Summary of Day 4

An introduction to survival analysis

Mark Stevenson

Faculty of Veterinary and Agricultural Sciences

The University of Melbourne, Parkville Victoria 3010 Australia

mark.stevenson1@unimelb.edu.au

THE UNIVERSITY OF MELBOURNE

Faculty of Veterinary and Agricultural Sciences
The University of Melbourne

OIE Collaborating Centre
Diagnostic Test Validation Science

Topics covered

- Piecewise Cox models
- Penalised Cox models

Piecewise Cox models

What we're talking about here is when the <u>effect</u> of a covariate changes over time

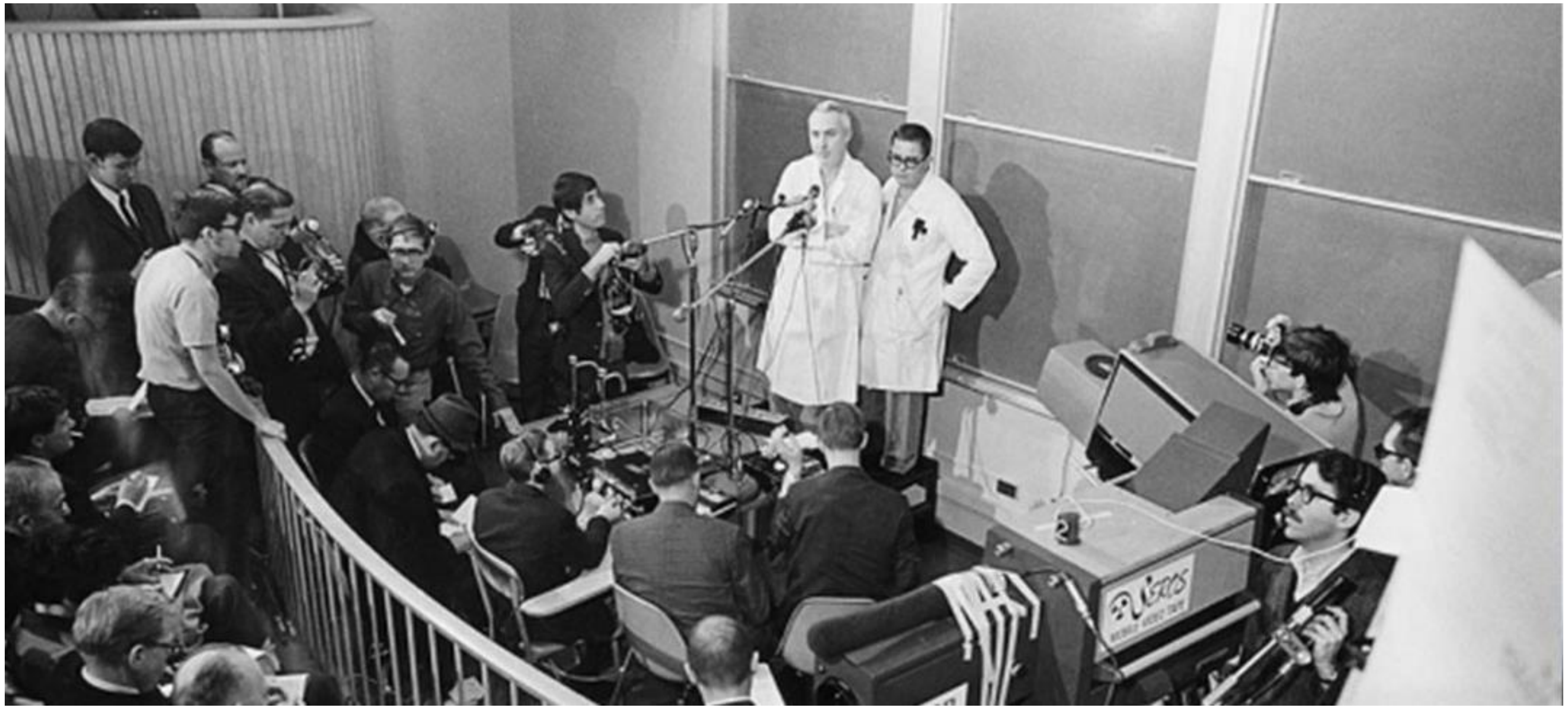
- Methods for dealing with non proportional hazards
  1. Stratification
  2. Time-dependent covariates

- How do we handle the situation when the <u>explanatory variable itself</u> changes over time?
  - repeated measurements on a subject
  - change in a subject's treatment

Piecewise Cox models

- Explanatory variables that change over time
  - the survival period for each individual is divided up into a sequence of shorter 'survival spells', each characterised by an entry and an exit time, and within which covariate values remain fixed
  - take the `addict` data set and suppose that the dose of methadone is reduced by 50% after 365 days into the program

id	start	stop	status	clinic	prison	dose
1	0	365	0	1	0	50
1	365	428	1	1	0	25
2	0	275	1	1	1	55
3	0	262	1	1	0	55
4	0	183	1	1	0	30
5	0	259	1	1	1	65



```
heart.cph03 <- coxph(Surv(start, stop, event) ~ (age + year) *
transplant, data = dat, method = "breslow");
summary(heart.cph03);
```

```
                    coef exp(coef) se(coef)      z      p
age               0.0155     1.016   0.0173  0.895 0.3700
year             -0.2735     0.761   0.1058 -2.585 0.0097
transplant       -0.5884     0.555   0.5427 -1.084 0.2800
age:transplant    0.0339     1.034   0.0279  1.211 0.2300
year:transplant   0.2013     1.223   0.1425  1.413 0.1600

                exp(coef) exp(-coef) lower .95 upper .95
age                 1.016      0.985     0.982     1.051
year                0.761      1.315     0.618     0.936
transplant          0.555      1.801     0.192     1.609
age:transplant      1.034      0.967     0.979     1.093
year:transplant     1.223      0.818     0.925     1.617

Rsquare= 0.083   (max possible= 0.969 )
Likelihood ratio test= 14.8  on 5 df,   p=0.0111
Wald test            = 13.8  on 5 df,   p=0.0172
Score (logrank) test = 14.0  on 5 df,   p=0.0153
```

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

Unit increases in age at time of entry into the program increased the hazard of death by a factor of 1.02.

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

With advancing years the hazard of death decreased once patients were accepted into the program. Implies an ↑ in patient 'quality' over time.

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

Over the entire study period transplantation had a beneficial effect on survival.

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

For transplanted patients, unit increases in age at time of acceptance into the program was associated with an increased hazard of death.

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

But as time progressed transplanted patients had an increased hazard of death. Survival of transplanted patients was not improving at the same rate as patient quality.

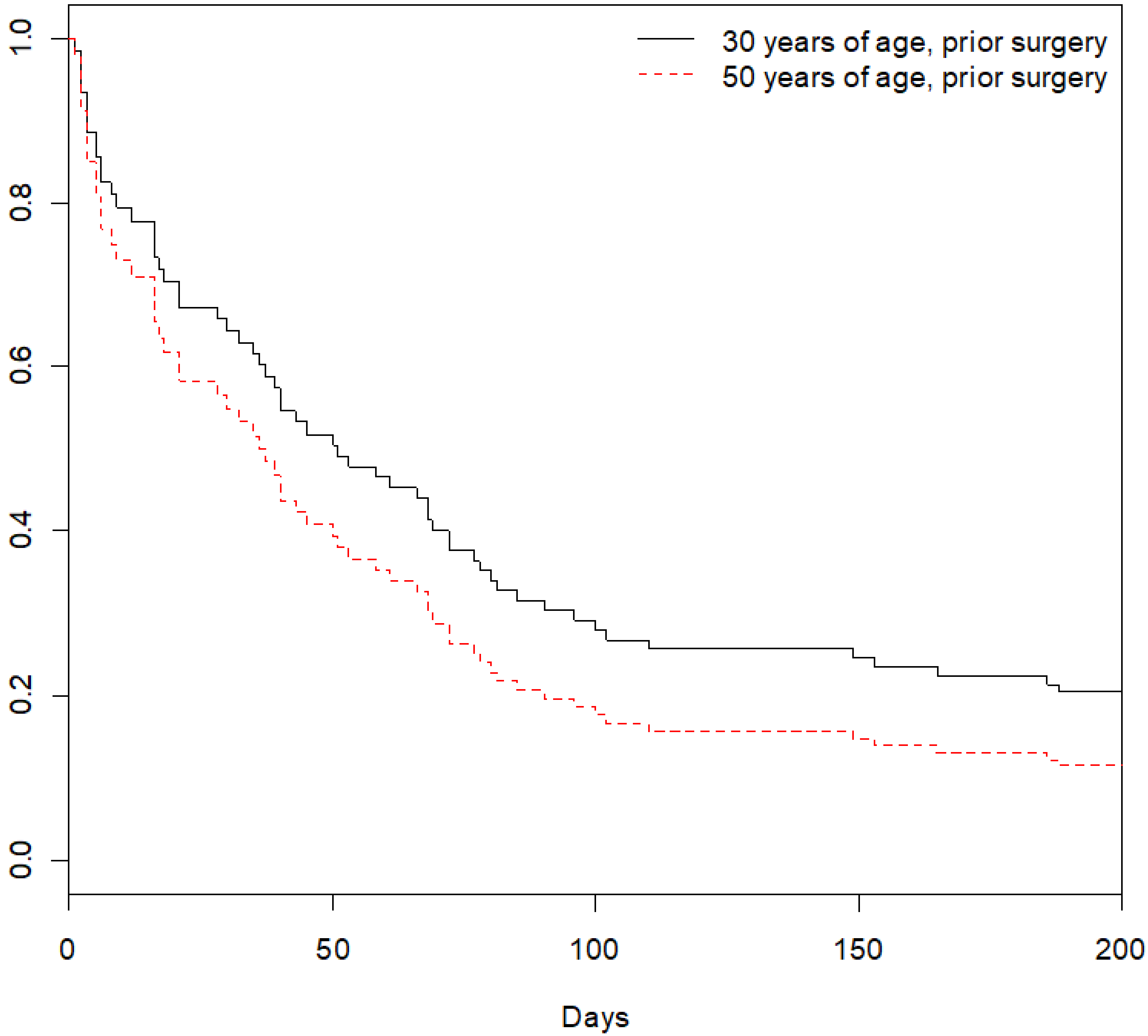
```
age30.dat <- data.frame(start = 0, stop = 183, age = 30 - 48, year =
0, surgery = 1, transplant = 0)
age50.dat <- data.frame(start = 0, stop = 183, age = 50 - 48, year =
0, surgery = 1, transplant = 0)
head(age50.dat)

start  stop   event  age year surgery transplant
0      183    1      -18    0       1          0
0      183    1        2    0       1          0

surv30 <- survfit(heart.cph03, newdata = age30.dat, individual =
FALSE, se = FALSE)
surv50 <- survfit(heart.cph03, newdata = age50.dat, individual =
FALSE, se = FALSE)
```

```
plot(surv30, lwd = 1, lty = 1, xlim = c(0, 200), xlab = "Days")
lines(surv50, lwd = 1, lty = 2, type = "s", col = "red")
legend(x = "topright", legend = c("30 years of age, prior surgery",
"50 years of age, prior surgery"), col = c("black", "red"), lwd =
c(1,1), lty = c(1,2), bty = "n")
```

Stanford heart transplant data (Crowley and Hu 1977). Predicted survival curve for a patient of 30 years at time of entry into the transplant program and a patient 50 years of age at time of entry.



Topics covered

- Piecewise Cox models
- <u>Penalised Cox models</u>

Penalised Cox models

- What do we do when our continuous explanatory variable is <u>not</u> linear in its log hazard?

- Two options
  - re-code the variable into categories and treat as a factor
  - parameterise the explanatory variable using smoothing functions

Penalised Cox models

- Penalised Cox models offer a means for dealing with non linearity in log hazards by fitting non-parametric functions (for example, spline smoothers) to account for relationships between explanatory and outcome variables

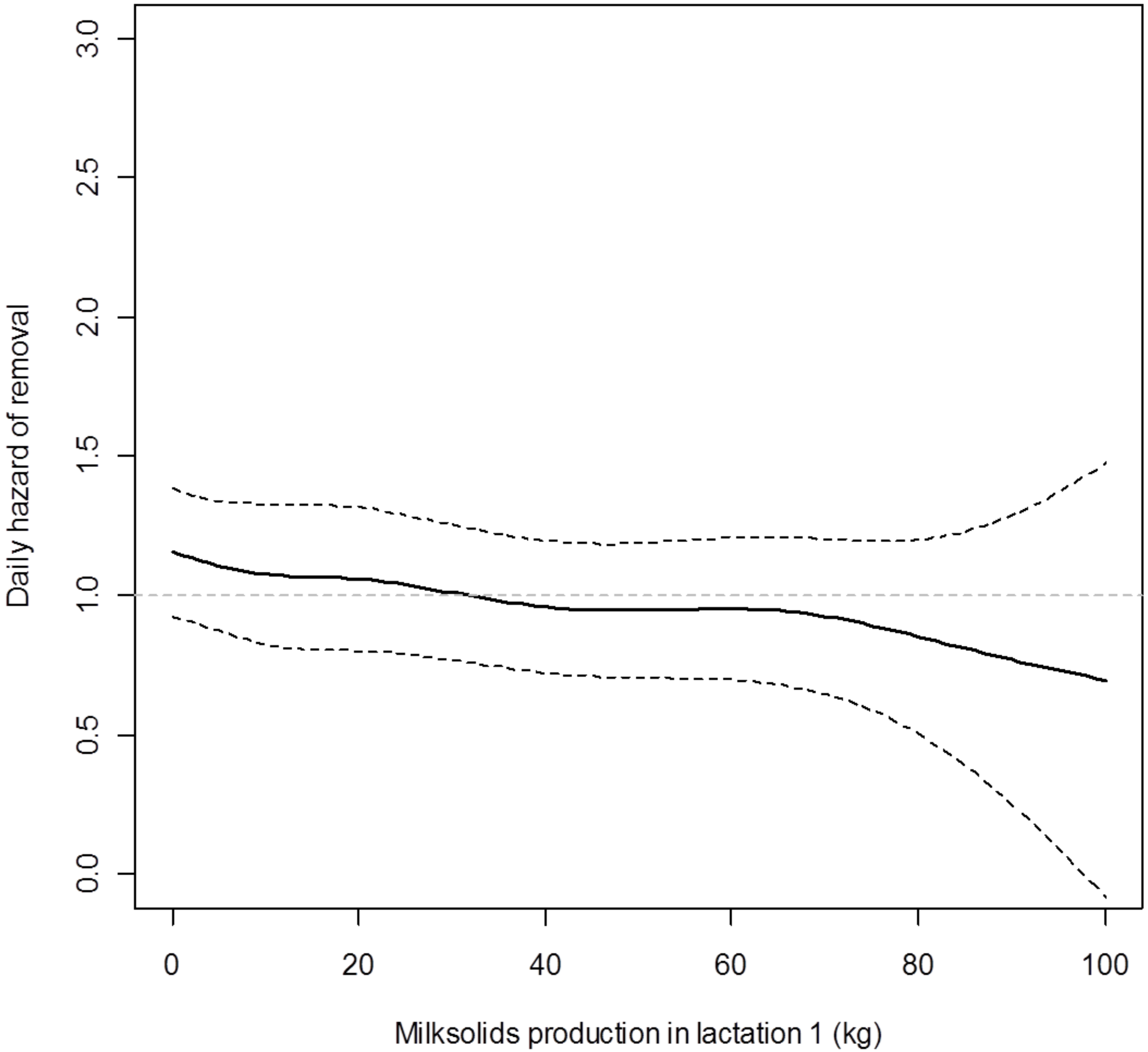
- A nice feature of this technique is that results can be displayed graphically to illustrate the multivariable functional form of these relationships (e.g. linear, quadratic or cubic)

Penalised Cox models

- Penalised Cox models offer a means for dealing with non linearity in log hazards by fitting non-parametric functions (for example, spline smoothers) to account for relationships between explanatory and outcome variables

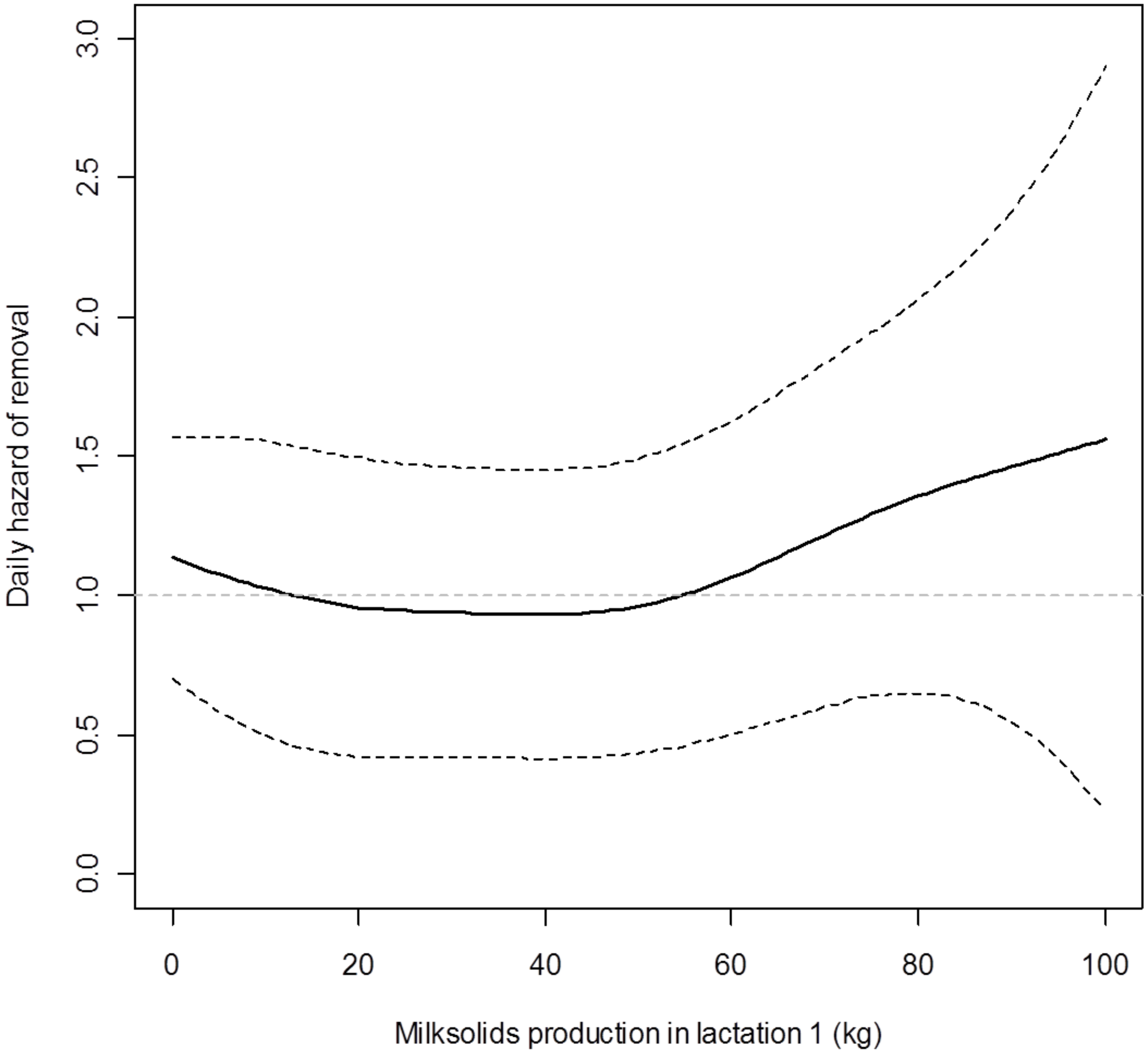
- A nice feature of this technique is that results can be displayed graphically to illustrate the multivariable functional form of these relationships (e.g. linear, quadratic or cubic)

Effect of L1 MS yield on daily hazard of removal, 0 to 730 days (P < 0.05)



Interpretation: during the first two years after L1, you're less likely to be culled if you were a high producer in L1.

Effect of L1 MS yield on daily hazard of removal, > 730 days (P > 0.05)



Interpretation: beyond two years after L1, high L1 producers have an increased hazard of culling.

THE UNIVERSITY OF MELBOURNE