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

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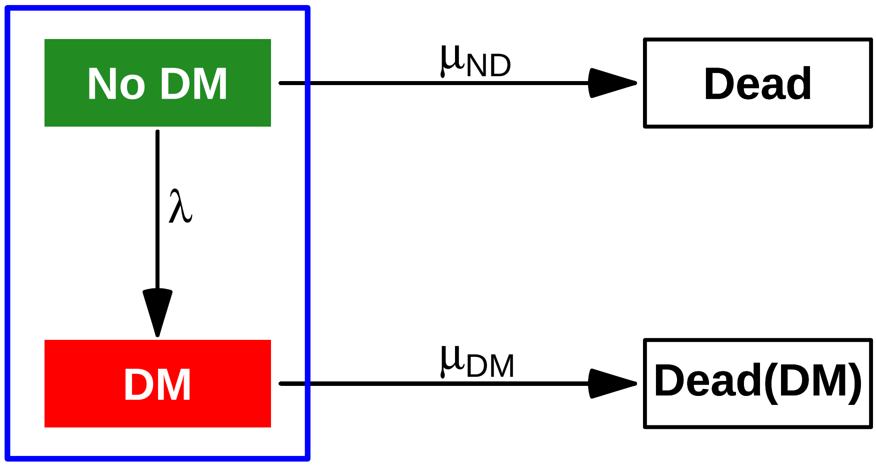
Demography of diabetes in DK

- How does diabetes spread in the population?
- Life time risk of DM
- . . . and complications

Prevalence of diabetes

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

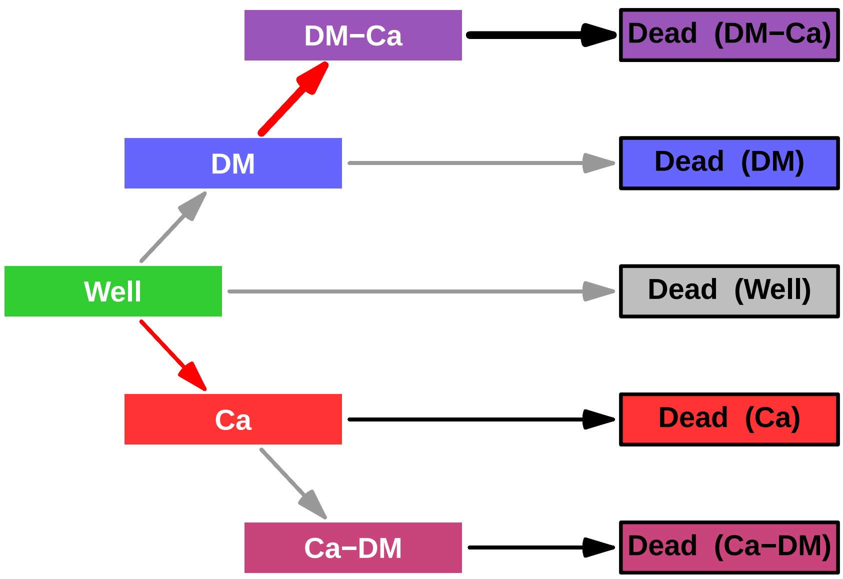
Demographic scenario



Cancer among diabetes patients

- Cancer is about 15% higher in DM ptt
- Life-time risk of cancer and DM both in the range 30–40%
- Assess:
  - Lifetime risk of DM and Cancer (and both) in DK
  - Changes in these 1995–2012
  - Impact of the DM vs noDM cancer incidence RR

Demographic scenario



Multistate models

- Distribution across boxes (states) is completely determined by:
- 1) Initial state distribution
- 2) Transition intensities
- Time scale?
- . . . or rather, what shall we call it?
- **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:

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

Transition probabilities for an interval of length ℓ:

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

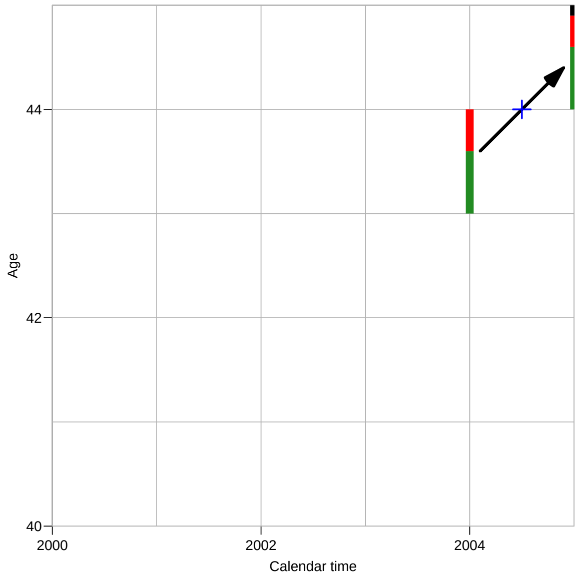
$$P_{\text{ND,ND}}(\ell) = \exp\big(-(\lambda+\mu_{\text{ND}})\ell\big)$$

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

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

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

Prevalence of DM — updating



Where do we get the rates from?
— and —
Why are the formulae wrong?
and how do we rectify that?

Transition intensities revisited — assumptions

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

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

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

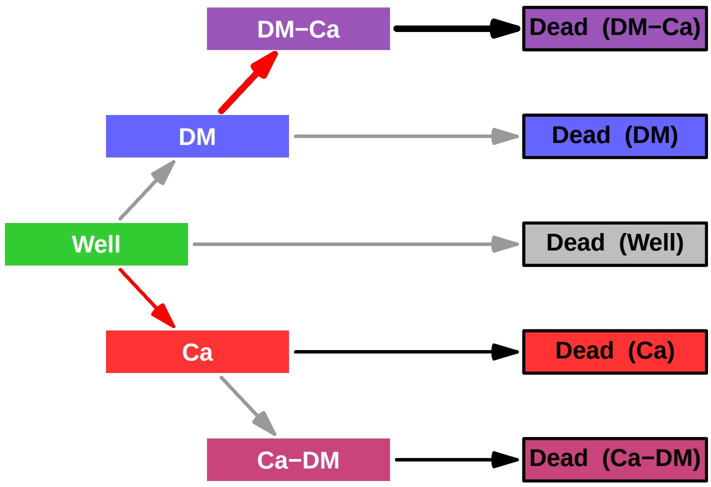
$$P_{\text{DM,Dead}}(\ell) = 1 - \exp(-\mu_{\text{DM}}\ell)$$

Assumes that ℓ is so small so that:

- the approximations are valid
- the probability of 2 or more transitions during ℓ is negligible.
- $\Rightarrow$ 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 $70 \rightarrow 75$,
based on 1, 3 and 6-month intervals respectively



Accuracy of multistate calculations

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

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	.

Rule of thumb for multistate calculations

- Transition probabilities over each interval should be less than **2%**,
- if they exceed that, use **shorter** intervals for calculations,
- 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
- Danish Cancer Register, 1943–2011
- Mortality, Statistics Denmark
- Population, Statistics Denmark

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)
- Similarly for the study with cancer states

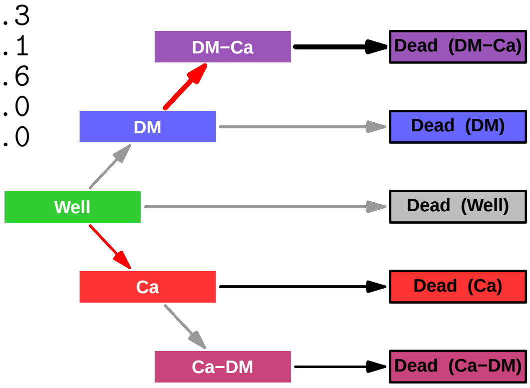
Incidence and mortality rates: Models

- Incident cases / deaths from each state
- Person-years in each state
- Classified 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

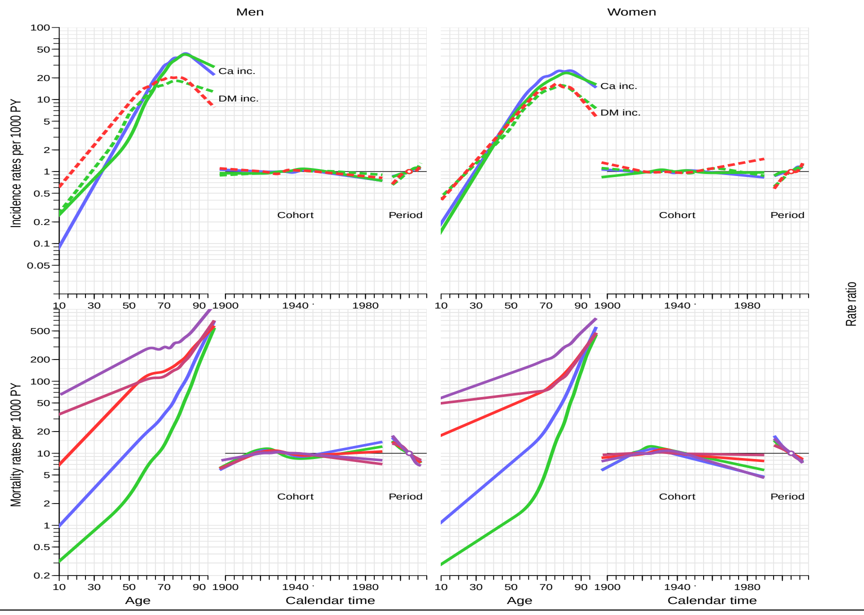
Events and risk time

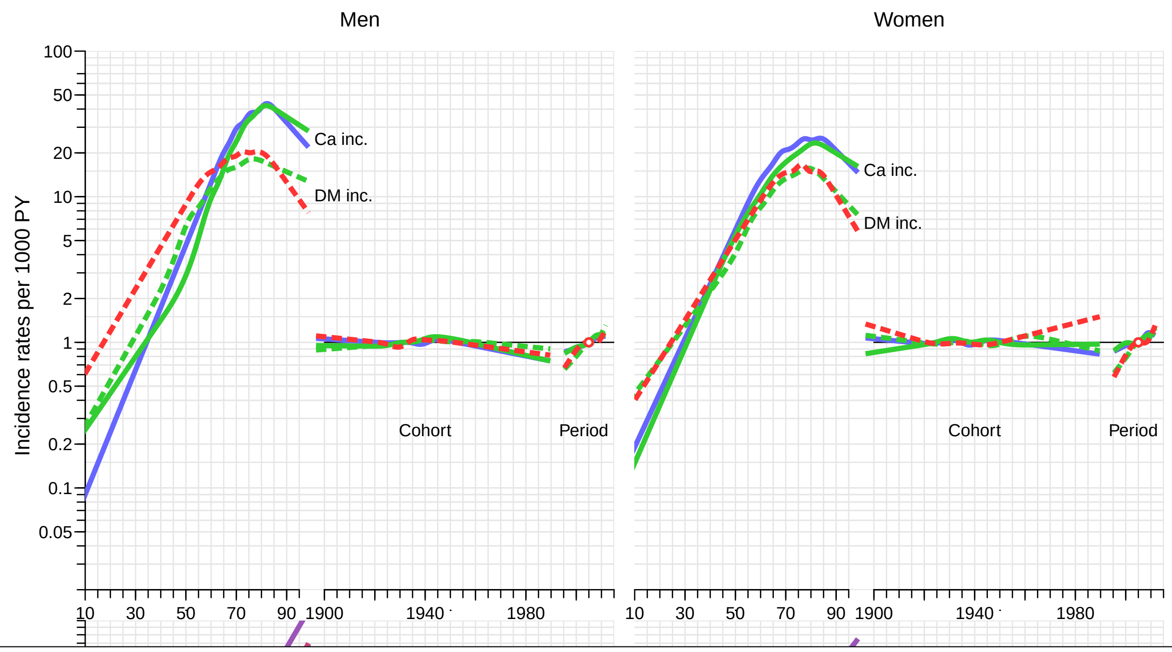
```
> cbind(
+ xtabs( cbind( D.ca, D.dm, D.dd ) ~ state, data=dcd ), round(
+ xtabs( Y/1000 ~ state, data=dcd ), 1 ) )

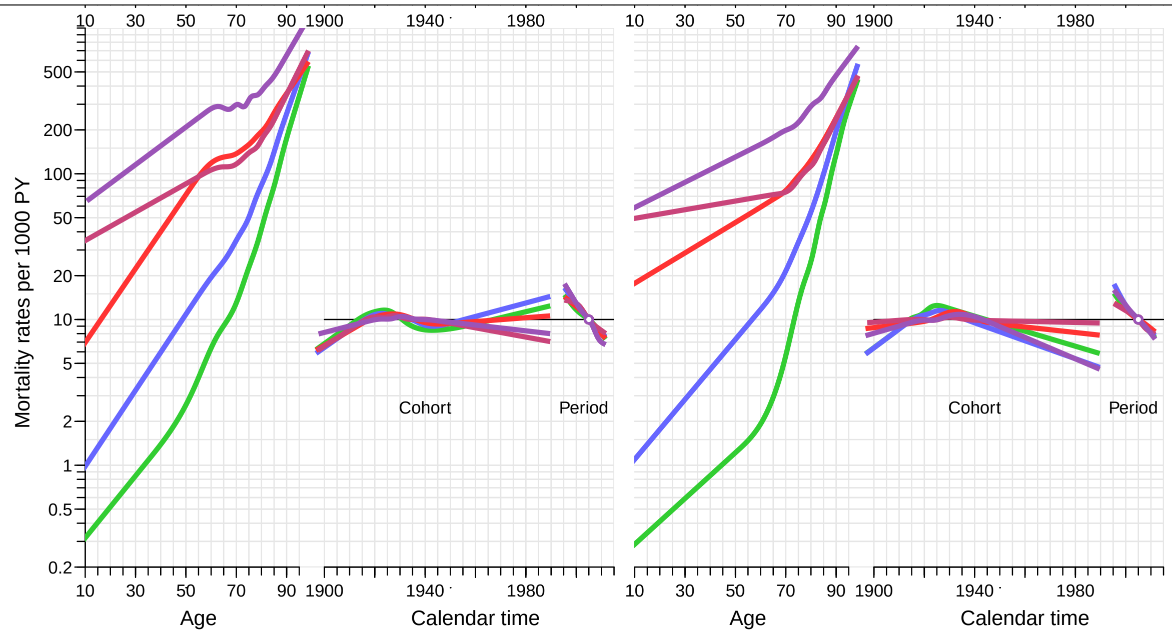
        D.ca   D.dm   D.dd       Y
Well  447419 345400 628705 87502.9
DM     35145      0  73480  2031.3
DM-Ca      0      0  24153    89.1
Ca         0  23508 222966  1973.6
Ca-DM      0      0  14703   117.0
Dead       0      0      0     0.0
```



Incidence and mortality rates







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
```

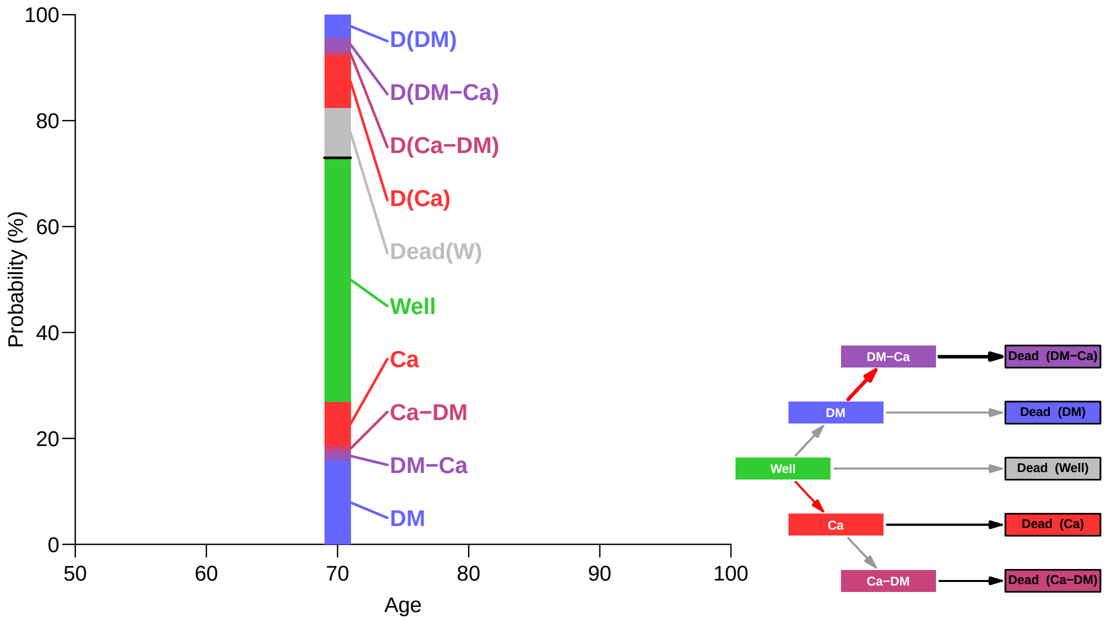

State occupancy probabilities

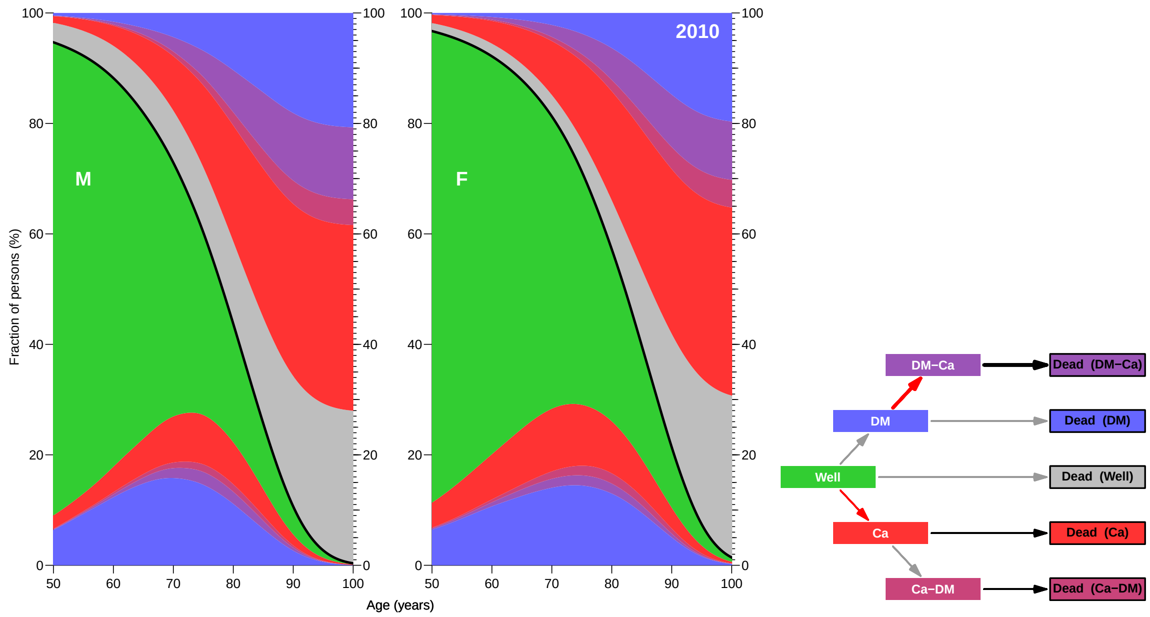
```
> PV <- PR[1,,,,]*0

> 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**"
- 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





Cancer rates among DM-ptt inflated 20% 50%

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]
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```


Transition rates

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> int <- 1/12
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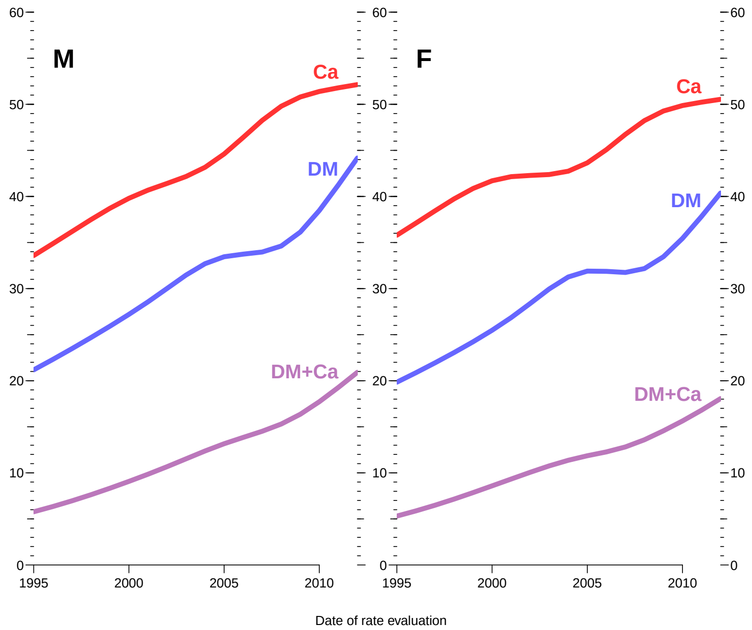
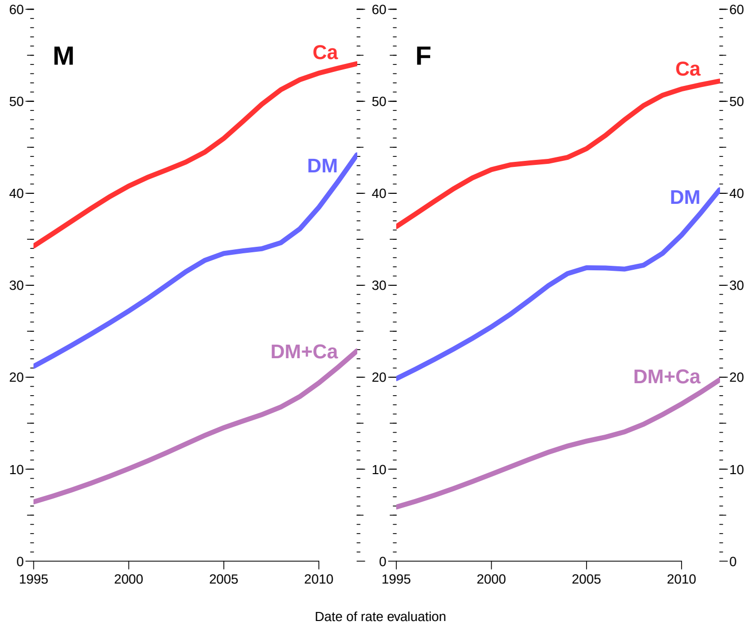
+ PR["Well" ,"D-W"  ,,yy,"M"] <- ci.pred( M.w2dd$model , newdata=nd )[,1]
+ PR["DM"   ,"DM-Ca",,yy,"M"] <- ci.pred( M.dm2ca$model, newdata=nd )[,1] * 1.5
+ PR["DM"   ,"D-DM" ,,yy,"M"] <- ci.pred( M.dm2dd$model, newdata=nd )[,1]
+ PR["Ca"   ,"Ca-DM",,yy,"M"] <- ci.pred( M.ca2dm$model, newdata=nd )[,1]
+ 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]
```

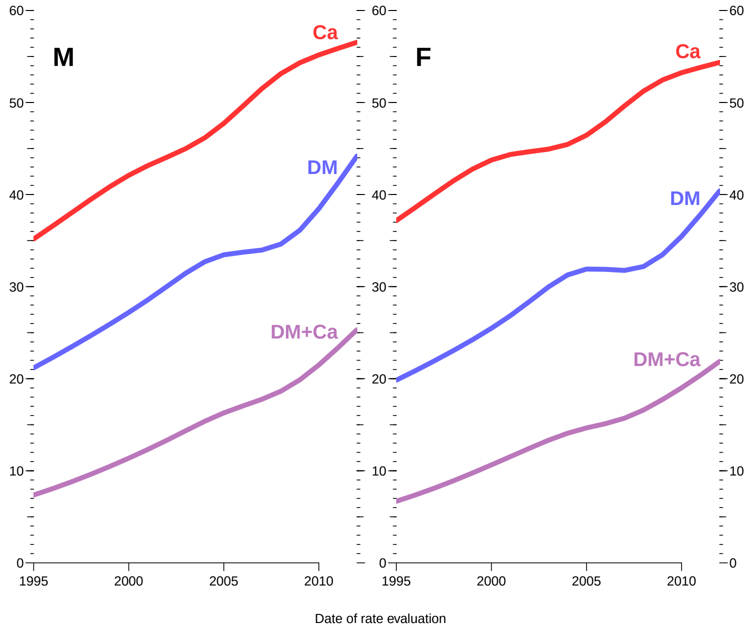

Lifetime risks



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

- 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%

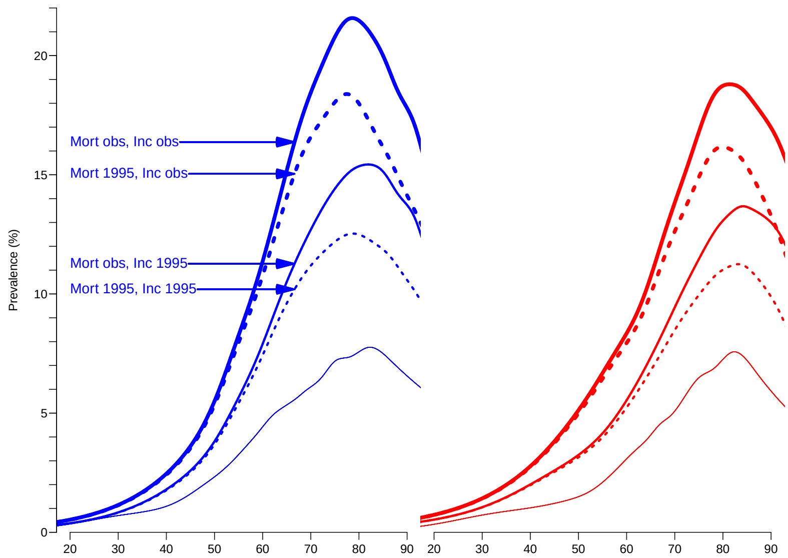
Conclusion — DM & Cancer

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

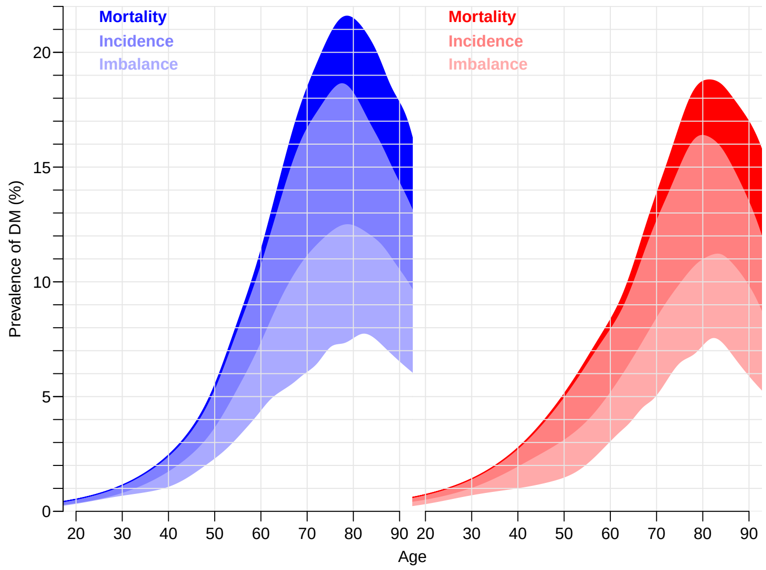
Prevalence of DM — updating

- 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.

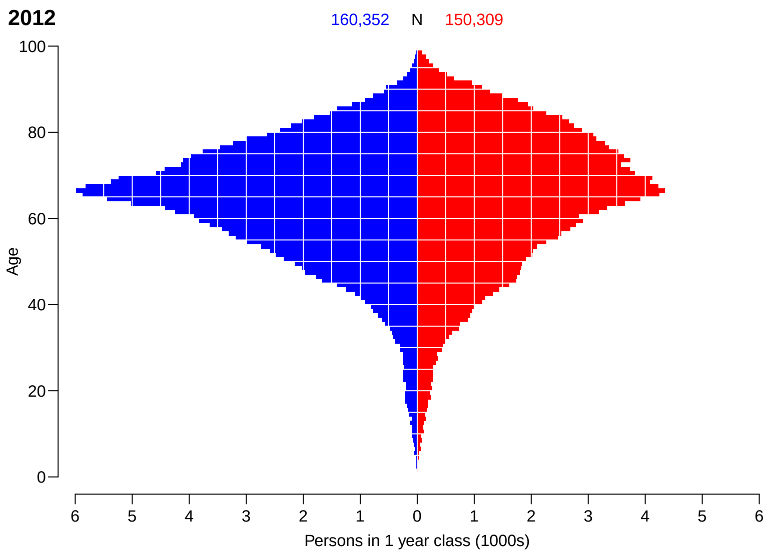
Prevalence of DM — updating



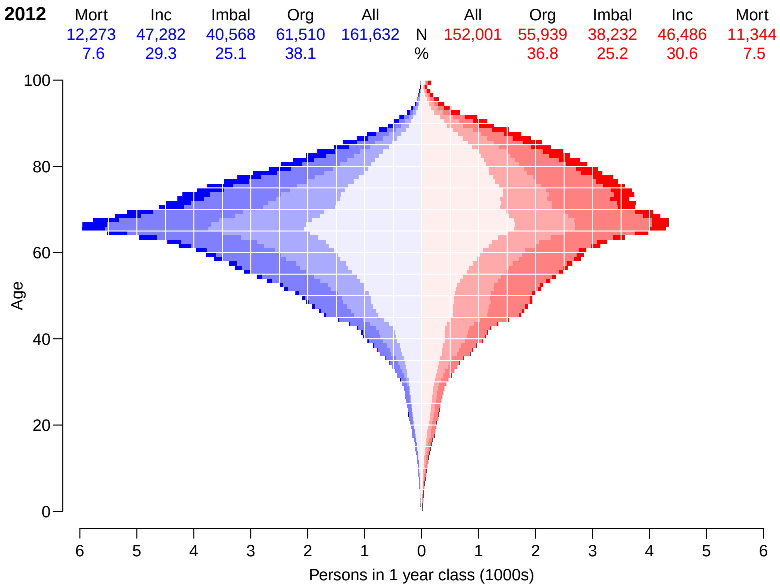
Components of prevalent cases



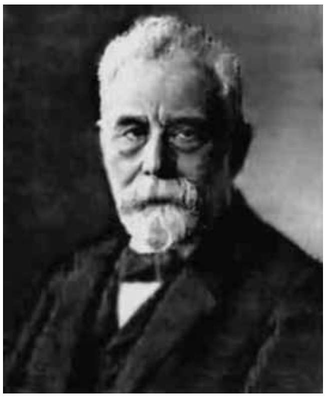
Prevalent cases

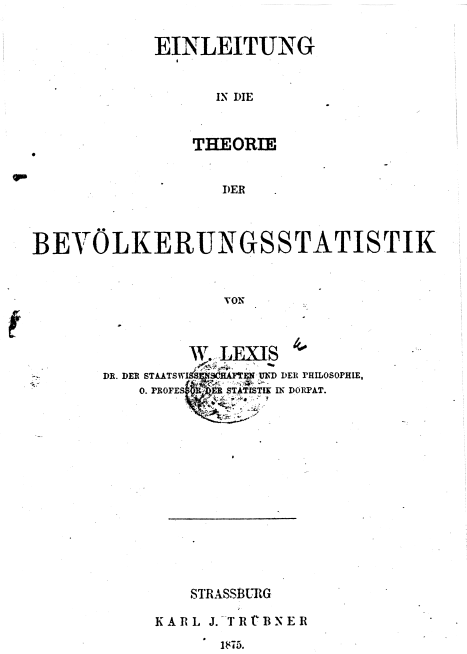


Components of prevalent cases



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.