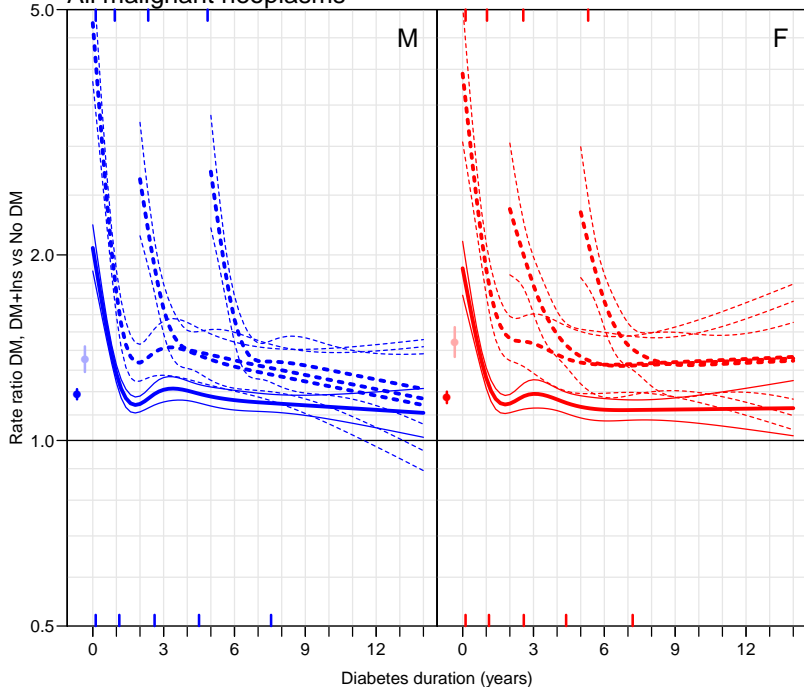


Epidemiology of Diabetes and cancer

Bendix Carstensen Steno Diabetes Center
Gentofte, Denmark
<http://BendixCarstensen.com>

Danish Cancer Society, 7 March 2014

All malignant neoplasms



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H. O. Adami, J. McLaughlin, A. Ekblom, C. Berne, D. Silverman, D. Hacker, and I. Persson.

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C. La Vecchia, E. Negri, S. Franceschi, B. D'Avanzo, and P. Boyle.

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The Danish Cancer Registry—history, content, quality and use.

Dan Med Bull, 44:535–539, Nov 1997.



B. Carstensen, J. K. Kristensen, B. Ottosen, and K. Borch-Johnsen

Diabetes and Cancer

Persons with diabetes have long been known to have increased incidence rates and mortality rates from cancer [1, 2, 3, 4]:

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

Aims of the Danish study [5]

- ▶ Describe cancer incidence rates among diabetes patients in Denmark.

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 - ▶ duration of insulin use

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- ▶ — for all types of cancer

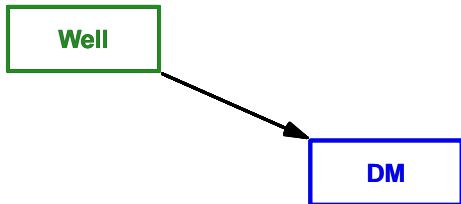
Aims of the Danish study [5]

- ▶ Describe cancer incidence rates among diabetes patients in Denmark.
- ▶ How cancer incidence rates vary relative to the non-DM population with:
 - ▶ duration of diabetes
 - ▶ duration of insulin use
- ▶ — for all types of cancer
- ▶ — and for specific sites of cancer

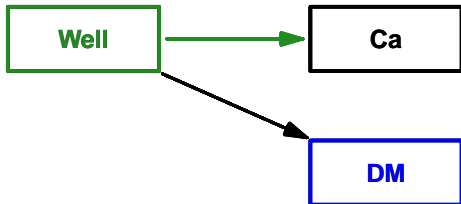
Follow-up of the Danish population

Well

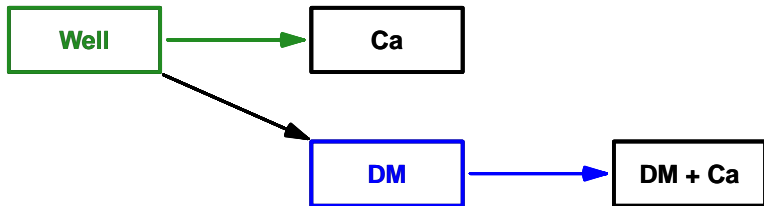
Follow-up of the Danish population



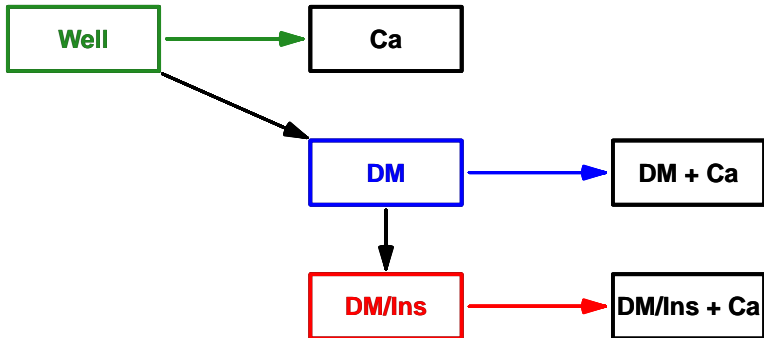
Follow-up of the Danish population



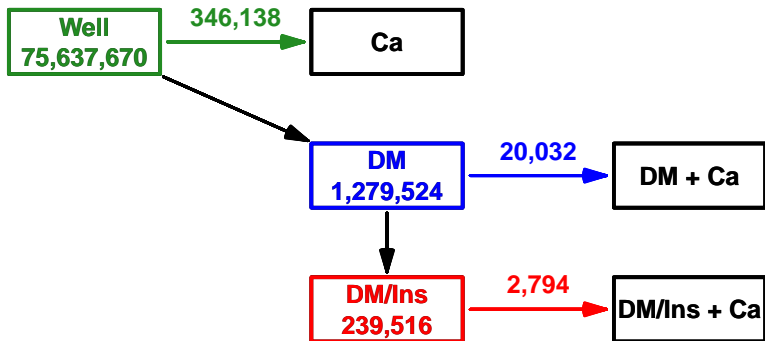
Follow-up of the Danish population



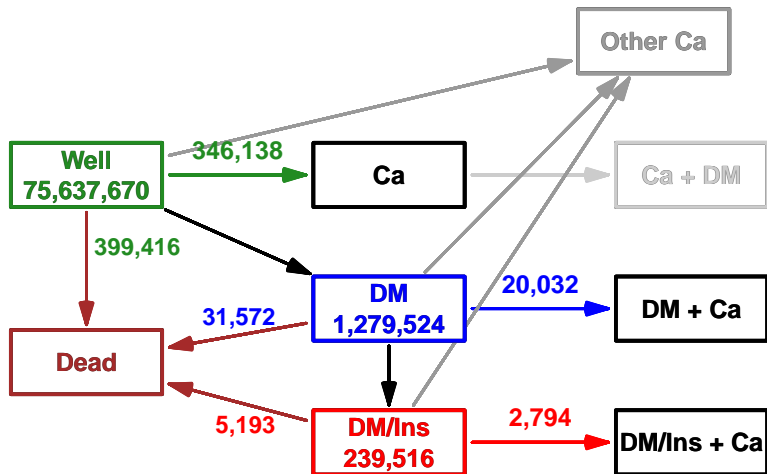
Follow-up of the Danish population



Follow-up of the Danish population



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Register linkage

The study is based on the linkage of



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- ▶ Danish Cancer Register [6]



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- ▶ “Insulin use” defined only by date of 2nd purchase of insulin.

Follow-up & analysis

Persons are followed 1 Jan 1995 to:

Follow-up & analysis

Persons are followed 1 Jan 1995 to:

event: first primary cancer of a given type

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- ▶ death

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- ▶ diagnosis of any other primary cancer
- ▶ death
- ▶ 31 Dec 2007

Follow-up & analysis

Persons are followed 1 Jan 1995 to:

event: first primary cancer of a given type

censoring:

- ▶ diagnosis of any other primary cancer
- ▶ death
- ▶ 31 Dec 2007

Follow-up tabulated in 1-year classes by age, calendar time, date of birth, and duration of **diabetes** and **insulin use** (6 mths).
Analysis by Poisson regression, separately by sex.

Model for cancer incidence rates

rate

Model for cancer incidence rates

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

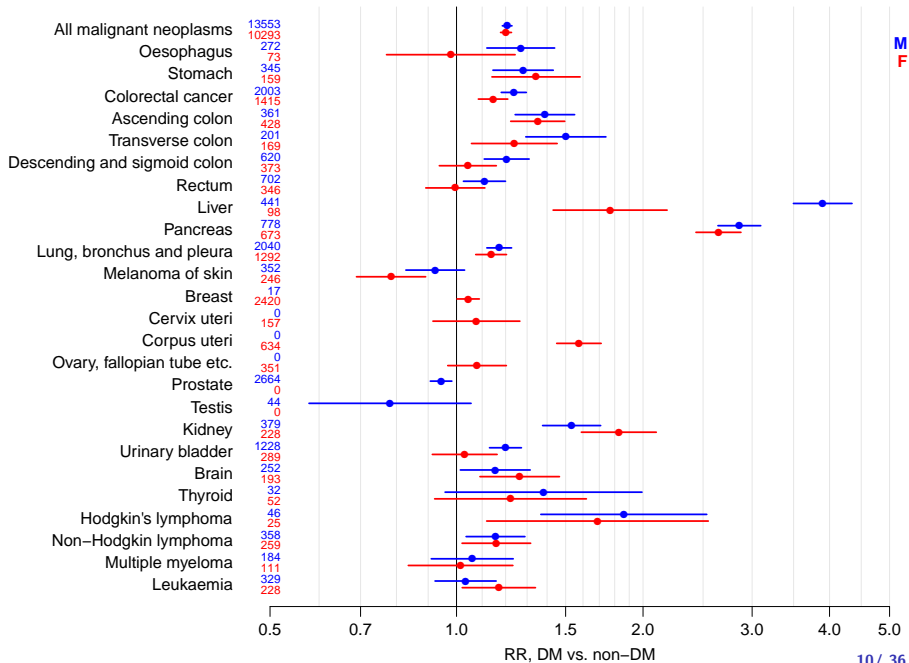
Model for cancer incidence rates

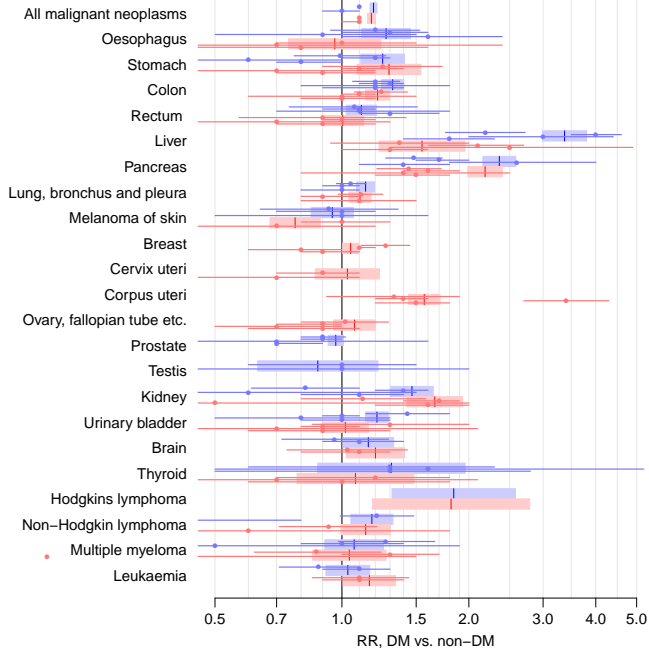
$$\text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ \times \text{RR}_{\text{DM}}$$

Model for cancer incidence rates

$$\begin{aligned} \text{rate} &= f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ &\quad \times \text{RR}_{\text{DM}} \\ &\quad \times \text{RR}_{\text{Ins}} \end{aligned}$$

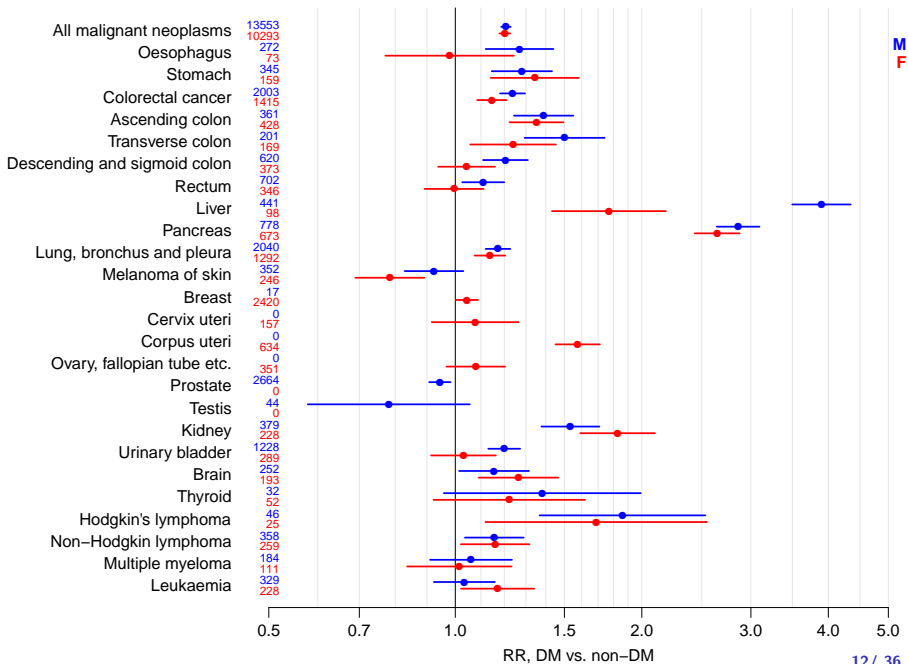
DM prevalent at 1.1.1995 excluded



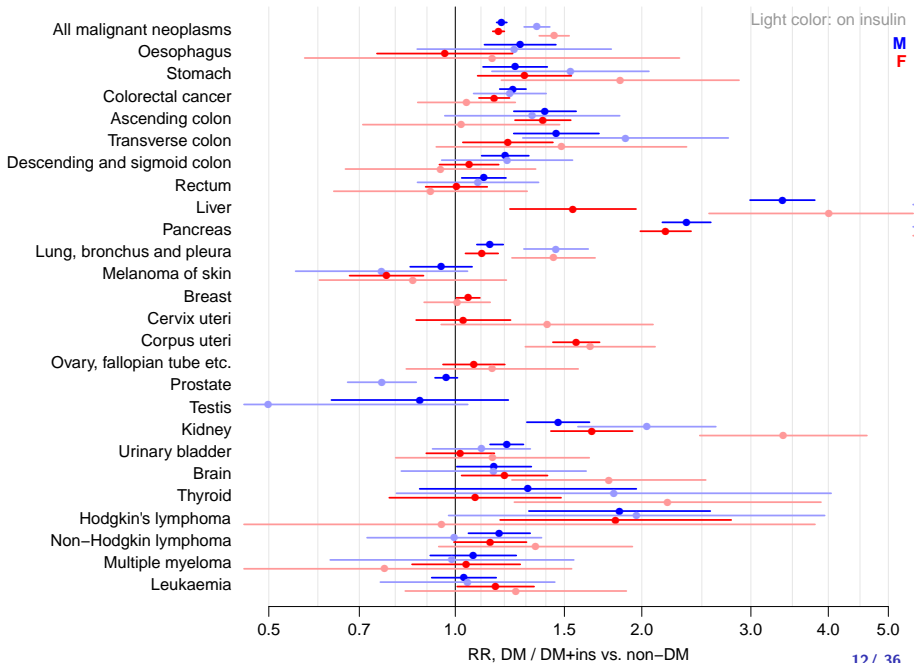


Top to bottom: Adami [1], la Vecchia [2], Wideroff [3], Coughlin [4]

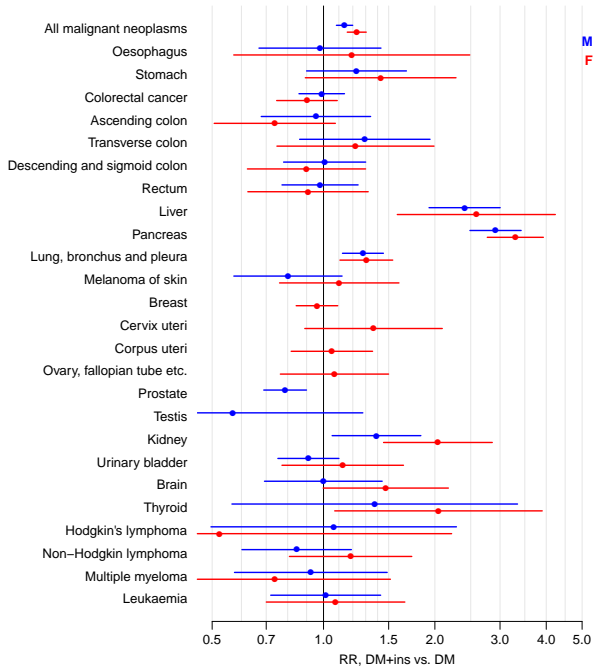
DM prevalent at 1.1.1995 excluded



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Model for cancer incidence rates

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Model for cancer incidence rates

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

Model for cancer incidence rates

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

Model for cancer incidence rates

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

Model for cancer incidence rates

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

- ▶ duration / cumulative dose
(slowly increasing/decreasing from time 0)

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

- ▶ duration / cumulative dose
(slowly increasing/decreasing from time 0)
- ▶ allocation (jump at time 0)
(confounding by indication)

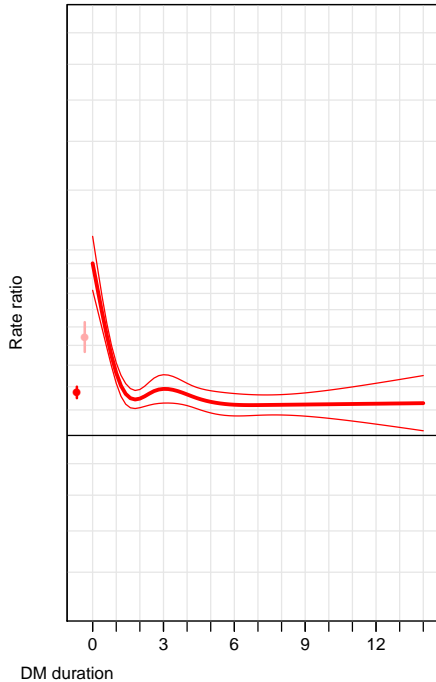
Model for cancer incidence rates

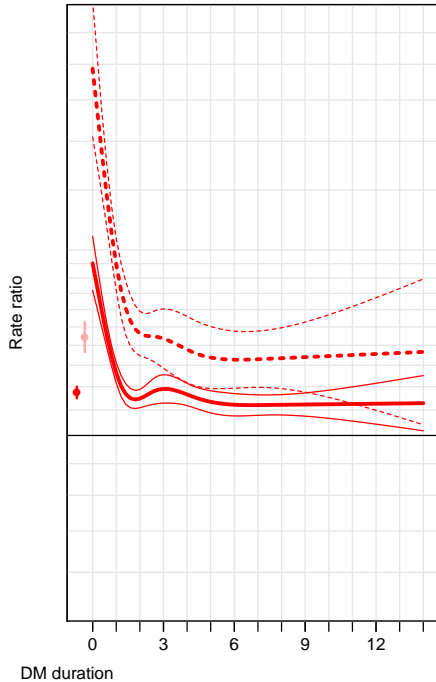
$$\text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ \times t(\text{DM-duration}) \\ \times s(\text{Ins-duration})$$

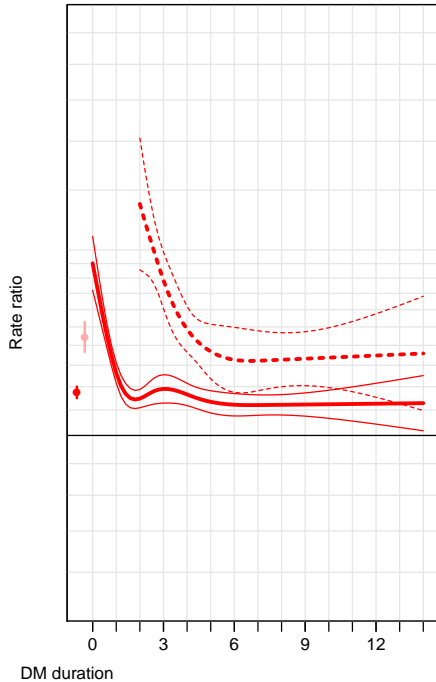
Functions t and s give the **combined** effects of:

- ▶ duration / cumulative dose
(slowly increasing/decreasing from time 0)
- ▶ allocation (jump at time 0)
(confounding by indication)

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







All cancers

Cumulative
risk, ages
65–75 (%):

M	F
20.9	15.4
22.3	16.1
23.7	19.5

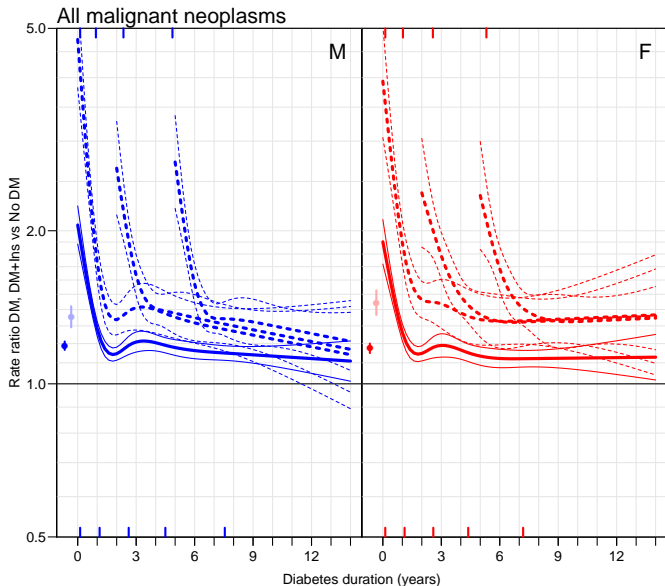
cases:

163,332	168,469
9,441	6,961
1,242	858

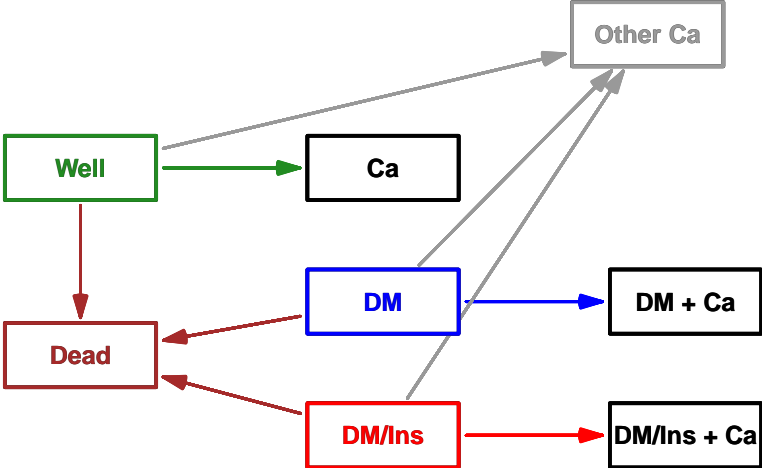
No DM

DM, no insulin

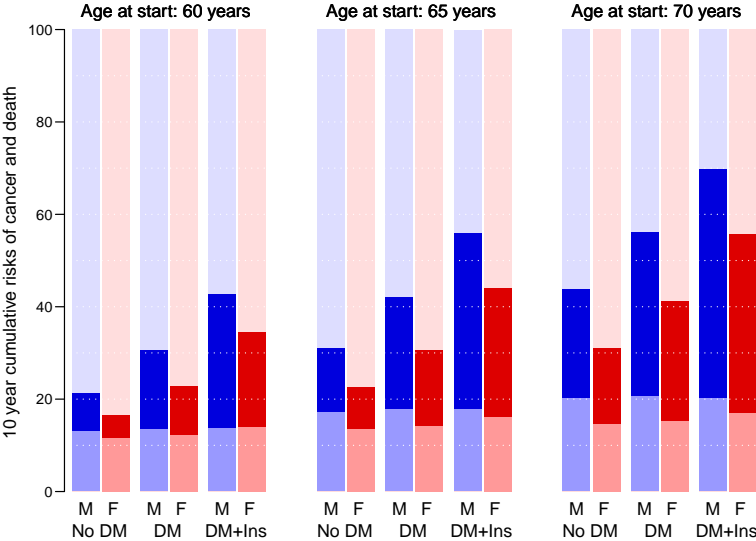
Insulin user



Cumulative risk



Cumulative risk



Colorectal

Cumulative risk, ages 65–75 (%):

M	F
2.9	1.9
3.4	2.2
3.0	2.2

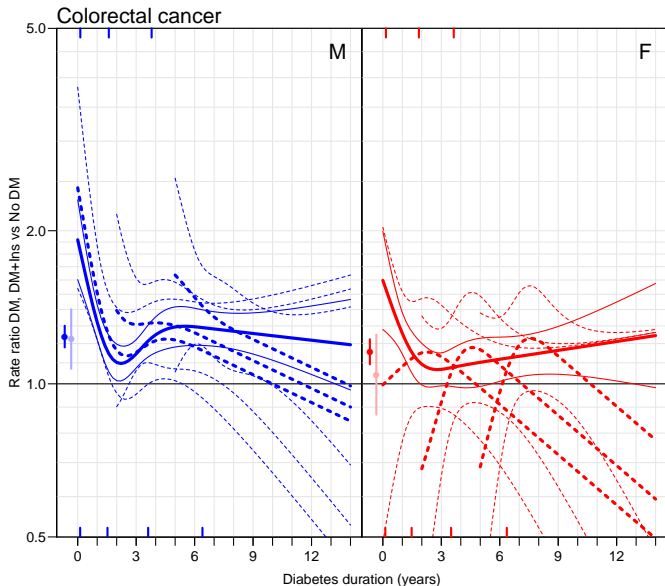
cases:

18,382	16,859
1,253	904
134	74

No DM

DM, no insulin

Insulin user



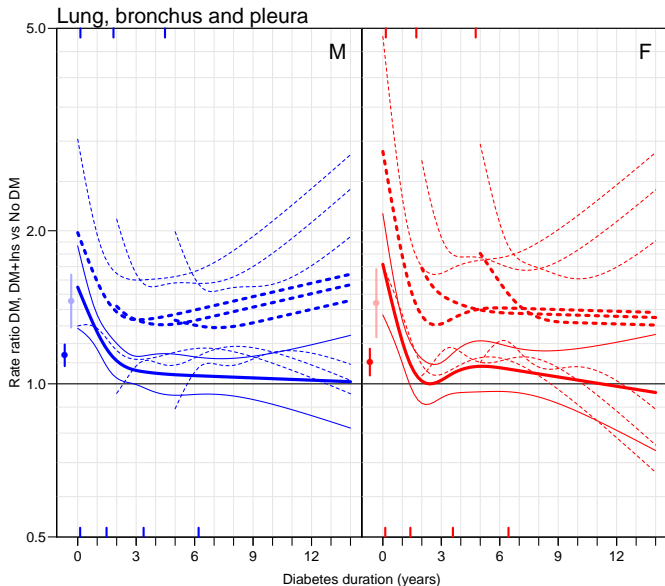
Lung

Cumulative
risk, ages
65–75 (%):

M	F
3.7	2.3
3.8	2.3
5.1	3.7

# cases:	
20,678	15,146
1,244	705
175	98

No DM
DM, no insulin
Insulin user



Pancreas

Cumulative
risk, ages
65–75 (%):

M	F
0.5	0.4
0.9	0.9
4.5	3.7

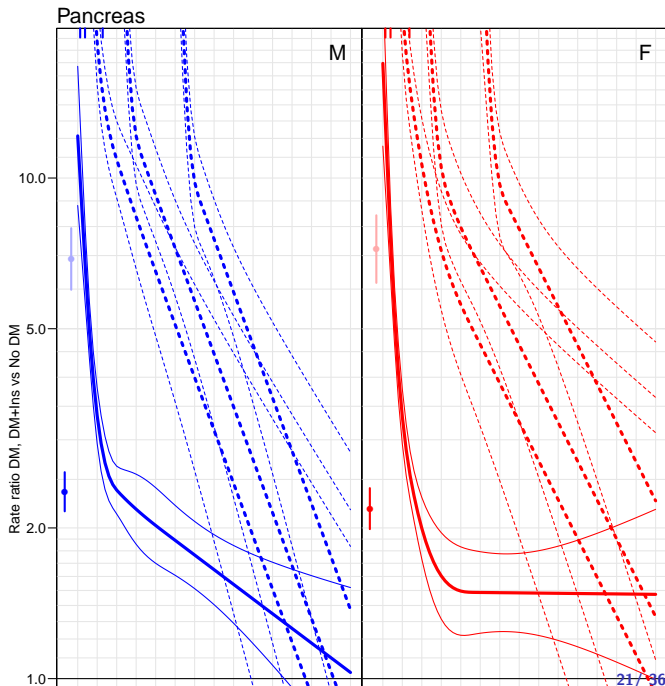
cases:

3,308	3,434
423	379
149	117

No DM

DM, no insulin

Insulin user



Liver

Cumulative
risk, ages
65–75 (%):

M	F
0.2	0.1
0.8	0.2
2.0	0.3

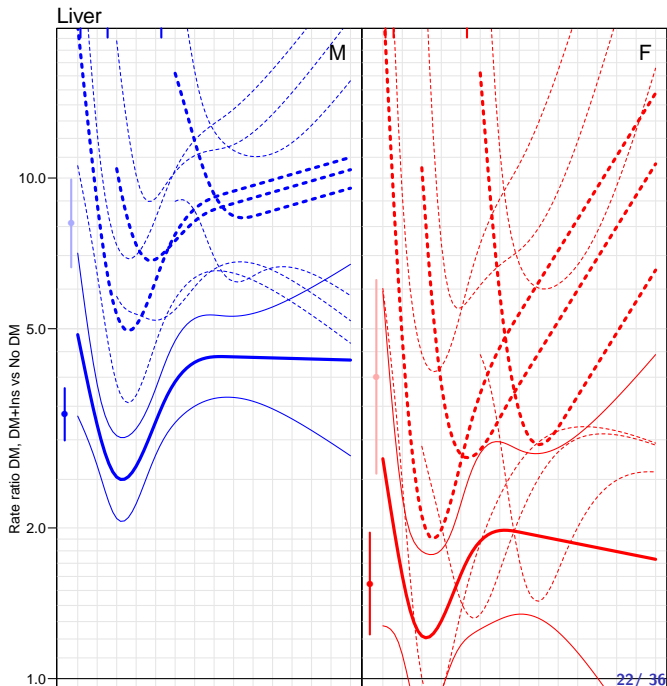
cases:

1,452	881
229	57
65	11

No DM

DM, no insulin

Insulin user



Prostate

Cumulative risk, ages 65–75 (%):

M

4.2

4.0

2.8

F

—

—

—

cases:

22,885

1,567

145

—

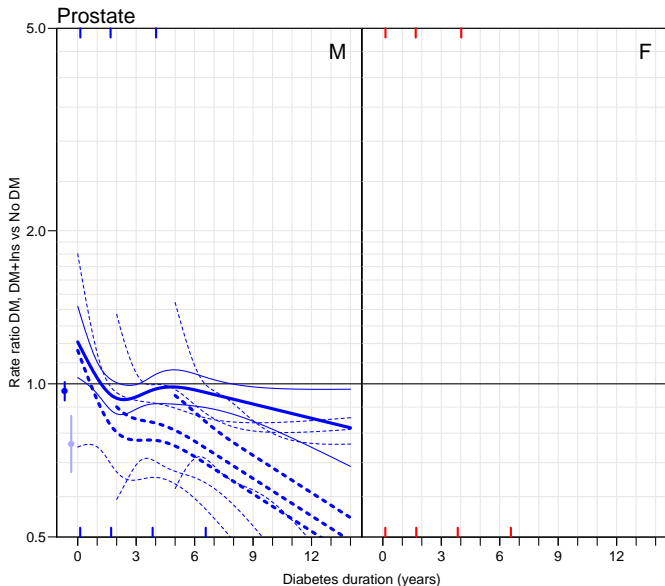
—

—

No DM

DM, no insulin

Insulin user



Limitations

- ▶ Only 2nd prescription of insulin is used here

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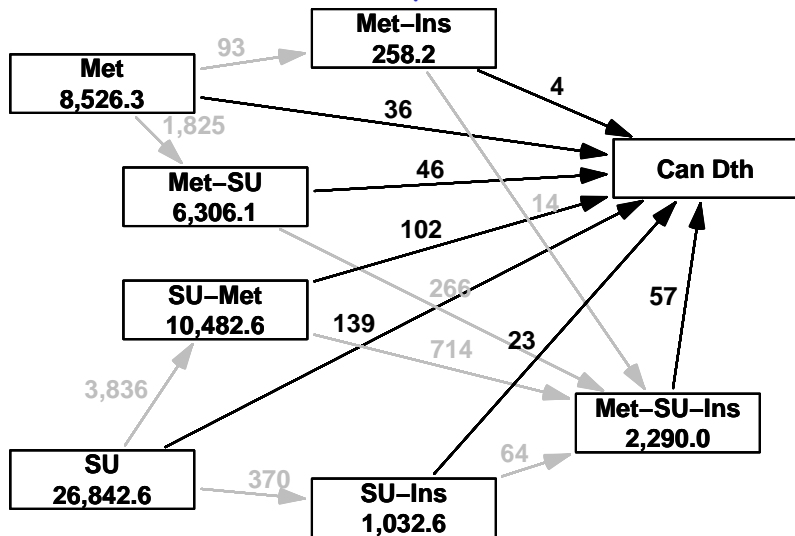
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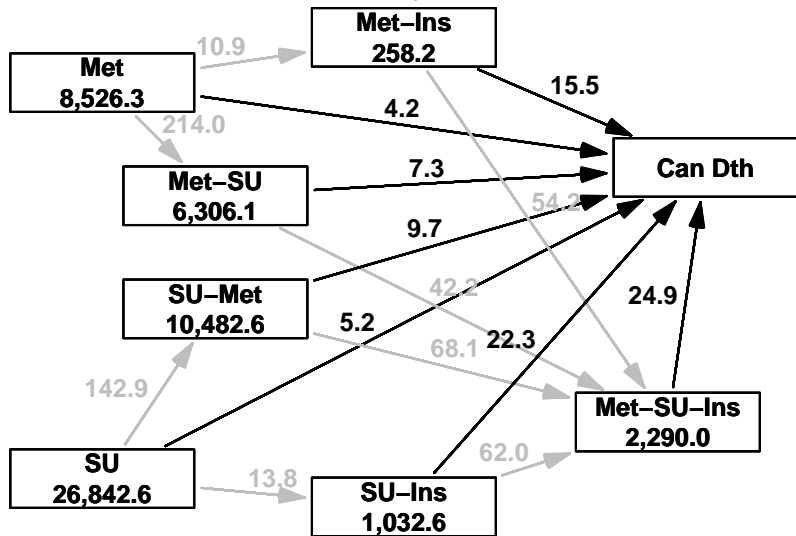
Limitations

- ▶ Only 2nd prescription of insulin is used here
- ▶ No dosage or actual duration of therapy is available in the NDR
- ▶ 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 be a limitation of **any** study.

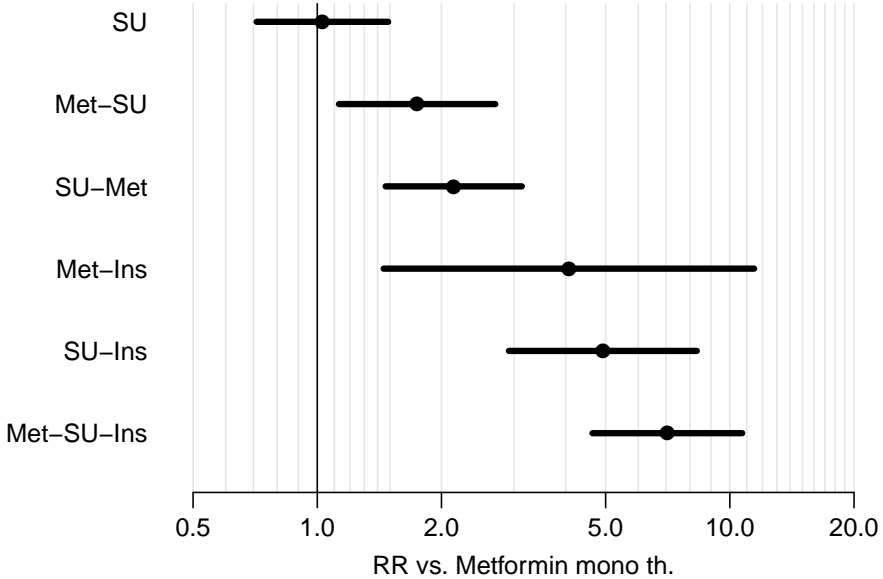
Different medications / cancer mortality



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Different medications

Andersson *et al.* [8]:

- ▶ Danish population > 35 years

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- ▶ Cancer defined by NDR (**not** the DCR)

Different medications

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- ▶ Only “all cancers”

Different medications

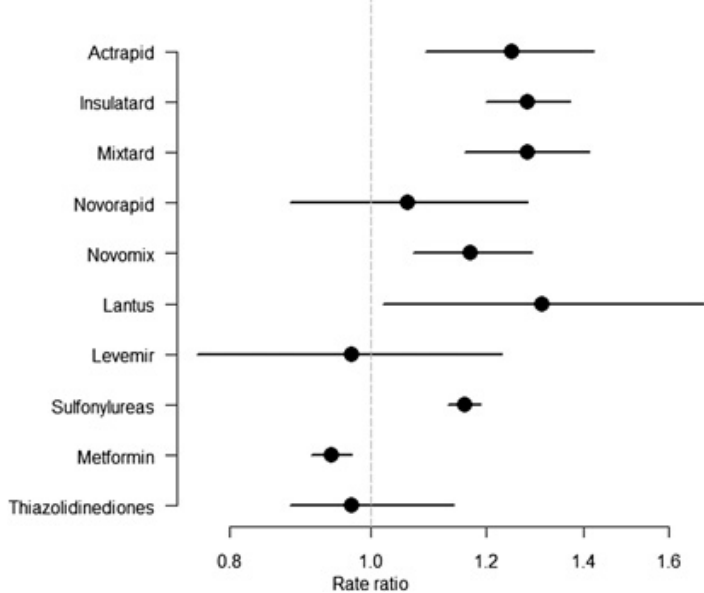
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- ▶ Cancer defined by NDR (**not** the DCR)
- ▶ Only “all cancers”
- ▶ Exposure: “currently using medication”
— of any kind

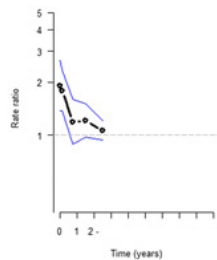
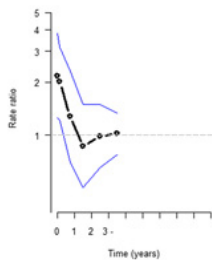
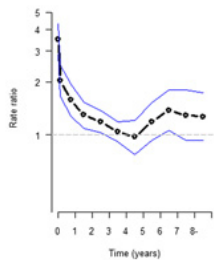
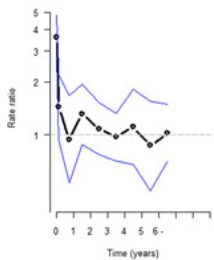
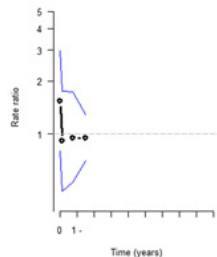
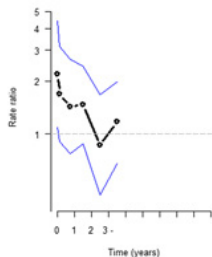
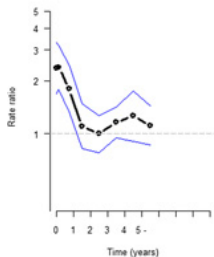
Different medications

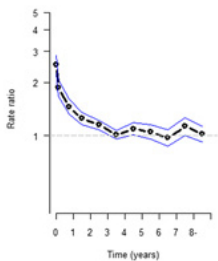
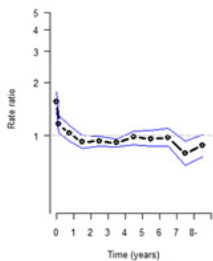
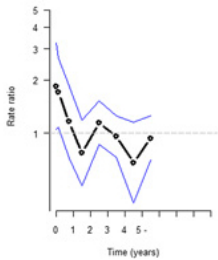
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— of any kind
- ▶ Cancer rates as a function of time since 1st prescription



Andersson *et al.* [8]

A**Actrapid****Insulatard****B****Novorapid****Novomix****Mixtard****Lantus****Levemir**Andersson *et al.* [8]

C**Sulfonylureas****Metformin****Thiazolidinediones**

Andersson *et al.* [8]

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Different medications

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- ▶ Only assignment effect

Conclusion

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 - ▶ insulin duration
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- ▶ Long term users of insulin show cancer rates higher than the non-DM population ($RR = 1.25$).

Interpretation

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

Interpretation

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Strong cumulative effect of insulin increasing cancer risk is unlikely as RR decrease by insulin duration for most cancer sites.

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I own shares in NovoNordisk

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