Practical aspects of large register studies: Multiple states and timescales

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Danish Cancer Society

DSBS, Copenhagen,
21 February 2011

Outline

Diabetes and Cancer

Persons with diabetes have long been known to have increased incidence rates and mortality rates from cancer [1, 2, 3]:

- Pancreas
- Liver
- Colon / Rectum
- Corpus uteri
- Lung
- Kidney
- ...

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  - duration of diabetes
  - duration of insulin use
- for all types of cancer
- and for specific sites of cancer

Follow-up of the Danish population

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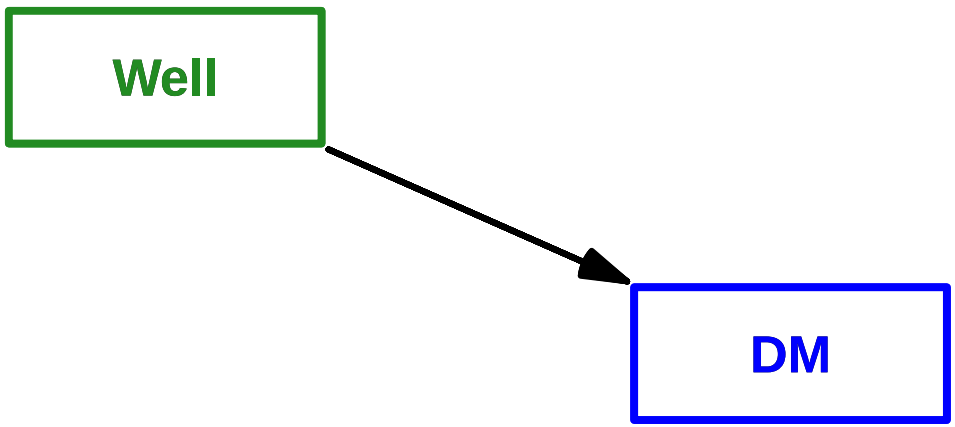

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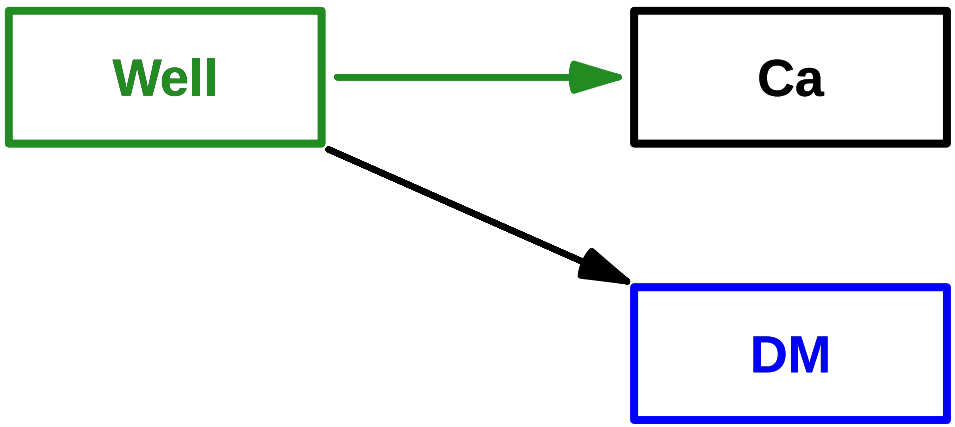

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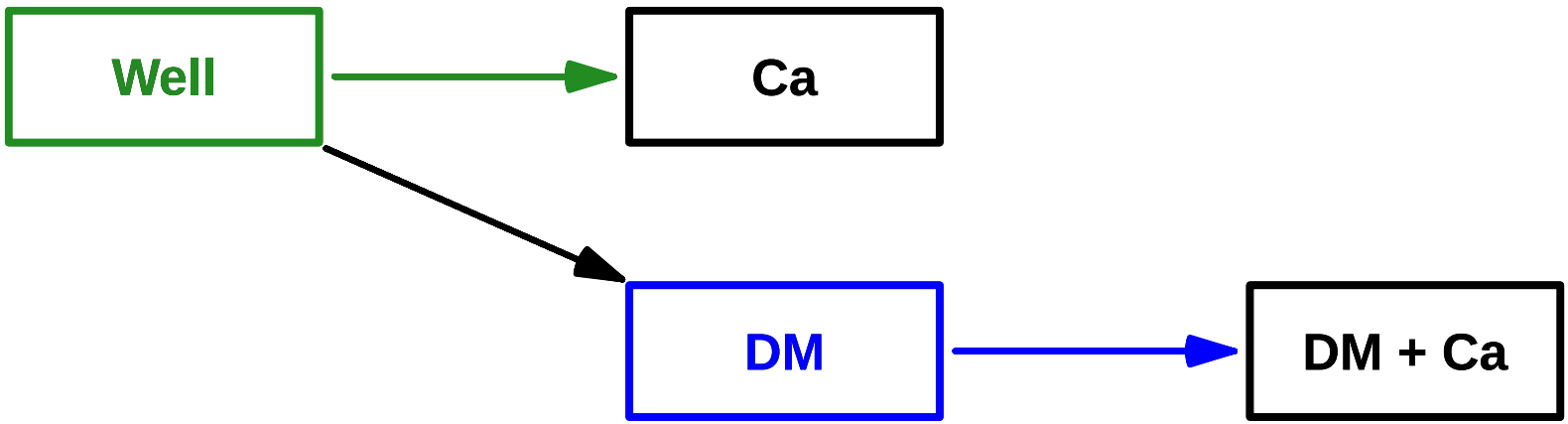

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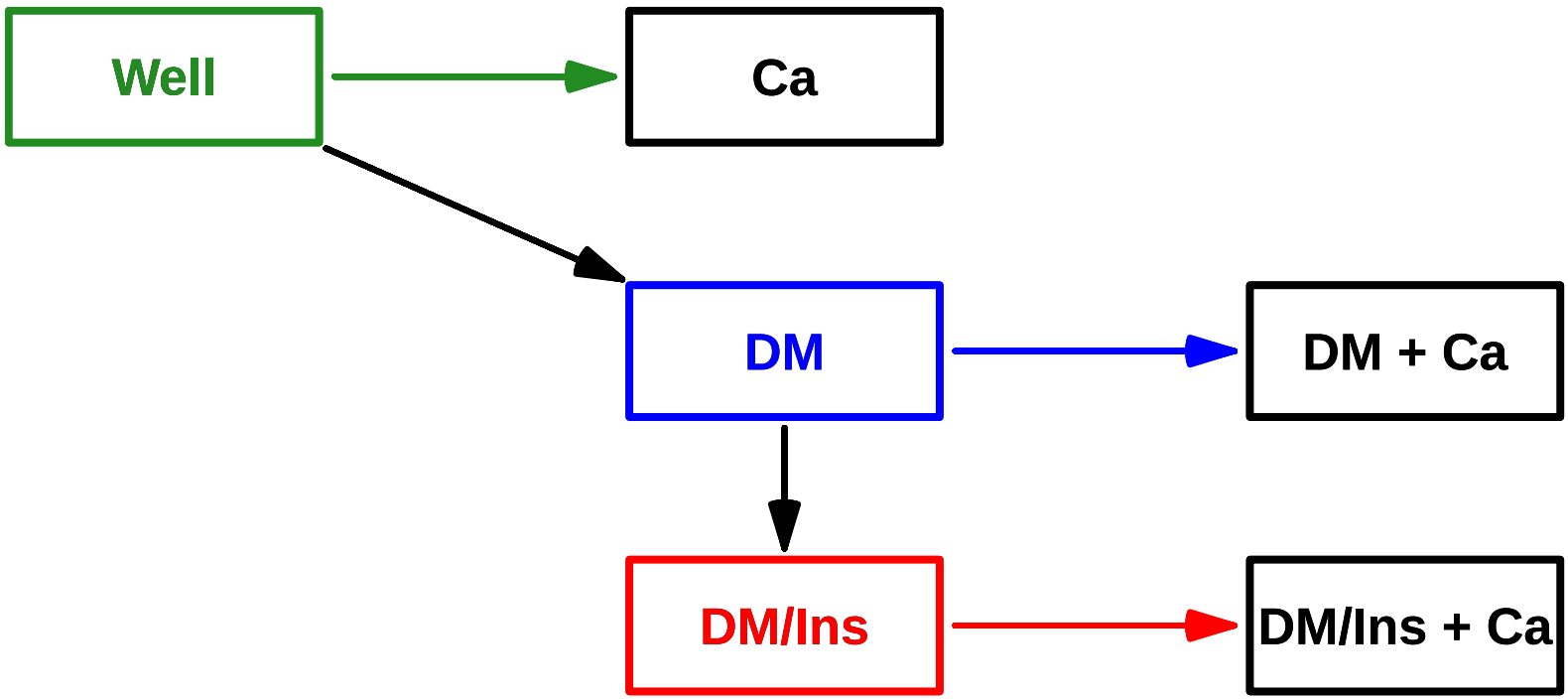

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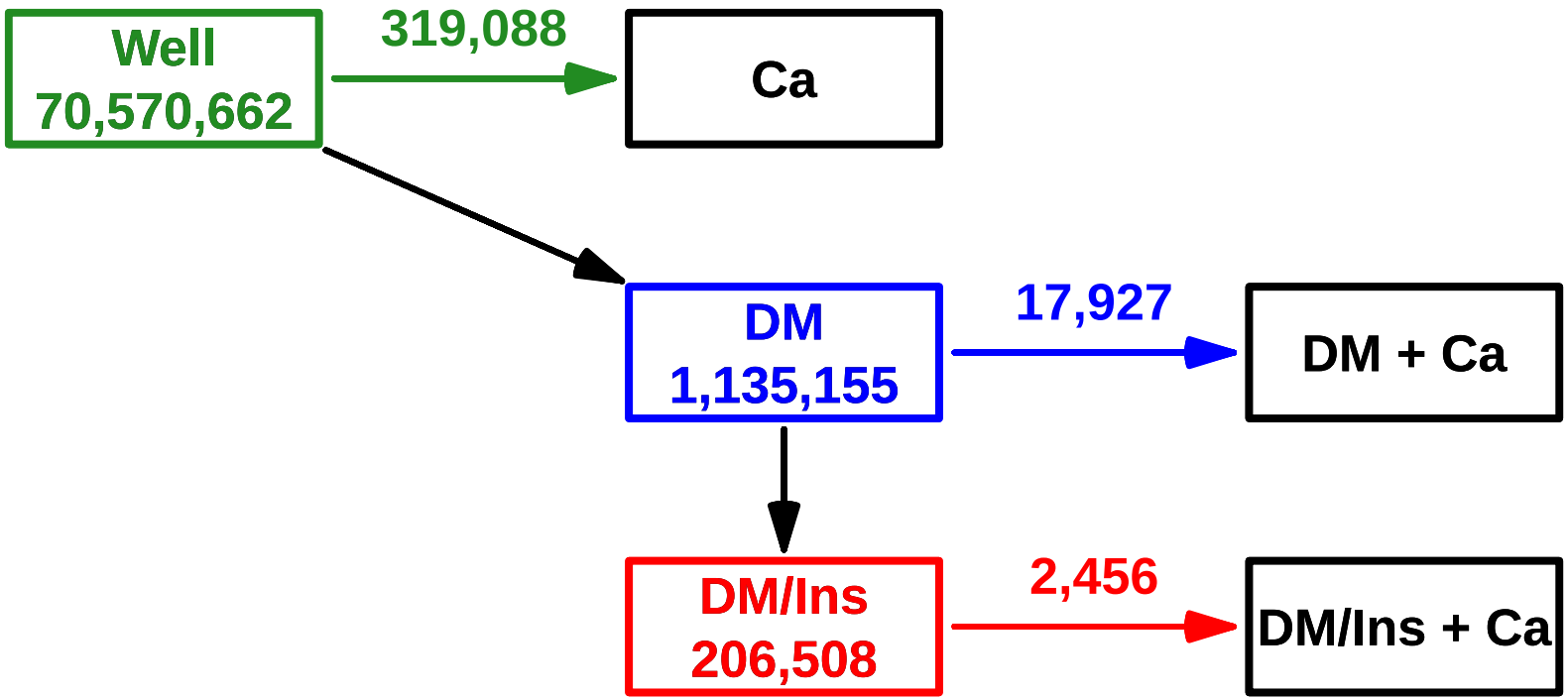

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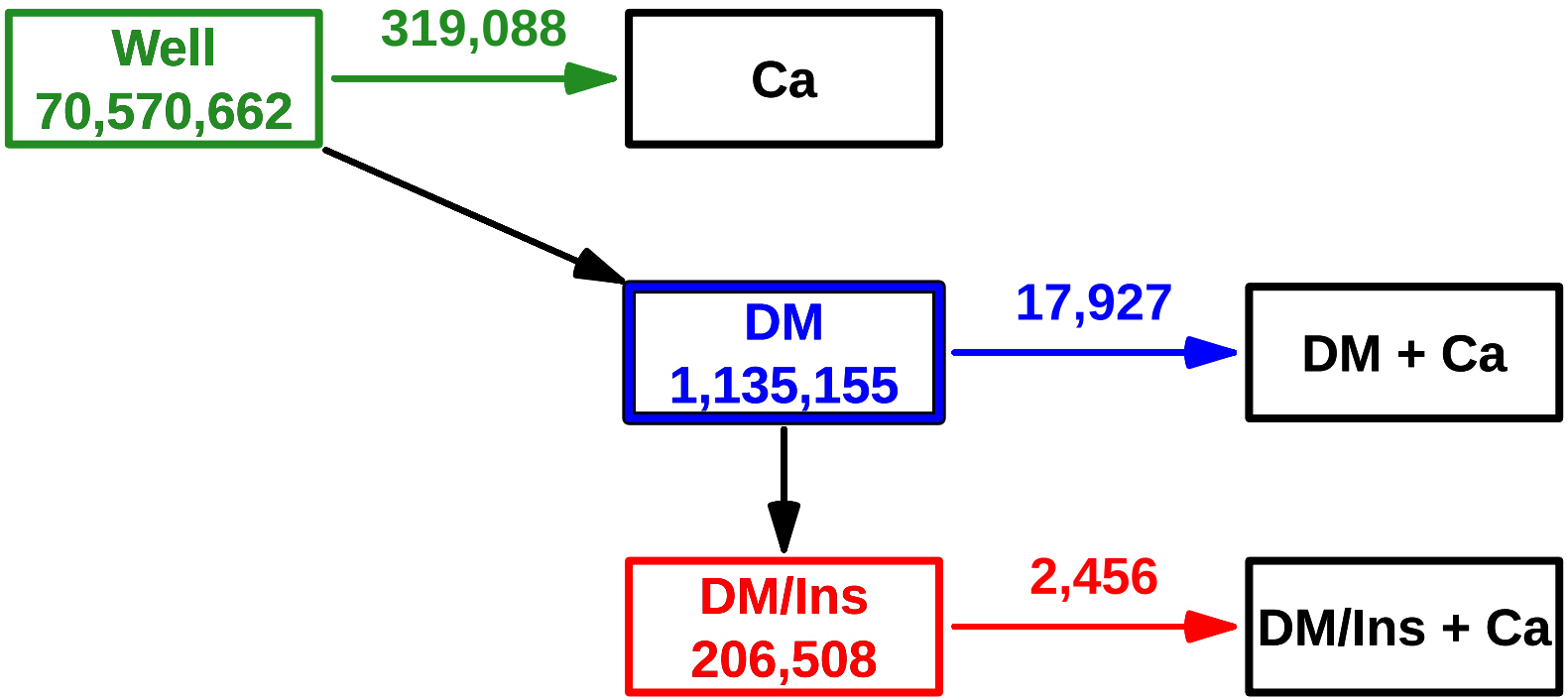

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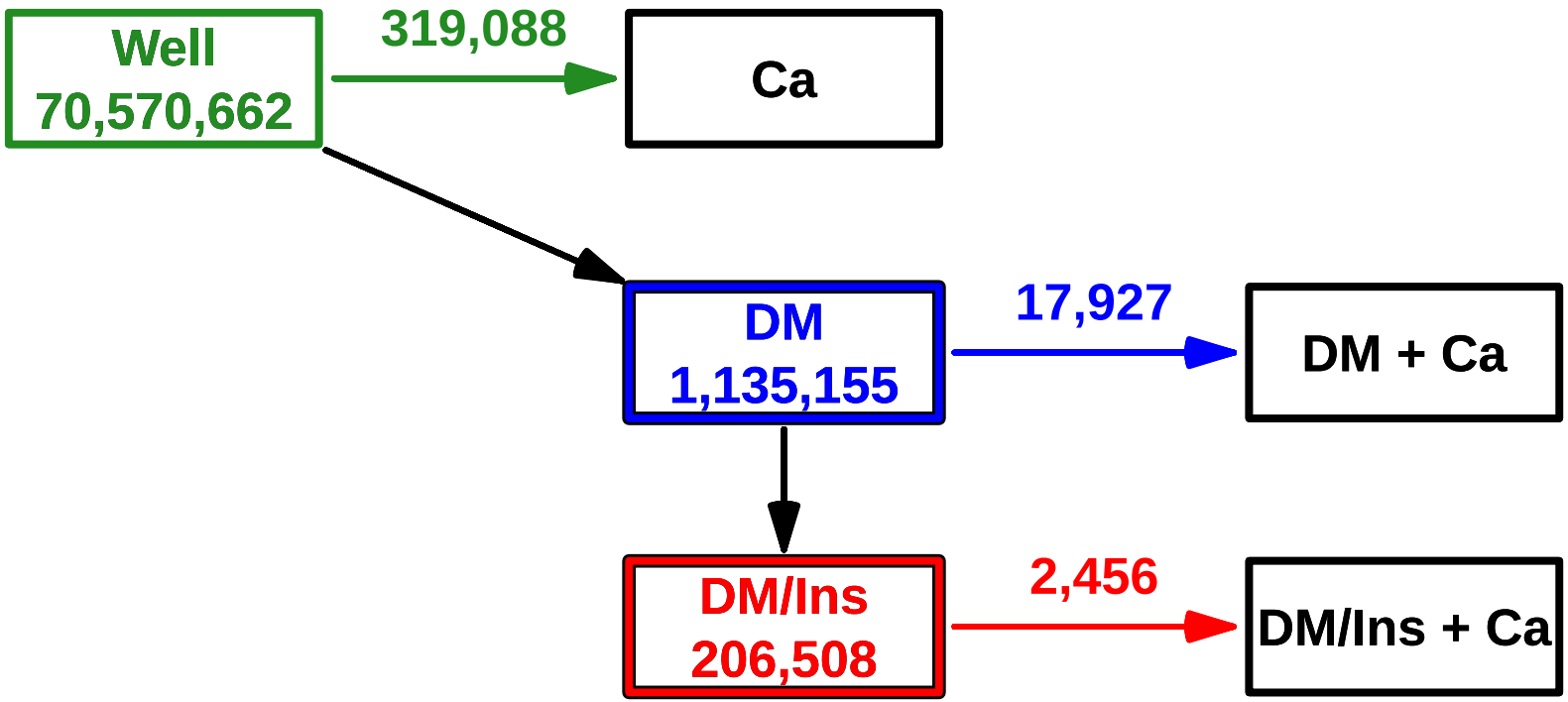

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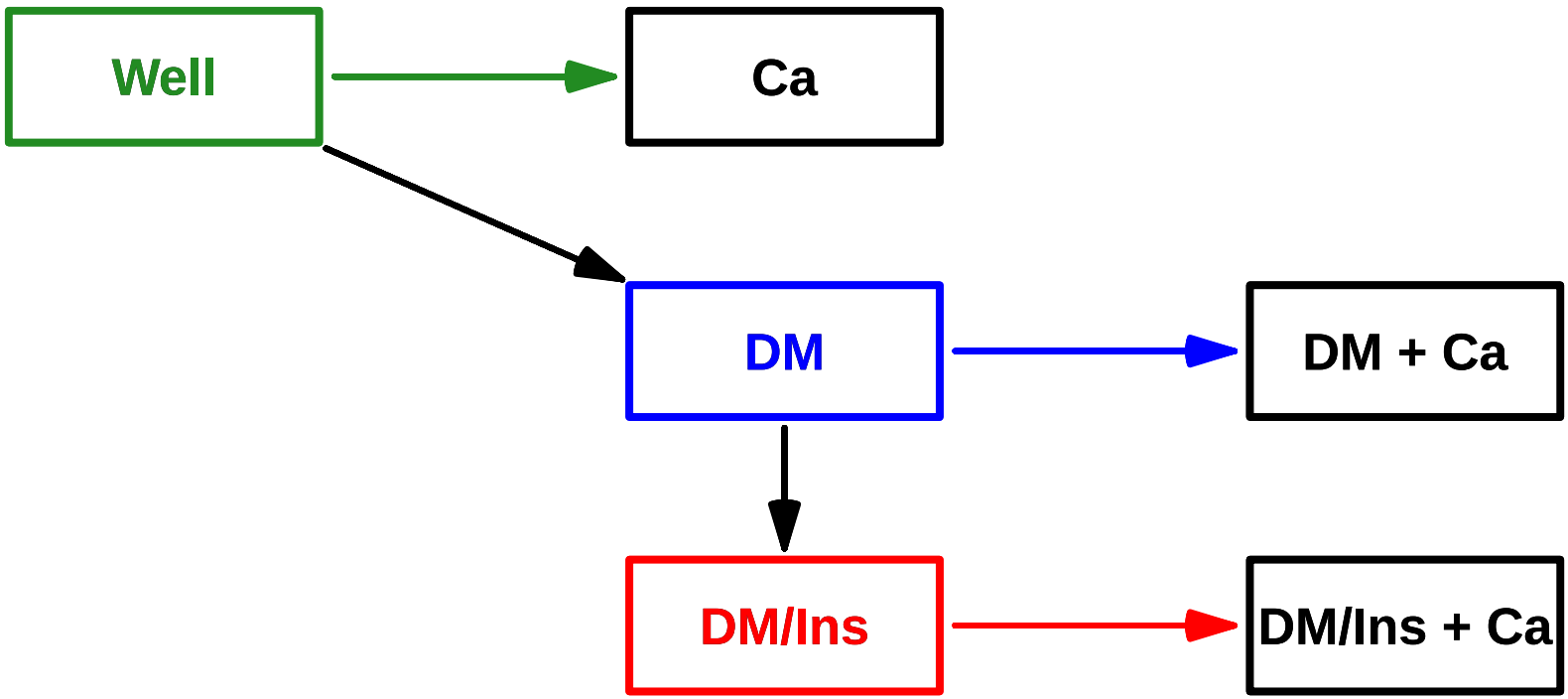

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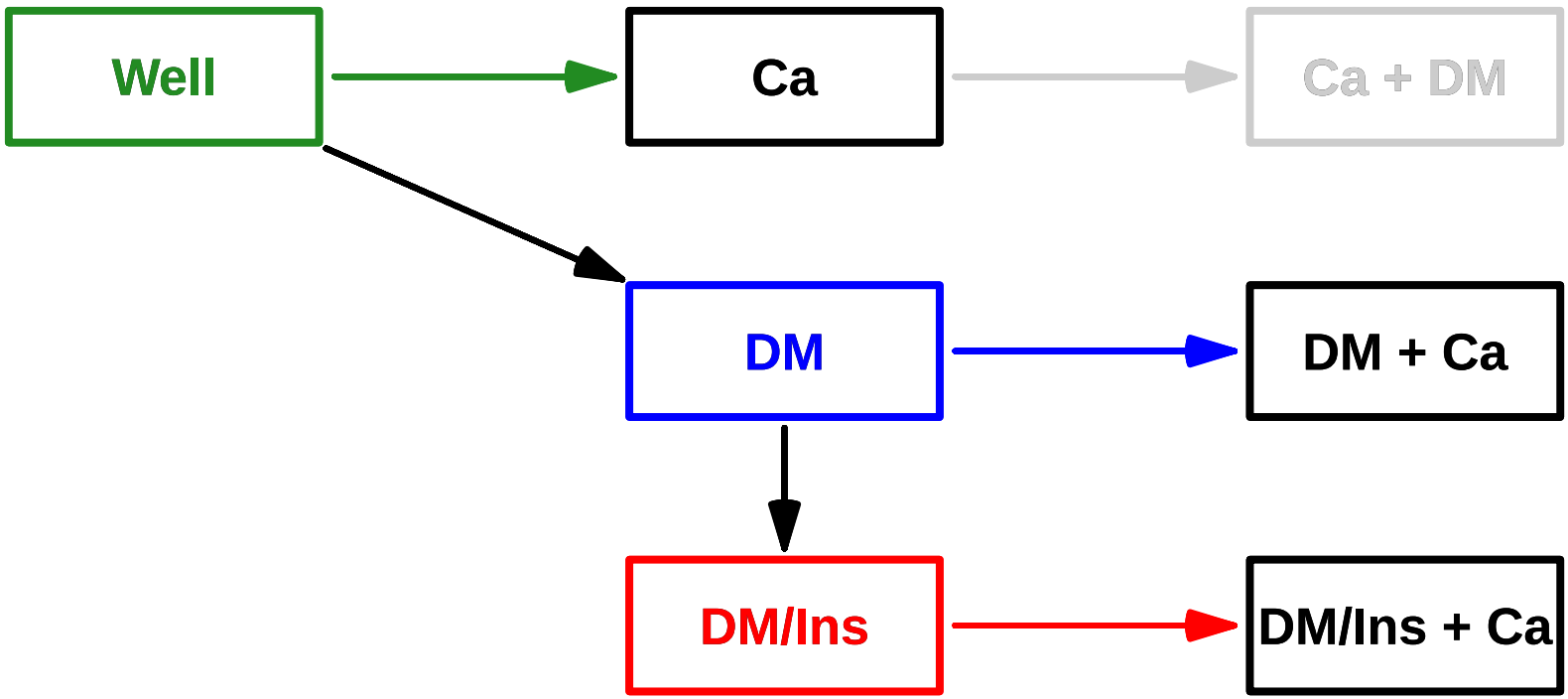

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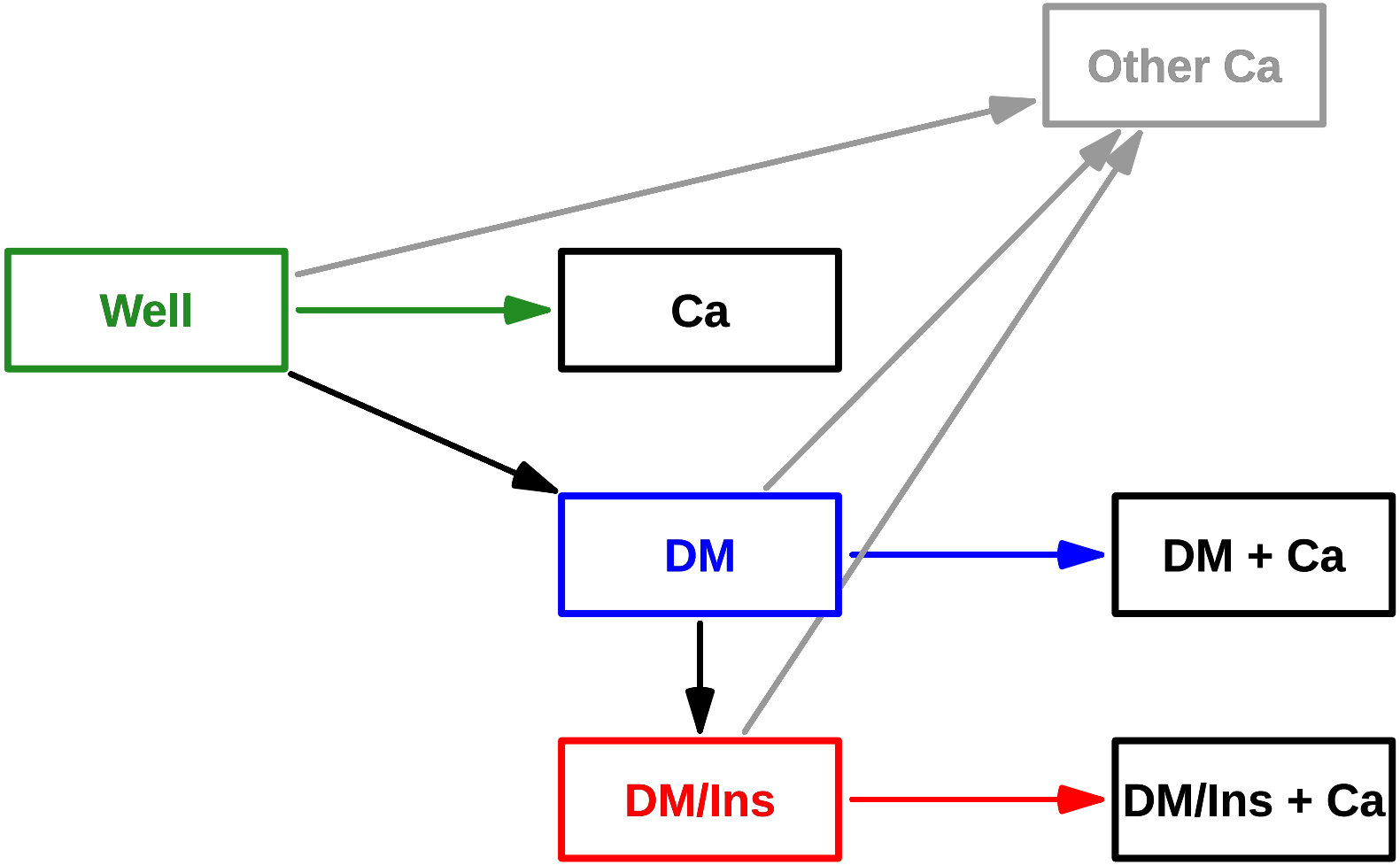

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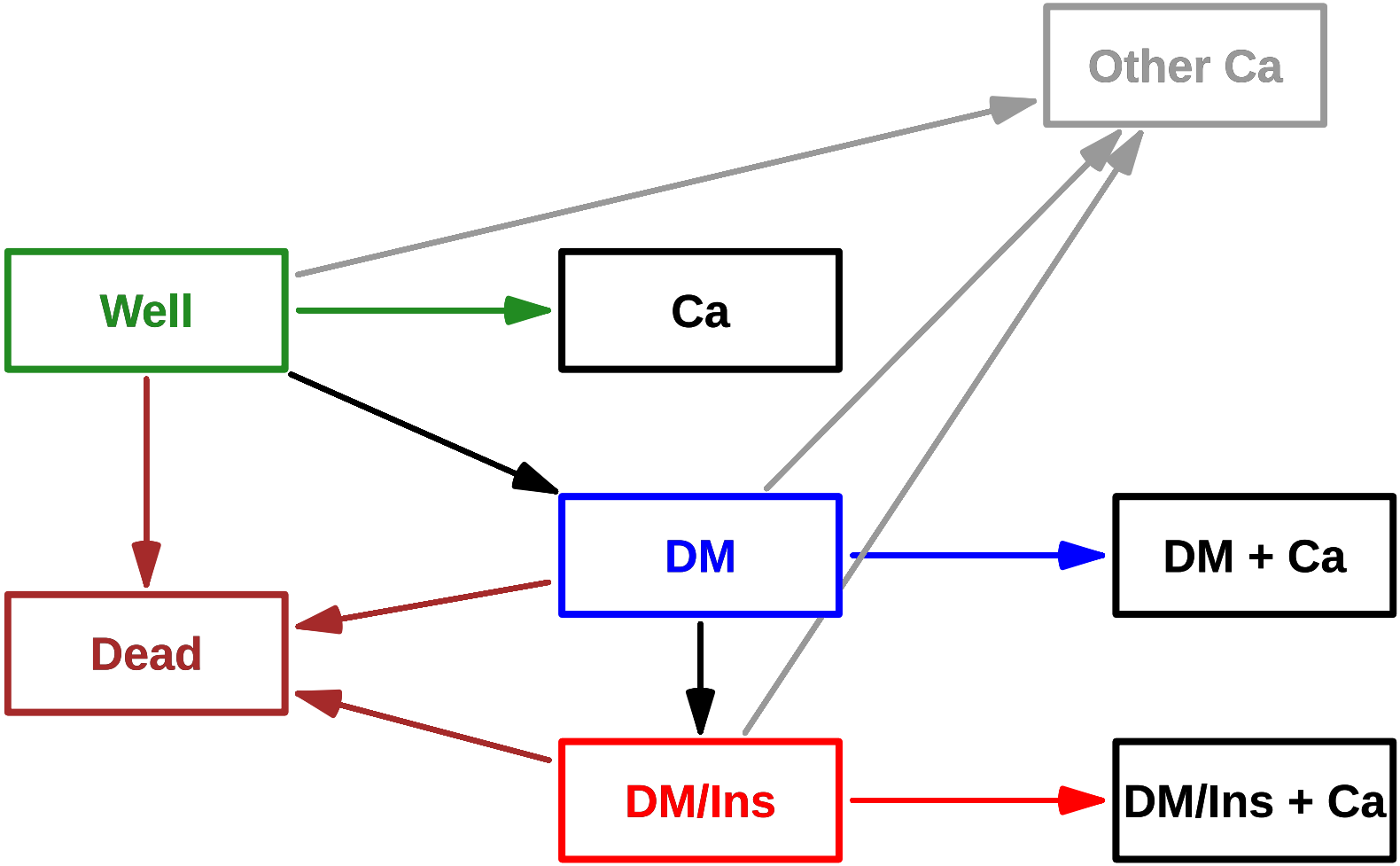

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- Note: "Insulin use" defined only by date of 2nd purchase of insulin.

Follow-up in the population

Persons are followed 1 Jan 1995 to:

Follow-up in the population

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event: first primary cancer of a given type

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Tabulation & analysis

Follow-up time (person-years) and events (cancer diagnosis) were classified by:

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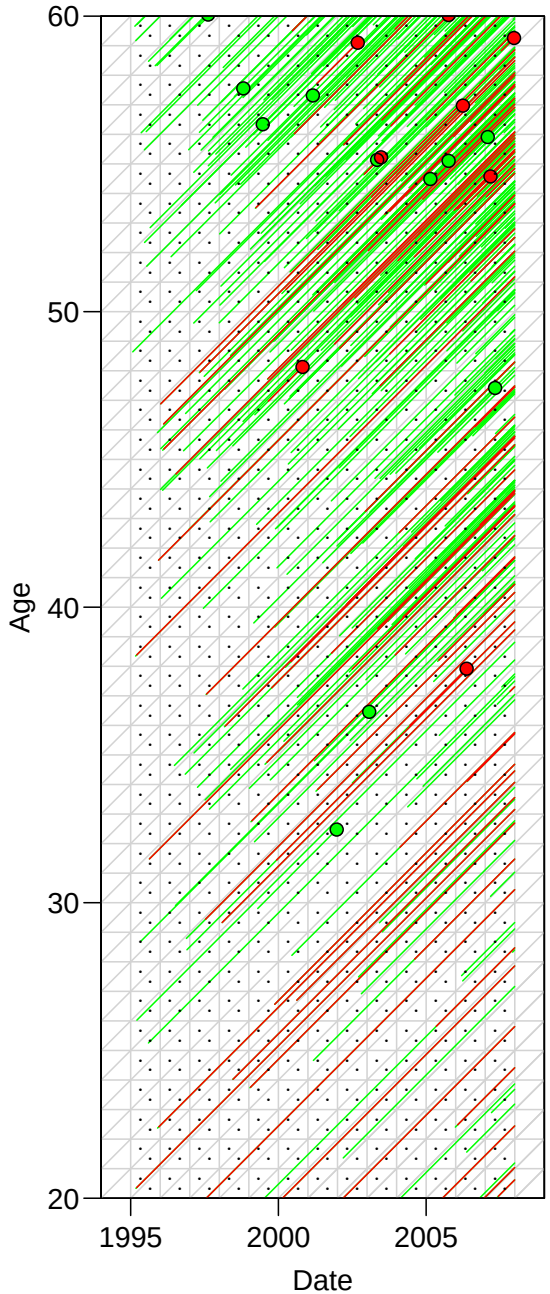
Poisson analysis using class midpoints as continuous variables.

Follow-up by age and time



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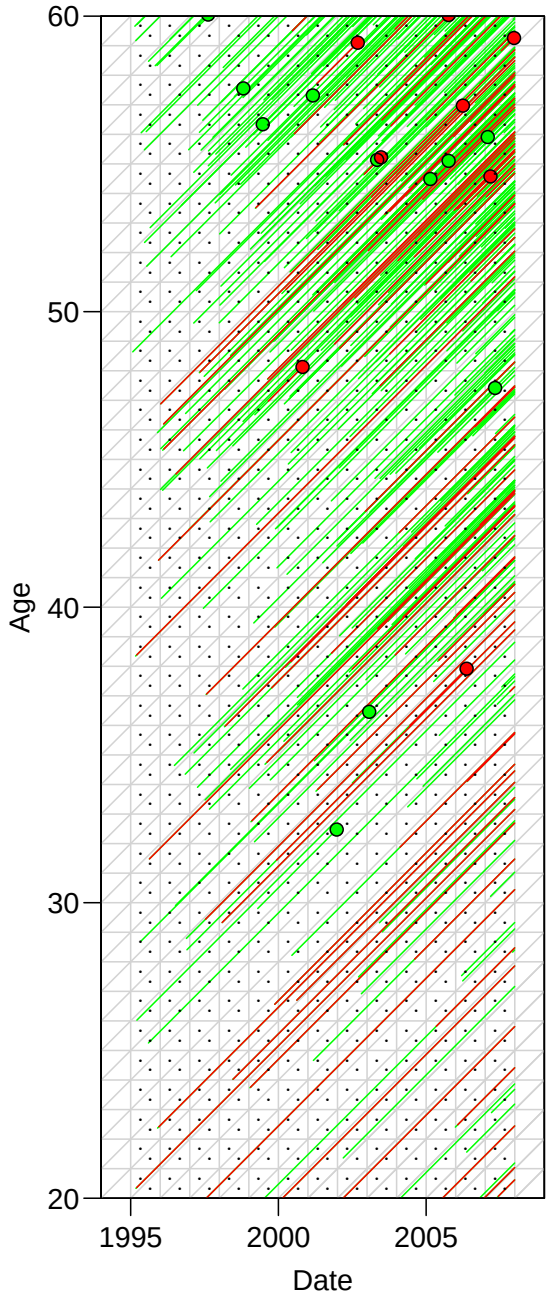

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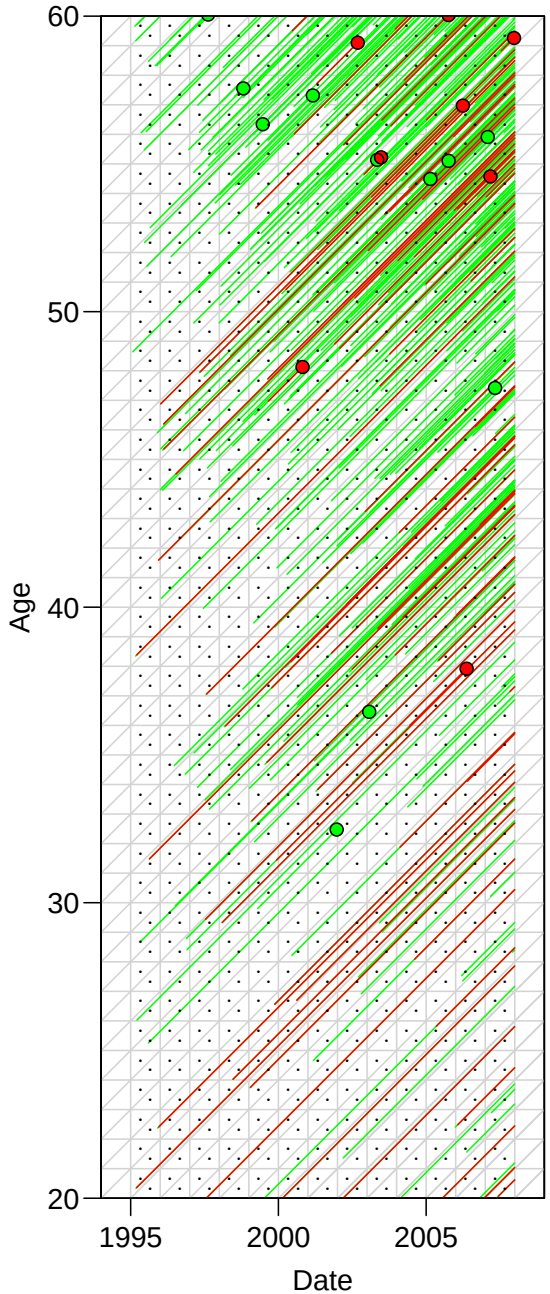

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Lexis diagram, after the German statistician, economist and demographer Wilhelm Lexis (1837–1914).

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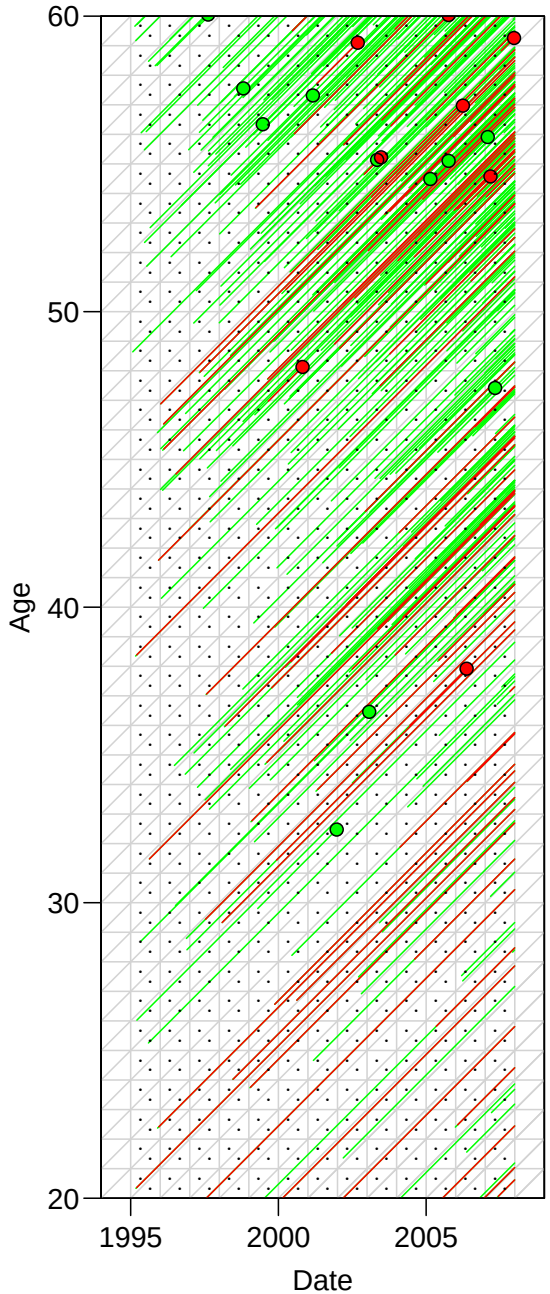

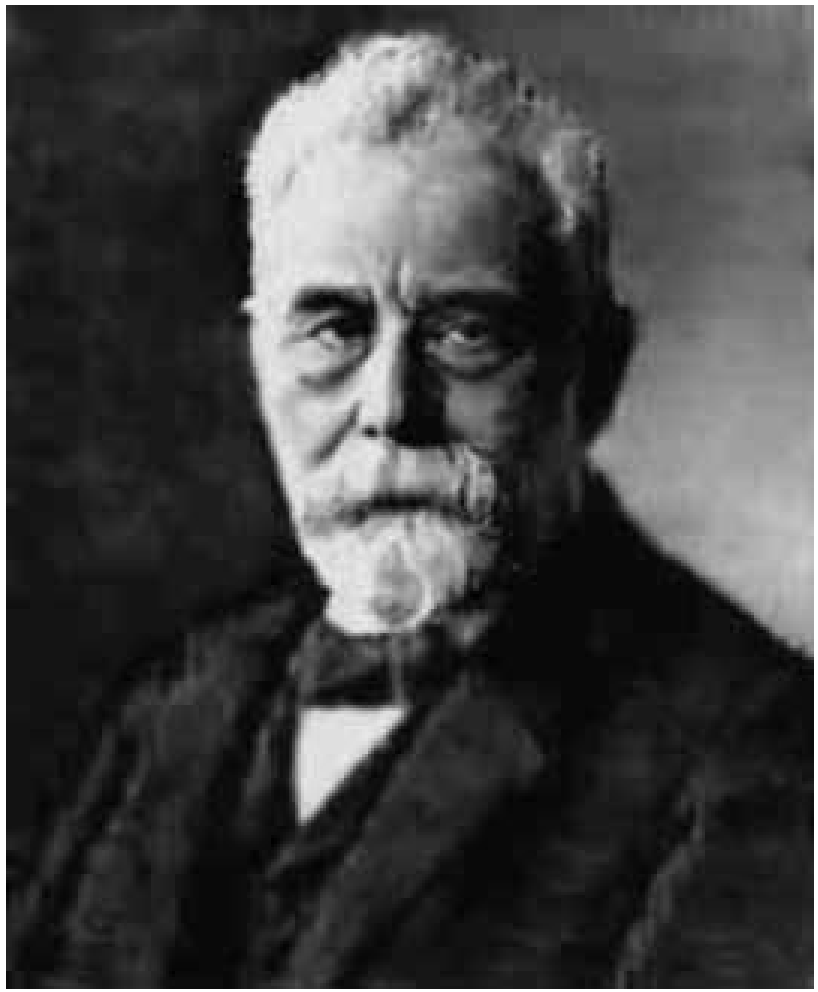

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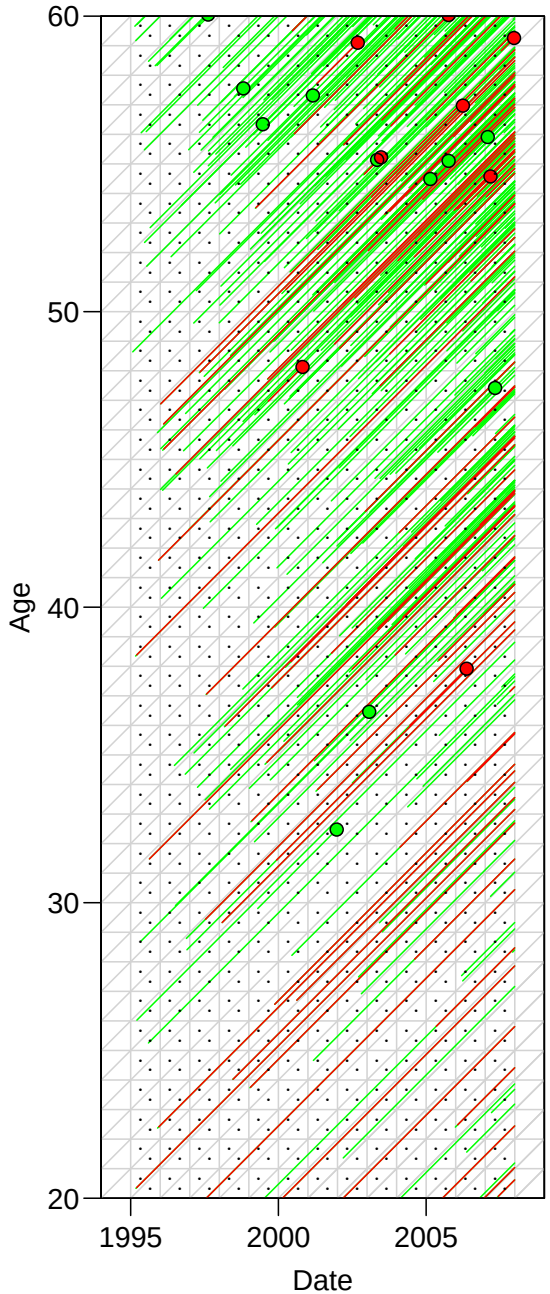

EINLEITUNG

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.

How the data looks — records

	Diabetes duration			Insulin duration		
	Well	DM	DM/Ins	Well	DM	DM/Ins
0	5600	12404	18081	5600	73288	82205
1	0	9448	29700	0	0	70101
2	0	8526	35351	0	0	59107
3	0	7668	39025	0	0	49215
4	0	6842	41267	0	0	40245
5	0	6045	42058	0	0	32231
6	0	5241	41572	0	0	25563
7	0	4496	39644	0	0	19841
8	0	3774	36354	0	0	15011
9	0	3082	31905	0	0	10921
10	0	2397	26331	0	0	7494
11	0	1741	20190	0	0	4745
12	0	1116	13064	0	0	2373
13	0	508	5130	0	0	620
Sum	5600	73288	419672	5600	73288	419672

How the data looks — events

	Diabetes duration			Insulin duration		
	Well	DM	DM/Ins	Well	DM	DM/Ins
0	319088	4331	255	319088	17927	781
1	0	2703	196	0	0	407
2	0	2322	222	0	0	329
3	0	1917	238	0	0	248
4	0	1714	210	0	0	181
5	0	1356	211	0	0	133
6	0	1023	216	0	0	132
7	0	828	231	0	0	85
8	0	633	169	0	0	61
9	0	479	180	0	0	46
10	0	297	131	0	0	22
11	0	194	120	0	0	17
12	0	100	62	0	0	11
13	0	30	15	0	0	3
Sum	319088	17927	2456	319088	17927	2456

Model for cancer incidence rates

rate

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$$\text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth})$$

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Functions t and s give the **combined** effects of:

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There is **no way** to separate these two effects.

Modelling in R

```
m1 <- glm( D ~ Ns(ax,knots=a.kn) +
               detrend( Ns(px,knots=p.kn), px ) +
               Ns(cx,knots=c.kn) +
               state +
               Ns( DMDur,knots=d.kn) +
               Ns(InsDur,knots=d.kn) +
               offset( log(y) ),
               family = poisson,
               data = subset(data,sex==sx) )
```

Simple analysis

- Assume that duration have no effect

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- Only two parameters to describe the effects:

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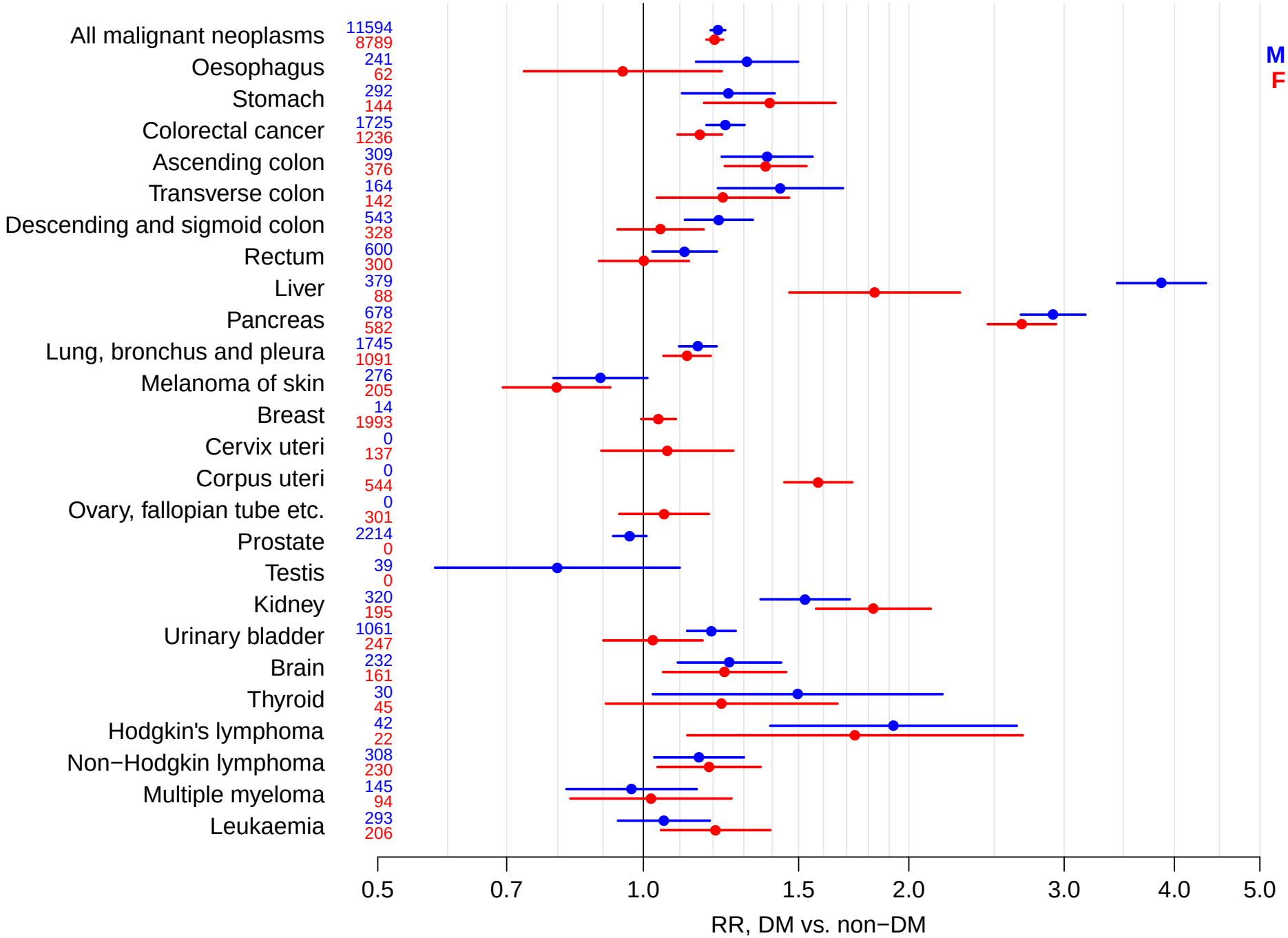
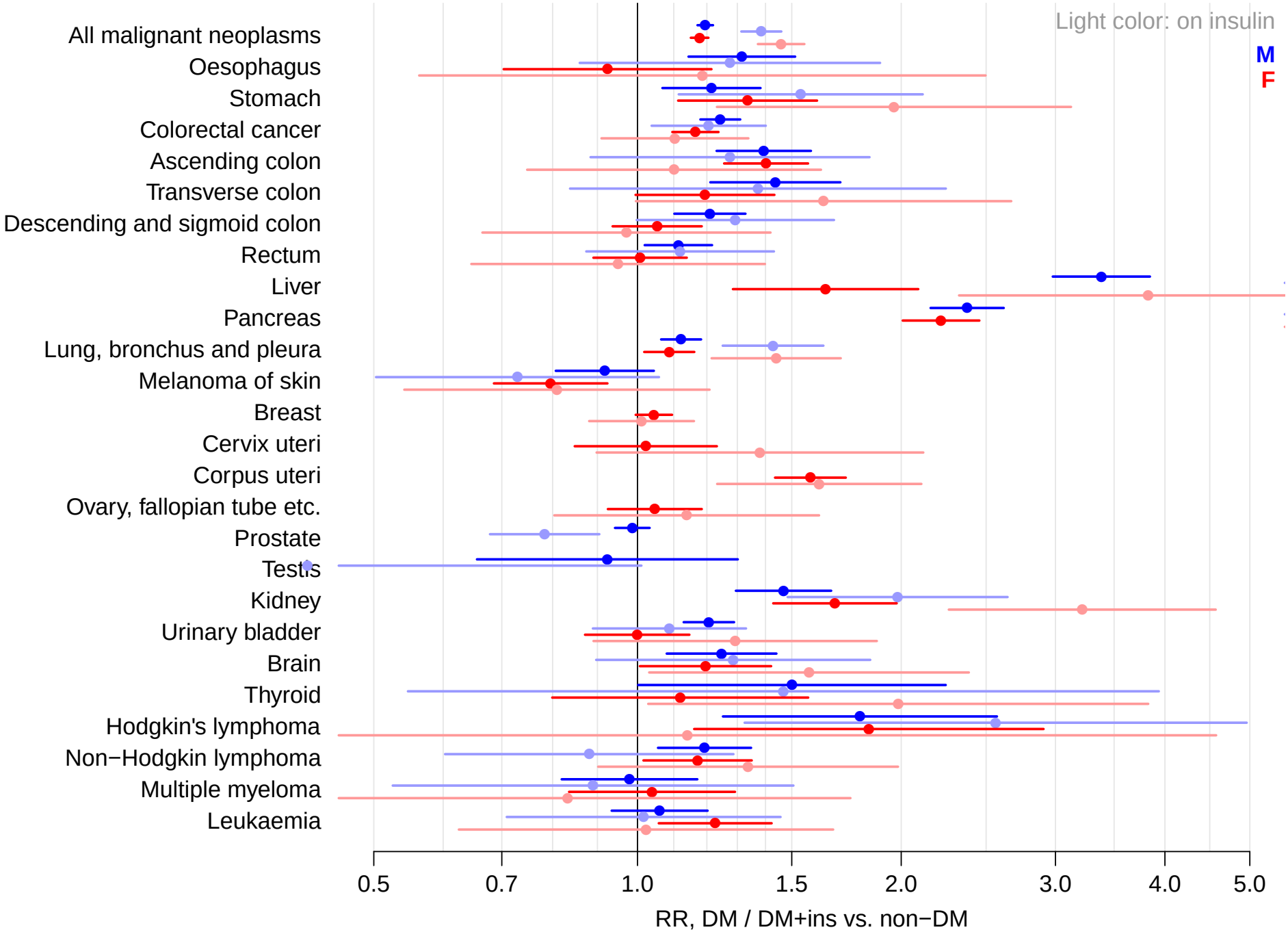
- Duration information is irrelevant for this model.
  (that is, if the model is true!)


All malignant neoplasms
Oesophagus
Stomach
Colorectal cancer
Ascending colon
Transverse colon
Descending and sigmoid colon
Rectum
Liver
Pancreas
Lung, bronchus and pleura
Melanoma of skin
Breast
Cervix uteri
Corpus uteri
Ovary, fallopian tube etc.
Prostate
Testis
Kidney
Urinary bladder
Brain
Thyroid
Hodgkin's lymphoma
Non−Hodgkin lymphoma
Multiple myeloma
Leukaemia
11594
8789
241
62
292
144
1725
1236
309
376
164
142
543
328
600
300
379
88
678
582
1745
1091
276
205
14
1993
0
137
0
544
0
301
2214
0
39
0
320
195
1061
247
232
161
30
45
42
22
308
230
145
94
293
206
M
F
0.5
0.7
1.0
1.5
2.0
3.0
4.0
5.0
RR, DM vs. non−DM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Thyroid
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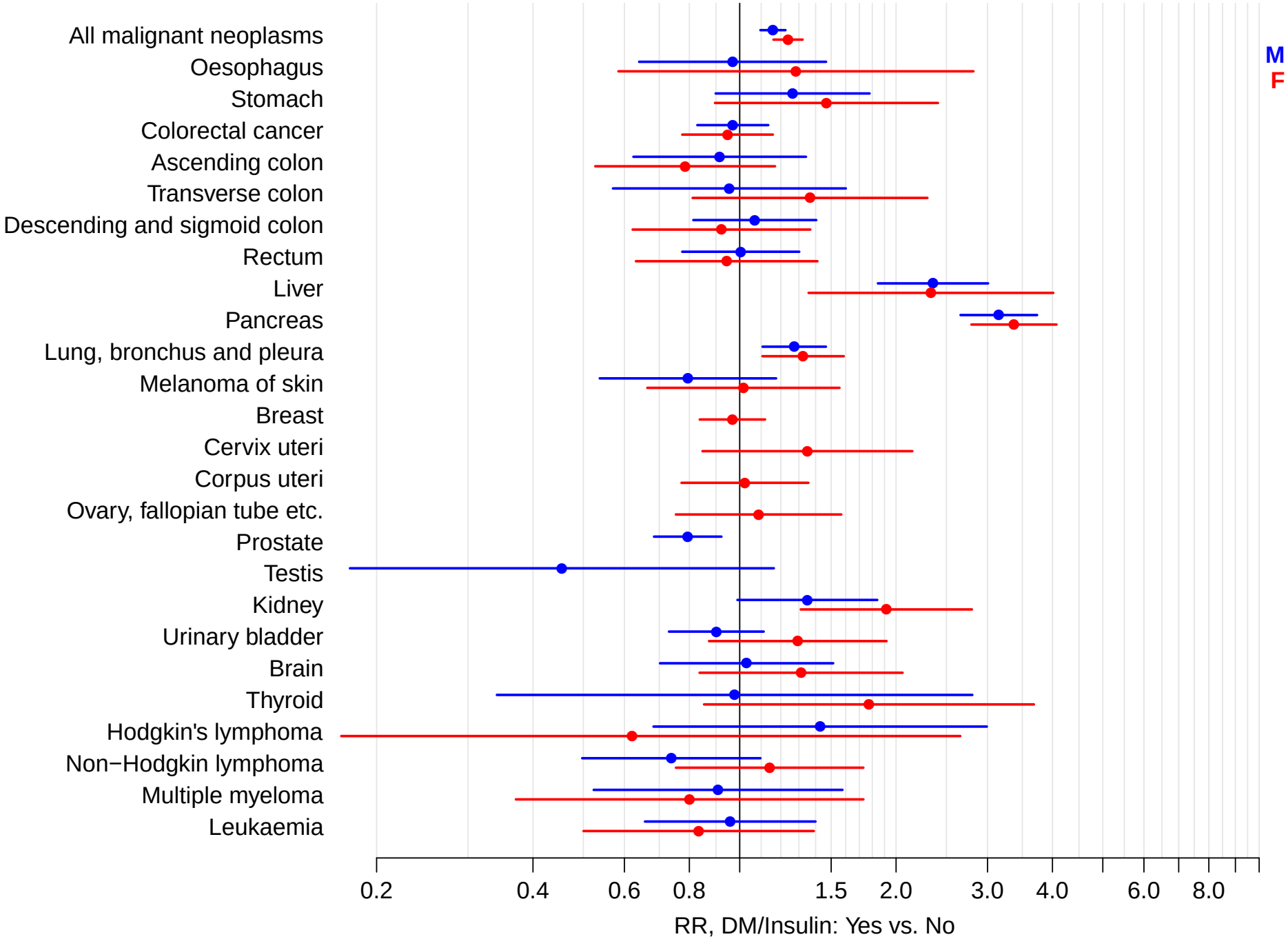
Multiple myeloma
Leukaemia
Light color: on insulin
M
F
0.5
0.7
1.0
1.5
2.0
3.0
4.0
5.0
RR, DM / DM+ins vs. non−DM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M
F
0.2
0.4
0.6
0.8
1.5
2.0
3.0
4.0
6.0
8.0
RR, DM/Insulin: Yes vs. No

Back to the duration model

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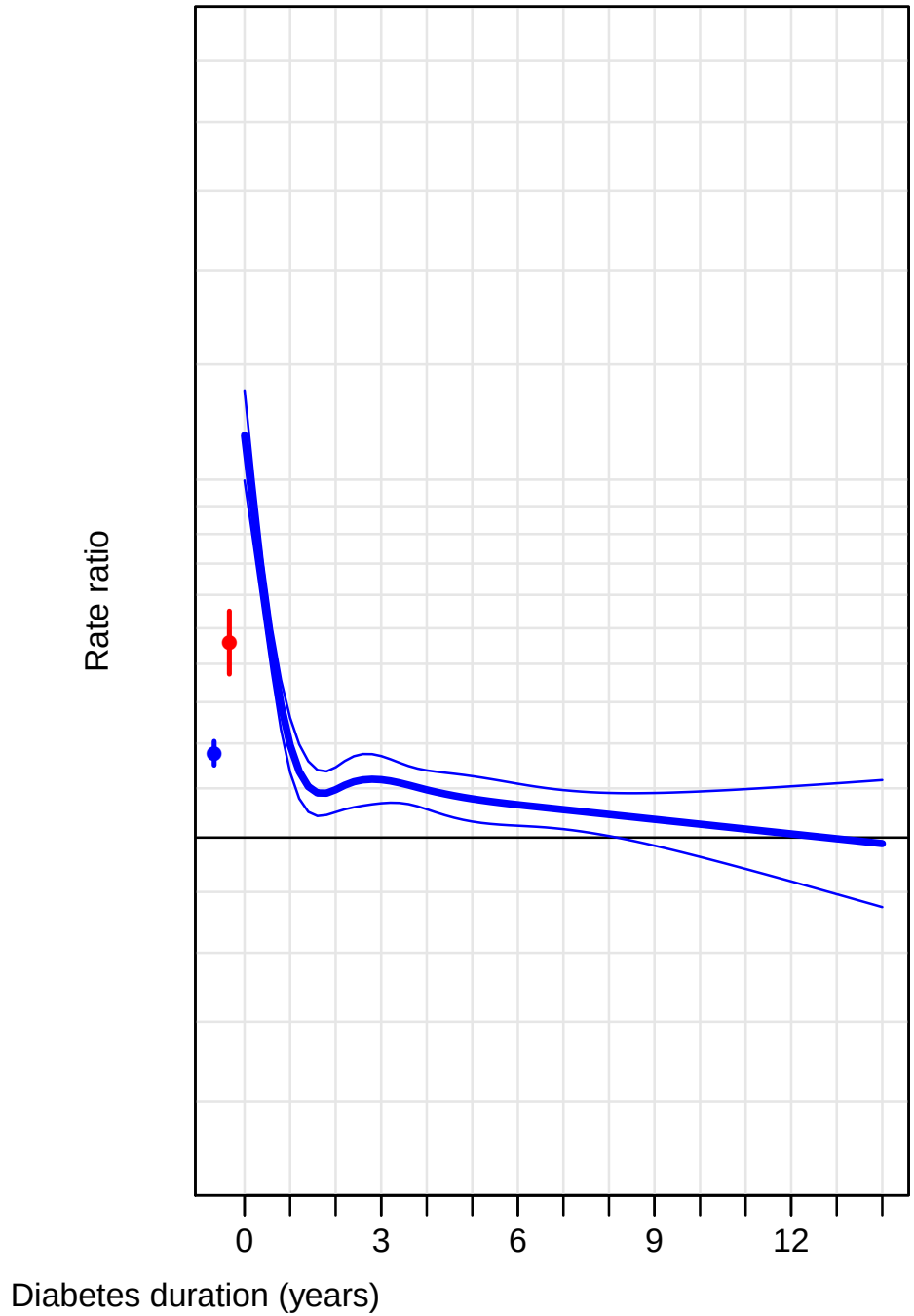
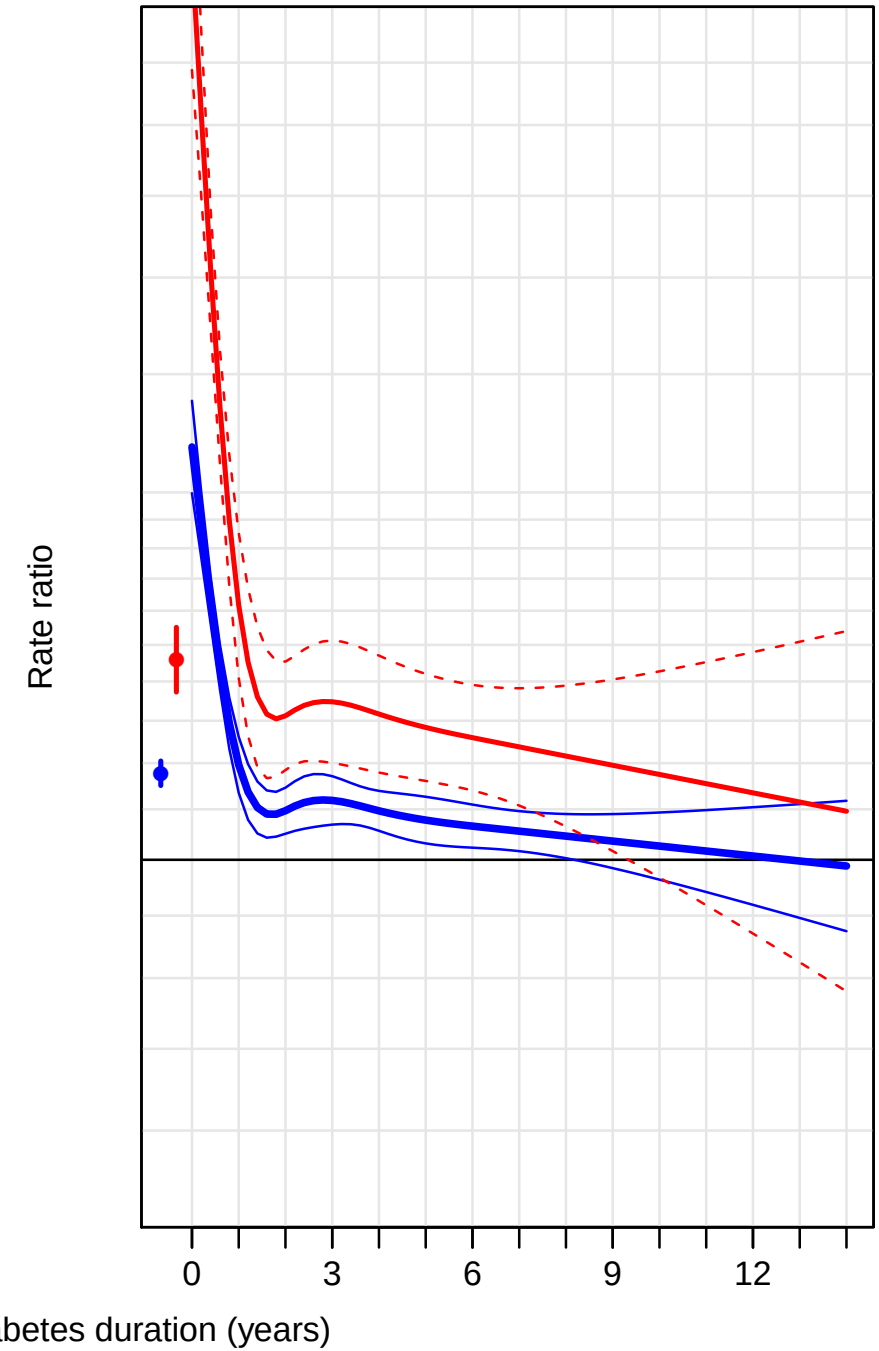

Rate ratio
0
3
6
9
12
Diabetes duration (years)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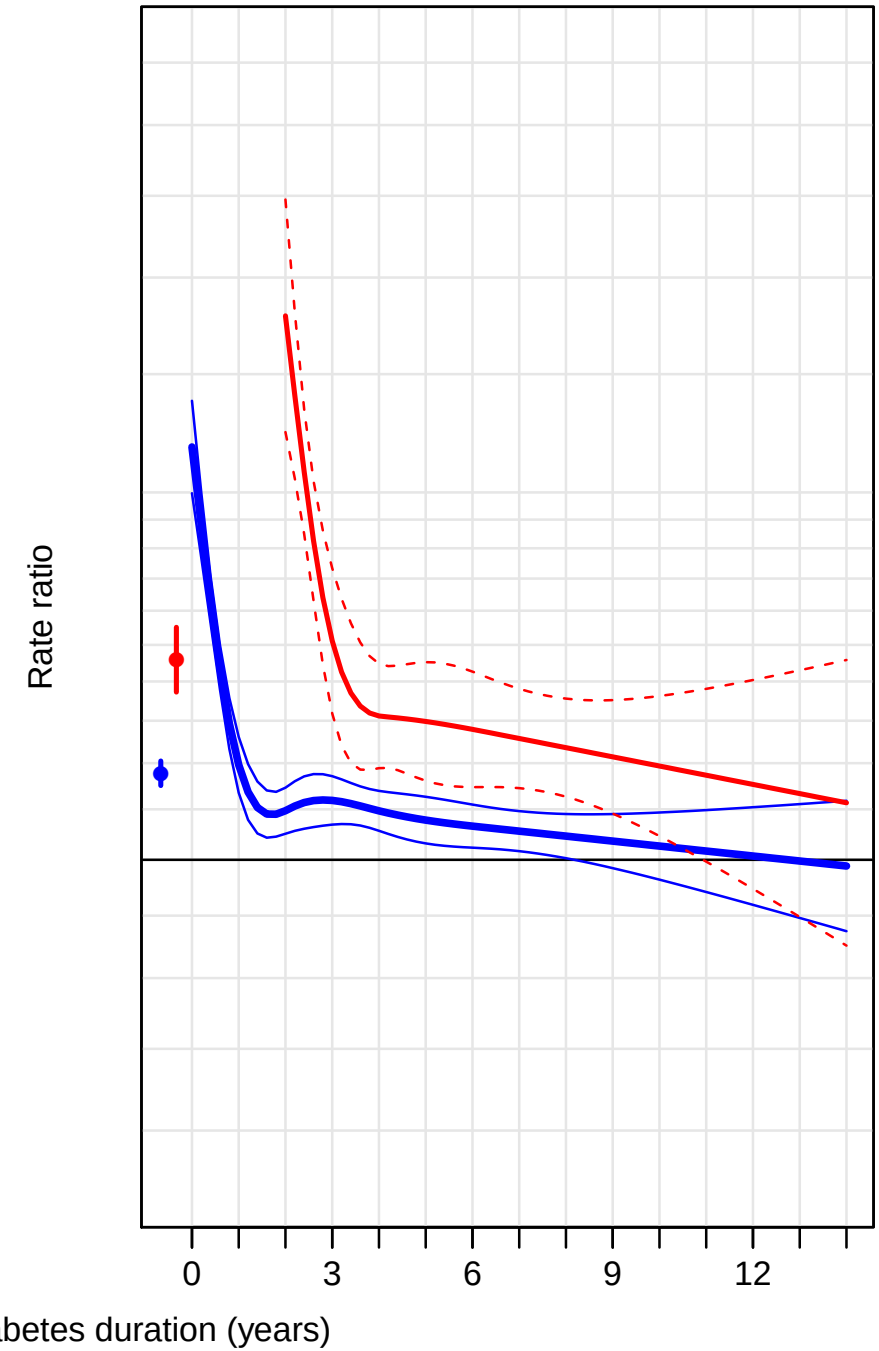
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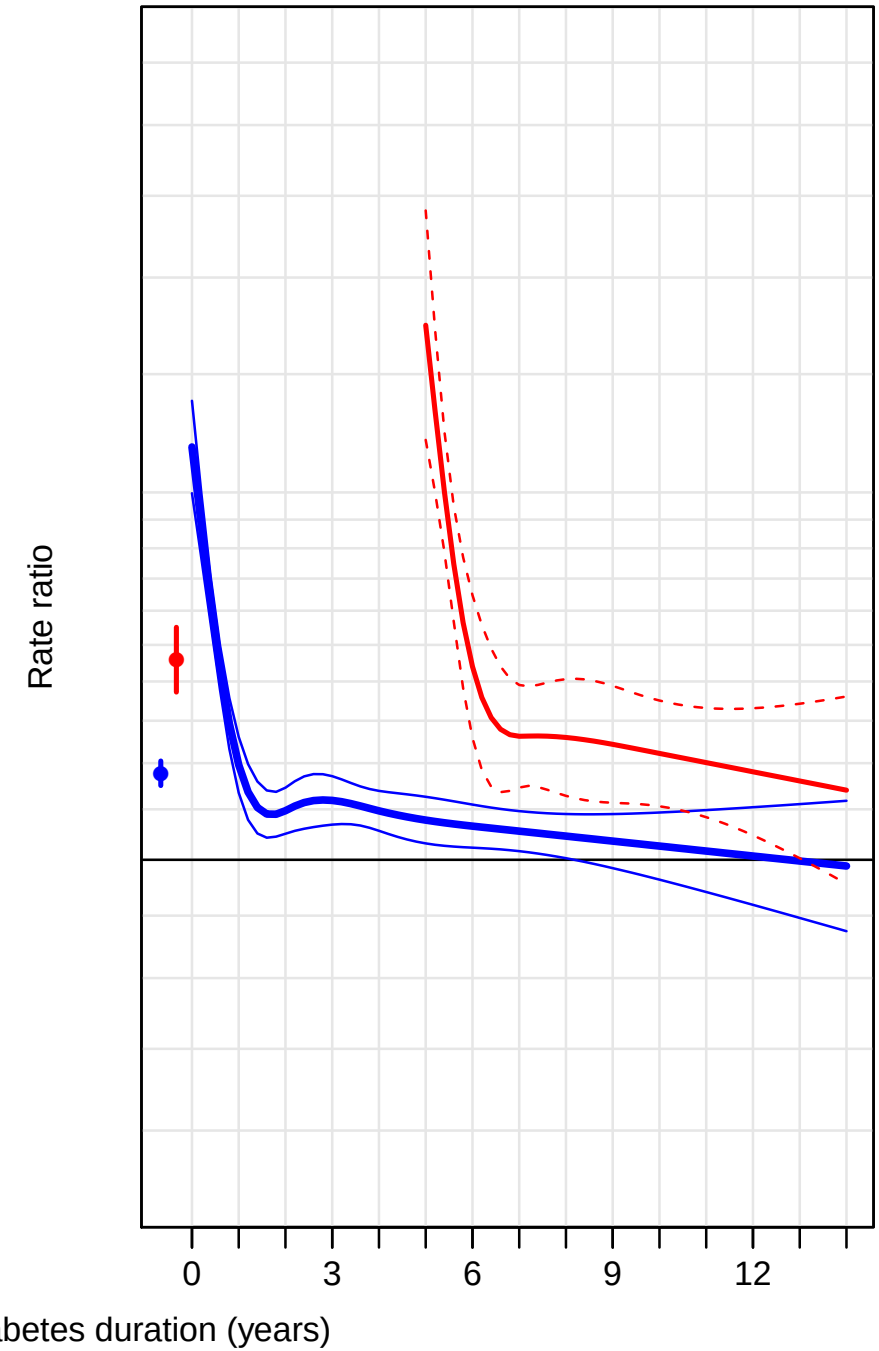
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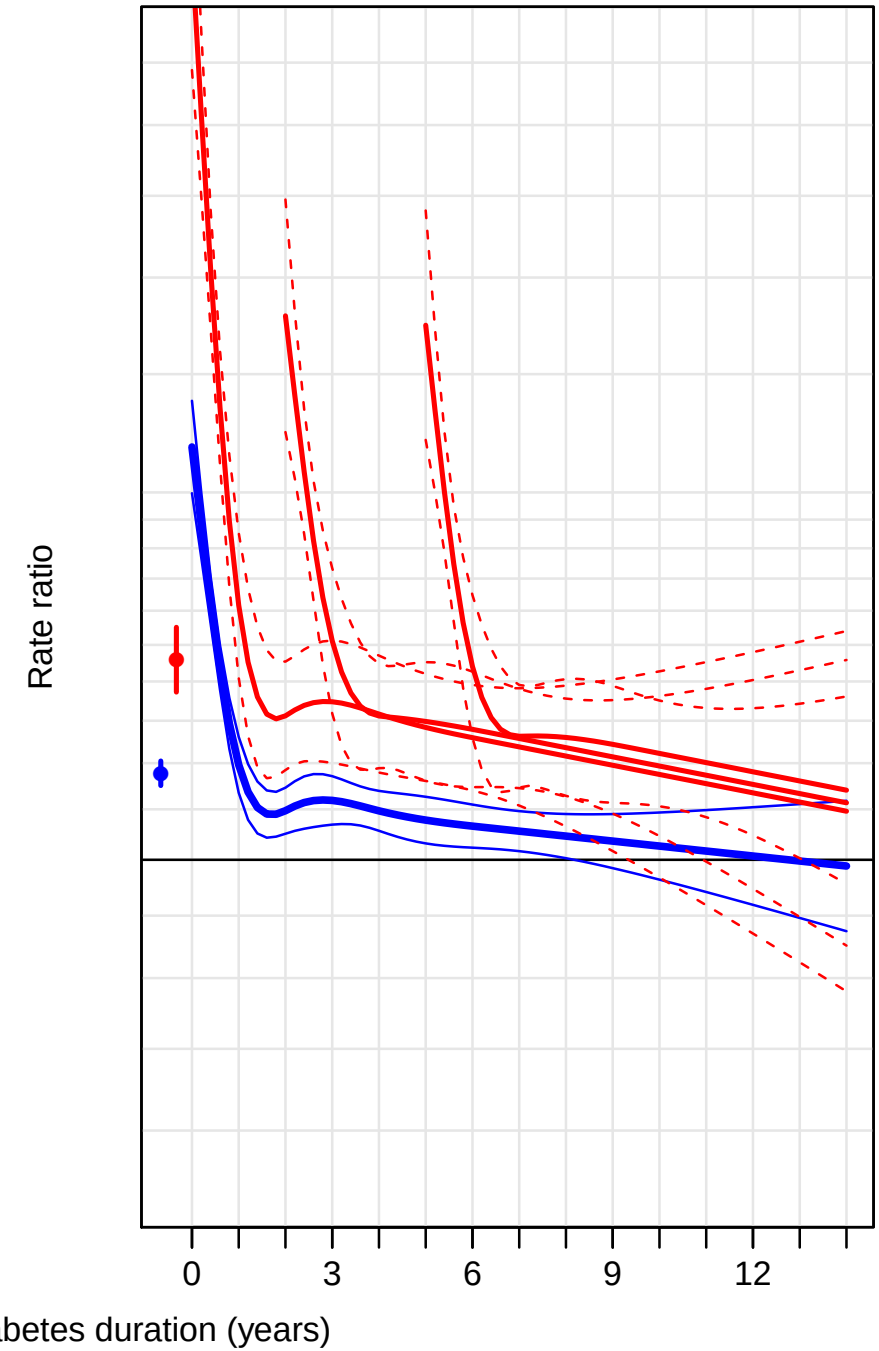
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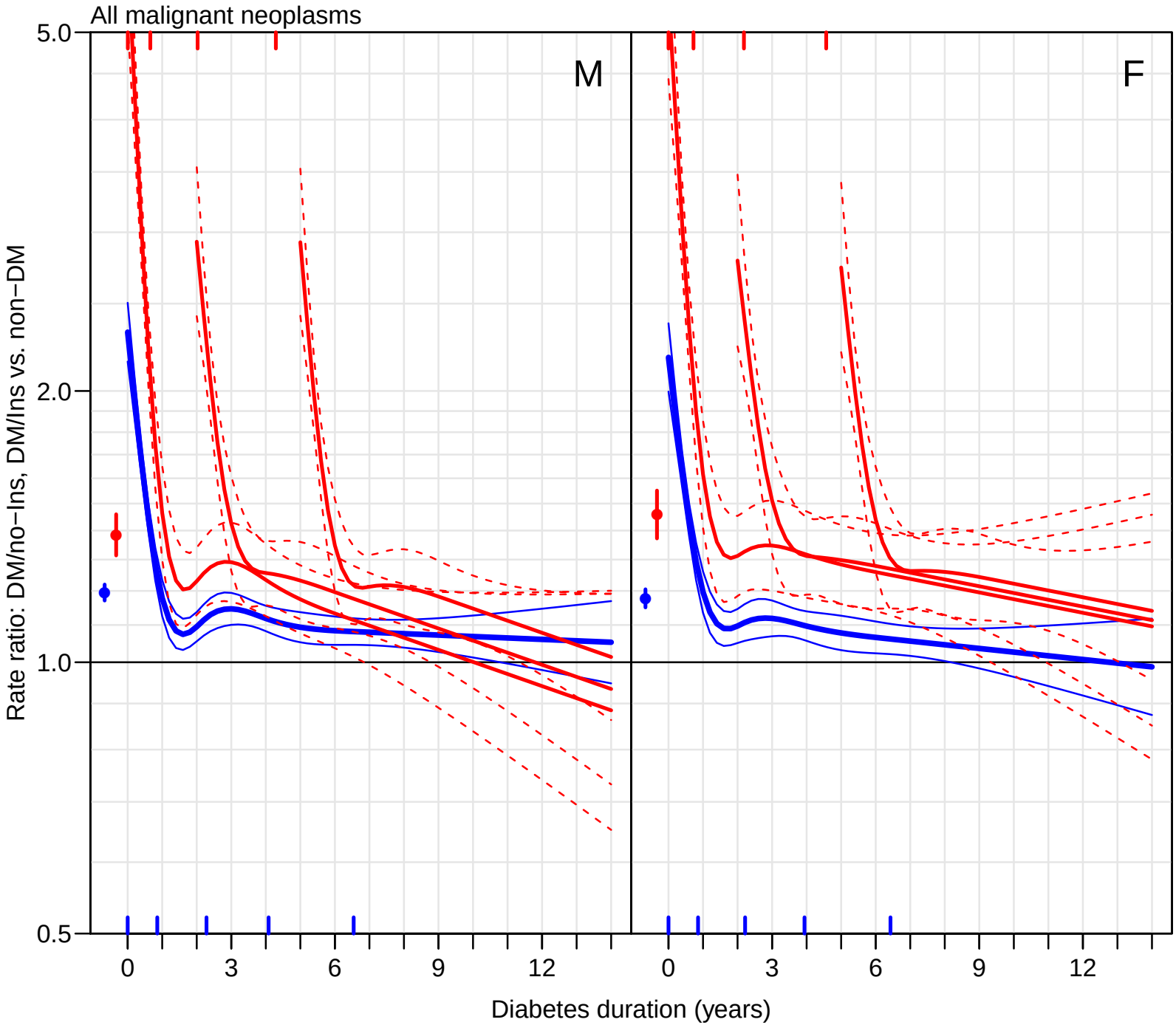
All malignant neoplasms
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
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12
Diabetes duration (years)

Extending the duration model

$$\begin{aligned}\text{rate} = & f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ & \times t(\text{DM-duration}) \\ & \times s(\text{Ins-duration})\end{aligned}$$

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$$\begin{aligned}\text{rate} = & f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ & \times t(\text{DM-duration}) \\ & \times s(\text{Ins-duration}) \\ & \times \beta(\text{DM-duration} - \text{Ins-duration})\end{aligned}$$

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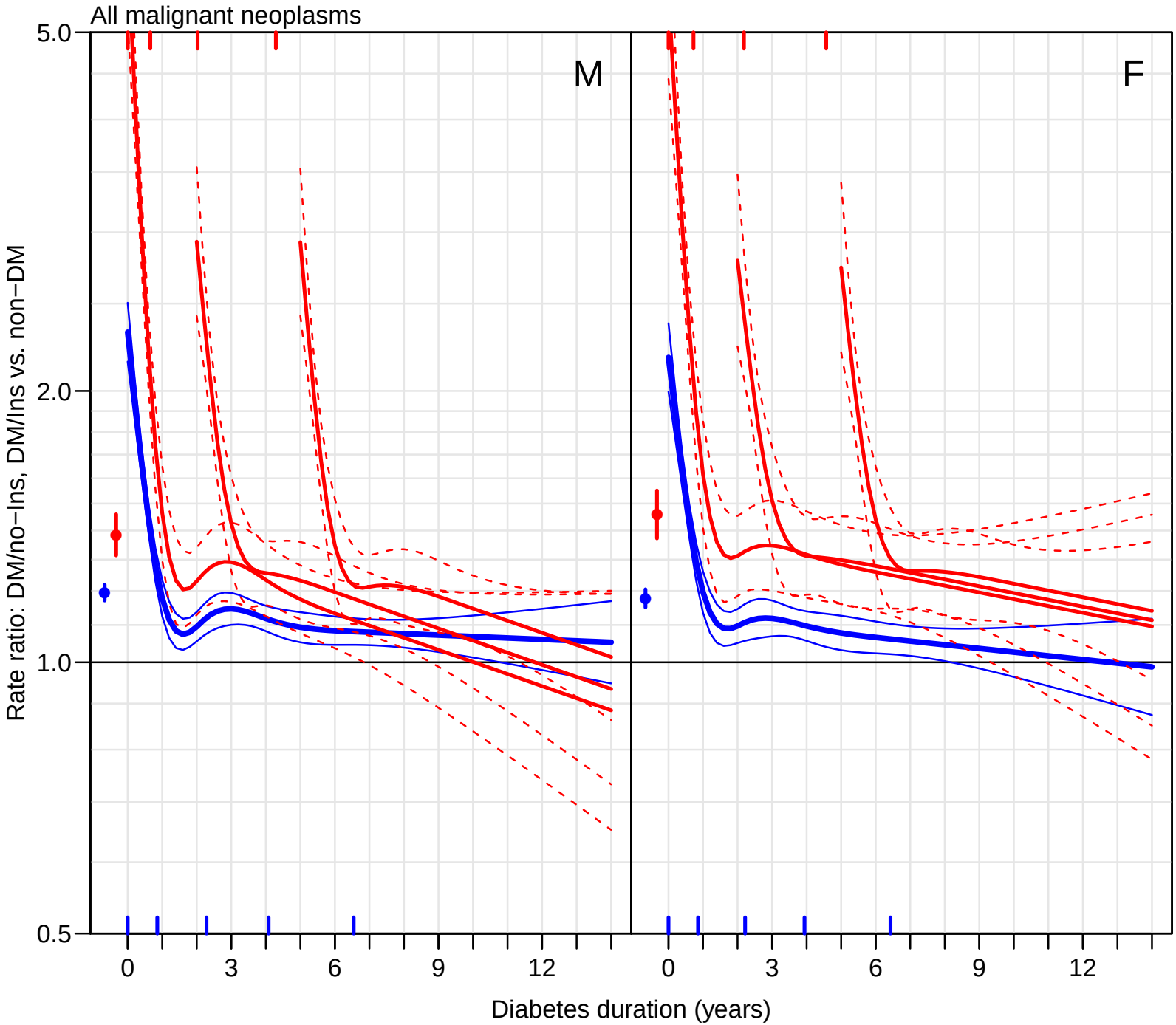
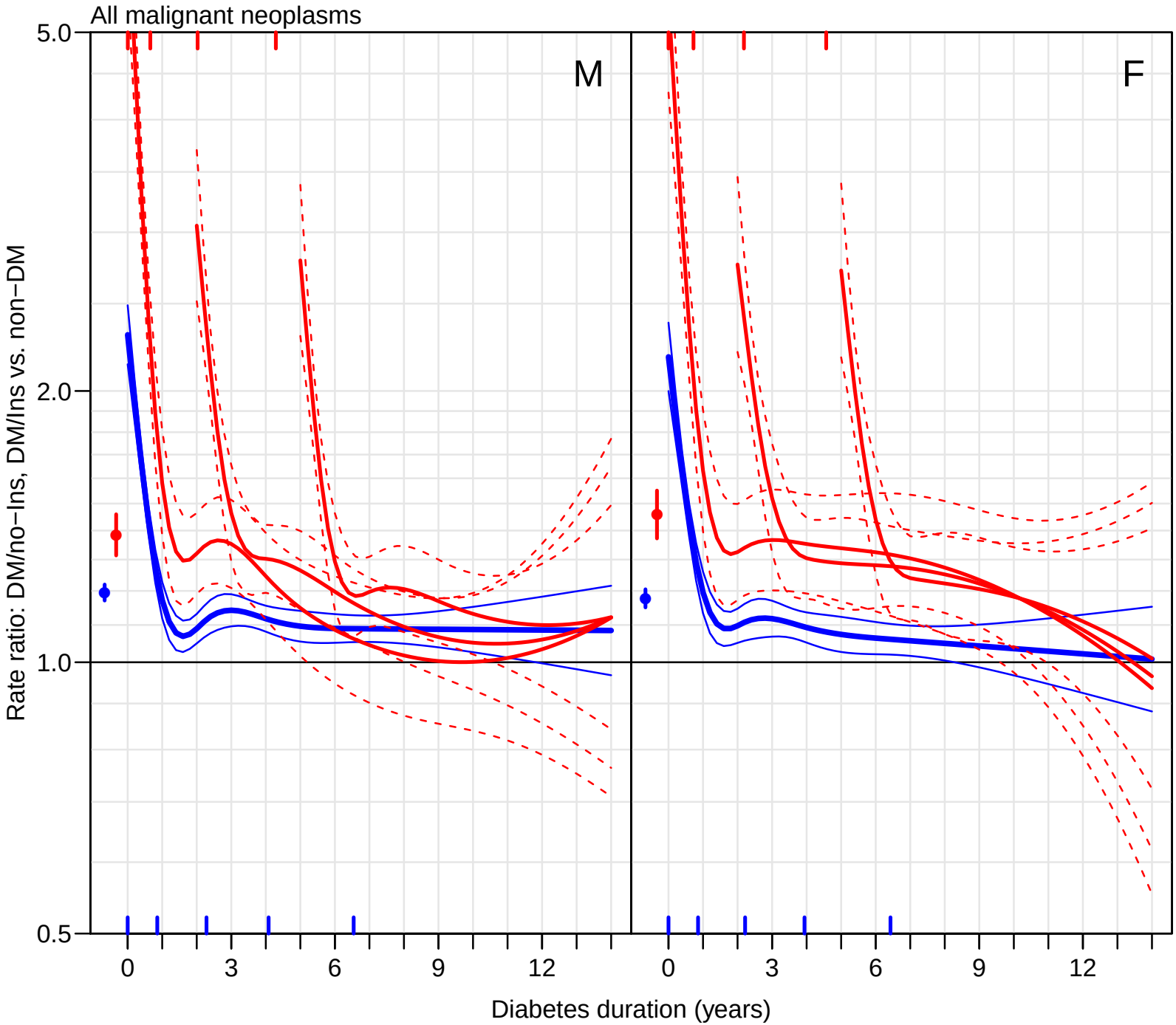
Two interaction terms:

- β: DM-duration at insulin start
- γ: Synergy between diabetes and insulin duration

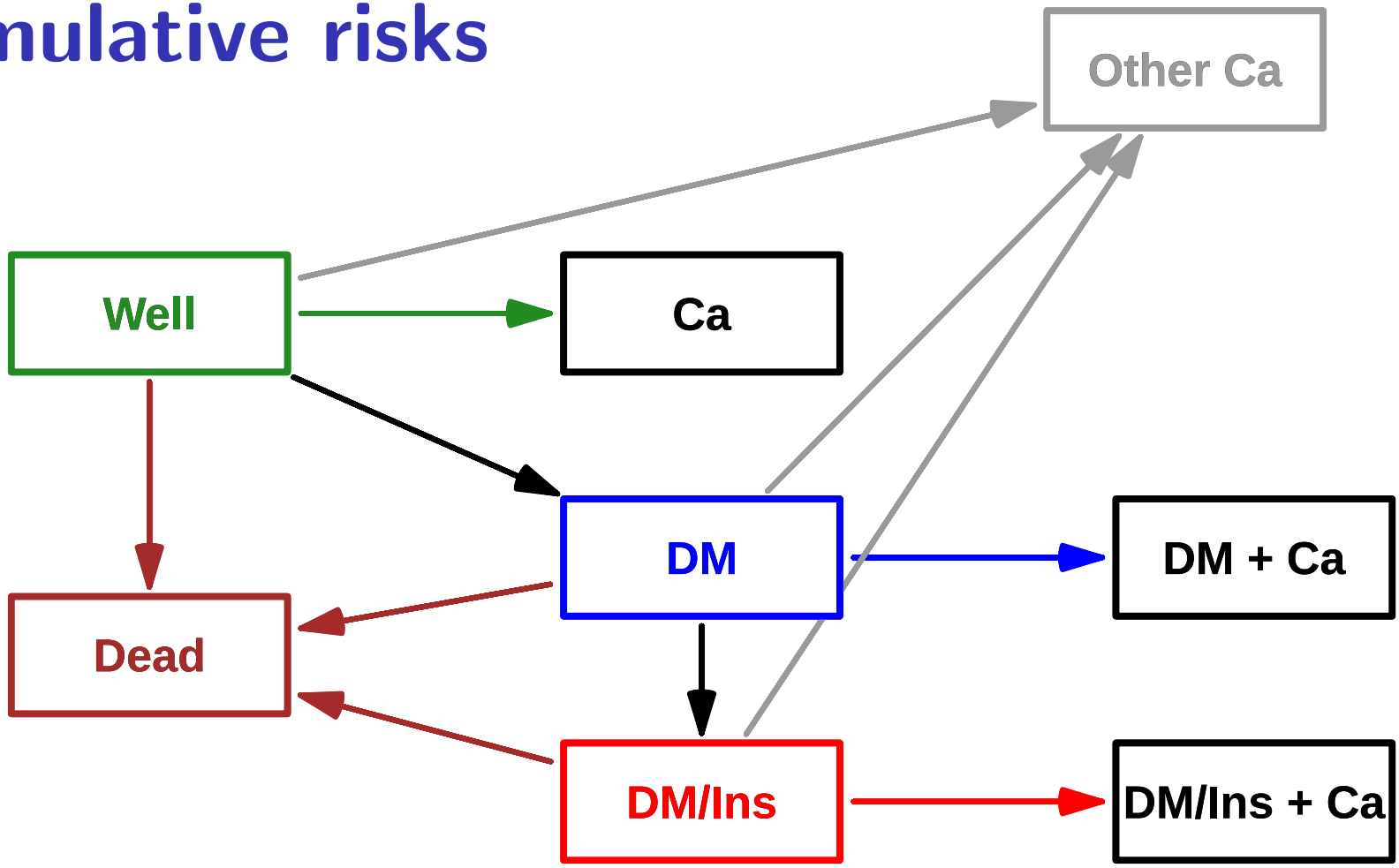
Modelling in R

```
mi <- update( m1, . ~ . +
                  I((DMDur-InsDur)*(state=="InsDur")) +
                  I( DMDur*InsDur) )
```

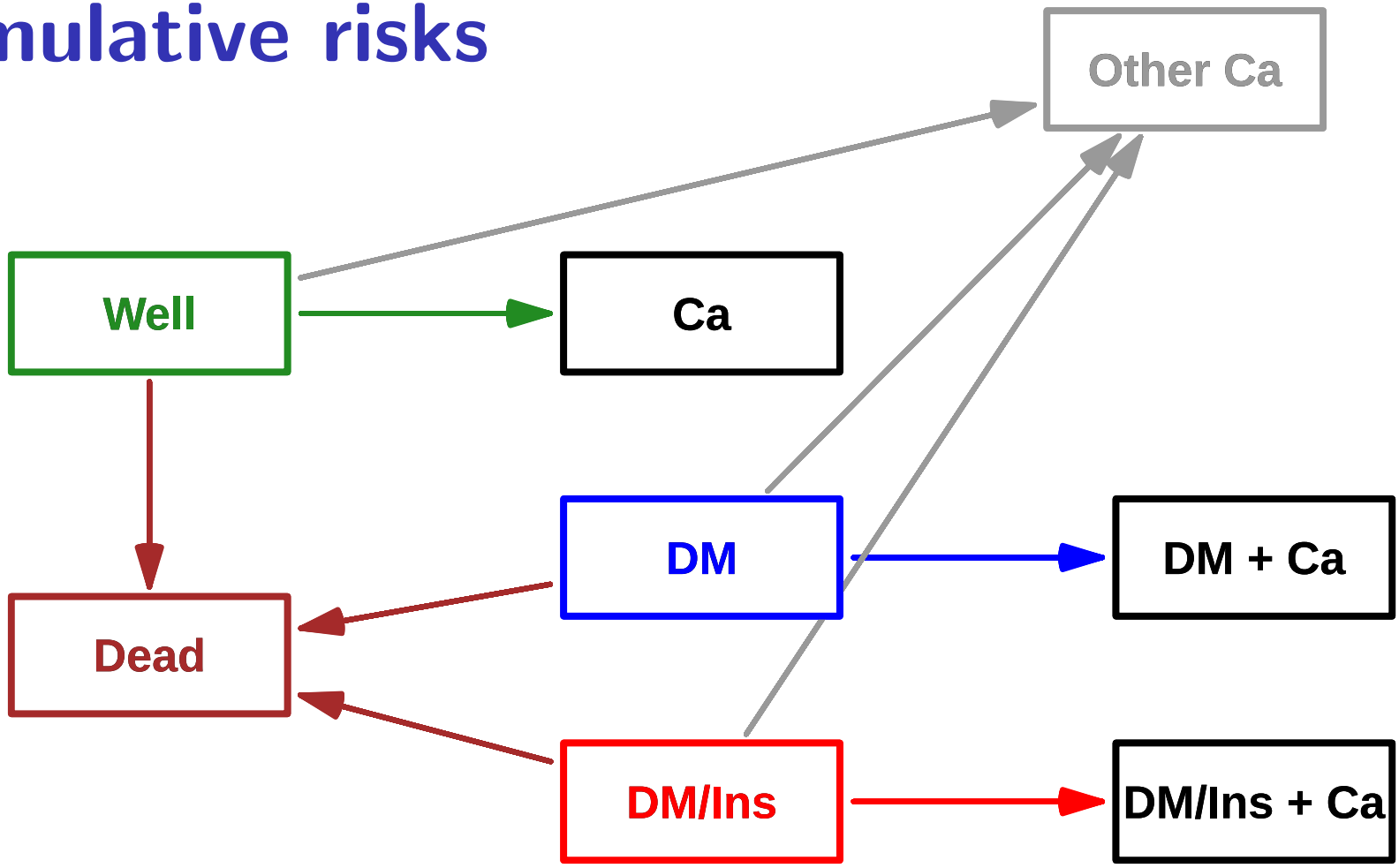

All malignant neoplasms
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)


All malignant neoplasms
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)

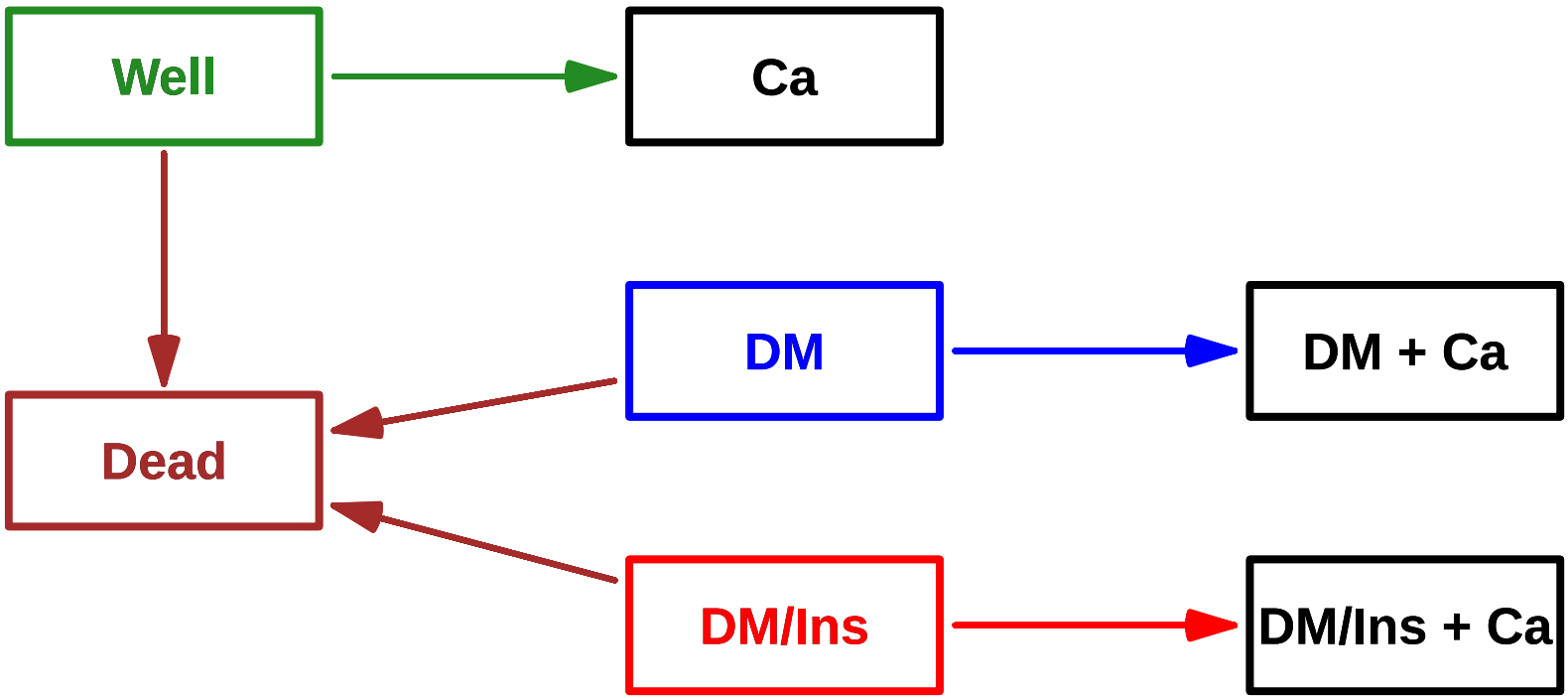
Cumulative risks



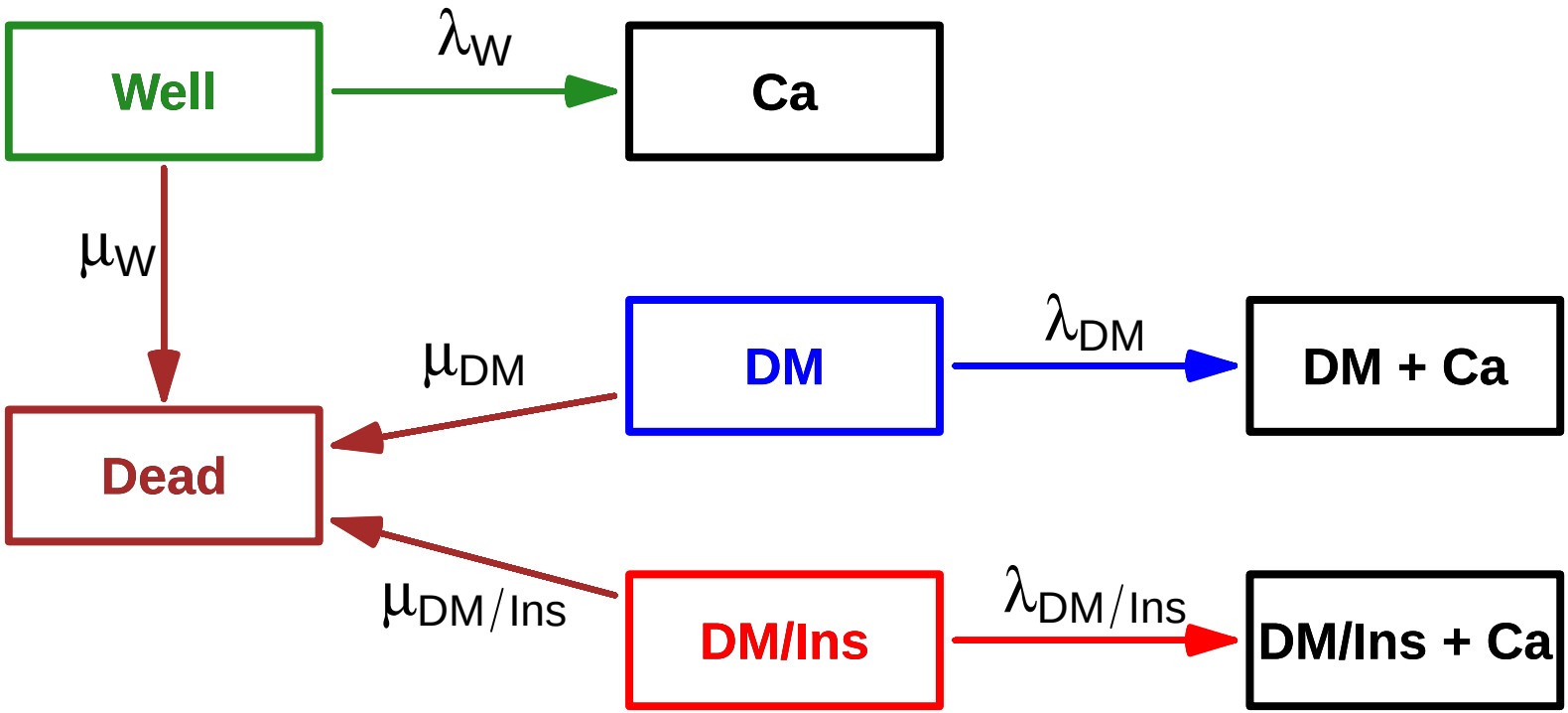
Cumulative risks



Cumulative risks

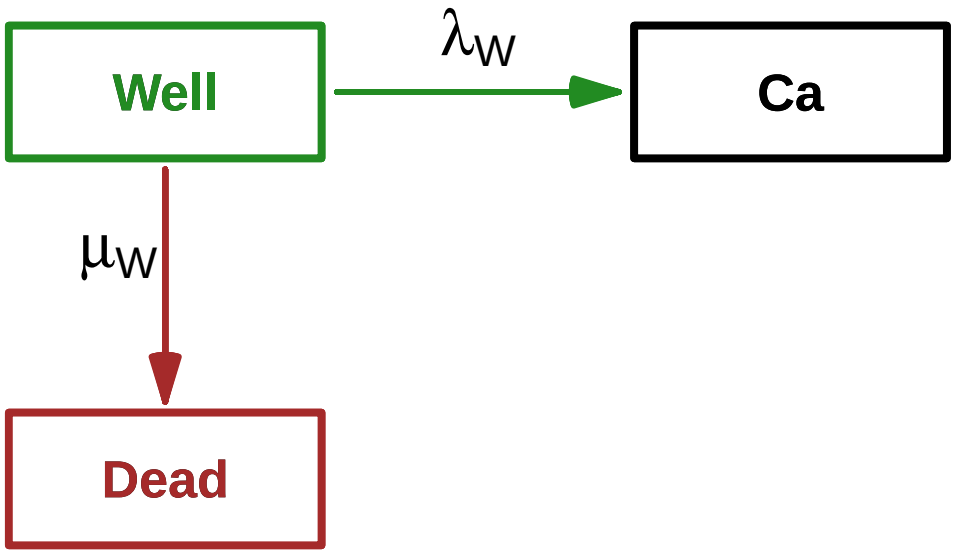


Cumulative risks



Note: **All** covariates must be given to specify rates.

Competing risks



Note: **All** covariates must be given to specify rates.

Competing risks:

- Probability of being alive without cancer:

$$S(t) = \exp\left(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\right)$$

- Probability of being dead without previous cancer:

$$p_{\text{dead}}(t) = \int_0^t S(u)\mu(u)\,\mathrm{d}u$$

- Probability of having had cancer disregarding subsequent death:

$$p_{\text{cancer}}(t) = \int_0^t S(u)\lambda(u)\,\mathrm{d}u$$

Computing the integrals

- The model:

$$\begin{aligned}\text{rate} = & f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ & \times t(\text{DM-duration}) \times s(\text{Ins-duration}) \\ & \times \beta(\text{DM-duration} - \text{Ins-duration}) \\ & \times \gamma(\text{DM-duration} \times \text{Ins-duration})\end{aligned}$$

  gives a closed form expression for the incidence rates (λ_{W}, λ_{DM}, $\lambda_{\text{DM/Ins}}$).
- A similar model fitted for deaths, giving a closed form expression for the mortality rates (μ_{W}, μ_{DM}, $\mu_{\text{DM/Ins}}$).

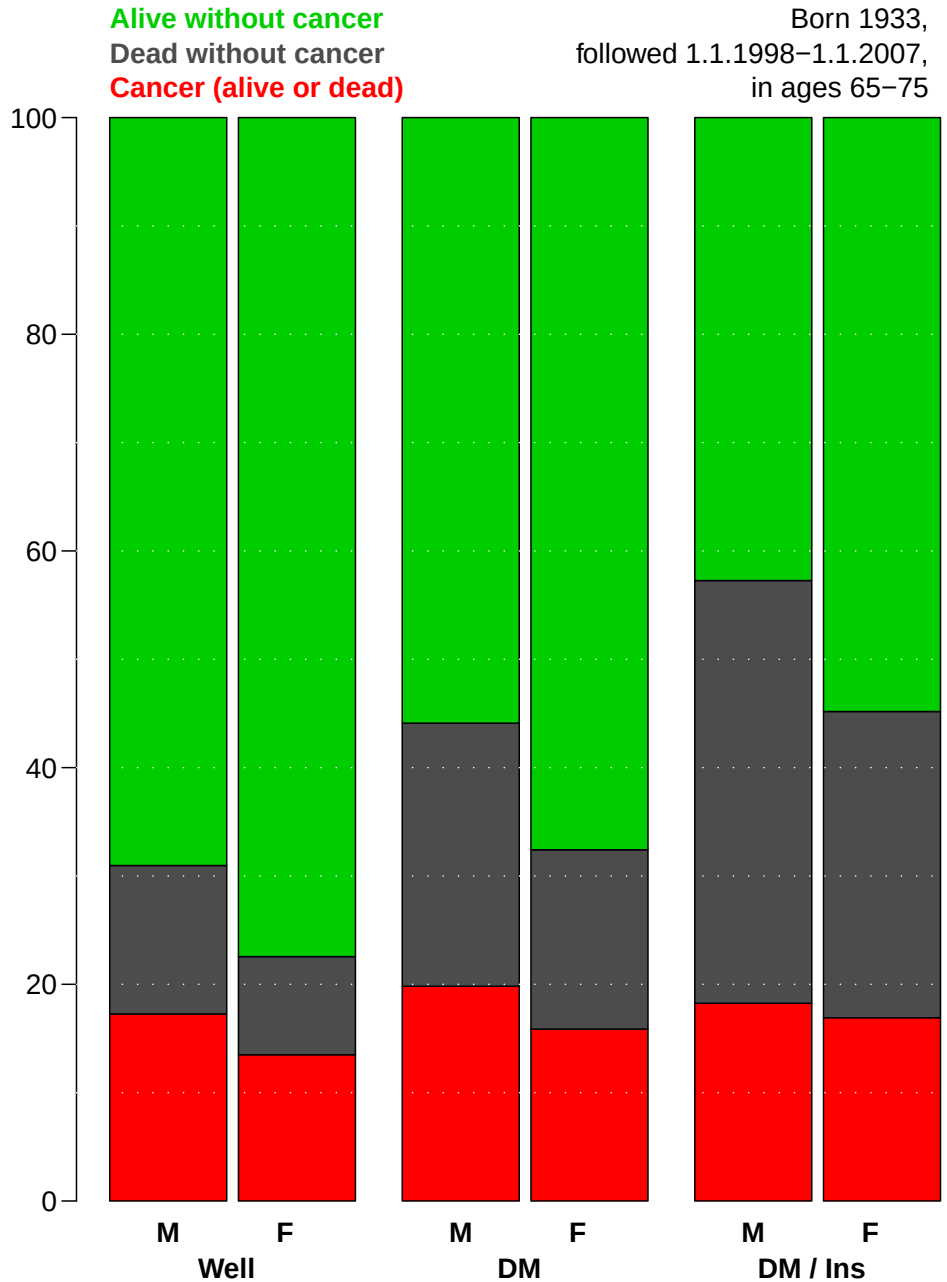
Computing the integrals

- Make a (model based) prediction of:
  - incidence rates
  - mortality rates

  for occurring combinations of:
  - Ages 65–75
  - Date of F.U. 1998–2008
  - Duration 0–10

  . . . for every $1/20$ year — 200 prediction points.
- Integrals are sums of these (multiplied by $1/20$)

Compute the cumulative risks for a 10-year period for the same type of person in each box.



Computing it in R

The mortality rates are in the vector mm and the cancer incidence rates in the vector cc:

```
surv <- exp( -cumsum( cc + mm ) )
prca <- cumsum( surv * cc )
prdd <- cumsum( surv * mm )
```

— for accuracy, check they sum to 1!

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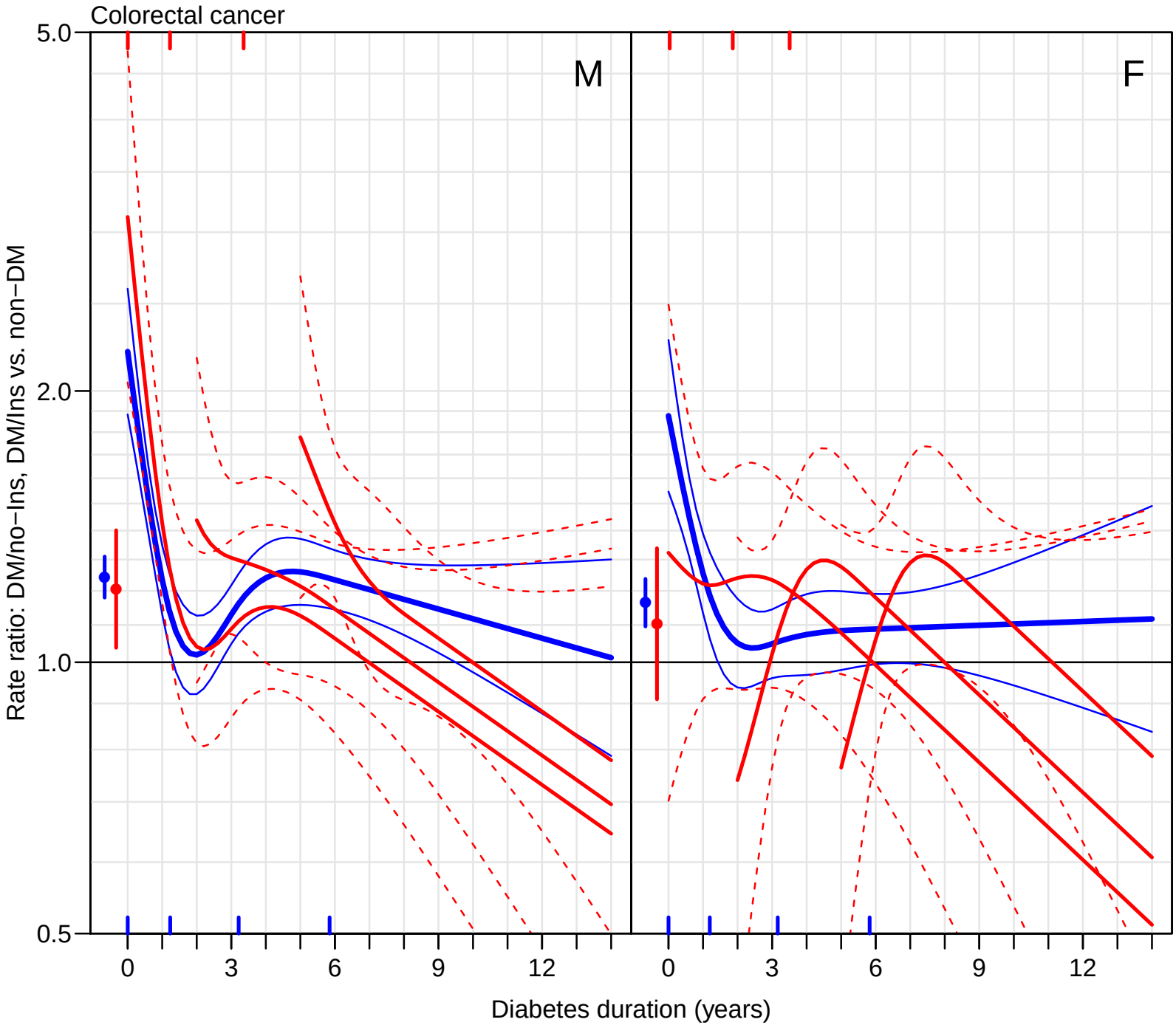
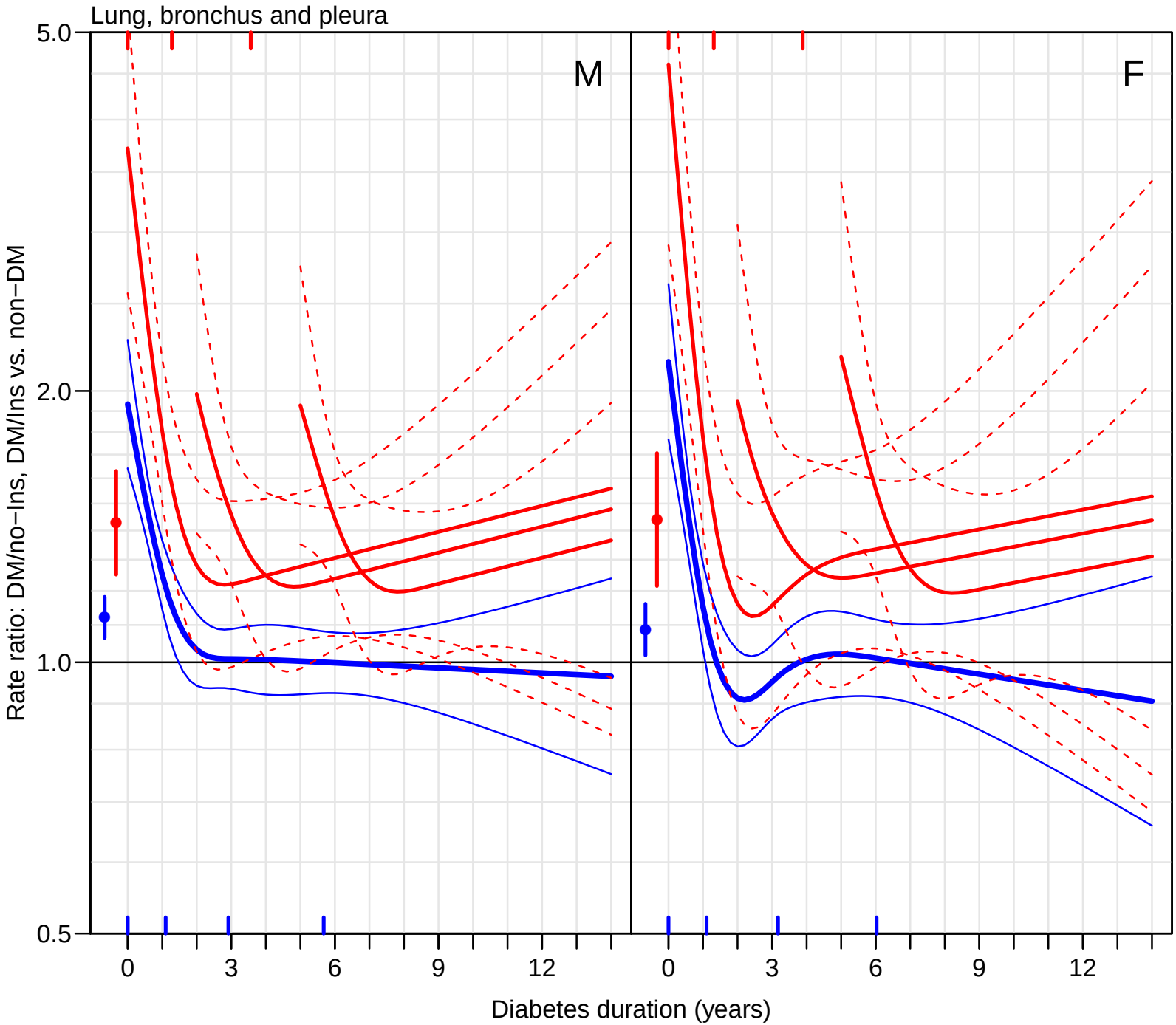
prdd <- cumsum( surv * mm )
```

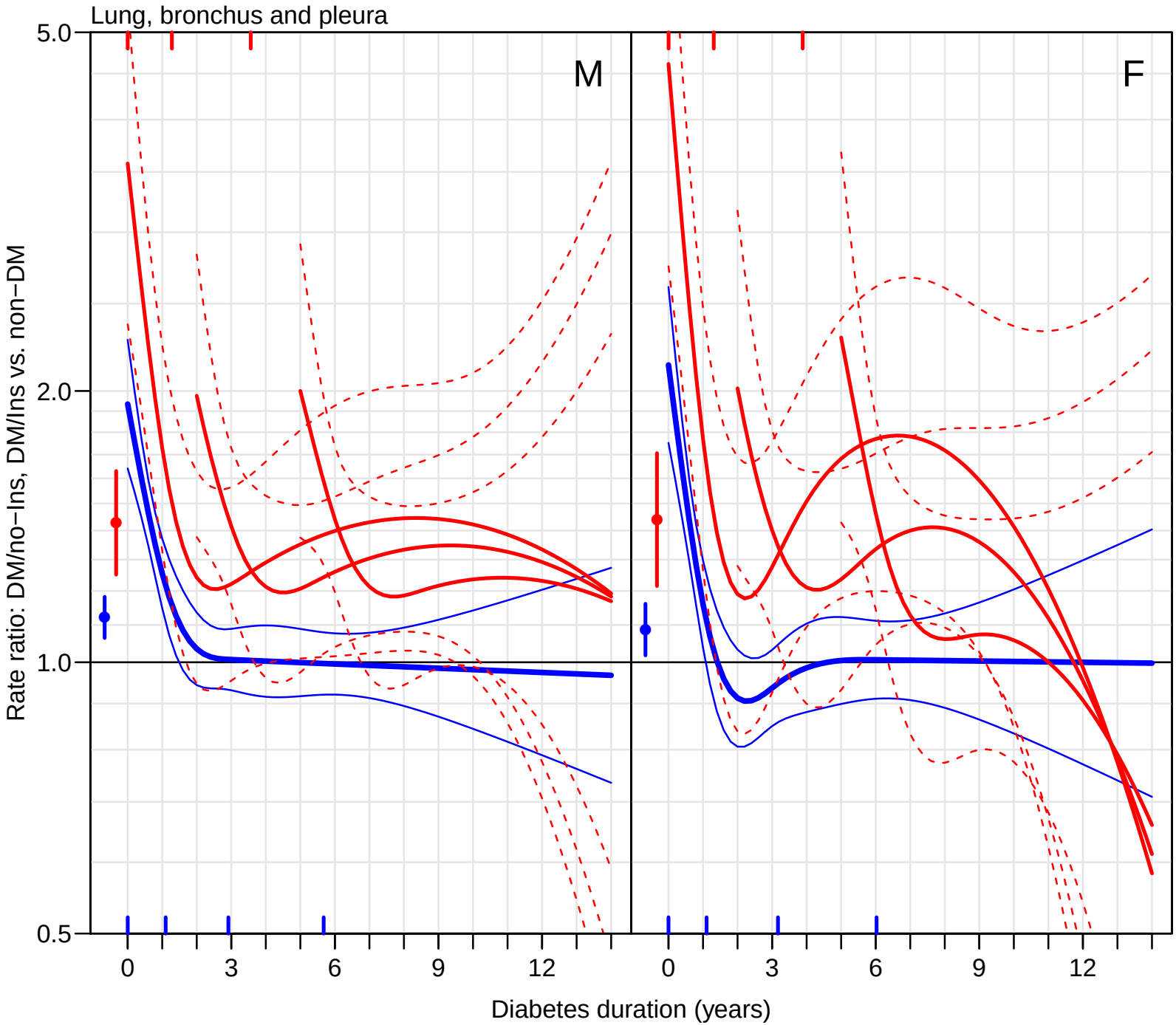
— for accuracy, check they sum to 1!

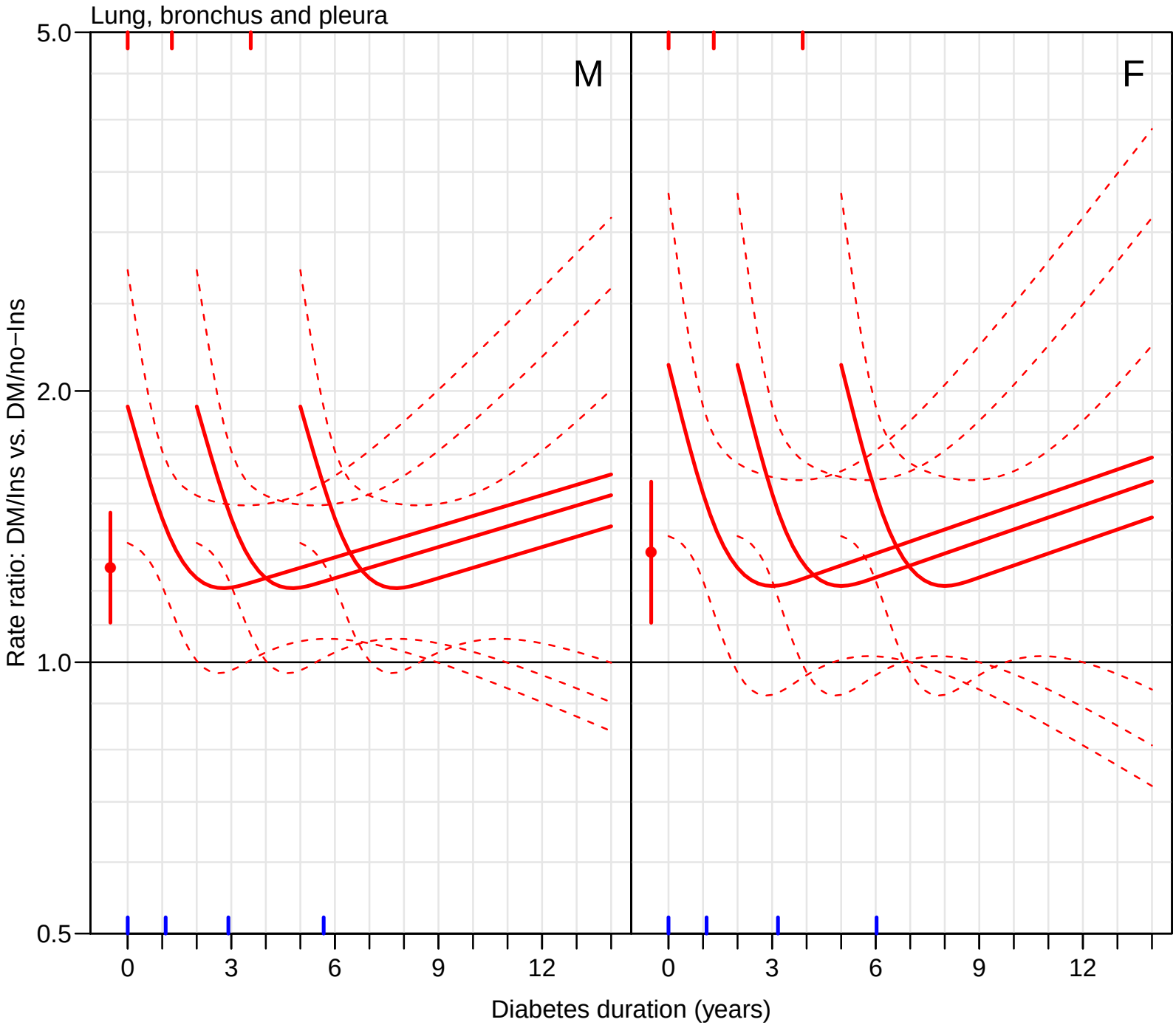
Actually it was:

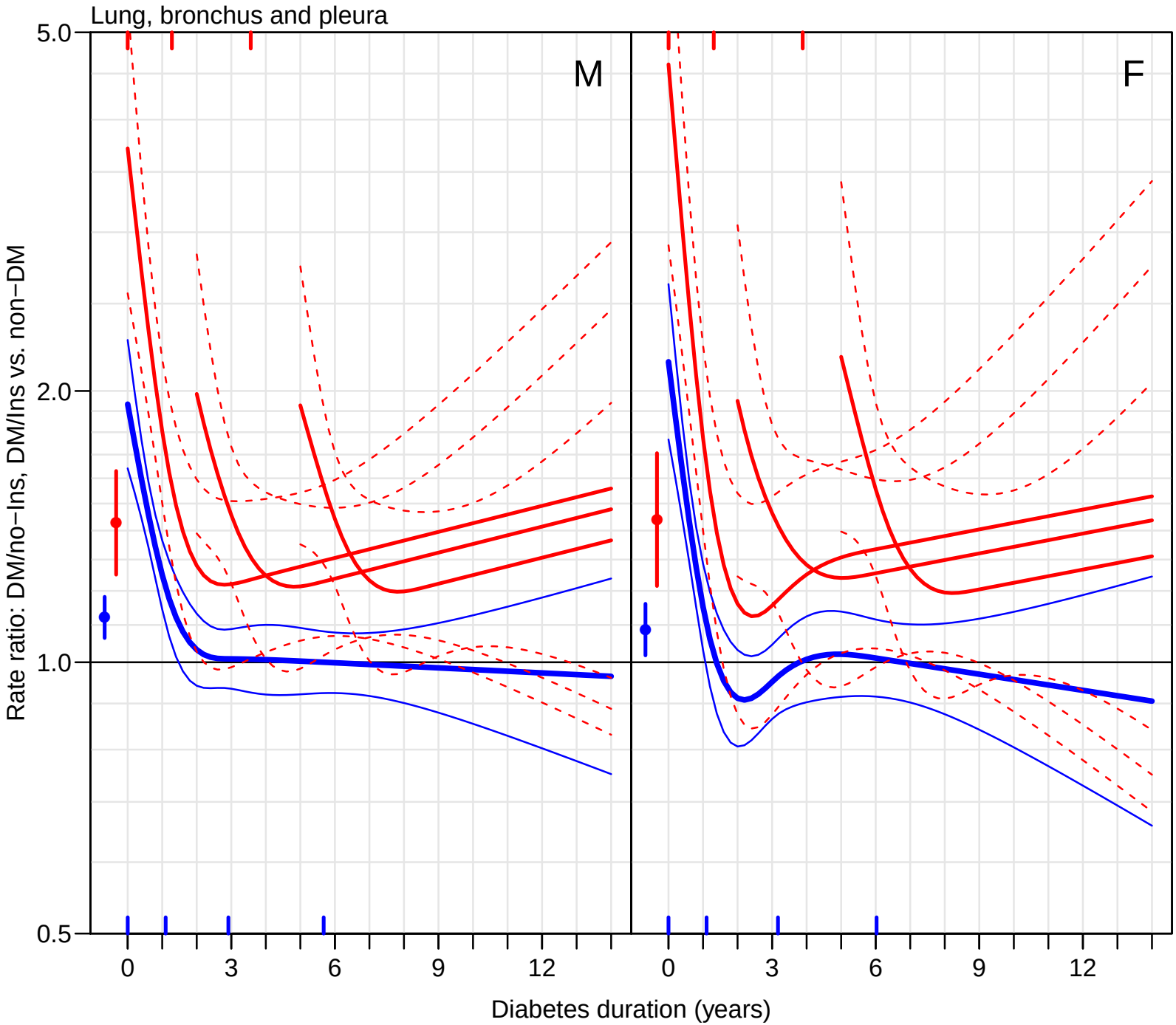
```
surv <- exp( -cumsum( exp(prr["Allm",sx,mo,,st])+
                      exp(prr["Dead",sx,mo,,st]) ) )
s.can[dg,sx,mo,,st] <-
                cumsum( surv * exp(prr[dg,sx,mo,,st]) )
```

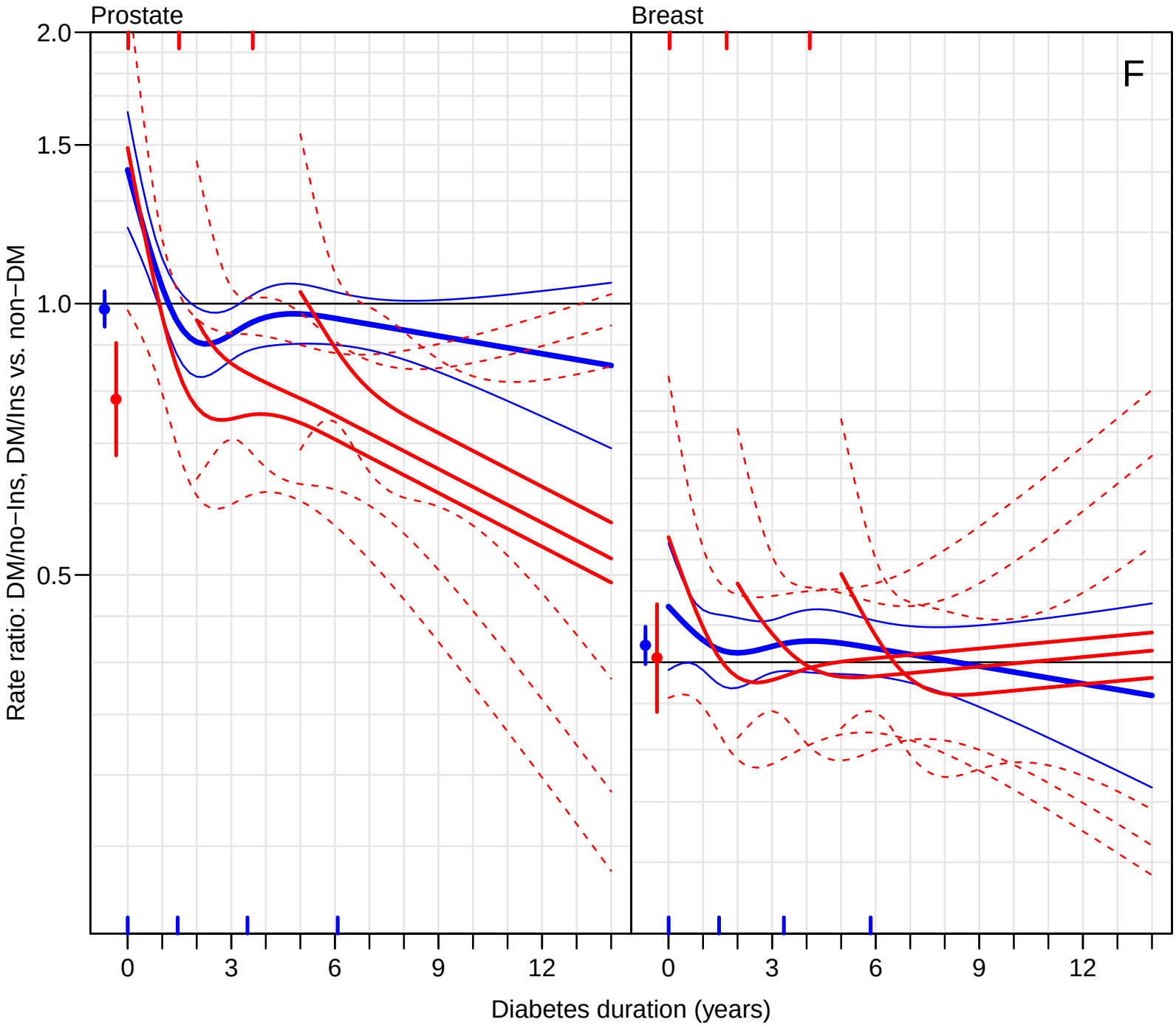

Colorectal cancer
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)

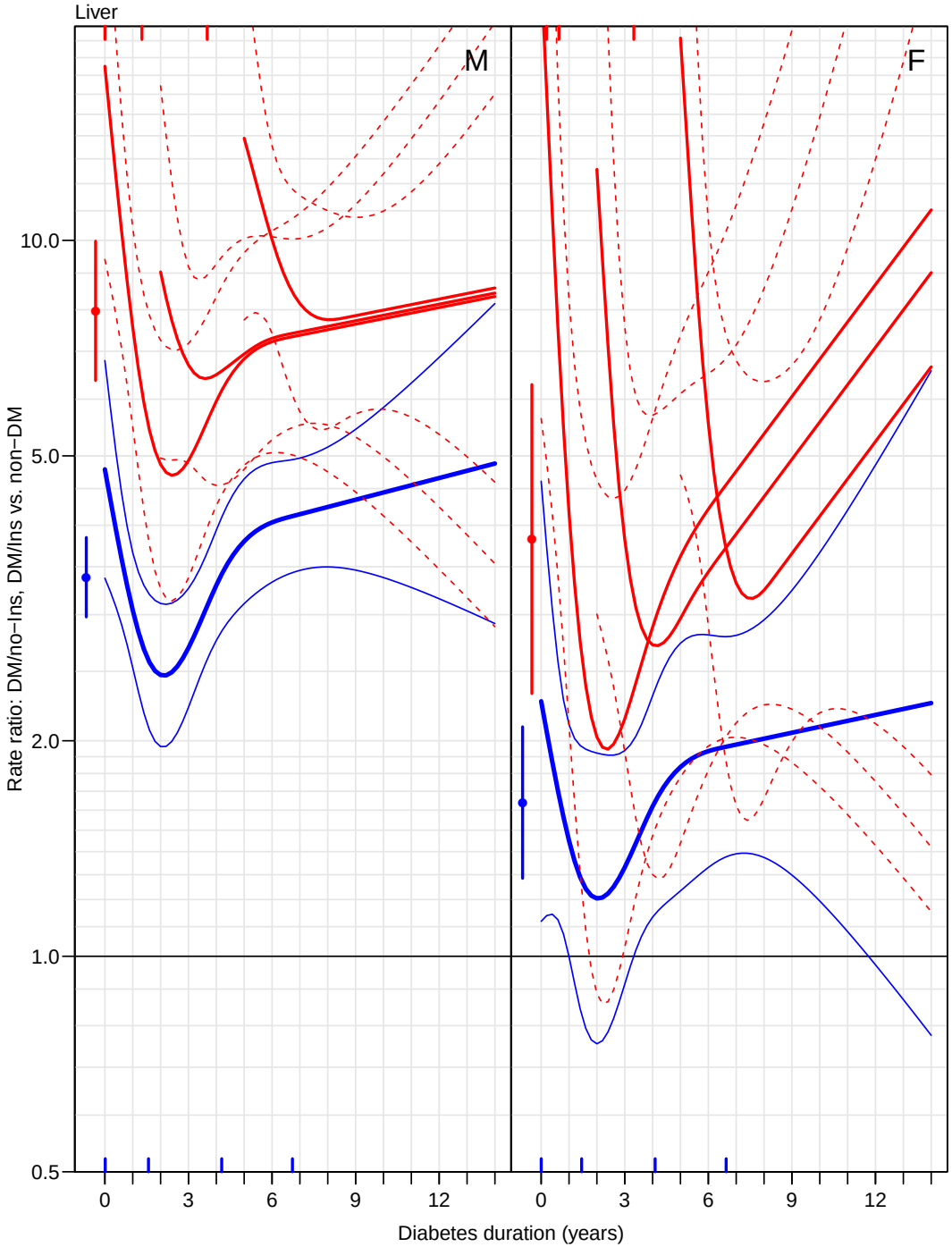

Lung, bronchus and pleura
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)

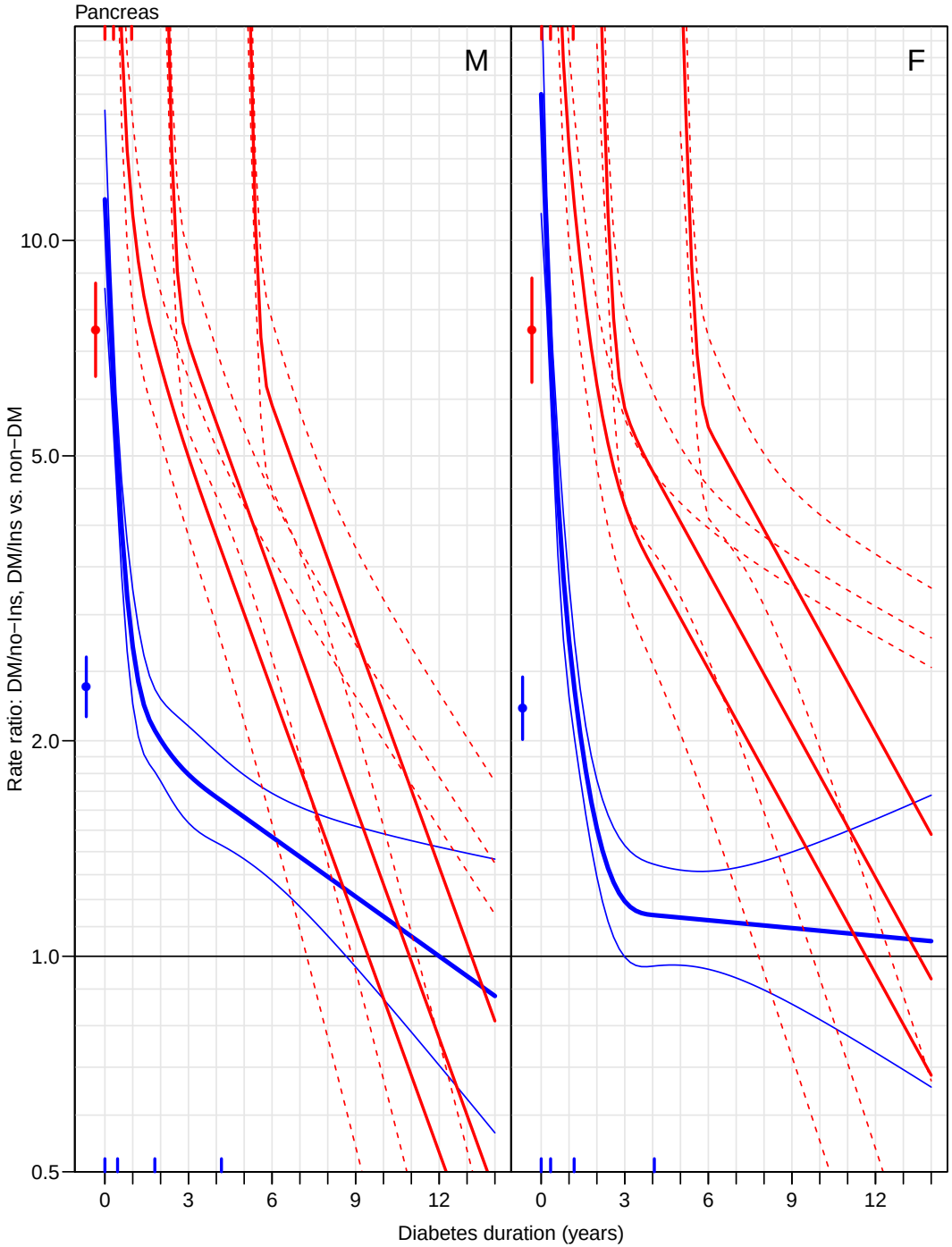

Lung, bronchus and pleura
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)

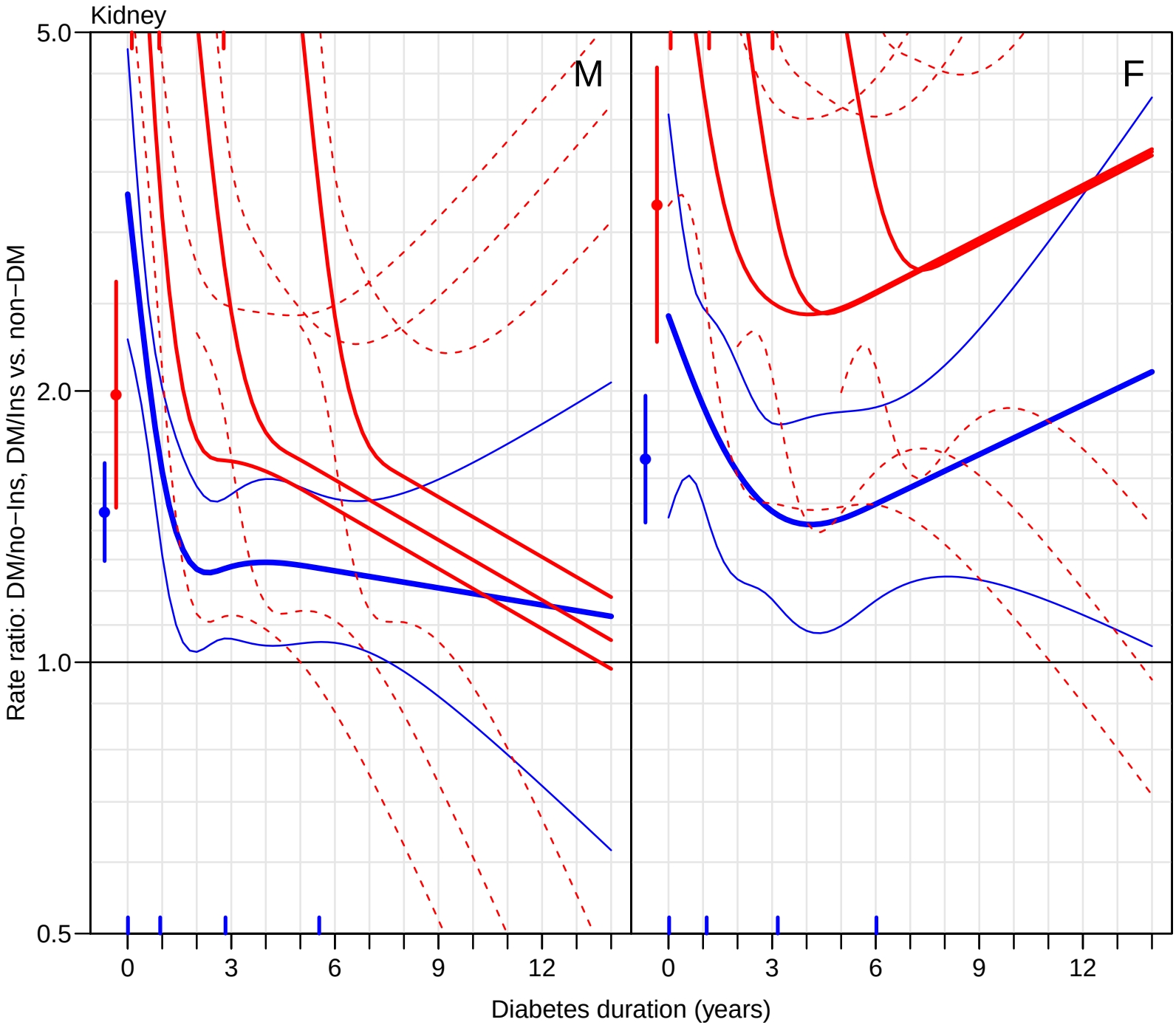

Lung, bronchus and pleura
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/Ins vs. DM/no−Ins
0
3
6
9
12
Diabetes duration (years)


Lung, bronchus and pleura
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)


Prostate
Breast
F
2.0
1.5
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
0
3
6
9
12
Diabetes duration (years)


Liver
M
F
10.0
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)


Pancreas
M
F
10.0
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)


Kidney
M
F
5.0
2.0
1.0
0.5
Rate ratio: DM/no−Ins, DM/Ins vs. non−DM
0
3
6
9
12
Diabetes duration (years)

DM-Cancer pattern seen previously

Overall findings broadly consistent with what has been reported in the literature:

- Wideroff *et al.* [3] used a Danish material too, with a less specific definition of DM, with about 9000 cancers among DM patients.
- Adami *et al.* [1] used a Swedish material, — 2400 cancers among DM ptt.
- LaVecchia [2] used a case-control study, with about 3000 cancers among DM ptt.

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- Oral anti-diabetic therapies not taken into account
- No clinical measurements are available
- Effects of DM duration / insulin use cannot be separated from allocation effects.
  This will a limitation of **any** study.

Conclusion

- Cancer rates in diabetes patients depend on:

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Conclusion

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  - insulin duration

Conclusion

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- Cancer rates in diabetes patients depend on:
  - diabetes duration
  - insulin duration
- Strong diagnosis / allocation effects (jumps at duration 0)
- RR decrease by duration (mostly)
- DM patients not on insulin have cancer rates similar to the non-DM population after about 3 years of DM.
- Long term users of insulin show cancer rates higher than the non-DM population.

Summary

Previously known

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Summary

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- Primarily elevated rates for liver, pancreas, colorectal, kidney, ...

This study adds

- Incidence rates primarily increased shortly after diagnosis / start of insulin.
- No excess risk for non-insulin users after 3 years
- Insulin users' rates do not approach non-DM rates

Interpretation

Findings are consistent with:

- Common risk factors for DM and cancer (obesity, lack of physical exc., eating habits ...)

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Findings are consistent with:

- Common risk factors for DM and cancer (obesity, lack of physical exc., eating habits ...)
- More intense surveillance for cancer following DM diagnosis
- Reverse causation: Undiagnosed cancers lead to DM diagnosis
- Effect of insulin in either direction

  A cumulative effect of insulin increasing cancer risk cannmot be excluded even if RR decrease by insulin duration for most cancer sites — there is a strong mortality selection.

Methodological points for FU-studies

- Follow all persons till death or exit from study — never censor persons due to status change, model effect of the status change.

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- Tabulate follow-up finely (1-year classes)
- Parametric models for rates makes it easy to compute state probabilities.
- — and your assumptions painfuly explicit.

The recent scare

- Diabetologia published 4 papers and an editorial in the summer 2009, pointing (weakly) to a possible promoting effect of Glargine, an insulin analog from Sanofi-Avensis.
  [6, 7, 8, 9, 10].
- All based on 1–4 years of follow-up after drug initiation.
- All based on comparison of heavily selected subgroups of patients.
- Some were methodologically flawed.

There is biological reason to suspect insulin/analogs for a role in cancer promotion.
But evidence is weak and data are limited.

Future studies in DK

- Aims:
  - Estimate association with different oral therapies (SU, Metformin, ...)
  - Estimate association with different insulin (analogs)
  - Estimate association with dosage of either
- The study in DK will include **all** follow-up time of Danish DM-patients and all persons without cancer.

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