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UCL

SPLINE FUNCTIONS TO MODEL POLYPHARMACY EXPOSURE

The studies discussed in this presentation are published here:

Jeffery A, Bhanu C, Walters K, Wong ICK, Osborn D, Hayes JF. **Polypharmacy and Antidepressant Acceptability in Comorbid Depression and Type 2 Diabetes.** British Journal of General Practice 31 October 2022. DOI: 10.3399/BJGP.2022.0295

Jeffery A, Bhanu C, Walters K, Wong ICK, Osborn D, Hayes JF. **Association between polypharmacy and depression relapse in individuals with comorbid depression and type 2 diabetes: a UK electronic health record study. British Journal of Psychiatry.** 2022 Dec 1:1-7. DOI: 10.1192/bjp.2022.160

How does polypharmacy effect antidepressant treatment in people with physical comorbidities?

Population: comorbid depression and type 2 diabetes (T2DM)

Outcome: Antidepressant treatment in people with T2DM

We already know:

- Antidepressants are effective in short-term

We don't know:

- If antidepressants are acceptable (relevant side effects e.g. weight gain, cardiac disturbances, nausea, etc.)
- Long-term effectiveness

Outcome: Antidepressant treatment in people with T2DM

Outcome 1: Antidepressant acceptability
(measured by stopping antidepressants before the recommended duration)

Outcome 2: Depression relapse
(measured by restarting antidepressants after stopping)

How does exposure to polypharmacy effect antidepressant treatment?

- Polypharmacy = the use of multiple medications
- Common in people with T2DM
- Evidence polypharmacy can increase risk of side effects, drug interactions, treatment burden, poor quality of life, depression, poor medication adherence…
- No evidence of how polypharmacy effects antidepressant treatment in people with T2DM
- Hypothesis – polypharmacy makes antidepressants less acceptable and at higher risk of depression relapse

Methods: Cohort study

Inclusion criteria:
- Comorbid depression and T2DM
- Starting first antidepressant

Study 1 entry:
First antidepressant prescription

Outcome 1 measured:
Time to stopping first antidepressant

Study 2 entry:
First antidepressant stopped

Outcome 2 measured:
Time to restarting antidepressant treatment

Methods: cox regression

Investigates the effect of an exposure on the time taken for an event to happen:

1 – Time taken to stop antidepressants (acceptability)

2 – Time taken to restart antidepressants (relapse)

Exposure: Polypharmacy – the number of medications concurrently prescribed:

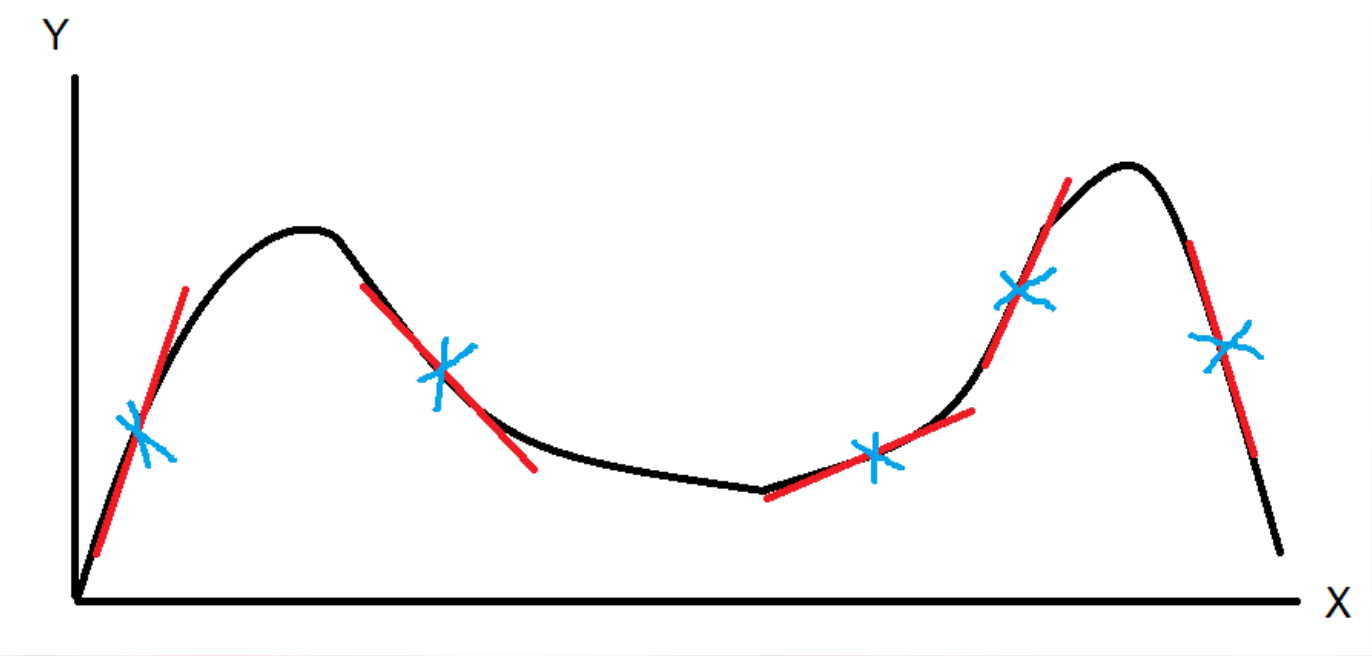
- Count of each different pharmaceutical agent prescribed alongside antidepressant treatment
- Exposure period – 90 days within index date
- Sensitivity analysis – repeat prescriptions (2 prescriptions within 180 days, 1 within 90)

Assumptions for cox regression:

- Effect of exposure is proportional over time…i.e. linear relationship between exposure and outcome

Spline functions

- Enable use of linear models, when linear assumptions fail
- Fit a linear function at certain intervals to fit individual hazard ratio point estimates
- Often used in time series analysis



Penalised B-splines

- Penalised fit = defines optimal point where spline should be fit hazard ratio
  - ➔ balances flexibility with overfitting
  - ➔ removes bias from user-selected splines (e.g. quartiles, clinically relevant intervals)

- B-splines = piecewise defined
  - ➔ i.e. a spline point at integer values only, overcomes numerical instability

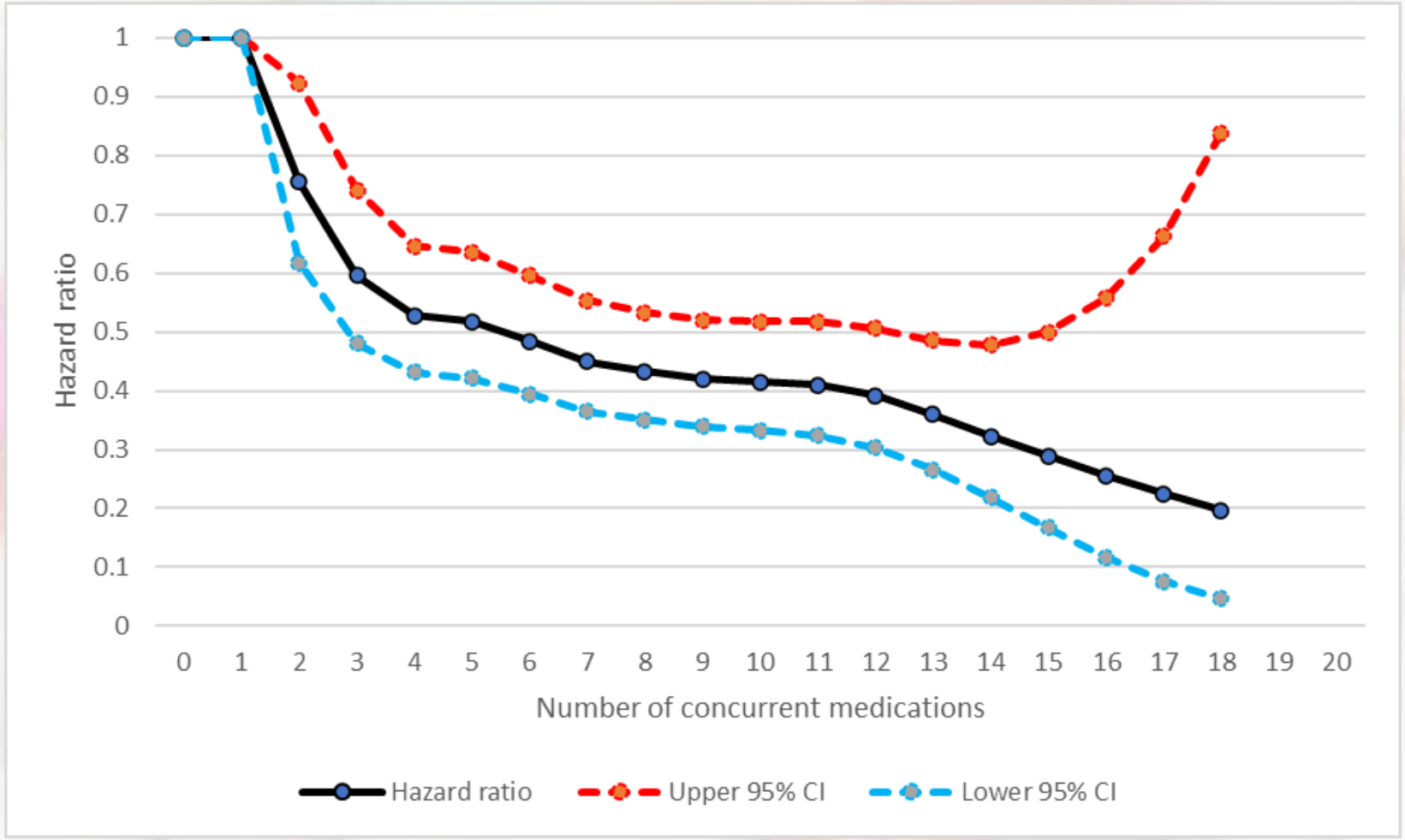
```
library(survival)

coxph(Surv(time, outcome) ~ pspline(polypharmacy_count, df = 0, caic = T) + confounders,
 data = dataset)
```

How does exposure to polypharmacy effect antidepressant treatment?

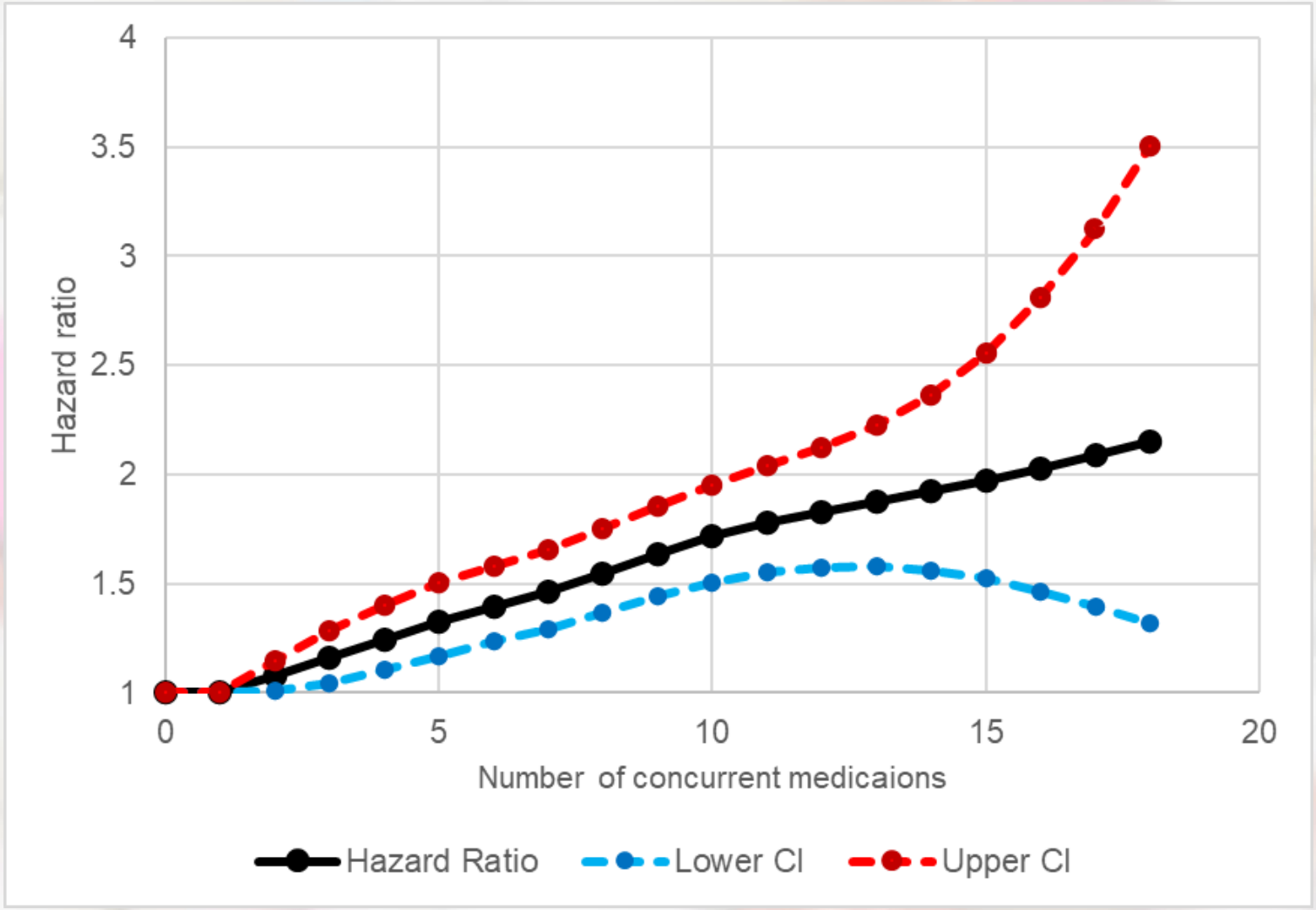
1) Stopping antidepressants before the recommended duration (acceptability)

2) Restarting antidepressants (relapse)

Stopping antidepressants



Restarting antidepressants



Benefits of using penalised B-splines

- Can identify change in hazard ratio at statistically relevant intervals
- Can see the first and last value for which an association exists

LIMITATION: May require large sample size

Interpretation of results

- More concurrent medications = more likely to continue antidepressant treatment
- More concurrent medications = more likely to restart antidepressant treatment
- More concurrent medications ➔ maybe more unwell, more severely depressed
- More concurrent medications ➔ maybe more accepting of pharmacological treatment

Any questions about the studies? Email annie.jeffery.09@ucl.ac.uk

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