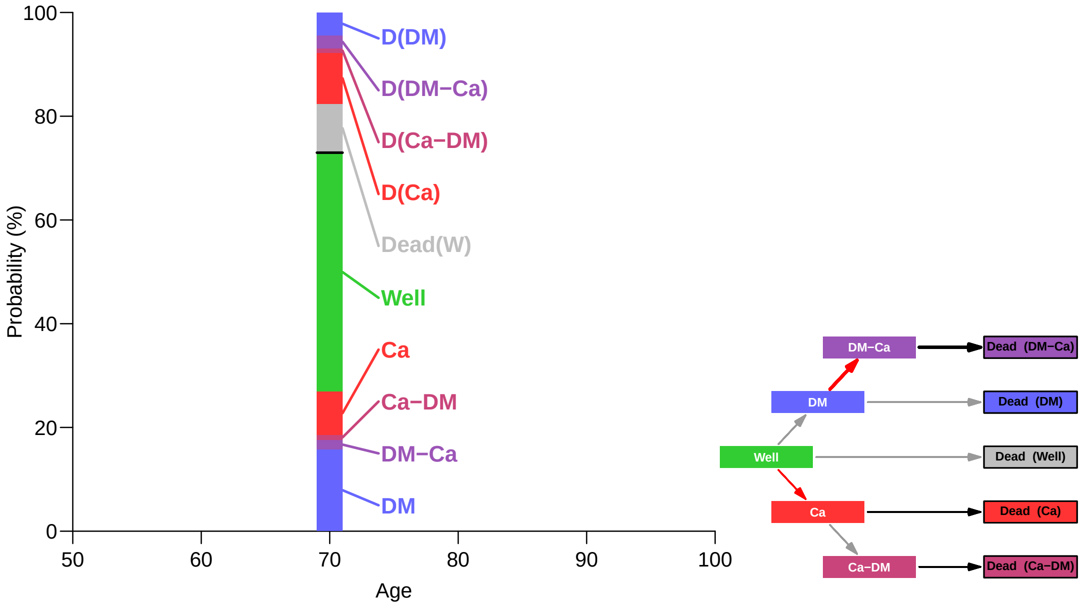
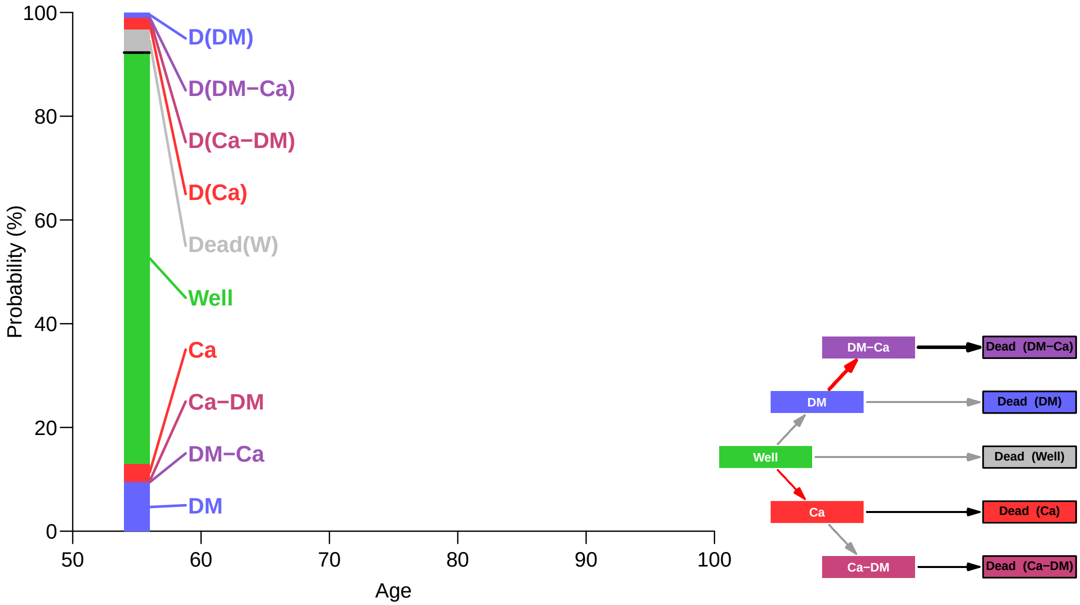
- Compute fraction in each state at each age

Prediction methods

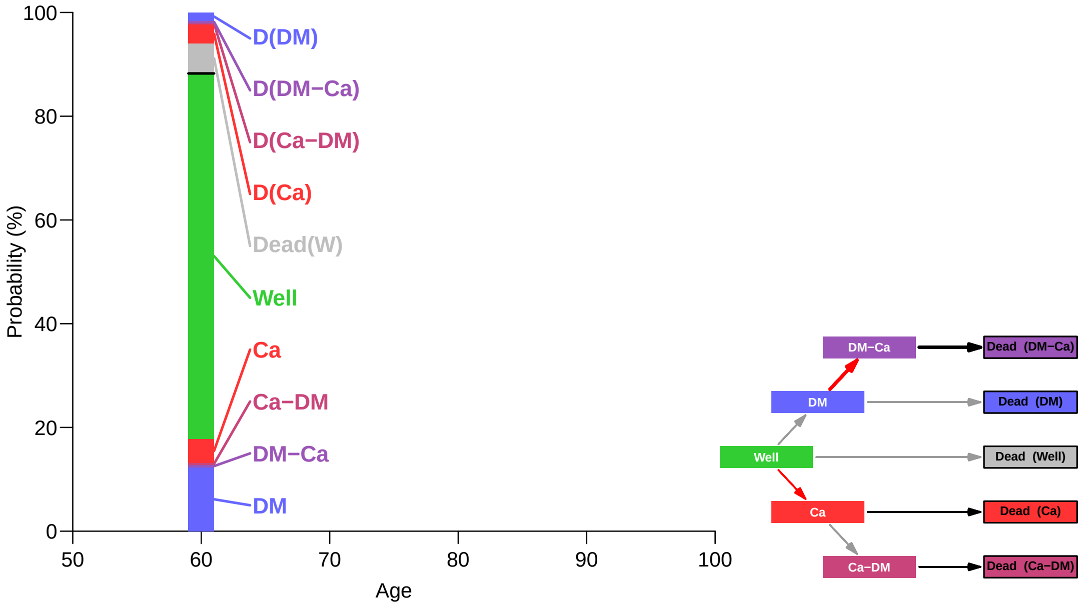
- Start all in age 0 in state "**Well**"
- Use rates to predict how many transfer to "**DM**", "**Ca**", "**Dead**" during a small interval
- Transfer to next possible states in next interval
- Interval length: 1 month
- Compute fraction in each state at each age
- Different scenarios using
  estimated (cross-sectional) rates
  at 1 January 1995, 1996, . . . , 2012

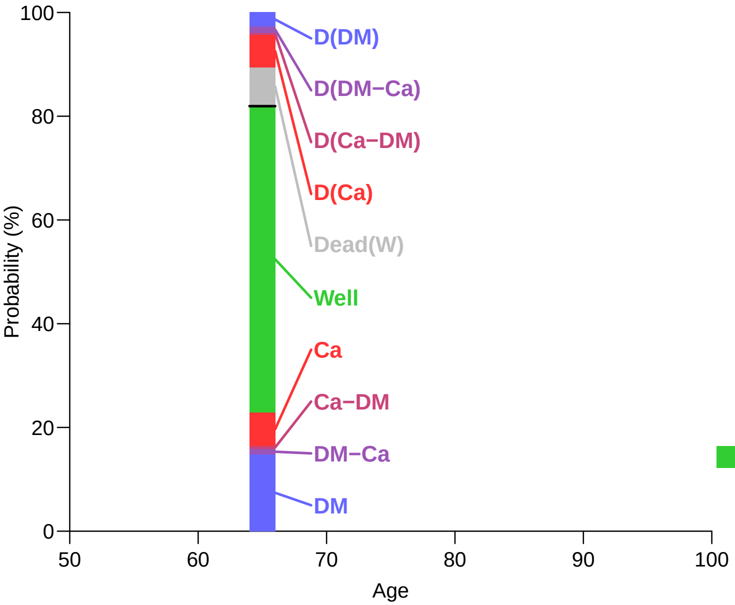


Probability (%)
100
80
60
40
20
0
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
Well
DM
DM−Ca
Ca
Ca−DM
Dead (DM−Ca)
Dead (DM)
Dead (Well)
Dead (Ca)
Dead (Ca−DM)

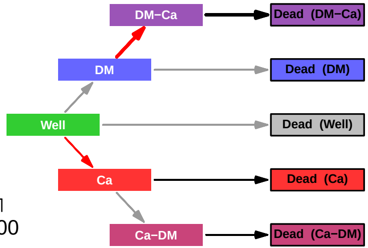


Probability (%)
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

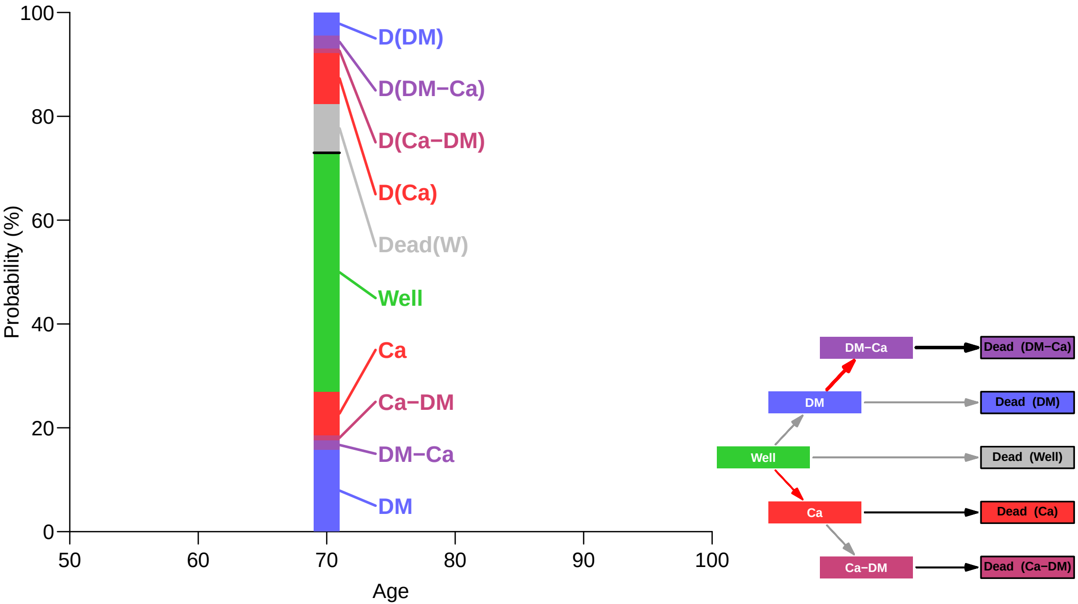

100
80
60
40
20
0
50
60
70
80
90
100
Probability (%)
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)



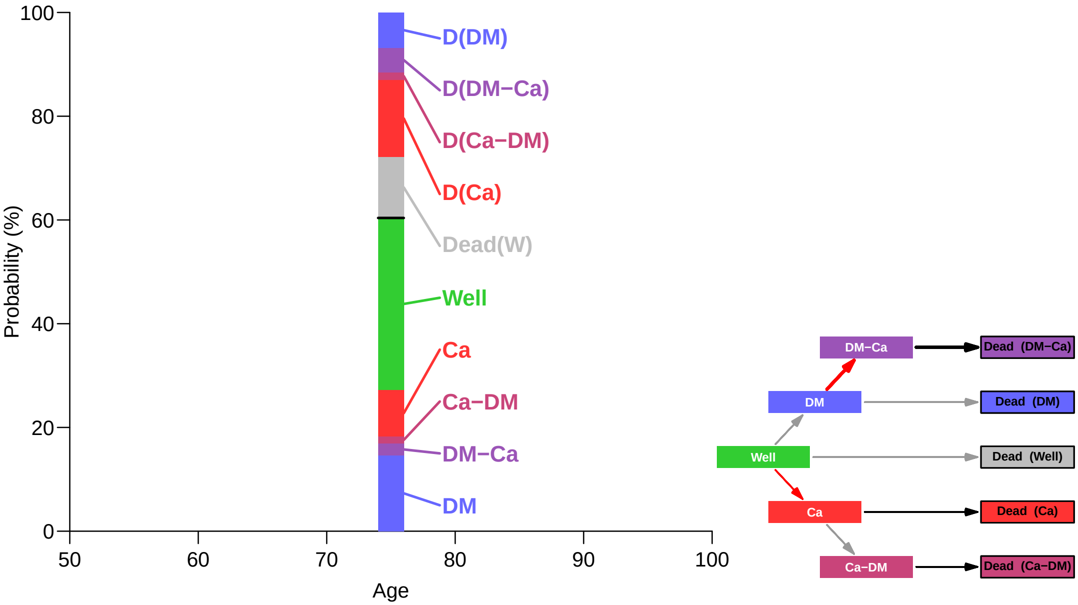
Probability (%)
100
80
60
40
20
0
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM



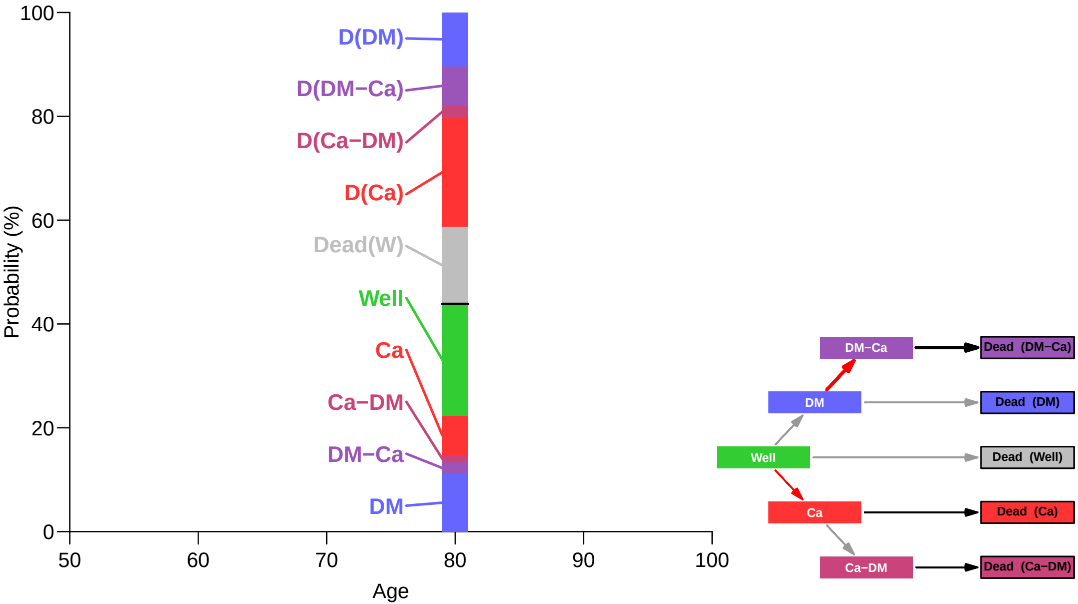
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

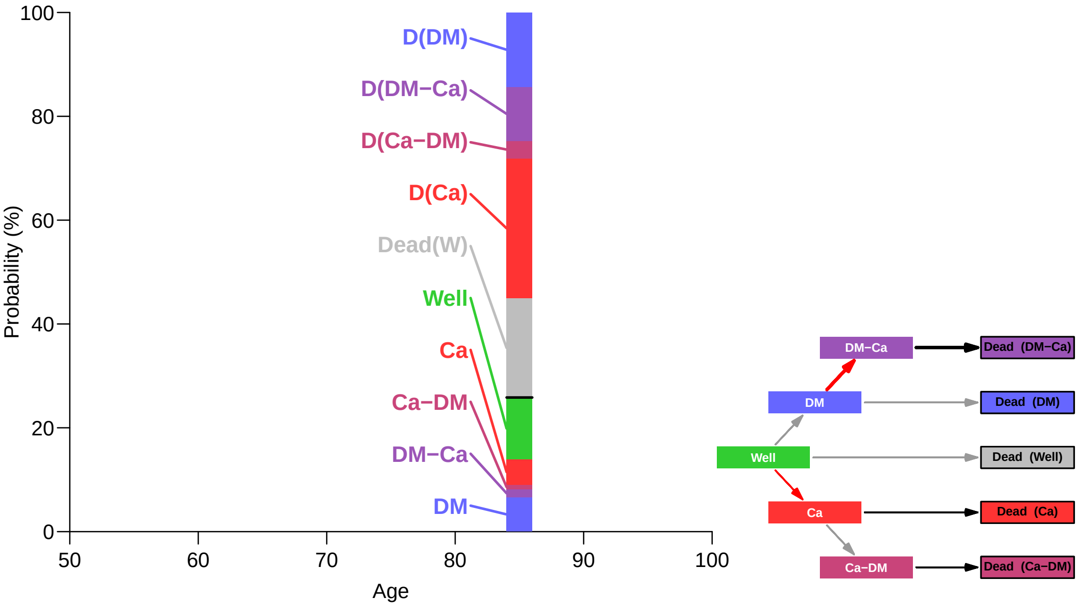


Probability (%)
100
80
60
40
20
0
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

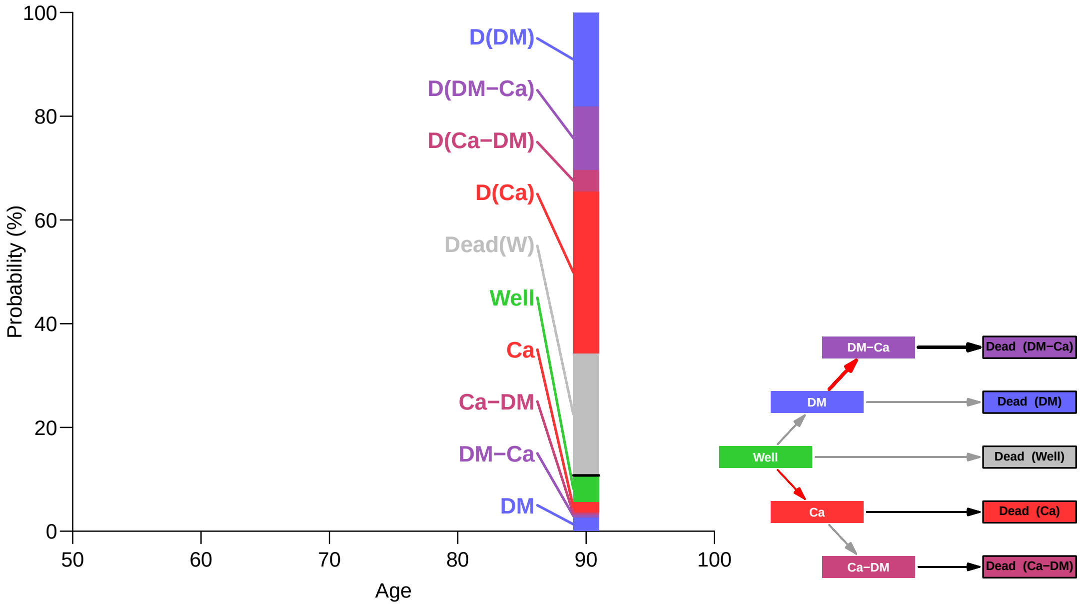


100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)

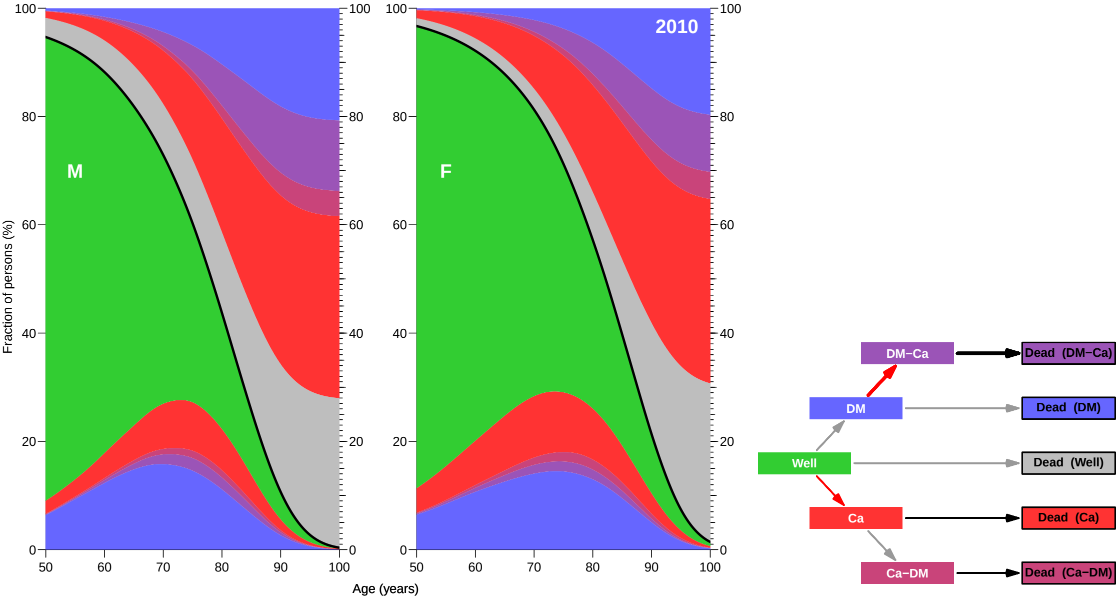

100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
DM
Well
Ca
Ca−DM
Dead (DM−Ca)
Dead (DM)
Dead (Well)
Dead (Ca)
Dead (Ca−DM)



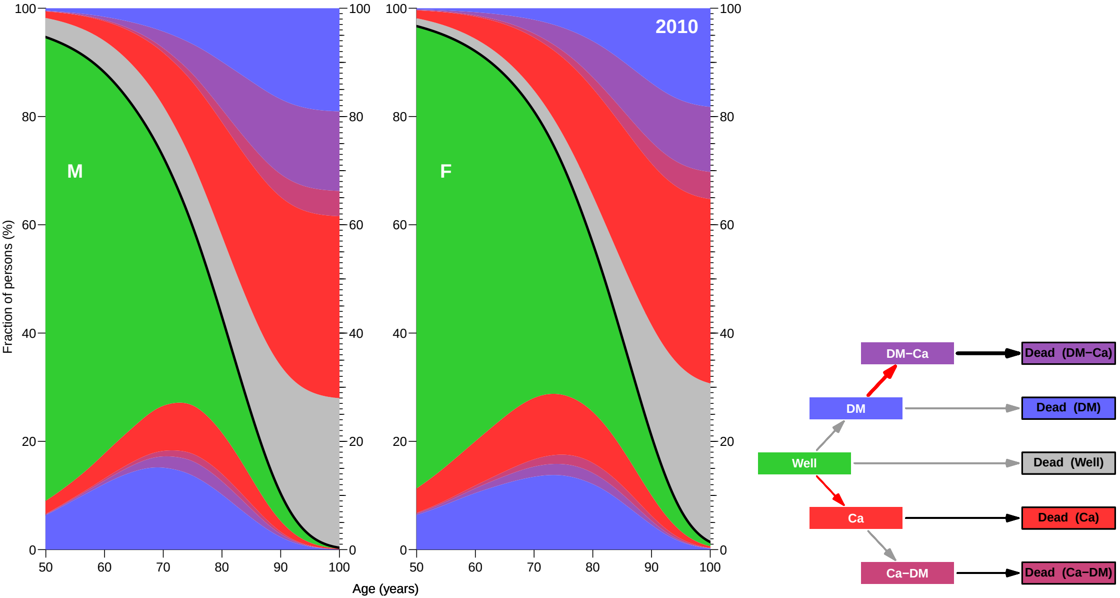
100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)



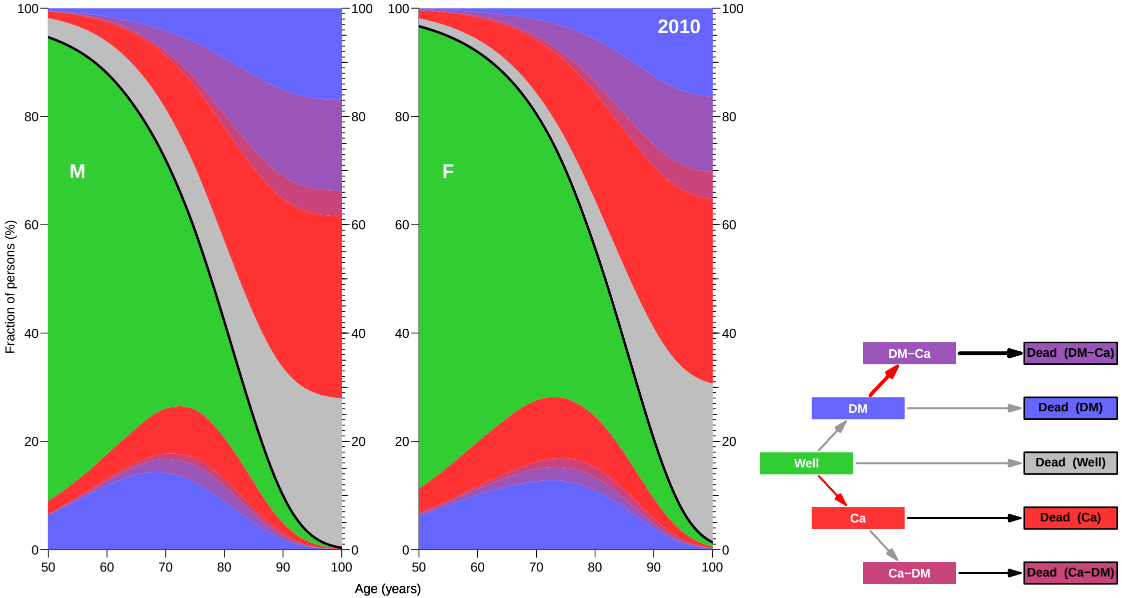
100
80
60
40
20
0
Probability (%)
50
60
70
80
90
100
Age
D(DM)
D(DM−Ca)
D(Ca−DM)
D(Ca)
Dead(W)
Well
Ca
Ca−DM
DM−Ca
DM
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
Dead (Ca−DM)



2010
M
F
Fraction of persons (%)
Age (years)
0
20
40
60
80
100
50
60
70
80
90
100
DM−Ca
Dead (DM−Ca)
DM
Dead (DM)
Well
Dead (Well)
Ca
Dead (Ca)
Ca−DM
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$model , newdata=nd )[,1]
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+ PR["DM-Ca","D-DC" ,,yy,"M"] <- ci.pred( M.dc2dd$model, newdata=nd )[,1]
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```

Transition rates

```
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+ 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]
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```
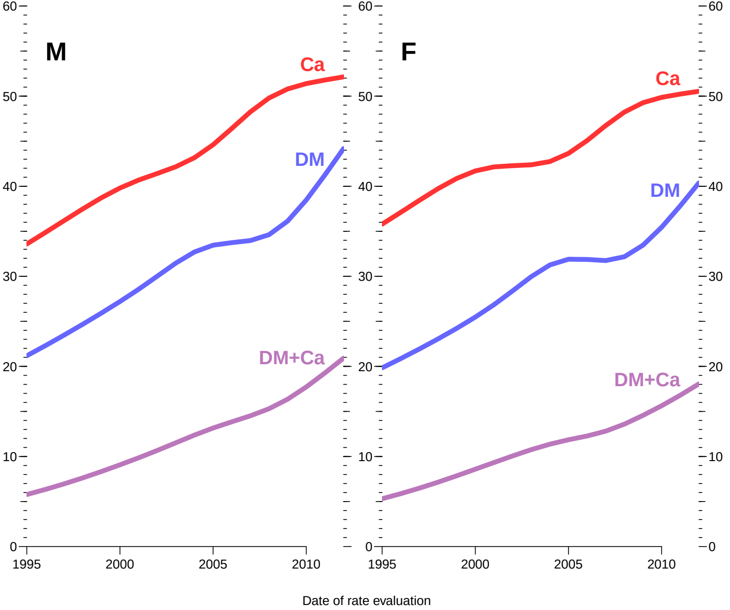
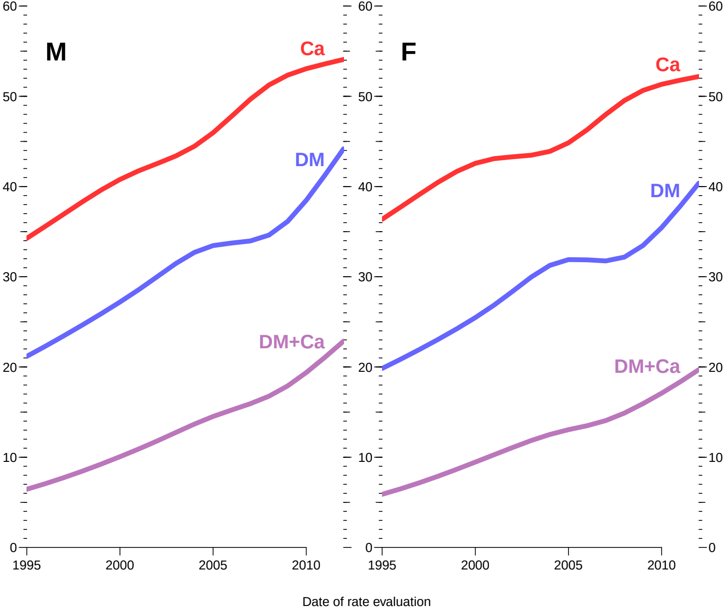
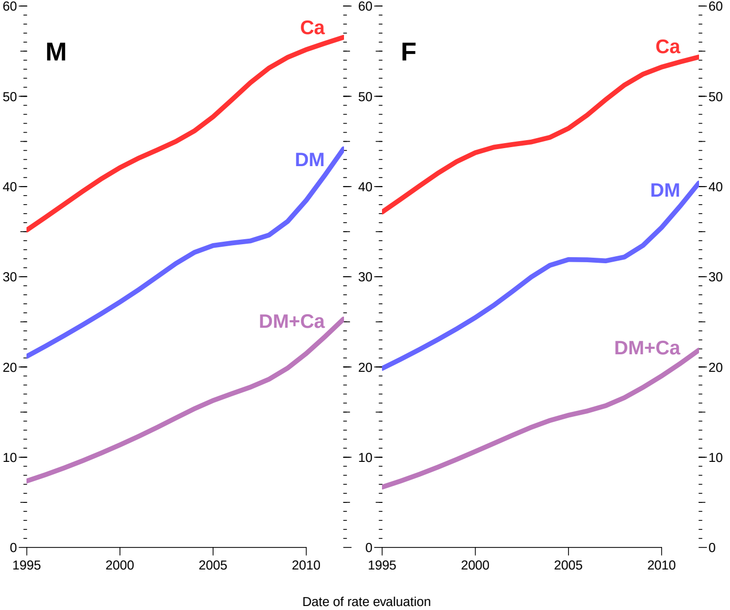

Lifetime risks



Lifetime risks - RR inflated 20%



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

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

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

- Changing **life-time risk** 1995–2012:

		+20% Ca | DM	+50% Ca | DM
Diabetes	**20%** to **42%**	20% to 42%	20% to 42%
Cancer	**35%** to **51%**	36% to 52%	36% to 55%
DM + Ca	**6%** to **20%**	6% to 21%	7% to 23%

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 age and calendar time — to predict prevalences 2012

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- 1-month intervals for updating
- Assume:

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  - Incidence rates had remained at 1995 level

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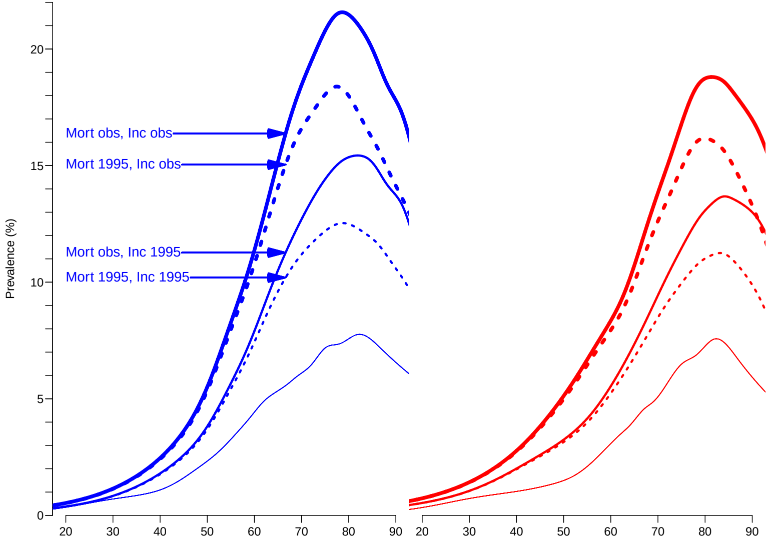
  - Mortality rates had remained at 1995 level
  - Both had remained at 1995 level

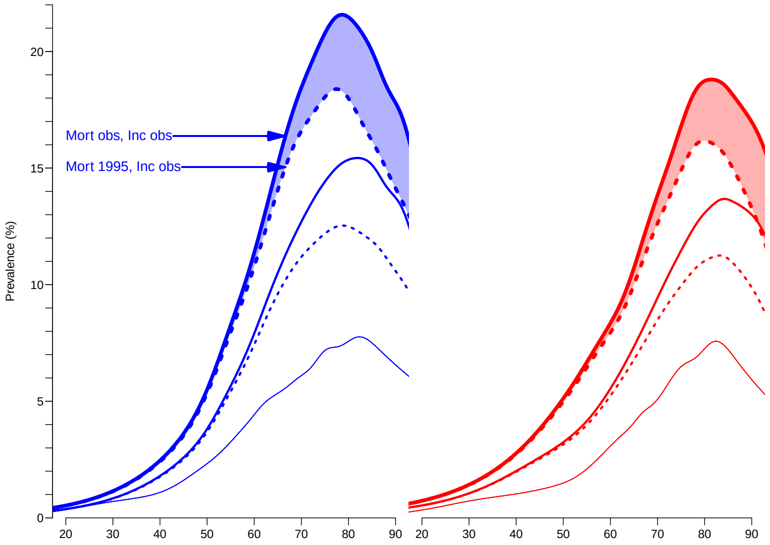
Prevalence of DM — updating

- Start with age-specific prevalences 1995
- Use fitted models for incidence and mortality - as function of age and calendar time — to predict prevalences 2012
- 1-month intervals for updating
- 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.

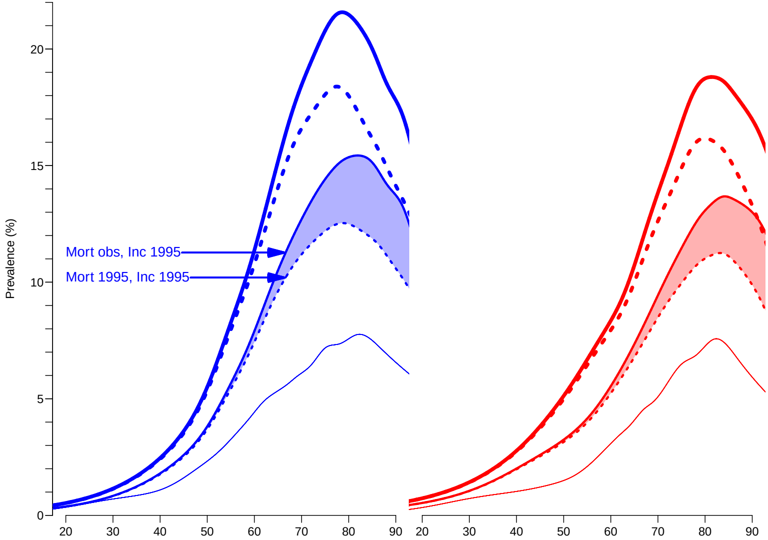
Prevalence of DM — updating



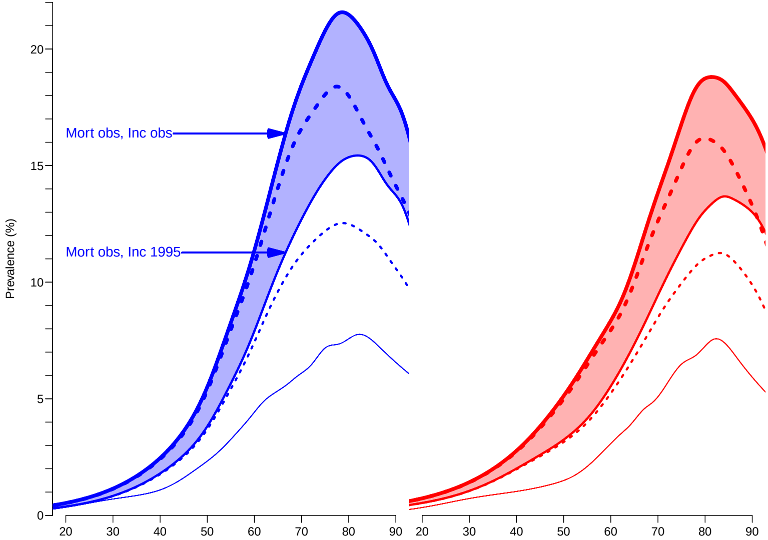
Prevalence of DM — updating



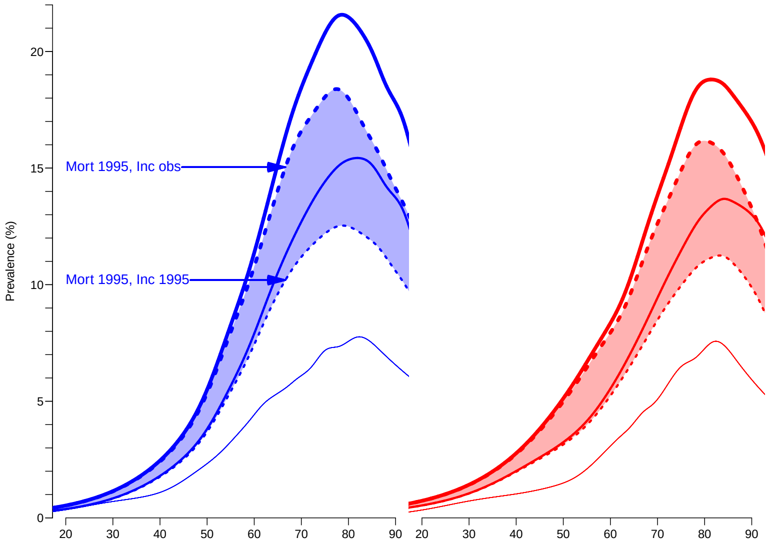
Prevalence of DM — updating



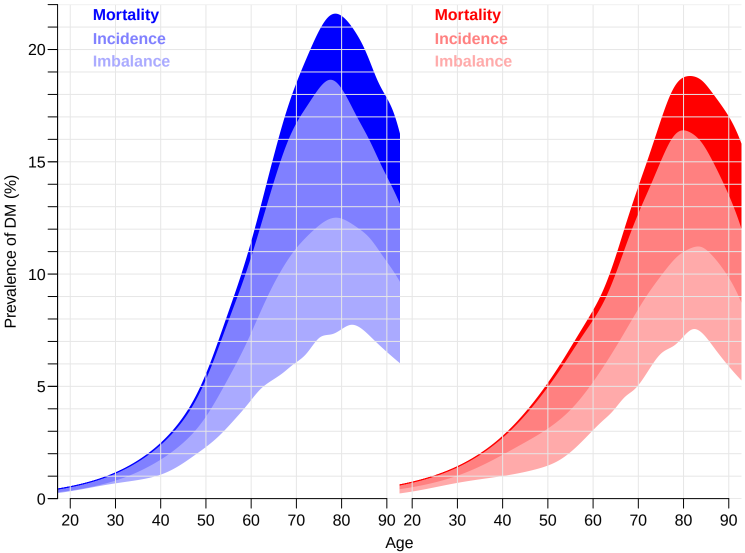
Prevalence of DM — updating



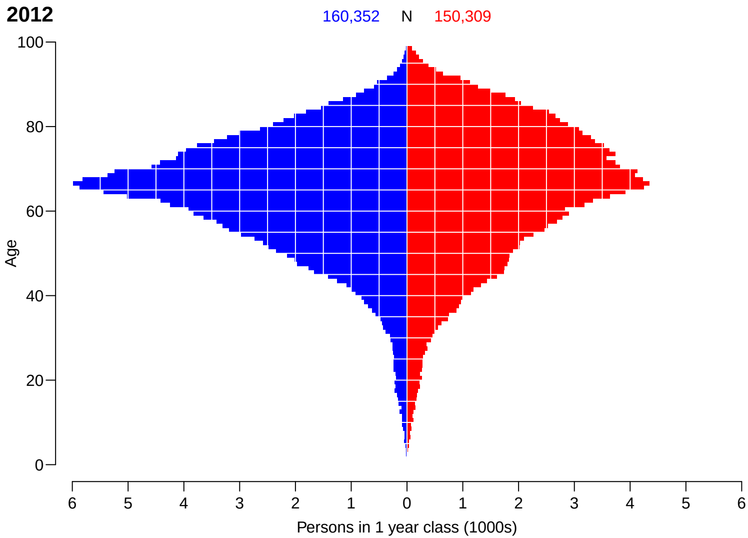
Prevalence of DM — updating



Componets of prevalent cases

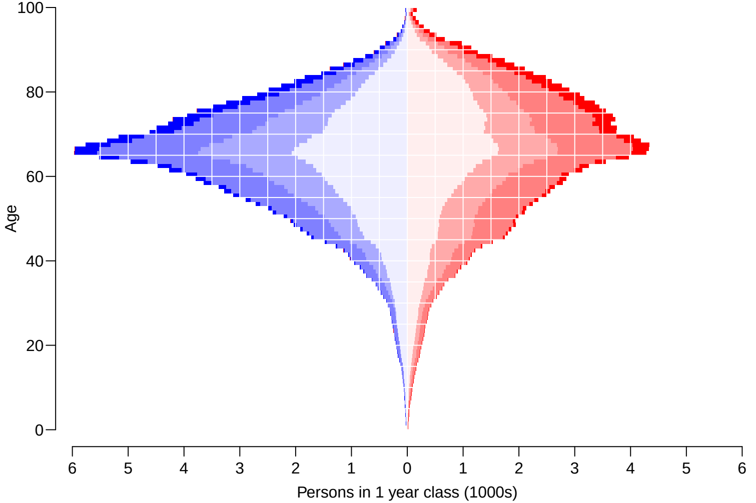


Prevalent cases

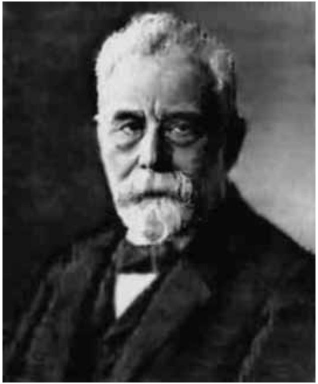


Components of prevalent cases

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



EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG
KARL J. TRÜBNER
1875.