Years of Life Lost to Diabetes

Bendix Carstensen Steno Diabetes Center
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http://BendixCarstensen.com

LEAD symposiun at EDEG, Dubrovnik,
6 May 2017

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Expected Lifetime

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Life lost to disease

- Persons with disease live shorter than persons without
- The difference is the life lost to disease — years of life lost
- Possibly depends on:
  - sex
  - age
  - duration of disease
  - definition of persons with/out disease
- Conditional or population averaged?
- . . . the latter gives a seductively comfortable single number
- . . . the former confusingly relevant insights
- YLL derives from Expected Lifetime

Expected Lifetime — the formals:

. . . the age at death integrated w.r.t. the distribution of age at death:

$$\mathrm{EL} = \int_0^\infty a\, f(a)\, \mathrm{d}a$$

The relation between the density f and the survival function S is $f(a) = -S'(a)$, so integration by parts gives:

$$\mathrm{EL} = \int_0^\infty a\big(-S'(a)\big)\, \mathrm{d}a = -\Big[aS(a)\Big]_0^\infty + \int_0^\infty S(a)\, \mathrm{d}a$$

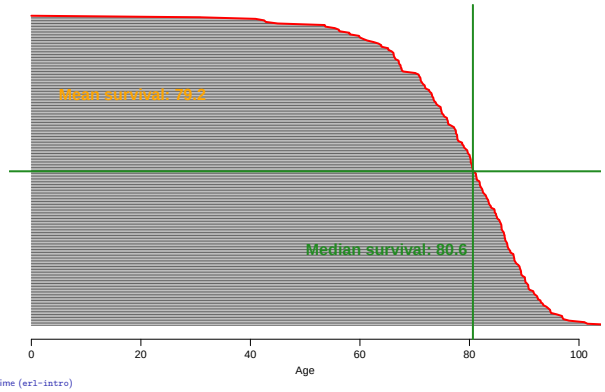
The first term is 0 so:

$$\mathrm{EL} = \int_0^\infty S(a)\, \mathrm{d}a$$

the area under the survival curve.

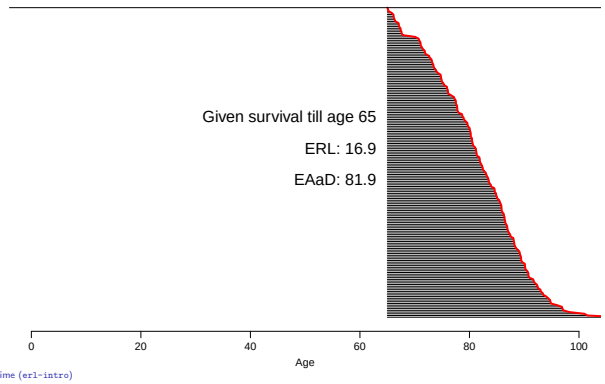
Expected life time — illustrated

- Take, say 200, persons
- follow till all are dead
- compute the mean age at death (life time)
- — that is the **life expectancy** (at birth)
- . . . so let's do it and see how it works



Expected residual life time

- Assume that persons already attained age 65 (say).
- What is the expected time they have left to live?
- Same experiment as before
- — except that we only look at those who attain age 65
- so we do not have 200 persons, only the 180 alive at 65
- re-scale to 100% at age 65



Expected lifetime and years lost

- ERL (**E**xpected **R**esidual **L**ifetime):
  Area under the survival curve
- YLL (**Y**ears of **L**ife **L**ost) (to diabetes, say):
  $\mathrm{ERL}_{\mathrm{pop}} - \mathrm{ERL}_{\mathrm{DM}}$
- **difference** between areas under survival curve for persons without DM and persons with DM
- $\Rightarrow$ area **between** the survival curves
- . . . but not all use this approach

Years of Life Lost

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Wikipedia: PYLL

Potential **Y**ears of **L**ife **L**ost

- Fix a threshold, T, (the population EL, or say 75)
- A person dead in age $a < T$ contributes $T - a$
- A person dead in age $a > T$ contributes 0

. . . seems to assume that the expected age at death is T regardless of attained age ?

WHO — Years of Life Lost

Rationale for use
Years of life are lost (YLL) take into account the age at which deaths occur by giving greater weight to deaths at younger age and lower weight to deaths at older age. The years of life lost (percentage of total) indicator measures the YLL due to a cause as a proportion of the total YLL lost in the population due to premature mortality.

Definition
YLL are calculated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs. The standard life expectancy used for YLL at each age is the same for deaths in all regions of the world (. . .)

`www.who.int/whosis/whostat2006YearsOfLifeLost.pdf`

$\Rightarrow$ a person dying in age a contributes $\mathrm{ERL}(a) > 0$

Comparing men and women

- When a man dies age a, say,
  - YLL is $\mathrm{ERL}_w(a) > 0$
  - — the expected residual life time of a woman aged a.
- When a woman dies age a, say,
  - YLL is $\mathrm{ERL}_m(a) > 0$
  - — the expected residual life time of a man aged a.
- . . . so each sex lose years relative to the other !
- So maybe not a terribly useful measure.

The *ad-hoc* measures do not work

- anyone who dies before age 75 (PYLL)
- anyone who dies (WHO YLL)
- . . . contribute a **positive** number to YLL
- $\Rightarrow$ **any** subgroup of the population have **positive** years of life lost when compared to the general population!
- . . . actually, compared to **any** population (ex: men vs. women)
- They only use the dead persons and ignore the living
- No shortcuts:
  - the YLL is a difference of expectations
  - use a statistical model (specify $f(a)$, that is)
  - a statistical model for all persons
  - We will use diabetes in Denmark as an example

YLL — the details

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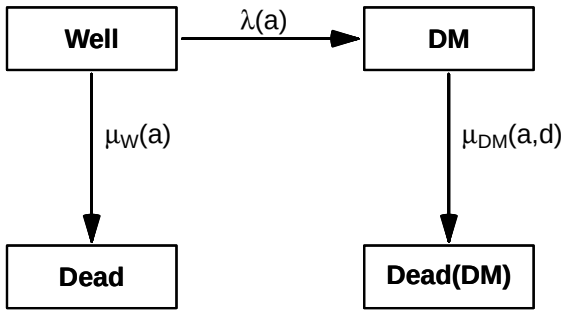
How the world looks



Comparing DM and well

$$\mathrm{YLL} = \int_0^\infty S_W(a) - S_D(a)\,\mathrm{d}a$$

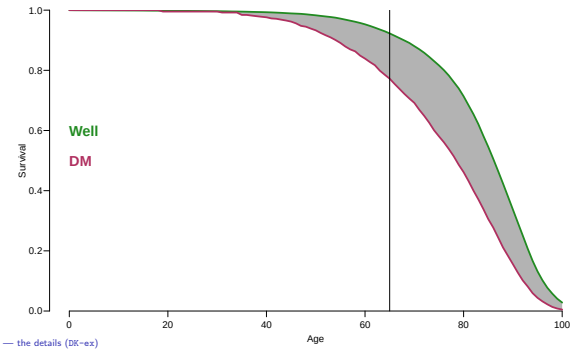
The survival functions we need are derived from mortality rates:

$$S_W(a) = \exp\left(-\int_0^a \mu_W(u)\,\mathrm{d}u\right), \qquad S_D(a) = \exp\left(-\int_0^a \mu_D(u)\,\mathrm{d}u\right)$$

Mortality rates from Denmark

```
> library( Epi )
> clear()
> data( DMepi )
> w15 <- subset( DMepi, sex=="F" & P==2015 )
> w15 <- w15[order(w15$A),]
> w15 <- transform( w15, mW =        D.nD / Y.nD,  # no DM mortality
+                        iW =          X / Y.nD,  # DM  incidence
+                        mD = pmax(0,D.DM / Y.DM,na.rm=TRUE), # DM mortality
+                        mT =  (D.nD+D.DM)/(Y.nD+Y.DM) ) # total mortality
> Sw <- surv1( 1, w15$mW )
> Sd <- surv1( 1, w15$mD )
> cbind( Sw, Sd )[65:70,]
   age        A0 age        A0
65  64 0.9297246  64 0.7853495
66  65 0.9226514  65 0.7721934
67  66 0.9149180  66 0.7547042
68  67 0.9070037  67 0.7381123
69  68 0.8990846  68 0.7214464
70  69 0.8909150  69 0.7061645
```


Survival curves (?)



Comparing DM and well

$$\mathrm{YLL} = \int_0^\infty S_W(a) - S_D(a)\,\mathrm{d}a$$

The survival functions we need are derived from mortality rates:

$$S_W(a) = \exp\left(-\int_0^a \mu_W(u)\,\mathrm{d}u\right), \qquad S_D(a) = \exp\left(-\int_0^a \mu_D(u)\,\mathrm{d}u\right)$$

For the **conditional** YLL given attained age A, just use:

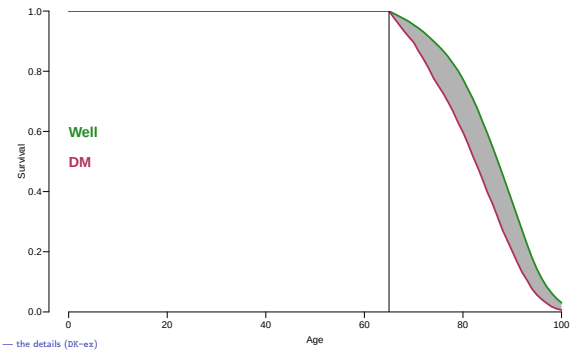
$$S_W(a|A) = S_W(a)/S_W(A), \qquad S_D(a|A) = S_D(a)/S_D(A)$$

Mortality rates from Denmark

```
> Sw <- surv1( 1, w15$mW, A=65 )
> Sd <- surv1( 1, w15$mD, A=65 )
> cbind( Sw, Sd )[65:70,]

   age        A0       A65 age        A0       A65
65  64 0.9297246 1.0000000  64 0.7853495 1.0000000
66  65 0.9226514 1.0000000  65 0.7721934 1.0000000
67  66 0.9149180 0.9916183  66 0.7547042 0.9773513
68  67 0.9070037 0.9830406  67 0.7381123 0.9558646
69  68 0.8990846 0.9744576  68 0.7214464 0.9342820
70  69 0.8909150 0.9656030  69 0.7061645 0.9144918
```


Conditional survival curves



Comparing DM and well

$$\text{YLL} = \int_0^\infty S_W(a) - S_D(a)\,\mathrm{d}a$$

The survival functions we need are derived from mortality rates:

$$S_W(a) = \exp\left(-\int_0^a \mu_W(u)\,\mathrm{d}u\right), \qquad S_D(a) = \exp\left(-\int_0^a \mu_D(u)\,\mathrm{d}u\right)$$

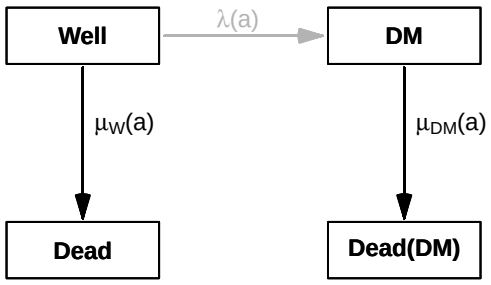
For the **conditional** YLL given attained age A, just use:

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

This implicitly assumes that persons in "Well" cannot contract "DM"

The immunity assumption — which is widely used in the literature

How the world looks



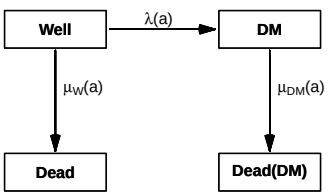
. . . with immunity to diabetes

Comparing DM and Well in the real world

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

still the same, but $S_W(t)$ should be:

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



Comparing DM and well in the real world

The survival function $S_W(a)$ is the sum of:

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

and

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

Comparing DM and well in the real world

The **conditional** survival function given **Well at** A is the sum of

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

$$\begin{aligned}\text{P}\{\text{DM}|\text{Well at } A\}(a) &= \int_A^a \lambda(s)\exp\left(-\int_A^s \mu_W(u) + \lambda(u)\,\mathrm{d}u\right) \\ &\qquad \times \exp\left(-\int_s^a \mu_D(u)\,\mathrm{d}u\right)\,\mathrm{d}s\end{aligned}$$

Note: This is **not** $S_W(a)/S_W(A)$ because we are not conditioning on being alive, but conditioning on being alive and well at age A

A brutal shortcut

. . . sooo hairy, so why don't we not just use the **total** population mortality, μ_T, and instead compare:

$$S_T(a) = \exp\left(-\int_0^a \mu_T(u)\,\mathrm{d}u\right), \qquad S_D(a) = \exp\left(-\int_0^a \mu_D(u)\,\mathrm{d}u\right)$$

- There is no simple relation between S_T and the correctly computed S_W so there is no guarantee that it will be useful, nor the direction of bias
- The comparison will be between a random person with diabetes and a random person (with or without diabetes)
- Empirical question whether this is a reasonable approximation

Practicals introduction

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`http://BendixCarstensen.com/Epi/Courses/EDEG2017`

Your turn to try:

- Not as bad as you may think:
- The `Epi` package has a couple of handy functions
  - `surv1` — computes a survival function from a mortality rate
  - `surv2` — computes a survival function for "Well" persons from two mortality rates and an incidence rate
  - `erl`, `yll` computes the expected residual life time and the years of life lost from two mortality rates and an incidence rate
  - access help by `?yll`.
- These are what you should use to do the calculations.
- — input is mortality and incidence rates in some form.
- Here is how to get your hands on those.

Danish diabetes data

```
> library( Epi )
> data( DMepi )
> dim( DMepi )

[1] 4000    8

> head( DMepi )

  sex A    P X D.nD     Y.nD D.DM       Y.DM
1   M 0 1996 1   28 35453.65    0  0.4757016
2   F 0 1996 9   19 33094.86    0  3.8767967
3   M 1 1996 4   23 36450.73    0  4.9199179
4   F 1 1996 7   19 34789.99    0  7.2484600
5   M 2 1996 7    7 35328.92    0 12.4743326
6   F 2 1996 2    8 33673.43    0  8.0951403

> w15 <- subset( DMepi, sex=="F" & P==2015 )
> w15 <- w15[order(w15$A),]
> dim( w15 )

[1] 100   8
```


Danish diabetes data

```
> w15 <- transform( w15, mW =        D.nD / Y.nD,  # no DM mortality
+                        iW =           X / Y.nD,  # DM  incidence
+                        mD = pmax(0,D.DM / Y.DM,na.rm=TRUE), # DM mortality
+                        mT =  (D.nD+D.DM)/(Y.nD+Y.DM) ) # total mortality
> Sw <- surv1( 1, w15$mW, A=65 )
> Sd <- surv1( 1, w15$mD, A=65 )
> cbind( Sw, Sd )[63:72,]

   age        A0       A65 age        A0       A65
63  62 0.9418470 1.0000000  62 0.8169978 1.0000000
64  63 0.9357472 1.0000000  63 0.7989680 1.0000000
65  64 0.9297246 1.0000000  64 0.7853495 1.0000000
66  65 0.9226514 1.0000000  65 0.7721934 1.0000000
67  66 0.9149180 0.9916183  66 0.7547042 0.9773513
68  67 0.9070037 0.9830406  67 0.7381123 0.9558646
69  68 0.8990846 0.9744576  68 0.7214464 0.9342820
70  69 0.8909150 0.9656030  69 0.7061645 0.9144918
71  70 0.8803810 0.9541860  70 0.6918332 0.8959326
72  71 0.8700207 0.9429572  71 0.6689975 0.8663601
```


Danish diabetes data exercise

- Exercises (which also contains the results you should see)
- pages 10–20: Simple calculations based on empirical rates
- — covered in the recap after coffee
- — link to the entire R-code on the course website `http://BendixCarstensen.com/Epi/Courses/EDEG2017`
- saves a lot of typing for you — but try to explore what you get
- pages 21–36: Calculations based on models for incidence and mortality 1996—2015.
- — partly covered in the recap, mainly the results on pp. 35–36.
- time permitting, recap will also cover more general aspects such as disease free time.

Practicals — recap

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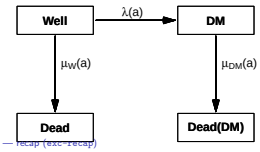
Recap: from probability theory to statistics:

- Data on:
  - diabetes and death events by diabetes status
  - risk time by diabetes status
- Fit models for the incidence and mortality rates
- Predict $\mu_W(a)$, $\lambda(a)$ and $\mu_D(a)$ at equidistant points of age
- Compute the YLL for say $A = 50, 60, \ldots$

Data

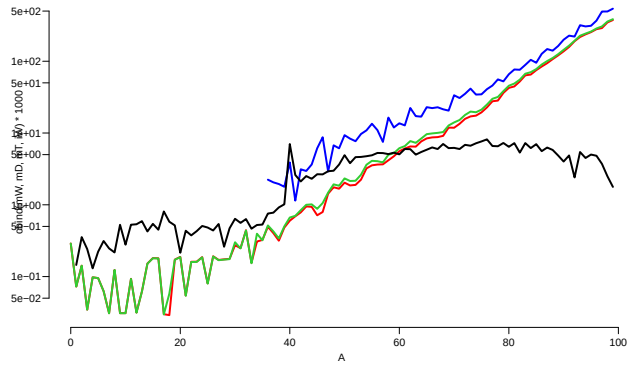
```
> library( Epi )
> data( DMepi )
> head( DMepi )

  sex A    P X D.nD     Y.nD D.DM       Y.DM
1   M 0 1996 1   28 35453.65    0  0.4757016
2   F 0 1996 9   19 33094.86    0  3.8767967
3   M 1 1996 4   23 36450.73    0  4.9199179
4   F 1 1996 7   19 34789.99    0  7.2484600
5   M 2 1996 7    7 35328.92    0 12.4743326
6   F 2 1996 2    8 33673.43    0  8.0951403
```



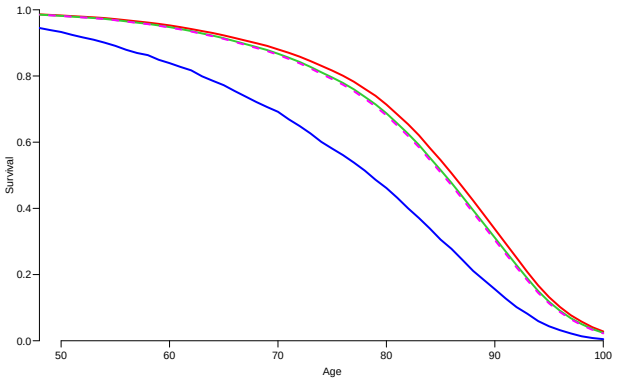

```
> w15 <- subset( DMepi, sex=="F" & P==2015 )
> w15 <- w15[order(w15$A),] # data ordered by age
> head( w15 )

     sex A    P  X D.nD     Y.nD D.DM      Y.DM
3802   F 0 2015  0    8 27692.48    0  0.000000
3804   F 1 2015  4    2 27558.64    0  3.532512
3806   F 2 2015 10    4 28204.69    0  9.576318
3808   F 3 2015  7    1 28916.24    0 14.725530
3810   F 4 2015  4    3 30704.35    0 13.488022
3812   F 5 2015  7    3 31504.41    0 22.655031

> w15 <- transform( w15, mW =        D.nD/Y.nD,
+                        iW =           X/Y.nD,
+                        mD = pmax(0,D.DM/Y.DM,na.rm=TRUE),
+                        mT = (D.nD+D.DM)/(Y.nD+Y.DM) )
> str( w15 )
```



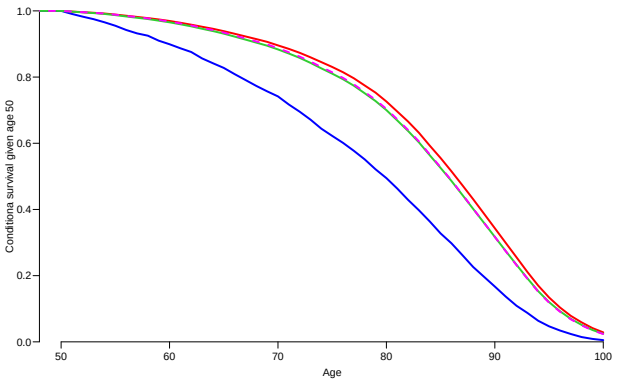
```
'data.frame': 100 obs. of  12 variables:
 $ sex : Factor w/ 2 levels "M","F": 2 2 2 2 2 2 2 2 2 2 ...
 $ A   : num  0 1 2 3 4 5 6 7 8 9 ...
 $ P   : num  2015 2015 2015 2015 2015 ...
 $ X   : num  0 4 10 7 4 7 10 8 7 17 ...
 $ D.nD: num  8 2 4 1 3 3 2 1 4 1 ...
 $ Y.nD: num  27692 27559 28205 28916 30704 ...
 $ D.DM: num  0 0 0 0 0 0 0 0 0 0 ...
 $ Y.DM: num  0 3.53 9.58 14.73 13.49 ...
 $ mW  : num  2.89e-04 7.26e-05 1.42e-04 3.46e-05 9.77e-05 ...
 $ iW  : num  0 0.000145 0.000355 0.000242 0.00013 ...
 $ mD  : num  0 0 0 0 0 0 0 0 0 0 ...
 $ mT  : num  2.89e-04 7.26e-05 1.42e-04 3.46e-05 9.77e-05 ...

> with( w15, matplot( A, cbind( mW, mD, mT, iW)*1000,
+                     log="y", lwd=3, type="l", lty=1,
+                     col=c("red","blue","limegreen","black") ) )
```


```
> head( surv1( 1, w15$mW, A=50 ) )

  age        A0 A50
1   0 1.0000000   1
2   1 0.9997112   1
3   2 0.9996386   1
4   3 0.9994968   1
5   4 0.9994623   1
6   5 0.9993646   1

> with( w15, matplot( surv1( 1, mW, A=50 )[,1],
+                cbind( surv1( 1, mW, A=50 )[,2],
+                       surv1( 1, mD, A=50 )[,2],
+                       surv1( 1, mT, A=50 )[,2],
+                       surv2( 1, mW, mD, iW, A=50 )[,2] ),
+                       lwd=3, type="l", lty=c(1,1,1,2), yaxs="i", ylim=0:1,
+                       xlab="Age", ylab="Survival",
+                       col=c("red","blue","limegreen","magenta"), xlim=c(50,100) )
```



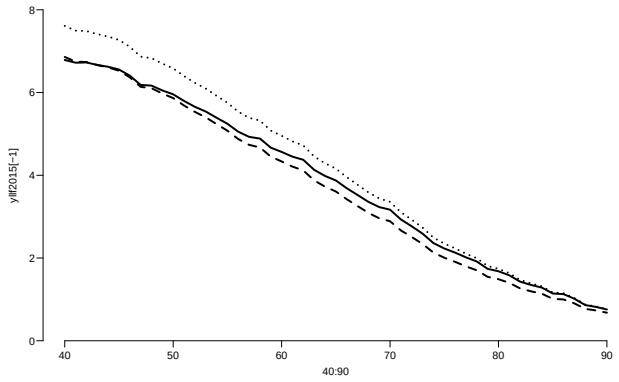

```
> with( w15, matplot( surv1( 1, mW, A=50 )[,1],
+               cbind( surv1( 1, mW, A=50 )[,3],
+                      surv1( 1, mD, A=50 )[,3],
+                      surv1( 1, mT, A=50 )[,3],
+                      surv2( 1, mW, mD, iW, A=50 )[,3] ),
+                      lwd=3, type="l", lty=c(1,1,1,2), yaxs="i", ylim=0:1,
+                      xlab="Age", ylab="Conditiona survival given age 50",
+                      col=c("red","blue","limegreen","magenta"), xlim=c(50,100) )
```


```
> with( w15, yll( int=1, muW=mW, muD=mD, lam=iW, A=c(40,50,60,70,80) ) )

       A0       A40       A50       A60       A70       A80
43.202977  6.787443  5.956740  4.564222  3.168186  1.680120

> with( w15, yll( int=1, muW=mW, muD=mD, A=c(40,50,60,70,80), n=F ) )

       A0       A40       A50       A60       A70       A80
44.155298  7.610837  6.584063  4.954874  3.358854  1.739498

> with( w15, yll( int=1, muW=mT, muD=mD, A=c(40,50,60,70,80), n=F ) )

       A0       A40       A50       A60       A70       A80
43.399315  6.859584  5.865477  4.333904  2.888800  1.488385



> yllf2015  <- with( w15, yll( int=1, muW=mW, muD=mD, lam=iW, A=c(40:90) ) )
> yllf2015x <- with( w15, yll( int=1, muW=mW, muD=mD, A=c(40:90) ) )
```



```
NOTE: Calculations assume that Well persons cannot get Ill (quite silly!).

> yllf2015t <- with( w15, yll( int=1, muW=mT, muD=mD, A=c(40:90), note=F ) )
>  plot( 40:90, yllf2015 [-1], type="l", lwd=3, ylim=c(0,8), yaxs="i" )
> lines( 40:90, yllf2015x[-1], type="l", lwd=3, lty="12" )
> lines( 40:90, yllf2015t[-1], type="l", lwd=3, lty="53" )
```

From probability theory to statistics: models

```
> # knots used for splines in all models
> a.kn <- seq(40,95,,6)
> p.kn <- seq(1996,2011,,4)
> c.kn <- seq(1910,1970,,6)
> #
> # APC-model for death for non-DM men
> mW.m <- glm( D.nD ~ Ns(  A,knots=a.kn) +
+                     Ns(P  ,knots=p.kn) +
+                     Ns(P-A,knots=c.kn),
+           offset = log(Y.nD),
+           family = poisson,
+             data = subset( DMepi, sex=="M" & A>29 ) )
> iW.m <- update( mW.m,    X ~ . )
> mD.m <- update( mW.m, D.DM ~ . , offset = log(Y.DM) )
```

. . . estimates mortality (and incidence) rates over the grid:

- age: $30 - 99$
- calendar time: $1996 - 2015$

From probability theory to statistics: predictions

Mortality rates for men in ages $30 - 100$ using rates from 2012:

```
> nd <- data.frame( A = seq(30,99.8,0.2)+0.1,
+                   P = 2012,
+                 Y.nD = 1,
+                 Y.DM = 1,
+                 Y.T  = 1 )
> muW.m <- ci.pred( mW.m, nd )[,1]
> muD.m <- ci.pred( mD.m, nd )[,1]
> lam.m <- ci.pred( iW.m, nd )[,1]
> cbind( nd$A, muW.m, muD.m, lam.m )[200+0:3,]

              muW.m      muD.m      lam.m
200 69.9 0.02017309 0.04012865 0.01191880
201 70.1 0.02056253 0.04076278 0.01195226
202 70.3 0.02096210 0.04141048 0.01198473
203 70.5 0.02137211 0.04207207 0.01201617
```

Rate representation when used as arguments in integrals:
Compute the function values in small equidistant intervals

From probability theory to statistics: YLL calculation

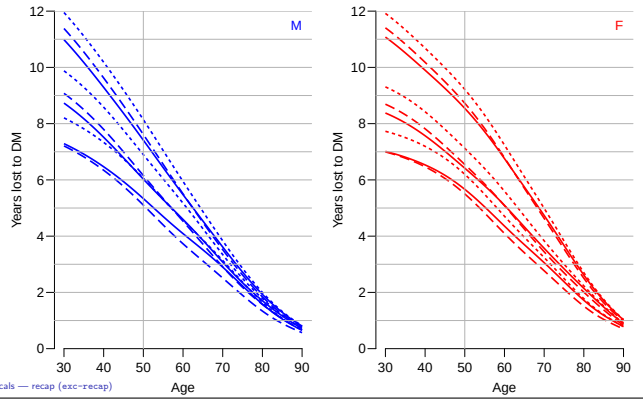
Epi package for **R** contains functions erl and yll that implements the formulae:

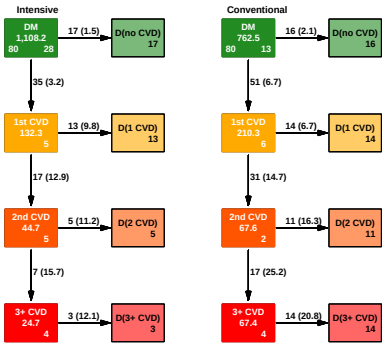
```
> ( YLL.m <- yll( int=0.2,
+                 muW=muW.m, muD=muD.m, lam=lam.m,
+                 A=c(50,55,60), age.in=30 ) )

     A30      A50      A55      A60
7.464539 5.273809 4.656095 4.040464
```

This is then done for different conditioning ages (A), men/women and based on predicted rates from 1996 – 2016.

YLL calculations

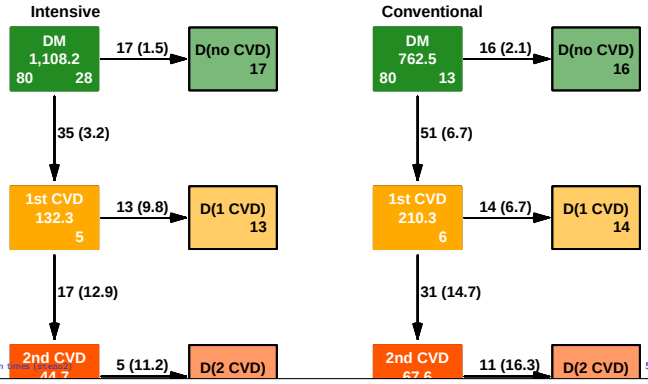
- Compute YLL for all combinations of:
  - sex
  - conditioning ages 30–90
  - dates 1996–2016
  - methods: Susceptible / Immune / Total approx.
- Show for select combinations





Years of Life Lost to diabetes: Conclusion

- Use a model
- for **all** your rates
- use your probability theory
- credible models for rates requires:
  smooth parametric function of age and calendar time
- continuous time formulation simplifies concepts and computing
- using non-DM mortality (immunity assumption) overestimates YLL
- If you cannot do it correctly for want of data:
  compare with the **total** population mortality
- but it may be misleading too. . .



Sojourn times

Years of Life Lost to Diabetes
LEAD symposiun at EDEG, Dubrovnik,
6 May 2017

`http://BendixCarstensen.com/Epi/Courses/EDEG2017`

Models

- As we did for mortality and incidence rates:
- Fit a model for each of the transitions
- We used proportional hazards for:
  - CVD-rates
  - mortality rates
- rates depending on age, sex, randomization group and CVD status

And now for something slightly different

- YLL is really difference in the time spent in the state "Alive"
- There might be more states than just "Alive" and "Dead"
- For example how much time is spent free of a particuar complication?
- Example here: Steno 2 study, and time spent with CVD.

Hazard ratios

	CVD event	Mortality
HR, Int. vs. Conv.	0.55 (0.39;0.77)	0.83 (0.54; 1.30)
H_0: PH btw. CVD groups	p=0.261	p=0.438
H_0: HR = 1	p=0.001	p=0.425
HR vs. 0 CVD events:		
0 (ref.)	1.00	1.00
1	2.43 (1.67;3.52)	3.08 (1.82; 5.19)
2	3.48 (2.15;5.64)	4.42 (2.36; 8.29)
3+		7.76 (4.11;14.65)

Diabetologia
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CrossMark

ARTICLE

Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

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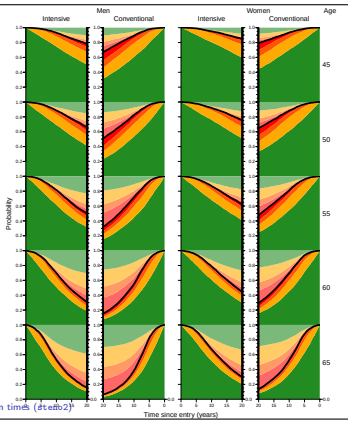
Abstract
Aims/hypothesis The aim of this work was to study the potential long-term impact of a 7.8 years intensified multifactorial pharmacological approaches. After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group. The pri-

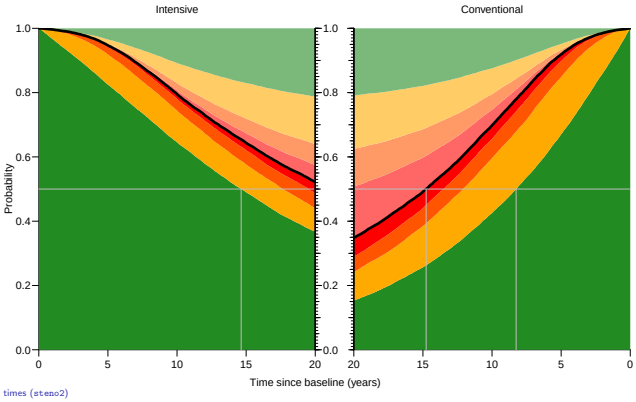
Practical modeling of rates

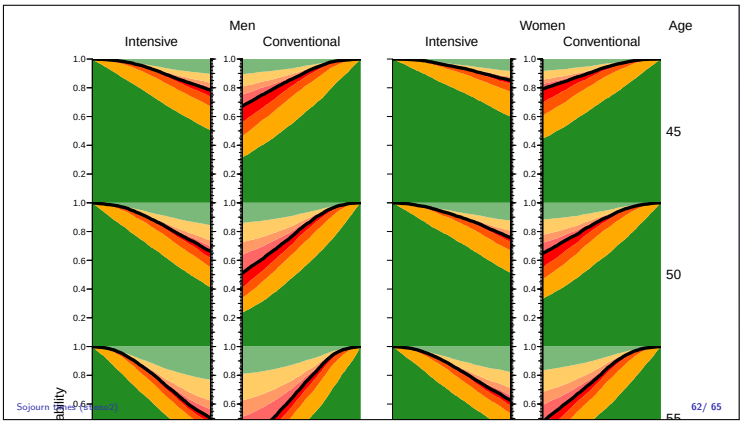
- Cut the follow-up time for each person by state
- Split the follow-up time in 1-month intervals
- Poisson model with smooth effect of time since randomization, sex and age at entry:
  - HR estimates
  - Estimates of baseline hazard
  - Hazard for any set of covariates
- Allows calcualtion of expected sojourn time in any state
- — analytically this is totally intractable. . .

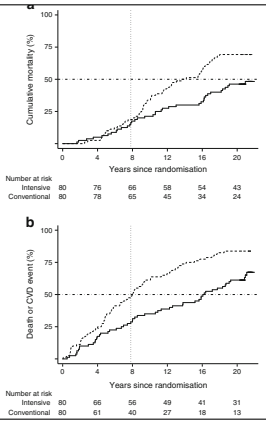
Estimating sojourn times

- Use simulation of the state occupancy probabilities:
- `Lexis` machinery in the `Epi` package for multistate representation
- `splitLexis` to subdivide follow-up for analysis
- `simLexis` for simulation to derive probabilities and sojourn times
- — simulates a cohort through the model, so probabilities are just empirical fractions









between groups (HR 0.83 [95% CI 0.54, 1.30]; $p=0.43$). Thus, the reduced mortality was primarily due to reduced risk of CVD.

The patients in the intensive group experienced a total of 90 cardiovascular events vs 195 events in the conventional group. Nineteen intensive-group patients (24%) vs 34 conventional-group patients (43%) experienced more than one cardiovascular event. No significant between-group difference in the distribution of specific cardiovascular first-event types was observed (Table 2 and Fig. 4).

Microvascular complications Hazard rates of progression rates in microvascular complications compared with baseline status are shown Fig. 3. Sensitivity analyses showed a negligible effect of the random dates imputation.

Progression of retinopathy was decreased by 33% in the intensive-therapy group (Fig. 5). Blindness in at least one eye was reduced in the intensive-therapy group with an HR of 0.47 (95% CI 0.23, 0.98, $p=0.044$). Autonomic neuropathy was decreased by 41% in the intensive-therapy group (Fig. 5). We observed no difference between groups in the progression of peripheral neuropathy (Fig. 5). Progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group (Fig. 5). Ten patients in the conventional-therapy groups vs five patients in the intensive-therapy group progressed to end-stage renal disease ($p=0.061$).

Discussion

Expected lifetime (years) and $-$YLL (YLG) during the first 20 years after baseline by sex, age, treatment group and CVD status.

sex		Men			Women		
state	age	Int.	Conv.	YLG	Int.	Conv.	YLG
Alive	45	18.5	17.5	1.0	19.1	18.4	0.7
	50	17.2	16.1	1.1	18.0	17.2	0.8
	55	15.6	13.8	1.8	17.4	15.9	1.6
	60	13.9	11.6	2.2	15.5	13.7	1.8
	65	11.2	9.5	1.8	13.3	11.4	2.0
No CVD	45	14.9	12.5	2.4	15.8	14.3	1.5
	50	14.0	11.1	2.9	15.1	12.9	2.2
	55	12.2	9.7	2.5	14.3	11.6	2.7
	60	10.9	8.2	2.7	12.4	9.9	2.6
	65	9.0	6.7	2.2	10.7	8.3	2.4

Expected lifetime and YLL (well, gained)

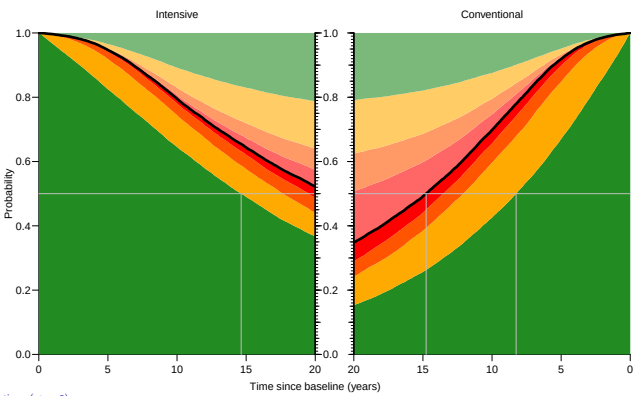
Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

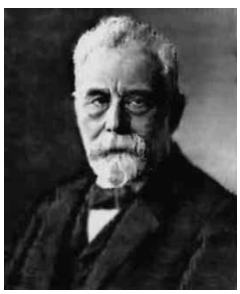
State	Intensive	Conventional	Int.$-$Conv.
Alive	15.6	14.1	1.5
No CVD	12.7	10.0	2.6
Any CVD	3.0	4.1	-1.1

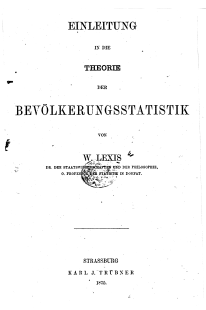
- Simulate a cohort with same covariate dist'n as the study
- **Population averaged** years gained alive / CVD-free
- Refer **only** to the Steno 2 trial population
- **Not** generalizable
- . . . but we have a **model**

History

- `Epi` package grew out of "Statistical Practice in Epidemiology with R" annually since 2002 in Tartu Estonia `http://BendixCarstensen.com/SPE`
- `Lexis` machinery conceived by Martyn Plummer, IARC
- Naming originally by David Clayton & Michael Hills, `stlexis` in Stata, later renamed `stsplit`
- David Clayton wrote a `lexis` function for the `Epi` package. Obsolete now.







Thanks for your attention