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Competing risks analysis of the Finnish diabetes prevention study

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Survival analysis

- Clinical studies usually consider one primary event of interest (disease-related) in the presence of other non-disease related events.

  - When one event prevents another event from happening or being observed => 'Competing risks'

    e.g. if a subject drops out (DO), later events are unobservable

  - If competing events are independent of each other, they are treated as independent censoring

Survival analysis

$$X = \min(T, U)$$

T = Time to event of interest

U = Censoring time

$$\lambda(t_i) = \frac{d_i \text{ (number of disease−related events at time } t_i)}{n_i \text{ (risk set: number of subjects known to survive just prior time } t_i)}$$

$$S(t) = \prod_{i:t_i \le t} (1 - \frac{d_i}{n_i}) \qquad S(t) = e^{(-\int_0^t \lambda(x)\partial x)}$$

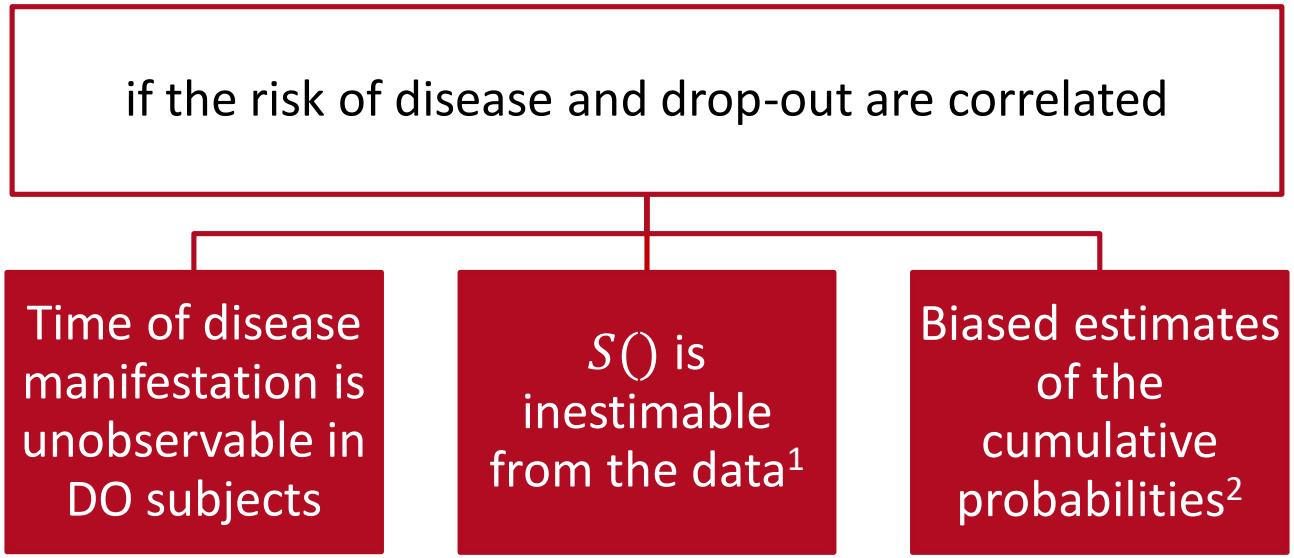
Survival analysis (Key assumptions)

1) n_i is a random sample of the population at risk at time t_i for all t, i.e. censoring is independent.
2) Outcome data $[X = \min(T, U)]$ is exact.

t_i	n_i	d_i	nd_i	$\lambda(t_i)$	$S(t_i)$
0	50	0	0	0	1
4	50	1	0	1/50	[1-(1/50)] * 1 = 0.98
5	49	0	**1**	0/49	[1-(0/49)] * 0.98 = 0.98
6	48	1	0	1/48	[1-(1/48)] * 0.98 = 0.96

This implies that the risk of subjects with censored time do not differ from that of subjects still in n_i

Dependence between censoring and event of interest



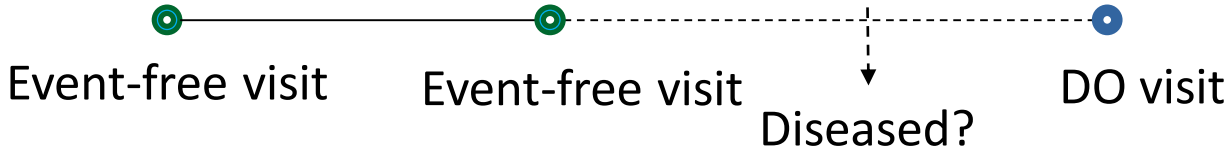
[1]Tsiatis A, Proc Natl Acad Sci. 1975; 72: 20-22; [2]Verdujin M *et al.*, Nephrol Dial Transplant. 2010; 26: 56-61

Exact (T, U) are unobservable

Clinical status is only observed at finite time points
e.g. at medical visits

Multiple events are possible within this interval

Biased estimates of the disease incidence[1,2]



[1]Joly P et al., Biostatistics. 2002; 3: 433-43; [2]Commenges D et al., Stat Med. 2004; 23: 199-210

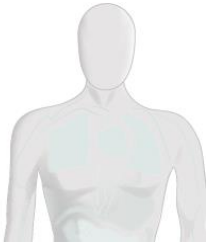
Competing risks with interval–censored data

- Multi-state model[1,2]
  - Hypothesis testing
  - Account for competing risks
  - Account for interval-censoring, i.e. the probability of developing non-terminal events in the interval between the medical visits
  - Allow simultaneous estimation of covariate effects on the different competing risks

[1]Joly P et al., Biostatistics. 2002; 3: 433-43; [2]Commenges D et al., Stat Med. 2004; 23: 199-210

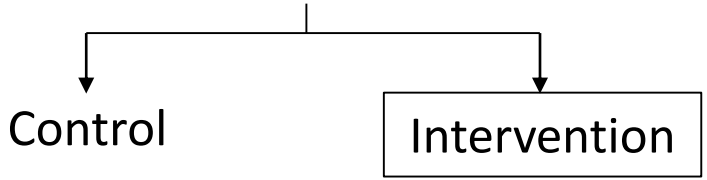
Finnish Diabetes Prevention Study (FDPS)

- Randomized controlled multicenter study carried out in Finland for 6 years with a follow-up of 10 years[1]



Overweight, middle-aged subjects with impaired glucose tolerance

- Investigate the effects of lifestyle intervention



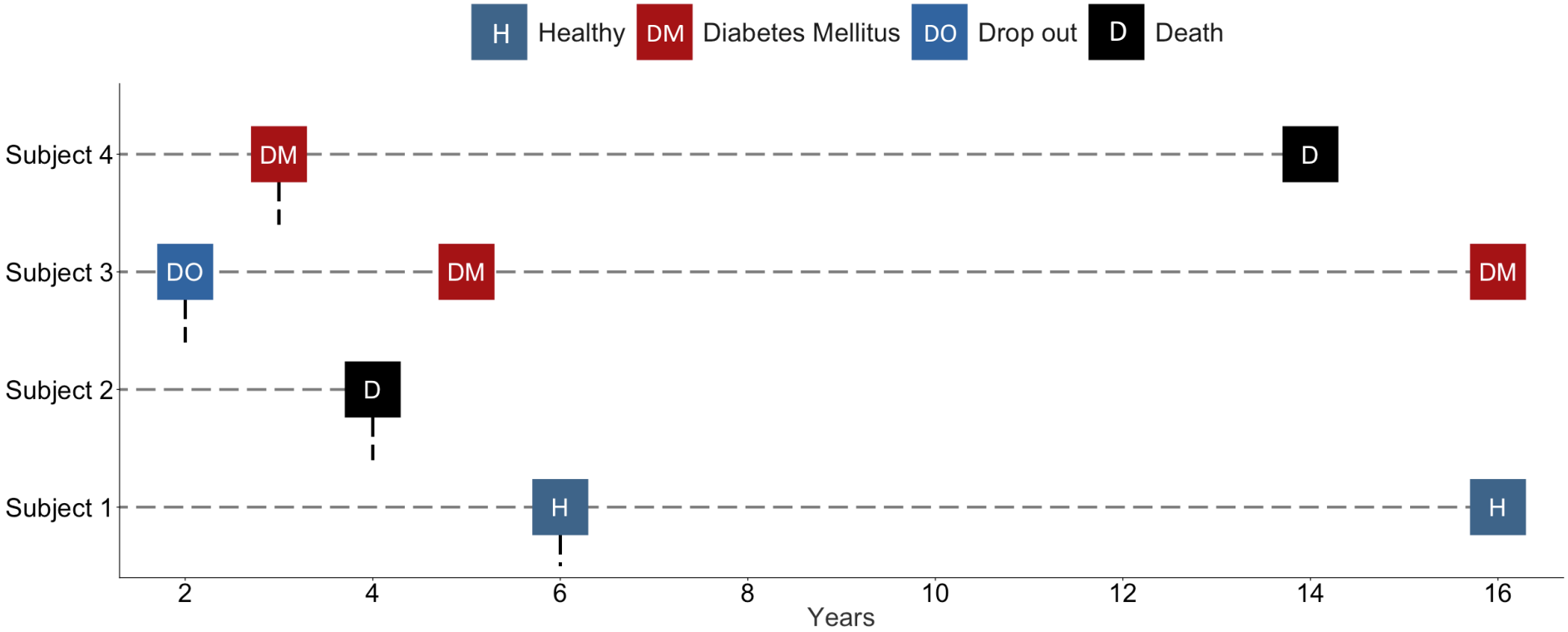
[1]Tuomilehto J et al., N Engl J Med 2001; 344:1343–50

Finnish Diabetes Prevention Study (FDPS)

- Clinical status assessed at yearly medical visits using OGTT*
  - Subjects who developed diabetes mellitus (DM) were excluded from the study at the visit of diagnosis
  - Yearly OGTT => Insulin sensitivity (S_I) by 9 surrogate methods[1]
    - QUICKI, HOMA, Avignon, Matsuda, etc

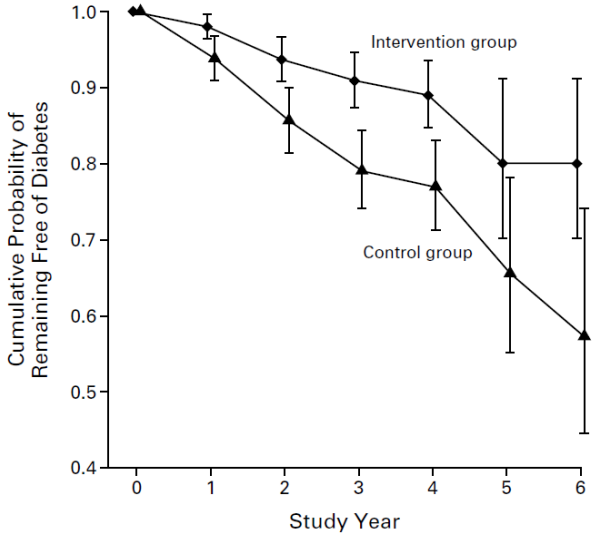
[1]Patarrão RS et al., Rev Port Endocrinol Diabetes Metab 2014; 9(1): 65–73; *OGTT – Oral Glucose Tolerance Test

Finnish Diabetes Prevention Study (FDPS)



Finnish Diabetes Prevention Study (FDPS)

- Previously analyzed by Kaplan-Meier estimator to obtain the survival curve[1]
  - Did not take interval-censoring into account
  - Regarded drop out as a non informative (independent censoring)
  - Did not have access to follow-up data



Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Figure 1. Proportion of Subjects without Diabetes during the Trial.

The vertical bars show the 95 percent confidence intervals for the cumulative probability of remaining free of diabetes. The relative risk of diabetes for subjects in the intervention group, as compared with those in the control group, was 0.4 ($P<0.001$ for the comparison between the groups).

[1]Tuomilehto J et al., N Engl J Med 2001; 344:1343–50

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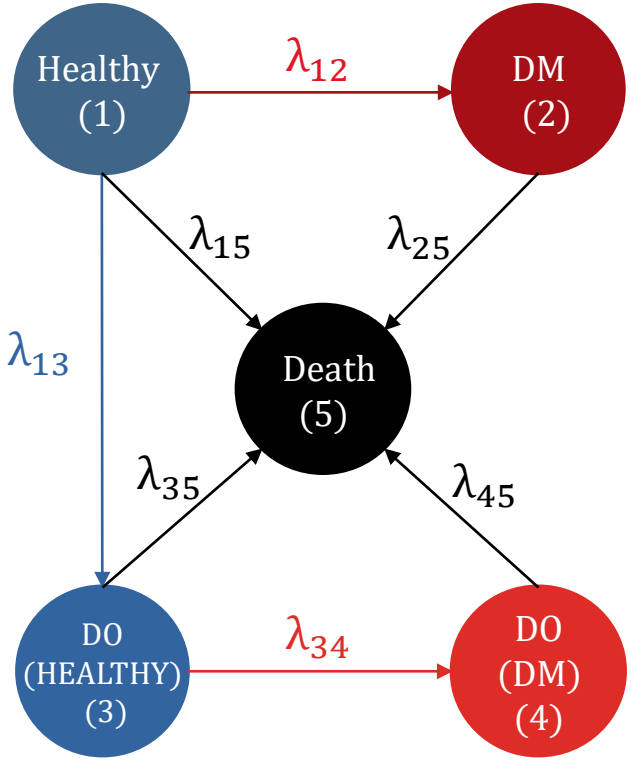
Aims

- Develop a multi-state model for competing risks analysis of data from FDPS and its follow-up
- Use the model to investigate
  - covariate effects on the different competing risks
  - predictiveness of methods of S_I assessment for the onset of diabetes

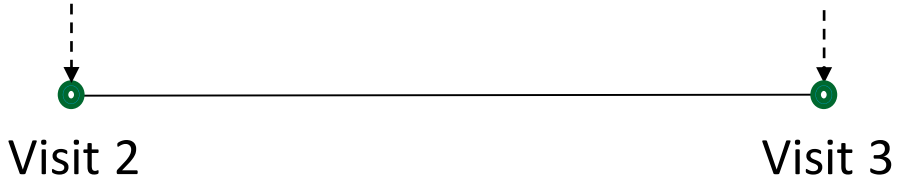
Model building & assumptions

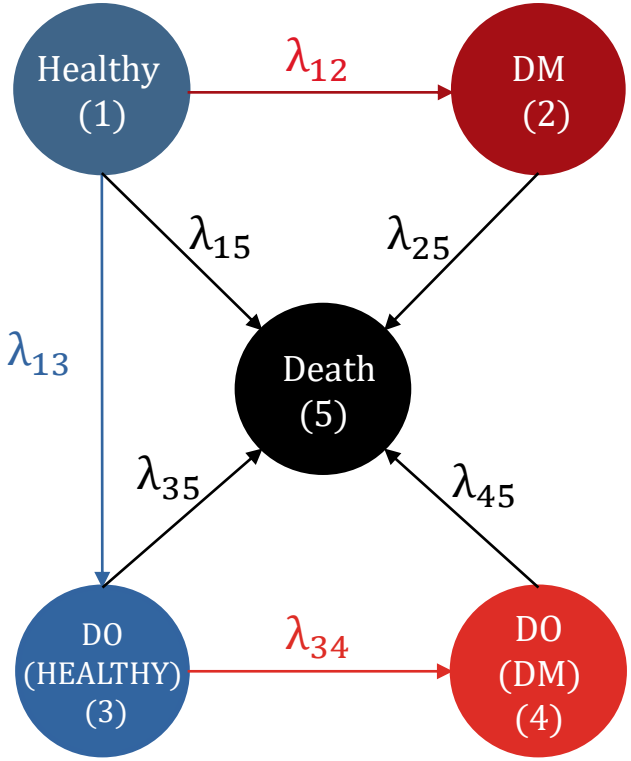
- Multi-state model
  - Hypothesis testing:
    - $\lambda_{H-D} = \lambda_{DO(H)-D}$
      $(\lambda_{15} = \lambda_{35})$
    - $\lambda_{DM-D} = \lambda_{DO(DM)-D}$
    - $\lambda_{H-DM} = \lambda_{DO(H)-DO(DM)}$
  - λ = Constant, Weibull, etc



Model building & assumptions

- Multi-state model
  - Covariates testing:
    - Base line covariates: No risk of selection/immortal bias.
    - Not the case for time-varying covariates





Model building & assumptions

- Multi-state model

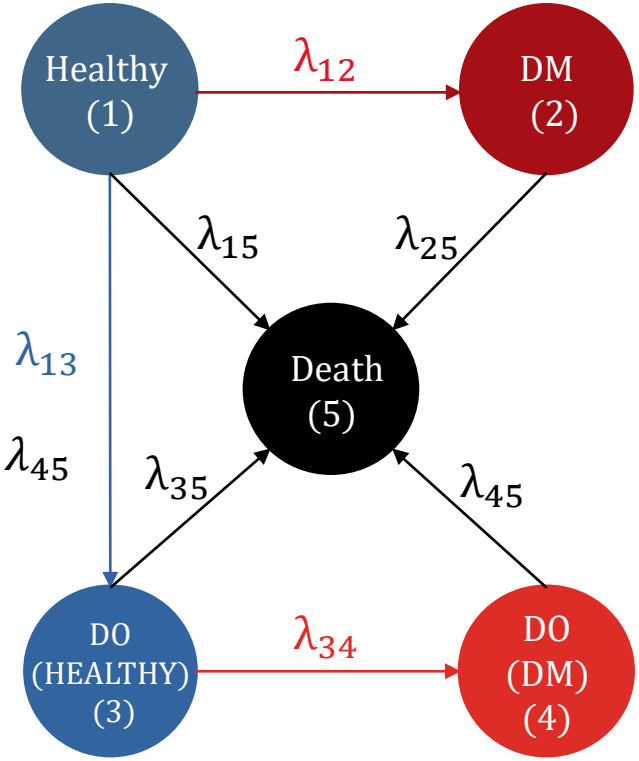
$$dP_1/dt = -P_1 \cdot (\lambda_{12} + \lambda_{13} + \lambda_{15})$$

$$dP_2/dt = -P_2 \cdot \lambda_{25} + P_1 \cdot \lambda_{12}$$

$$dP_3/dt = -P_3 \cdot \lambda_{34} - P_3 \cdot \lambda_{35} + P_1 \cdot \lambda_{13}$$

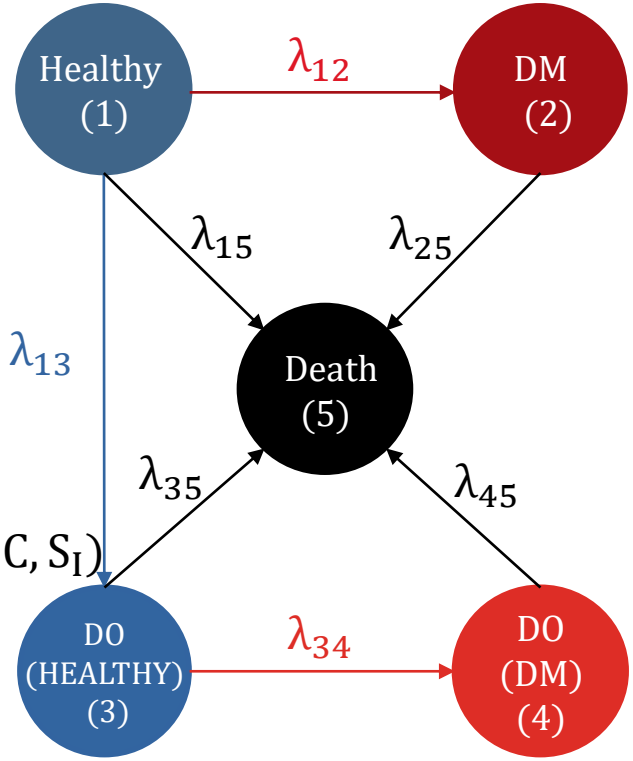
$$dP_4/dt = -P_4 \cdot \lambda_{45} + P_3 \cdot \lambda_{34}$$

$$dP_5/dt = P_1 \cdot \lambda_{15} + P_2 \cdot \lambda_{25} + P_3 \cdot \lambda_{35} + P_4 \cdot \lambda_{45}$$



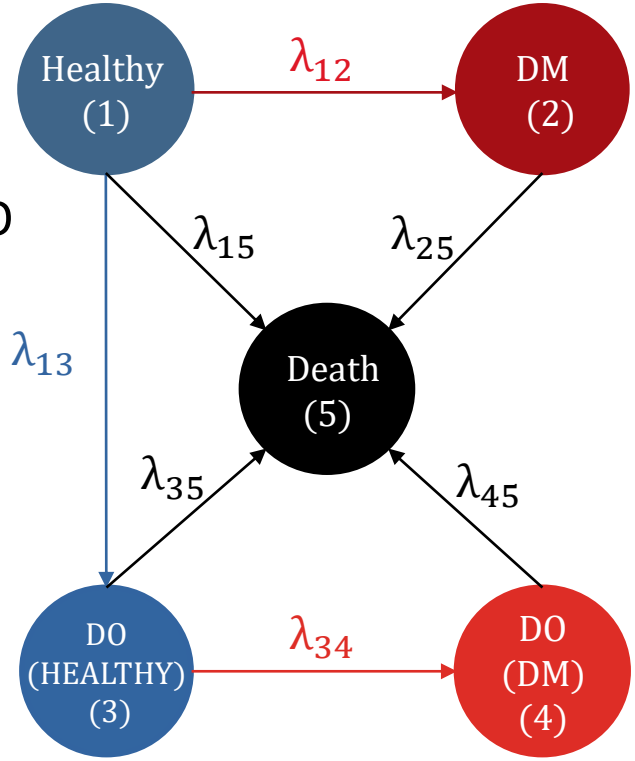
Results

- Multi-state model
  - Stationary
    - $\lambda_{H-DO(H)}$ & $\lambda_{DO(H)-DO(DM)}$
    - $\mathrm{COV}_{H-DO(H)} = f(\mathrm{Intervention}, \mathrm{BMI})$
  - Non-stationary
    - λ_{H-DM} & λ_{i-D}
    - $\mathrm{COV}_{H-DM} = f(\mathrm{Intervention}, \mathrm{BMI}, \mathrm{HbA1C}, \mathrm{S_I})$
    - λ_{i-D} followed Gompertz-Makeham formula



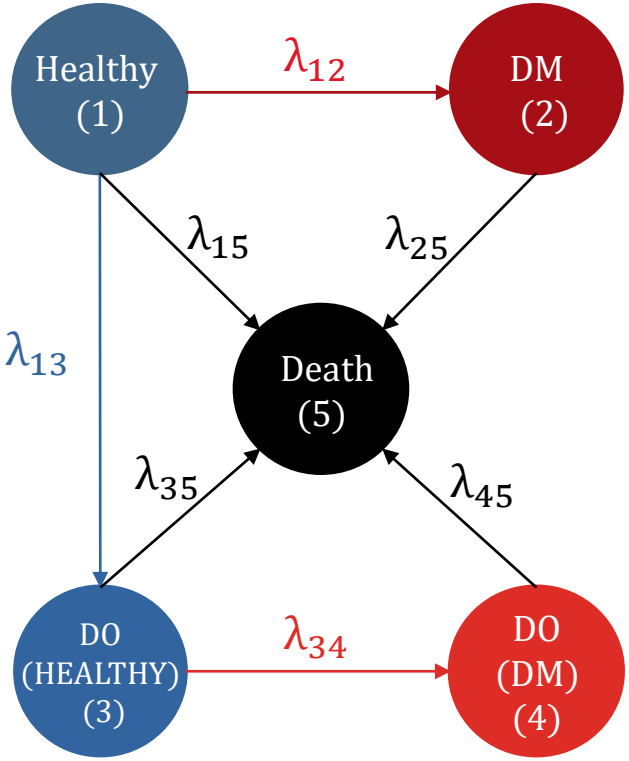
Results

- Multi-state model
  - Hypothesis testing:
    - λ_{i-D} were indeed independent of DO
    - No significant difference between
      - λ_{H-D} & $\lambda_{DO(H)-D}$
      - λ_{DM-D} & $\lambda_{DO(DM)-D}$



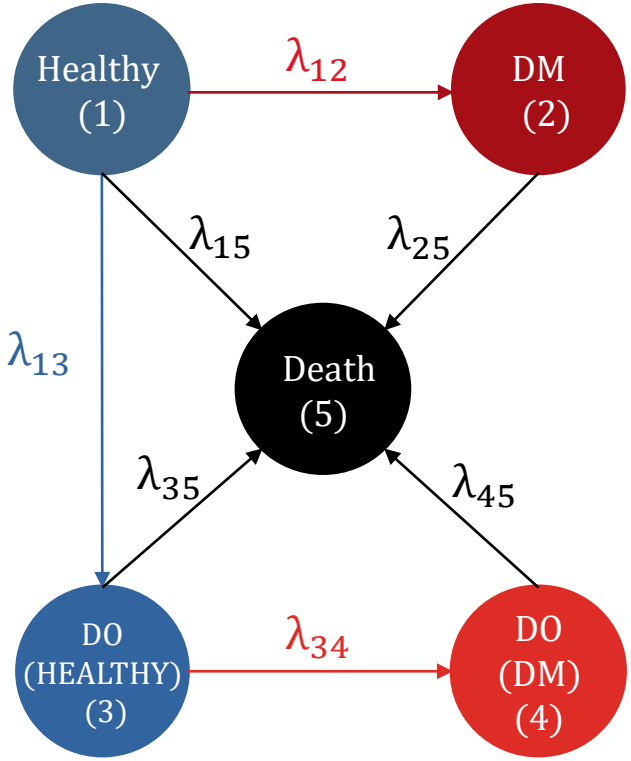
Results

- Multi-state model
  - Hypothesis testing:
    - DO was an informative process
      - $\lambda_{H-DM} \neq \lambda_{DO(H)-DO(DM)}$
    - After DO, subjects were at ~3.5 times lower risk of developing DM
    - Subjects in the intervention group
      - 2 times higher risk of DO
      - 1.5 times lower risk of DM



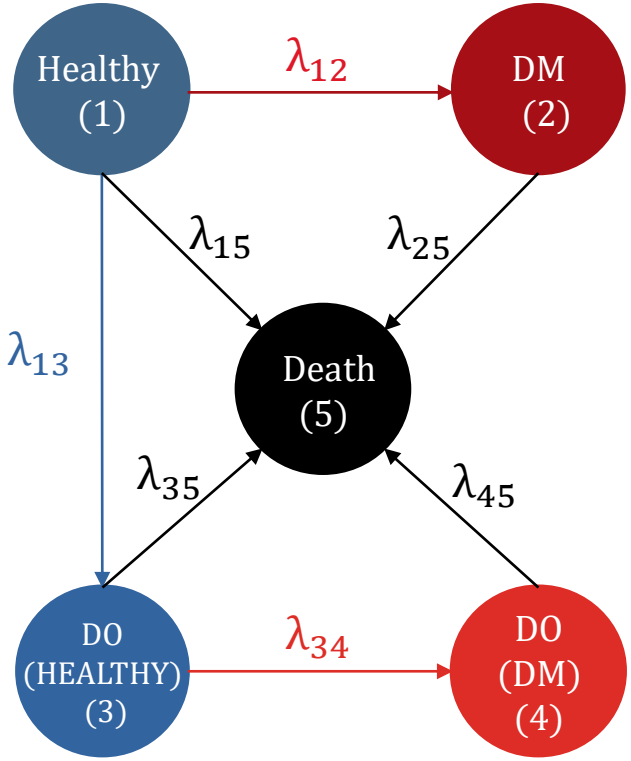
Results

- Multi-state model
  - Hazard of dying 20% higher among patients
    - $\lambda_{H-D} = \alpha + \beta \cdot e^{k \cdot (\theta_{15,\text{scale}} \cdot age)}$
    - $\lambda_{DM-D} = \alpha + \beta \cdot e^{k \cdot (\theta_{25,\text{scale}} \cdot age)}$
    - $\lambda_{H-D} = \lambda_{DO(H)-D}$
    - $\lambda_{DM-D} = \lambda_{DO(DM)-D}$

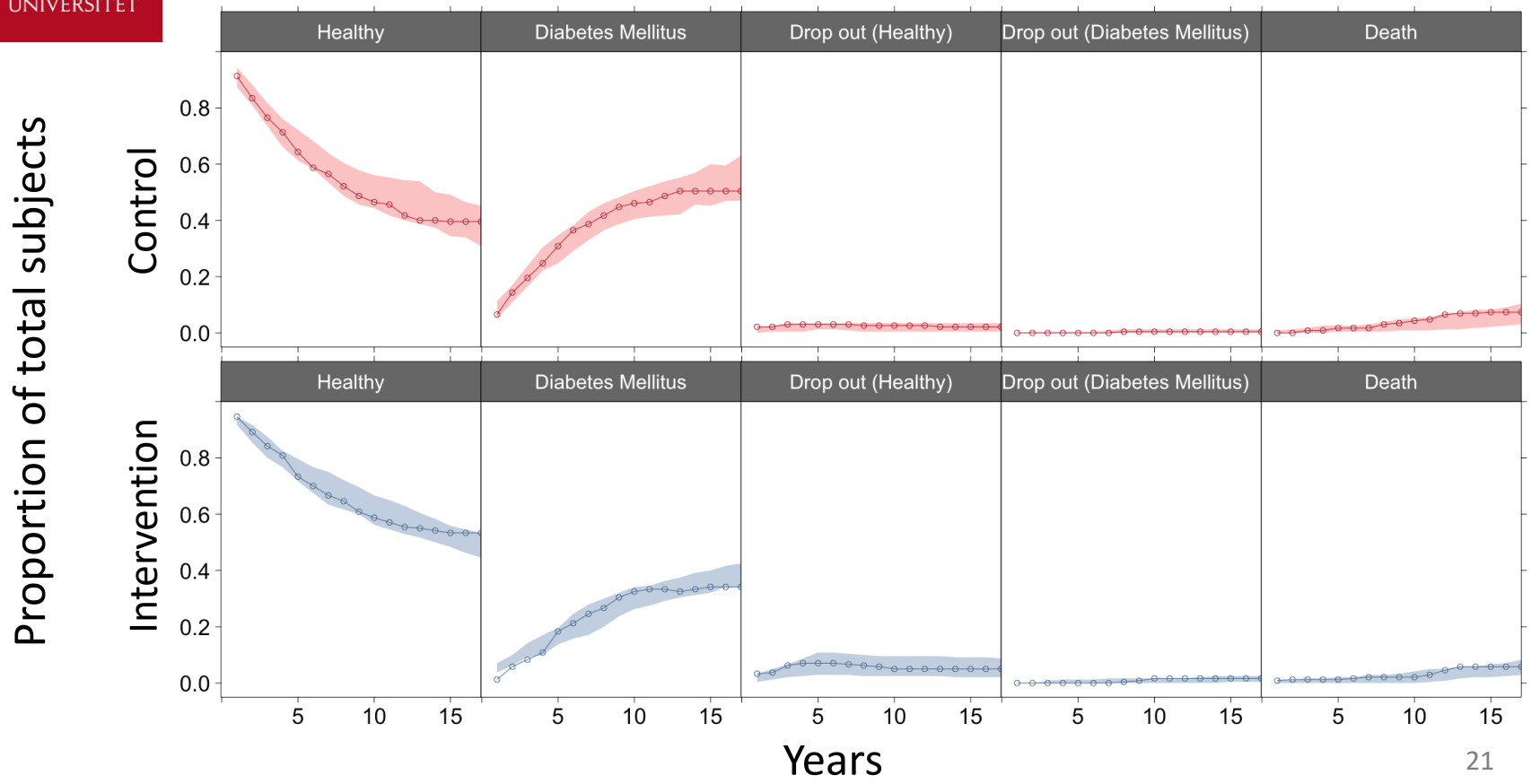


Results

- Multi-state model
  - Measurements of S_I
    - $QUICKI, HOMA, Avignon$
  - Effects of significant covariates at different combinations can be assessed
    - HbA_{1c}=7% ~ 2.5 times higher risk of DM than HbA_{1c}=6%

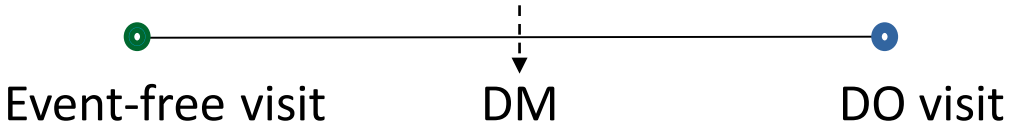


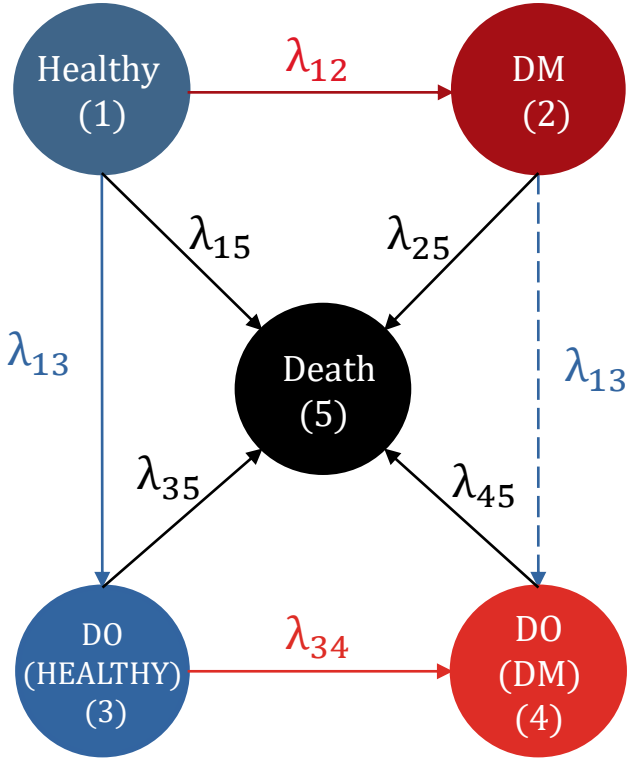
Results


Healthy
Diabetes Mellitus
Drop out (Healthy)
Drop out (Diabetes Mellitus)
Death
Control
Intervention
Proportion of total subjects
0.0
0.2
0.4
0.6
0.8
5
10
15
Years

Remarks

- Thanks to follow up data, we knew that all DO subjects were healthy first:
  - allow DM manifestation in the interval between last healthy visit and the DO visit
    - $\lambda_{14} = \lambda_{13} \cdot \lambda_{12}$





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Conclusions

- Competing risks violates the standard survival analysis assumptions
- Interval censoring further complicates competing risks analysis
- Multi-state models:
  - Hypothesis testing & identifying influential assumptions
  - Describe the dependence of mechanisms leading to incomplete observations
  - Account for the occurrence probability of the non-terminal processes in the interval between visits
  - Allow simultaneous estimation of covariate effects on the different competing risks
  - extendable for PK/PD joint modeling and simulation of drugs, biomarkers and competing clinical outcomes

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Acknowledgements

All members of the Pharmacometrics Group at Uppsala University, Sweden

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Extras

Censoring is independent

- **Non-informative censoring** occurs if the distribution of censoring times U provides no information about the distribution of survival times T, and vice versa.
  - T with density $f()$ and survival $S()$;
    U with density $\mathrm{y}()$ and survival $\mathrm{Z}()$

$$L \propto \prod_{i=1}^{n} [f(x_i)]^{\delta_i} \cdot [S(x_i)]^{1-\delta_i}$$

Censoring is dependent

- Cause-specific hazard for k^{th} event:
  - The instantaneous risk of k^{th} event given that the subject survived all other events until t_i

$$\lambda_k(t_i) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t_i \leq T_k < t_i + \Delta t, K = k | T_k \geq t_i)$$

$$S_k(t) = e^{(-\int_0^t \lambda_k(x)\partial x)}$$

Describes a hypothetical world where patients can have only k^{th} event

Assumes independence

Little use for clinical decisions in the real world

Censoring is dependent

- The cumulative incidence function ($C_k(t)$):
  - The proportion of subjects who have k^{th} event, accounting for subjects failing from other events

$$C_k(t) = \int_0^t S(x)\lambda_k(x)\,\partial x$$

  - Break down probabilities of failure
  - Calculate real world probabilities