

Short Course in Epidemiology Advanced Stream

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Types of measures

- ▶ **Status measures:**
what is the **state of affairs** at a given date (or age, say)
Prevalence
- ▶ **Flow measures:**
what are **rates of change** at a given date (or age, say)
Incidence, Mortality

Population based epidemiology (epi-intro)

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Advanced stream overview

- ▶ 0a: About the stream and practicals
- ▶ 0b: Tally of computing resources
- ▶ 1a: Population Surveillance & cetera (EG)
- ▶ 1b: Population based Epidemiology, Prevalence (BxC)
- ▶ 1c: Prevalence practical (Section 1.2, p. 2)
- ▶ Break
- ▶ 1Ia: US Case examples (EG)
- ▶ 1Ib: Population dynamics, rates (BxC)
- ▶ 1Ic: Incidence practical (section 1.3, p. 4)
- ▶ 1Id: Mortality, survival and adherence to this world (BxC)
- ▶ III: Commercial

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Prevalence

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prev-ana

Population based epidemiology

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epi-intro

Prevalence

- ▶ What is the fraction with diabetes among all alive at a given date
— **empirical** prevalence
- ▶ What is the probability that a randomly chosen (living) person has diabetes
— **theoretical** prevalence

Prevalence (prev-ana)

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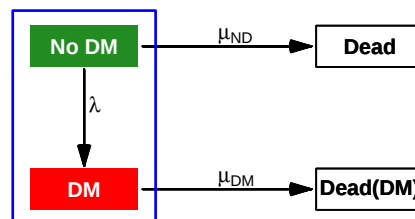
Population based epidemiology

- ▶ What goes on in the population **as such**
- ▶ Descriptive epidemiology
- ▶ Medical demography:
 - ▶ how many **are affected** by diabetes
— at a given date
 - ▶ how many **acquire** diabetes
— in a given timespan
 - ▶ how many **die** (w/o diabetes)
— in a given timespan
- ▶ Prevalence
- ▶ Incidence
- ▶ Mortality

Population based epidemiology (epi-intro)

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Components of diabetes prevalence



Prevalence (prev-ana)

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Prevalence — data

- ▶ **empirical** prevalence:
 - ▶ ratio of counts (affected / total)
 - ▶ requires a specific population
(e.g. 50–59 year old women at 1 Jan 2008)
- ▶ **theoretical** prevalence
 - ▶ requires a statistical model for binomial outcome, e.g.

$$P\{DM\} = f(a, p)$$

- ▶ "this is how data **could** have been generated"
- ▶ **Estimated** probability...
- ▶ based on data (X, N) for different values of a and p

Your turn — 1.2 Prevalence, p. 2

Prevalence (prev-ana)

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Analyzing prevalence

Assumptions in statistical model:

- ▶ Prevalence varies **continuously** with age
- ▶ Prevalence varies **smoothly** with age

Data for a statistical model:

- ▶ No. prevalent DM cases in age classes
- ▶ No. total population in age classes
- ▶ Quantitative age in each age class (midpoint, e.g.)

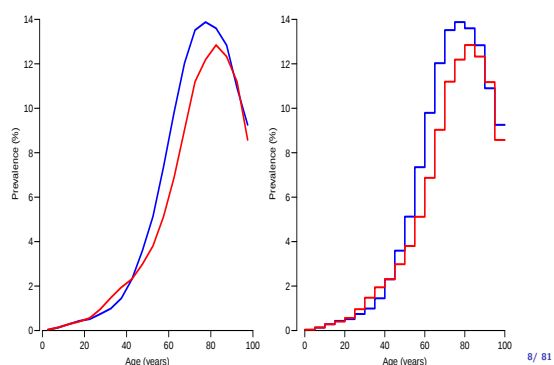
— age classes as small as possible

— modeling smooths the random variation between classes.

Prevalence (prev-ana)

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Analyzing prevalence



Prevalence (prev-ana)

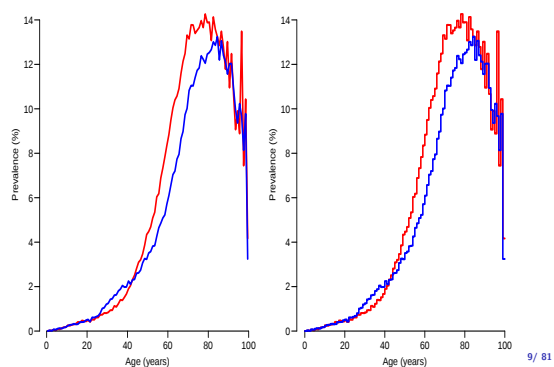
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Population dynamics

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pop

Analyzing prevalence



Prevalence (prev-ana)

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What goes on in a population?

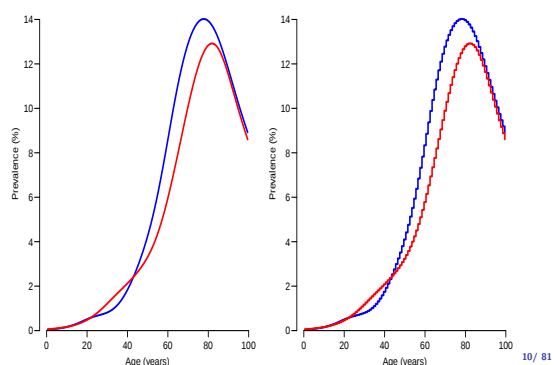
- ▶ Birth, death
- ▶ Birth, disease, death
- ▶ Birth, disease (duration), death
- ▶ Diseased persons (prevalence (p)):
 - ▶ increases by new cases (incidence rate, λ)
 - ▶ decreases by cases dying (mortality rate, μ)
 - ▶ increases by duration from disease to death, y
 - the longer duration the higher the prevalence.
- ▶ In a small interval dt :

$$p(t + dt) = p(t) - \mu dt + \lambda dt$$
- ▶ No change in prevalence if $\lambda = \mu$

Population dynamics (pop)

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Analyzing prevalence



Prevalence (prev-ana)

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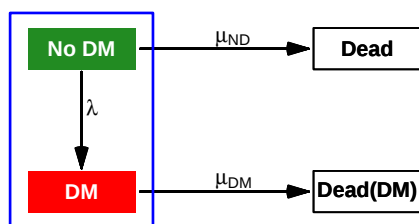
Relationships

- ▶ $p = \lambda \times y$:
prevalence equals incidence times duration.
 - ▶ X new cases per population N per year
 - ▶ $\lambda = X/N$
 - ▶ each case lasting y years: Xy cases present
 - ▶ Prevalence $p = Xy/N = \lambda y$
- ▶ — only in steady state
- ▶ — only if independent of age
- ▶ Mainly a **qualitative** relationship
- ▶ because populations are **not** in steady state.

Population dynamics (pop)

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Components of diabetes prevalence



Quantities determining prevalence are the rates

The DM register

One line is one person:

```

> load( file="../data/dr.Rda" )
> nrow( subset( dr, floor(doDM)==2006 &
+           (doDM-doBth)>=60 &
+           (doDM-doBth)< 65 ) )
[1] 3480
  
```

Rates determine all

If we know the rates, then we know:

- ▶ prevalence
- ▶ survival
- ▶ lifespan with DM
- ▶ lifespan without DM
- ▶ years of life lost
- ▶ lifespan with DM and CVD
- ▶ etc. . .

. . . meaning that we can **simulate** everything from rates.

Note: rates depend on age, duration, calendar time . . .

Population data I

One line is one age×period class

```

> load( file="../data/Ydk.Rda" )
> str( Ydk )
'data.frame': 8400 obs. of  4 variables:
 $ sex: Factor w/ 2 levels "M","F": 1 2 1 2 1 2 1 2 1 2 ...
 $ A  : num  0 0 1 1 1 2 2 3 3 4 4 ...
 $ P  : num  1971 1971 1971 1971 1971 1971 ...
 $ Y  : num  37139 35129 36134 34223 37113 ...
> head( Ydk )
  sex A  P      Y
1  M  0 1971 37139.17
2  F  0 1971 35128.83
3  M  1 1971 36133.67
4  F  1 1971 34223.00
5  M  2 1971 37113.00
6  F  2 1971 34926.33
  
```

Incidence rates

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Population data II

```

> subset( Ydk, A>=60 & A<65 & P==2006 )
  sex A  P      Y
7121 M 60 2006 40160.17
7122 F 60 2006 39678.17
7123 M 61 2006 38069.33
7124 F 61 2006 37952.83
7125 M 62 2006 35100.50
7126 F 62 2006 35562.67
7127 M 63 2006 32311.67
7128 F 63 2006 32980.00
7129 M 64 2006 29321.67
7130 F 64 2006 30069.83
> sum( subset( Ydk, A>59 & A<65 & P==2006 )$Y )
[1] 351206.8
  
```

Incidence rate of DM

- ▶ **Rate**: events per time
- ▶ **Events**: New cases of DM
- ▶ **(risk) Time**: Time lived by persons susceptible to the event

Events by age and sex I

Tables of events and PY by sex:

```

> ( D <- with( subset(dr,floor(doDM)==2006),
+             table( floor((doDM-doBth)/5), sex ) ) )
  sex
    M  F
0   26 29
5   41 38
10  79 85
15  55 101
20  73 101
25 107 158
30 178 275
35 352 317
40 597 608
45 882 614
50 1307 894
55 1659 1152
  
```

Events by age and sex II

60	2038	1442
65	1583	1342
70	1195	1175
75	950	1096
80	634	834
85	245	470
90	70	153
95	12	31
100	0	2

Incidence data II

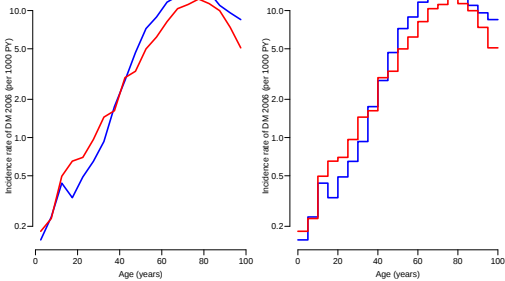
60	2038	1442	174963.333	176243.500	11.648	8.182
65	1583	1342	121788.167	129678.000	12.998	10.349
70	1195	1175	91038.500	105248.833	13.126	11.164
75	950	1096	68313.833	88990.167	13.906	12.316
80	634	834	45502.167	73541.667	13.933	11.341
85	245	470	22305.833	47119.833	10.984	9.975
90	70	153	7295.500	20757.833	9.595	7.371
95	12	31	1413.667	6093.667	8.489	5.087

Person-years by age and sex I

Tables of events and PY by sex:

```
> ( Y <- xtabs( Y ~ I(floor(A/5)*5) + sex, data=subset(Ydk,P==2006) ) )
I(floor(A/5) * 5)      sex      M      F
0 166333.333 158679.833
5 173061.833 164956.500
10 180623.833 171379.833
15 163695.000 154952.667
20 149068.000 144681.333
25 164809.667 163738.500
30 191372.167 189887.167
35 200951.833 194950.833
40 212268.000 205365.000
45 188801.833 184550.167
50 181232.333 179168.000
55 186422.833 186106.500
60 174963.333 176243.500
```

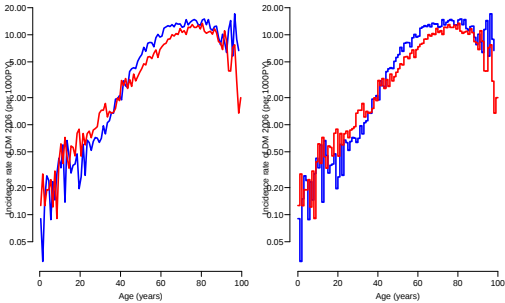
Incidence curves



Person-years by age and sex II

65	121788.167	129678.000
70	91038.500	105248.833
75	68313.833	88990.167
80	45502.167	73541.667
85	22305.833	47119.833
90	7295.500	20757.833
95	1413.667	6093.667

Incidence curves

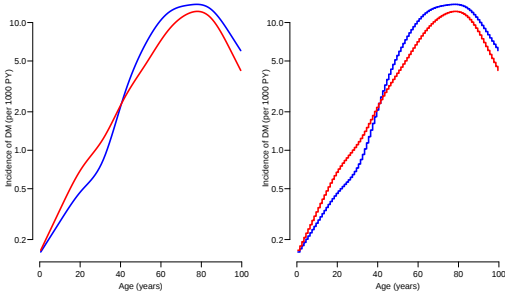


Incidence data I

Divide tables of events and PY by sex:

```
> D <- D[1:20,]
> inc <- D/Y * 1000
> round( cbind( D, Y, inc ), 3 )
      M      F      M      F      M      F
0 26 29 166333.333 158679.833 0.156 0.183
5 41 38 173061.833 164956.500 0.237 0.230
10 79 85 180623.833 171379.833 0.437 0.496
15 55 101 163695.000 154952.667 0.336 0.652
20 73 101 149068.000 144681.333 0.490 0.698
25 107 158 164809.667 163738.500 0.649 0.965
30 178 275 191372.167 189887.167 0.930 1.448
35 352 317 200951.833 194950.833 1.752 1.626
40 597 608 212268.000 205365.000 2.812 2.961
45 882 614 188801.833 184550.167 4.672 3.327
50 1307 894 181232.333 179168.000 7.212 4.990
55 1659 1152 186422.833 186106.500 8.899 6.190
```

Incidence curves



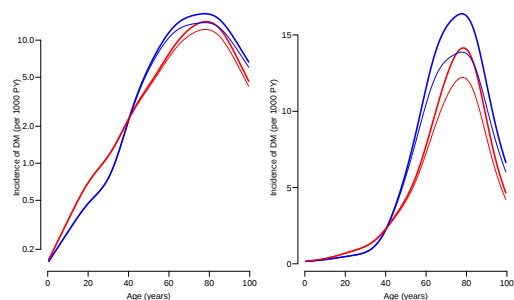
People only get diabetes once. . . I

- ▶ In our calculations we used the **entire** population-PY as denominator
- ▶ . . . but it should only be those **susceptible** to DM,
- ▶ that is, those without a diagnosis.
- ▶ So we should subtract the PY among in DM-persons from the population PY

Incidence rates (inc-ana)

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Incidence curves



Incidence rates (inc-ana)

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People only get diabetes once. . . I

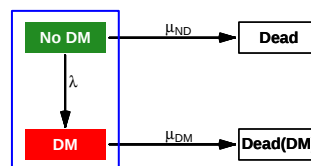
```
> dmY <- Y * 0
> for( sx in c("M","F") )
+ for( aa in 1:20 )
+ dmY[aa,sx] <- with( subset(dr,sex==sx),
+ sum( pmax( 0, pmin(2007,doBth+ aa *5,doDth,na.rm=TRUE) -
+ pmax(2006,doBth+(aa-1)*5,doDM ) ) ) )
> round( 100*t(dmY/Y), 1 )
      I(floor(A/5) * 5)
sex  0   5   10   15   20   25   30   35   40   45   50   55   60   65   70
M  0.0  0.1  0.3  0.4  0.5  0.7  1.0  1.5  2.3  3.8  5.5  7.7  10.6 12.8 14.9
F  0.0  0.1  0.3  0.4  0.6  0.9  1.5  2.1  2.5  3.2  4.2  5.5  7.3  9.6 12.1
      I(floor(A/5) * 5)
sex    95
M     9.3
F     8.3
```

Incidence rates (inc-ana)

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Analysis of rates

- ▶ Get the denominator right
- ▶ Count only the transitions of interest



Your turn — 1.3 Incidence, p 4.

Incidence rates (inc-ana)

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Incidence data I

Divide tables of events and PY by sex:

```
> round( cbind( D, Y-dmY, inc=D/(Y-dmY)*1000 ), 3 )
      M   F      M   F      M   F
0    26  29 166271.972 158616.314  0.156  0.183
5    41  38 172835.243 164710.285  0.237  0.231
10   79  85 180075.719 170846.886  0.439  0.498
15   55 101 162961.780 154280.319  0.338  0.655
20   73 101 148291.398 143828.127  0.492  0.702
25  107 158 163576.325 162209.046  0.654  0.974
30  178 275 189413.859 186995.975  0.940  1.471
35  352 317 197867.377 190940.455  1.779  1.660
40  597 608 207282.839 200196.856  2.880  3.037
45  882 614 181720.264 178650.303  4.854  3.437
50 1307 894 171227.261 171672.990  7.633  5.208
55 1659 1152 172004.168 175814.414  9.645  6.552
60 2038 1442 156393.482 163348.876 13.031  8.828
65 1583 1342 106147.963 117196.741 14.913 11.451
```

Incidence rates (inc-ana)

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Mortality rates

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mort-ana

Incidence data II

```
70 1195 1175 77472.789 92552.577 15.425 12.695
75 950 1096 58019.610 77074.413 16.374 14.220
80 634 834 38714.886 63474.716 16.376 13.139
85 245 470 19202.411 40731.951 12.759 11.539
90 70 153 6412.488 18248.537 10.916 8.384
95 12 31 1281.738 5585.846 9.362 5.550
```

Incidence rates (inc-ana)

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Mortality

- ▶ Mortality rates ↔ Survival
- ▶ . . . but **only** if we have an origin
- ▶ **rates** are instantaneous — independent of previous history
- ▶ **survival** is a cumulative measure:
- ▶ time **since** some time:
 - ▶ birth
 - ▶ DM diagnosis
 - ▶ Start of treatment
 - ▶ Inclusion in clinical trial
 - ▶ Inclusion in cohort study — meaningful?

Mortality rates (mort-ana)

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```
> library( Epi )
> load( file = "../data/dr.Rda" )
> load( file = "../data/dmY.Rda" )
> dd <- with( subset( dr, floor(doDth)==2006 ),
+           table( floor(doDth-doBth), sex ) )
> str( dd )
'table' int [1:88, 1:2] 0 1 1 0 2 0 1 1 0 2 ...
- attr(*, "dimnames")=List of 2
..$      : chr [1:88] "0" "12" "18" "20" ...
..$ sex:  chr [1:2] "M" "F"
> dmD <- dmY * 0 # a table of 0s with same structure as the person-years
> for( aa in intersect( dimnames(dd)[[1]], # fill in deaths where they are
+                     dimnames(dmD)[[1]] ) )
+   dmD[aa,] <- dd[aa,]
> cbind( dmD, dmY )
```

Mortality rates (mort-ana)

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```
65 97 63 3175.0308881 2444.3942450
66 104 60 3218.0856812 2411.1838445
67 147 74 3067.7435265 2471.9917799
68 136 67 3135.4591450 2565.0095692
69 131 84 3043.8849018 2588.6799548
70 141 90 2935.6734375 2583.8702941
71 145 93 2919.1940537 2572.7331335
72 150 101 2729.4571012 2578.1553072
73 147 123 2572.6509370 2454.7790567
74 169 101 2408.7354579 2506.7189450
75 180 129 2268.5285174 2500.4774297
76 175 127 2177.3356298 2400.9440466
77 197 141 2113.8368364 2421.5974775
78 183 172 1935.0518805 2343.8443926
79 185 174 1799.4706737 2248.8899836
80 212 196 1689.5302632 2199.1535400
81 195 154 1533.6681125 2165.9042405
82 197 203 1326.5886888 2017.5379713
83 186 209 1157.1877826 1880.7084905
84 149 201 1080.3061885 1803.6466494
85 161 227 944.8050421 1736.7338926
86 145 195 753.8669682 1501.4529501
```

Mortality rates (mort-ana)

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	M	F	M	F
0	0	2	0.5991139	0.8834697
1	0	0	2.2238462	5.1816978
2	0	0	10.0438410	14.6850286
3	0	0	17.0520062	16.4032660
4	0	0	31.4427208	26.3662713
5	0	0	25.4418535	36.5189540
6	0	0	34.6849836	40.7997248
7	0	0	41.2744337	51.0909042
8	0	0	52.6381848	56.9708197
9	0	0	72.5509094	60.8343396
10	0	0	85.3786136	85.2971495
11	0	0	97.2820296	92.0268266
12	1	0	120.0022359	111.8253605
13	0	0	115.8396328	129.0822457
14	0	0	129.6119440	114.7156362
15	0	0	131.8663390	121.9779585
16	0	0	137.7102903	121.6464603
17	0	0	146.4369793	137.8939167
18	1	0	157.8277979	142.3506072
19	0	0	159.3784021	148.4783878
20	0	1	149.7101520	154.7186798

Mortality rates (mort-ana)

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```
87 123 195 571.6494811 1213.5076211
88 118 190 479.8750475 1059.2705835
89 96 182 353.2254999 876.9174655
90 76 148 297.9148159 710.0238486
91 63 152 226.3693954 616.3634914
92 72 136 167.5491735 521.1093040
93 50 94 117.0354553 395.9485944
94 29 87 74.1429975 265.8511126
95 19 58 54.8777396 186.8722191
96 17 51 35.8853082 134.1148951
97 7 44 21.2913490 94.5064904
98 9 22 12.3662040 56.3150190
99 3 20 7.5076243 36.0117959
```

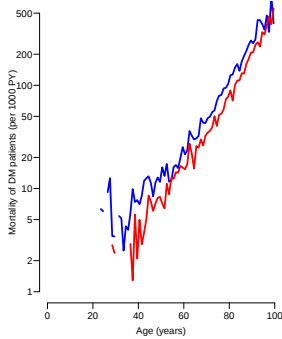
Mortality rates (mort-ana)

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21	2	0	159.8240811	167.7973905
22	0	1	142.4998350	147.8355276
23	1	0	158.2059093	181.0933141
24	1	0	166.3616880	201.7611598
25	0	1	198.0180497	219.7468375
26	2	0	217.0691592	241.7829944
27	3	0	238.0459089	292.6649769
28	1	1	289.0175594	354.5225200
29	1	1	291.1906626	420.7362345
30	0	0	337.3480178	465.0634935
31	2	1	369.8610480	535.5297856
32	2	0	388.2872535	575.6638541
33	1	0	399.5219924	644.9040345
34	2	2	463.2897195	670.0309441
35	2	0	503.4987334	697.1798589
36	3	2	519.7317942	691.0730864
37	6	1	608.5930030	777.7685538
38	5	5	675.9224563	891.2704106
39	6	2	776.7104921	953.0860758
40	6	5	851.7037109	1005.1466880
41	8	3	943.1357642	1043.2090555
42	12	4	1014.2465616	1074.4989623

Mortality rates (mort-ana)

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... not credible

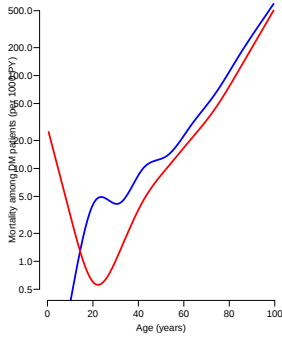
Mortality rates (mort-ana)

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43	13	5	1032.9122856	993.8265132
44	15	9	1143.1631323	1051.4625842
45	14	8	1236.7600363	1071.9565711
46	11	7	1311.7568816	1154.2537850
47	16	8	1408.1272657	1116.3735545
48	19	10	1486.4897341	1230.9328330
49	19	11	1638.4353889	1326.3465553
50	29	10	1806.6080278	1398.7197564
51	25	9	1889.1044999	1401.0834764
52	34	17	1965.9349339	1530.4011980
53	25	14	2144.9687562	1591.7855328
54	26	20	2198.4565389	1573.0196803
55	38	21	2356.6929735	1692.9809287
56	43	27	2547.1730908	1881.0030712
57	44	29	2794.6999525	2036.3213516
58	63	37	3185.4952440	2237.9205234
59	89	39	3534.6040233	2443.8599857
60	82	39	3830.5961627	2543.1885368
61	90	45	3853.8911425	2623.7722501
62	136	71	3782.6235474	2608.7045714
63	119	57	3657.8934755	2619.3721537
64	103	39	3444.8469698	2499.5860958

Mortality rates (mort-ana)

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Mortality rates (mort-ana)

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Mortality and duration I

Not meaningful without conditioning on age
What is the survival of a person diagnosed at age 60?

```
> dr60 <- subset( dr, floor(doDM-doBth)== 60 &
+               doDM >1995 )
> D60 <- with( dr60, table( floor(doDth-doDM), sex ) )
```

This is deaths among persons diagnosed in age 60

Survival curve I

$S(t) = (1 - \mu_0) \times (1 - \mu_1) \times (1 - \mu_2) \times \dots$

```
> ( p60 <- 1 - D60/Y60 )
sex      M      F
0  0.9665625 0.9693842
1  0.9745237 0.9823014
2  0.9765453 0.9810227
3  0.9740970 0.9826913
4  0.9753110 0.9824754
5  0.9661094 0.9817572
6  0.9700272 0.9822702
7  0.9543746 0.9737208
8  0.9631180 0.9754235
```

Mortality and duration I

But we also need PY

```
> Y60 <- D60 * 0
> for( sx in dimnames(Y60)[[2]] )
+ for( dd in dimnames(Y60)[[1]] )
+ Y60[dd,sx] <- with( subset( dr60, sex==sx ),
+                   sum( pmax( pmin(2012,      # end of FU
+                                doDth,      # in duration dd
+                                doDM+as.numeric(dd)+1,
+                                na.rm=TRUE) -
+                                (doDM+as.numeric(dd)), # start of FU
+                                0 ) ) ) # discard negative FU
> cbind( D60, round(Y60,1), round(1000*D60/Y60,1) )
```

Survival curve II

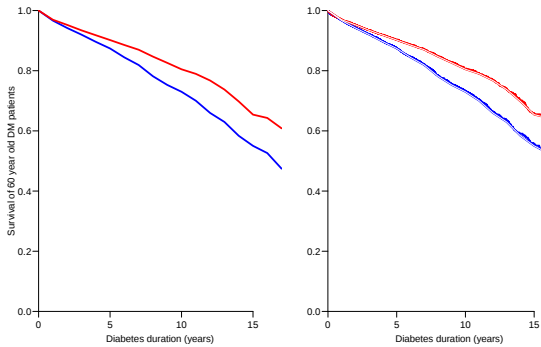
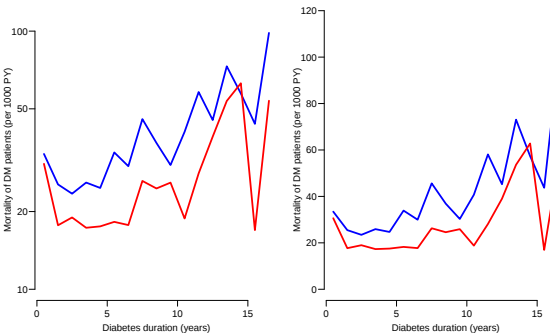
```
9  0.9697122 0.9741110
10 0.9592825 0.9811961
11 0.9419072 0.9718911
12 0.9547620 0.9609833
13 0.9269371 0.9463654
14 0.9426528 0.9371992
15 0.9562704 0.9830491
16 0.9015634 0.9462515
> ( S60 <- rbind( 1, apply( p60, 2, cumprod ) ) )
      M      F
0  1.0000000 1.0000000
0  0.9665625 0.9693842
1  0.9419381 0.9522275
2  0.9198452 0.9341568
3  0.8960185 0.9179877
4  0.8738967 0.9019004
5  0.8442798 0.8854472
6  0.8189743 0.8697484
7  0.7816083 0.8468921
```

Mortality and duration II

	M	F	M	F	M	F
0	178	117	5323.4	3821.6	33.4	30.6
1	121	61	4749.5	3446.6	25.5	17.7
2	99	59	4220.9	3109.0	23.5	19.0
3	97	48	3744.7	2773.2	25.9	17.3
4	81	43	3280.8	2453.7	24.7	17.5
5	96	39	2832.6	2137.8	33.9	18.2
6	72	33	2402.2	1861.3	30.0	17.7
7	89	41	1950.7	1560.2	45.6	26.3
8	58	31	1572.6	1261.4	36.9	24.6
9	37	26	1221.6	1004.3	30.3	25.9
10	39	15	957.8	797.7	40.7	18.8
11	43	18	740.2	640.4	58.1	28.1
12	25	19	552.6	487.0	45.2	39.0
13	28	18	383.2	335.6	73.1	53.6
14	14	13	244.1	207.0	57.3	62.8
15	6	2	137.2	118.0	43.7	17.0
16	4	2	40.6	37.2	98.4	53.7

Survival curve III

8	0.7527811	0.8260784
9	0.7299810	0.8046921
10	0.7002580	0.7895607
11	0.6595780	0.7673671
12	0.6297401	0.7374269
13	0.5837294	0.6978753
14	0.5502542	0.6540482
15	0.5261918	0.6429616
16	0.4743952	0.6084034



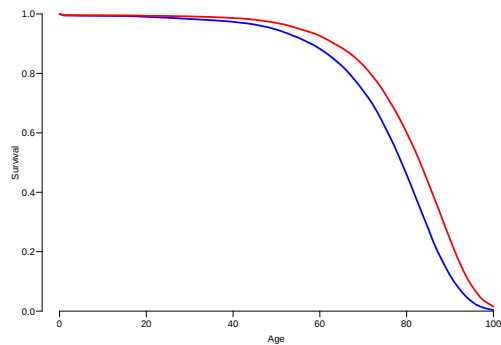
Mortality and survival

- ▶ Formally there is a one-to-one correspondence
- ▶ But survival requires a meaningful **origin**
- ▶ ... such as date of diagnosis or date of start of intervention
- ▶ Survival is time **since**...
- ▶ ... time since inclusion in a cohort is not meaningful

Mortality rates (mort-ana)

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How does the survival function look?



Population measures (measure-links)

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Population measures

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measure-links

Survival function in your computer I

$$S(t) = \exp\left(-\int_0^t \lambda(s) ds\right) = \exp(-\Lambda(s))$$

```
> library(Epi)
> data(M.dk)
> names(M.dk)
[1] "A" "sex" "p" "D" "Y" "rate"
> head( subset(M.dk,P==2005 & sex==1) )
```

Population measures (measure-links)

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Demographic measures

- ▶ Practicals chapter 2: "Basic concepts..."
- ▶ Rates
- ▶ Survival
- ▶ Competing risks
- ▶ Lifetime risk of ...
- ▶ Years lost to ...
- ▶ Time spent with...

Population measures (measure-links)

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Survival function in your computer II

```
      A sex    P    D      Y      rate
63    0    1 2005 167 33047.17 5.05338330
141    1    1 2005   9 33280.33 0.27042998
219    2    1 2005   3 33253.67 0.09021562
297    3    1 2005   9 33396.00 0.26949335
375    4    1 2005   7 34101.33 0.20527057
453    5    1 2005   3 34416.33 0.08716791
> mort.m <- subset(M.dk,P==2005 & sex==1)$rate
> mort.f <- subset(M.dk,P==2005 & sex==2)$rate
> age <- subset(M.dk,P==2005 & sex==1)$A
> Lamb.m <- cumsum(mort.m/1000)
> Lamb.f <- cumsum(mort.f/1000)
> Surv.m <- exp(-Lamb.m)
> Surv.f <- exp(-Lamb.f)
> cbind( age, mort.m, Lamb.m, Surv.m,
+       mort.f, Lamb.f, Surv.f )[1:10,]
```

Population measures (measure-links)

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Survival

- ▶ Normally estimated by the Kaplan-Meier estimator
- ▶ — or life table (actuarial) estimator
- ▶ In demography we want to address the survival of the **entire population**
- ▶ — or the population of diabetes patients
- ▶ ... is the latter meaningful?

Population measures (measure-links)

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Survival function in your computer III

```
      age    mort.m    Lamb.m    Surv.m    mort.f    Lamb.f    Surv.f
[1,] 0 5.05338330 0.005053383 0.9949594 3.57265182 0.003572652 0.9964337
[2,] 1 0.27042998 0.005323813 0.9946903 0.25196586 0.003824618 0.9961827
[3,] 2 0.09021562 0.005414029 0.9946006 0.12648288 0.003951101 0.9960567
[4,] 3 0.26949335 0.005683522 0.9943326 0.15702613 0.004108127 0.9959003
[5,] 4 0.20527057 0.005888793 0.9941285 0.15306591 0.004261193 0.9957479
[6,] 5 0.08716791 0.005975961 0.9940419 0.06069895 0.004321892 0.9956874
[7,] 6 0.08731718 0.006063278 0.9939551 0.03050765 0.004352399 0.9956571
[8,] 7 0.08596276 0.006149241 0.9938696 0.06039650 0.004412796 0.9955969
[9,] 8 0.16953702 0.006318778 0.9937011 0.08930210 0.004502098 0.9955080
[10,] 9 0.16586881 0.006484646 0.9935363 0.02917734 0.004531275 0.9954790
> plot( c(0,age+1), c(1,Surv.m),
+       type="l", lty=1, lwd=3, col="blue",
+       ylim=0:1, yaxs="i", xlab="Age", ylab="Survival" )
> lines( c(0,age+1), c(1,Surv.f),
+       type="l", lty=1, lwd=3, col="red" )
```

Population measures (measure-links)

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Survival function in your computer

Note:

- ▶ the survival curve is just at set of points $(a, S(a))$ where $a = 0, 1, 2, \dots$
- ▶ the cumulative rate $\Lambda(a)$ was just computed as the cumulative sum of the mortality rates (in units of rate per 1 year):

```
> Lamb.m <- cumsum( mort.m/1000 )
```

Population measures (measure-links)

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Years of life lost

- ▶ — to diabetes, at age a
- ▶ the expected lifetime at age a if no DM minus the expected lifetime at age a if DM
- ▶ So you need to compute the (residual) expected lifetime (at age a):
 - ▶ for persons with DM
 - ▶ for persons without DM
- ▶ The same calculations, but now using age-specific mortality for diabetes patients. . .

Population measures (measure-links)

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Expected lifetime

Computed as the area under the survival curve:

$$EL = \int_0^{\infty} S(t) dt$$

Expected **residual** lifetime at age a

computed as the area under the **conditional** survival curve:

$$EL = \int_a^{\infty} S(t)/S(a) dt$$

Integrals are just sums (cumsum() in R)

Population measures (measure-links)

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Measures of this world

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Cox

Expected lifetime I

This is just the integral of the survival function:

```
> EL.m <- sum( Surv.m * 1 ) + 0.5
> EL.f <- sum( Surv.f * 1 ) + 0.5
> round( c(EL.m, EL.f), 2 )
[1] 75.93 80.43
```

For the expected residual lifetime at age 50 we need the **conditional** survival from age 50:

```
> cbind( age, Surv.m, Surv.f )[48:52,]
   age  Surv.m  Surv.f
[1,]  47 0.9555531 0.9745701
[2,]  48 0.9514781 0.9725746
[3,]  49 0.9472553 0.9696475
[4,]  50 0.9426571 0.9670942
[5,]  51 0.9373919 0.9638805
```

Population measures (measure-links)

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Inference in Multistate models

P.K. Andersen & N. Keiding
Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med*, 2011 [1]:

1. Do not condition on the future
2. Do not regard individuals at risk after they have died
3. Stick to this world

Measures of this world (Cox)

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Expected lifetime II

```
> C50.m <- Surv.m[51:100]/Surv.m[51]
> C50.f <- Surv.f[51:100]/Surv.f[51]
> EL.m <- sum( C50.m * 1 )
> EL.f <- sum( C50.f * 1 )
> round( c(EL.m, EL.f), 2 )
[1] 27.90 31.44
```

Population measures (measure-links)

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Conditioning on the future

- ▶ ... also known as "Immortal time bias", see e.g. S. Suissa: Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [2].
- ▶ Wrongly including persons' follow-up in the wrong state (namely the one reached some time in the future).
- ▶ Frequently caused by classification of **persons** instead of classification of **follow-up time**

Measures of this world (Cox)

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Why these mistakes?

- ▶ Time is absent from survival analysis results
- ▶ Time is taken to be a **response** variable observed for each person
- ▶ Unit of analysis seems to be the person
- ▶ **Persons** classified by exposure
- ▶ The **real** unit of observation should be person-time

Measures of this world (Cox)

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A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x .

The covariate t has a special status:

- ▶ Computationally, because all individuals contribute to (some of) the range of t .
- ▶ ... the scale along which time is split (the risk sets)
- ▶ Conceptually it is less clear
 - t is but a covariate that varies within individual.
- ▶ Cox's approach profiles $\lambda_0(t)$ out.

Measures of this world (Cox)

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Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, "exposure")
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — "empirical rates"
 - ▶ (d_{it}, y_{it}) : (event, (sojourn) time) for individual i at time t .
 - ▶ y is the **response** time, t is the **covariate** time
- ▶ Covariates relate to each interval of follow-up
- ▶ Allows **multiple** timescales, e.g. age and disease duration.

Measures of this world (Cox)

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The Cox-likelihood as profile likelihood

- ▶ One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log(\lambda(t, x_i)) = \log(\lambda_0(t)) + \beta_1 x_{1i} + \dots + \beta_p x_{pi} = \alpha_t + \eta_i$$

- ▶ Profile likelihood:
 - ▶ Derive estimates of α_t as function of data and β s
 - assuming constant rate between death times
 - ▶ Insert in likelihood, now only a function of data and β s
 - ▶ Turns out to be Cox's partial likelihood

Measures of this world (Cox)

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"Stick to this world"

In the paper by Andersen & Keiding this is primarily aimed at the use of "net survival", that is the calculation of

$$\exp\left(-\int_0^t \lambda_c(s) ds\right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

Corresponds to the survival probability in the situation where:

1. all other causes of death are absent
 2. the mortality, λ_c from cause c is unchanged
- ... which is indeed **not** of this world.

Measures of this world (Cox)

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Splitting the dataset

- ▶ The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y .
- ▶ — much larger than the original dataset
- ▶ — each individual contributes many empirical rates
- ▶ (one per risk-set contribution in Cox-modeling)
- ▶ From each empirical rate we get:
 - ▶ Poisson-response d
 - ▶ Risk time y
 - ▶ Covariate value for the timescale (time since entry, current age, current date, ...)
 - ▶ other covariates
- ▶ Modeling is by standard glm Poisson

Measures of this world (Cox)

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Sticking to this world

- ▶ Do not make predictions based on unrealistic assumptions:
 1. Mortality is 0
 2. Diabetes rates remain as now
- ▶ or
 1. Smallpox is eradicated
 2. ... yet mortality remains the same
- ▶ I postulate a further specific feature of "this world":
 - ▶ — it is **continuous**
 - ▶ — in particular, death and disease rates vary **smoothly** by
 - ▶ age
 - ▶ calendar time
 - ▶ disease duration
 - ▶ ...

Measures of this world (Cox)

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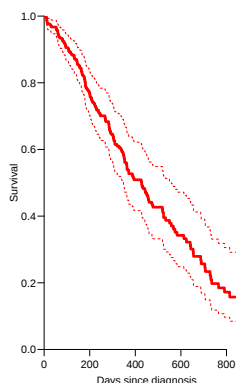
Example: Mayo Clinic lung cancer

- ▶ Survival after lung cancer
- ▶ Covariates:
 - ▶ Age at diagnosis
 - ▶ Sex
 - ▶ Time since diagnosis
- ▶ Cox model
- ▶ Split data:
 - ▶ Poisson model, time as factor
 - ▶ Poisson model, time as spline

Measures of this world (Cox)

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Mayo Clinic lung cancer 60 year old woman



Measures of this world (Cox)

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```
> CM <- cbind( 1, Ns( seq(10,1000,10)-5, knots=t.kn ), 60, 1 )
> lambda <- ci.exp( mls.pois.sp, ctr.mat=CM )
> Lambda <- ci.cum( mls.pois.sp, ctr.mat=CM, intl=10 )[-4]
> survP <- exp(-rbind(0,Lambda))
```

Measures of this world (Cox)

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Example: Mayo Clinic lung cancer I

```
> round( cmp, 5 )
```

	age	2.5%	97.5%	sex	2.5%	97.5%
Cox	1.01716	0.99894	1.03571	0.59896	0.43137	0.83165
Poisson-factor	1.01716	0.99894	1.03571	0.59896	0.43137	0.83165
Poisson-spline	1.01619	0.99803	1.03468	0.59983	0.43199	0.83287

Measures of this world (Cox)

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What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- ▶ dividing time very finely and
- ▶ modeling one covariate, the time-scale, with one parameter per distinct value.
- ▶ ⇒ difficult to access the baseline hazard
 - only the **cumulative hazard** (and survival) are accessible
- ▶ ⇒ uninitiated tempted to show survival curves where irrelevant
 - or forgetting to show it where it is relevant

Measures of this world (Cox)

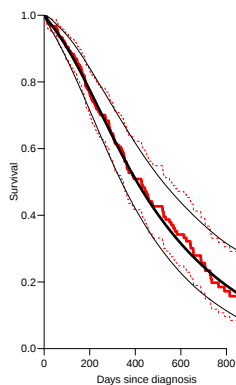
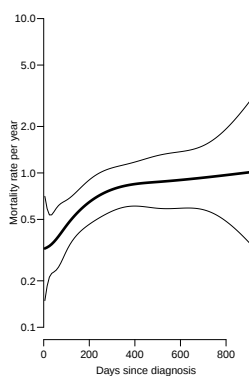
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Modeling in this world

- ▶ Replace the α_t s by a parametric function $f(t)$ with a limited number of parameters, for example:
 - ▶ Piece-wise constant
 - ▶ Splines (linear, quadratic or cubic)
 - ▶ Fractional polynomials
- ▶ Brings model into "this world":
 - ▶ smoothly varying rates
 - ▶ parametric closed form representation of baseline hazard
 - ▶ finite no. of parameters
- ▶ Makes it really easy to extract and use the **hazard**:
 - ▶ to see how it looks
 - ▶ expected residual life time
 - ▶ state occupancy probabilities in multistate models
 - ▶ ...

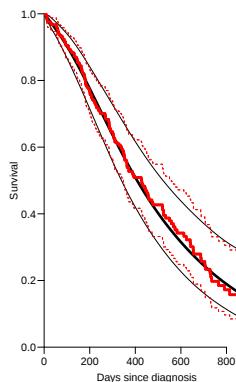
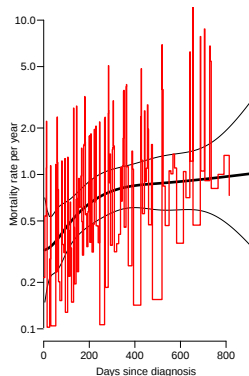
Measures of this world (Cox)

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Conclusions

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conc

Conclusions

- ▶ Population based epidemiology requires:
 - ▶ Population level data (beware of sampling issues)
 - ▶ Population level models
- ▶ Models for hazard rates (incidence, mortality, morbidity)
- ▶ Ability to show and interpret the rates
- ▶ ... using relevant derived measures:
 - ▶ RR relative to a given timepoint
 - ▶ Expected life time
 - ▶ etc.
- ▶ Survival models from clinical science almost always irrelevant.

References

-  [P. K. Andersen and N. Keiding.](#)
Interpretability and importance of functionals in competing risks and multistate models.
Stat Med, Nov 2011.
-  [S. Suissa.](#)
Immortal time bias in pharmaco-epidemiology.
Am. J. Epidemiol., 167:492–499, Feb 2008.