

Caution in time-to-event models where a pre-event state modifies time-varying exposure

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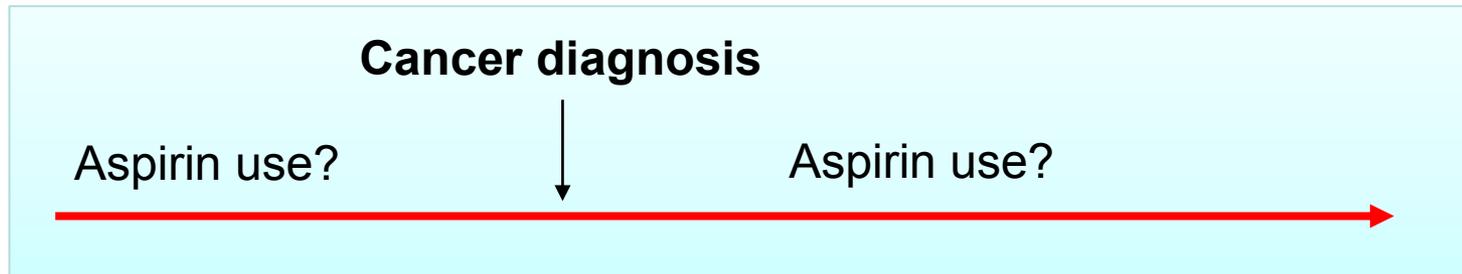
1. National Cancer Registry Ireland, 2. Trinity College Dublin



SPHeRE 2016, Dublin

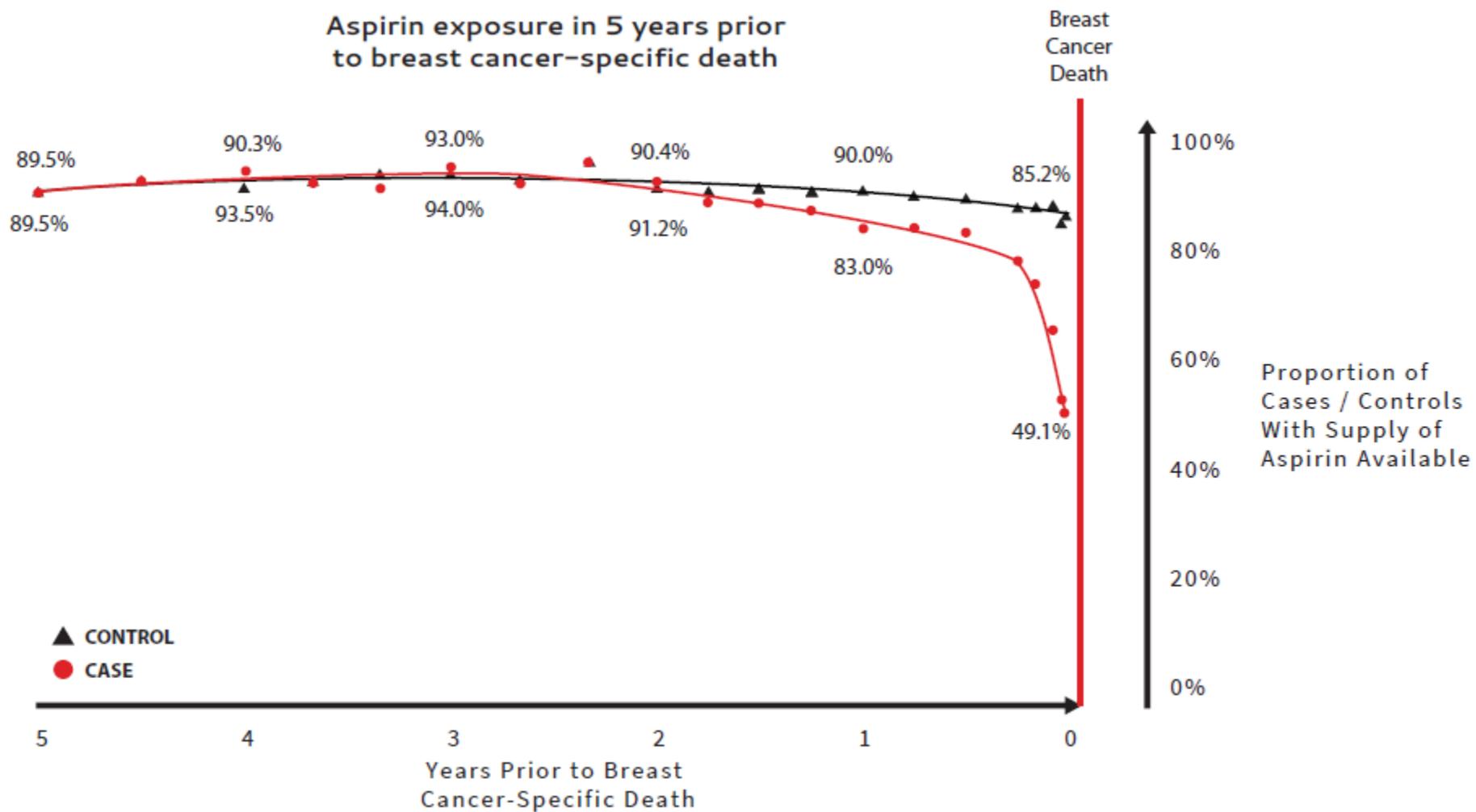


- In cancer outcome studies it is often important to distinguish between effects of pre- and post-diagnostic exposures.

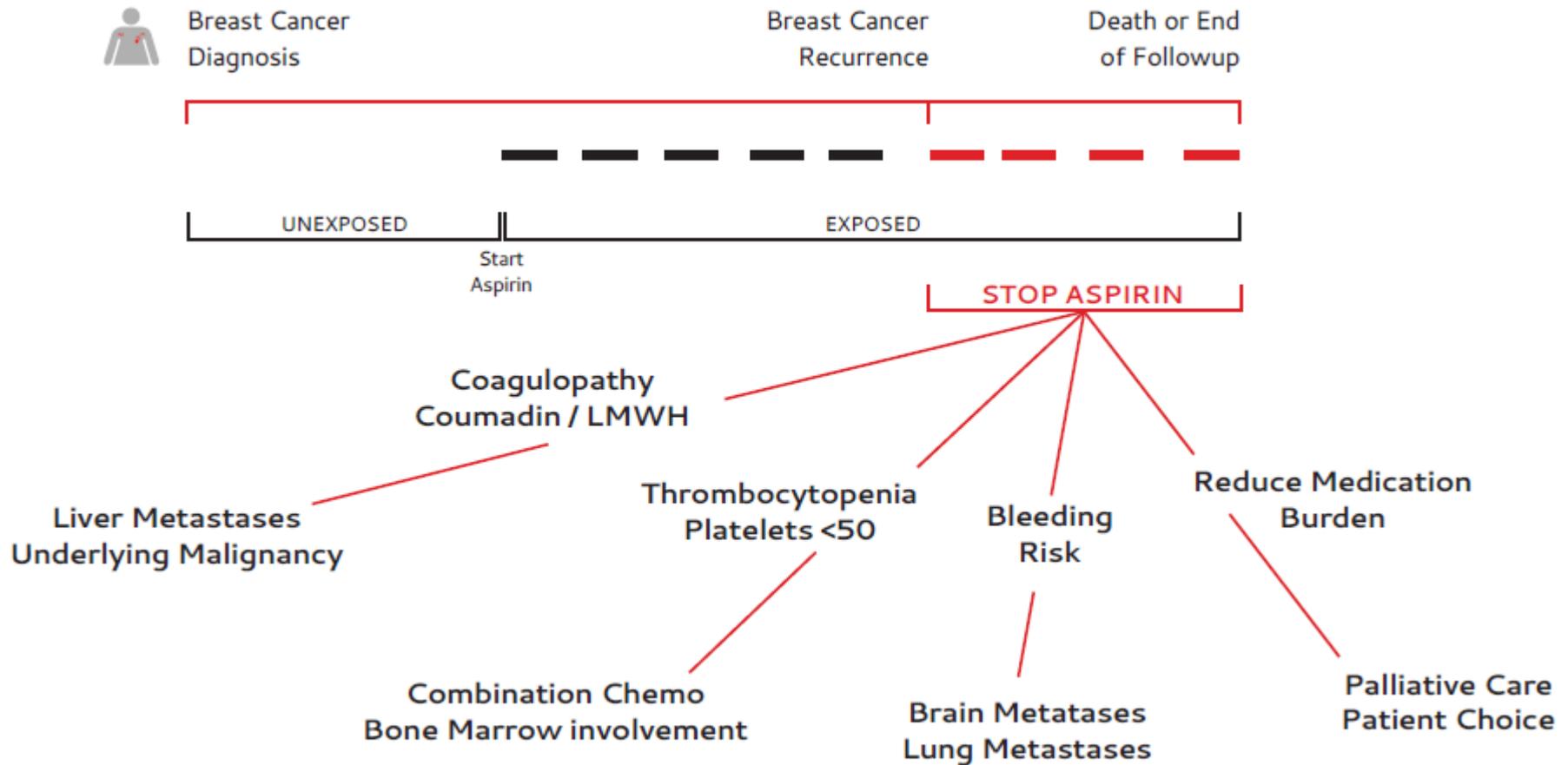


- Might be tempted to adjust a time-varying post-diagnosis exposure analysis by baseline status...

Aspirin exposure pre-death

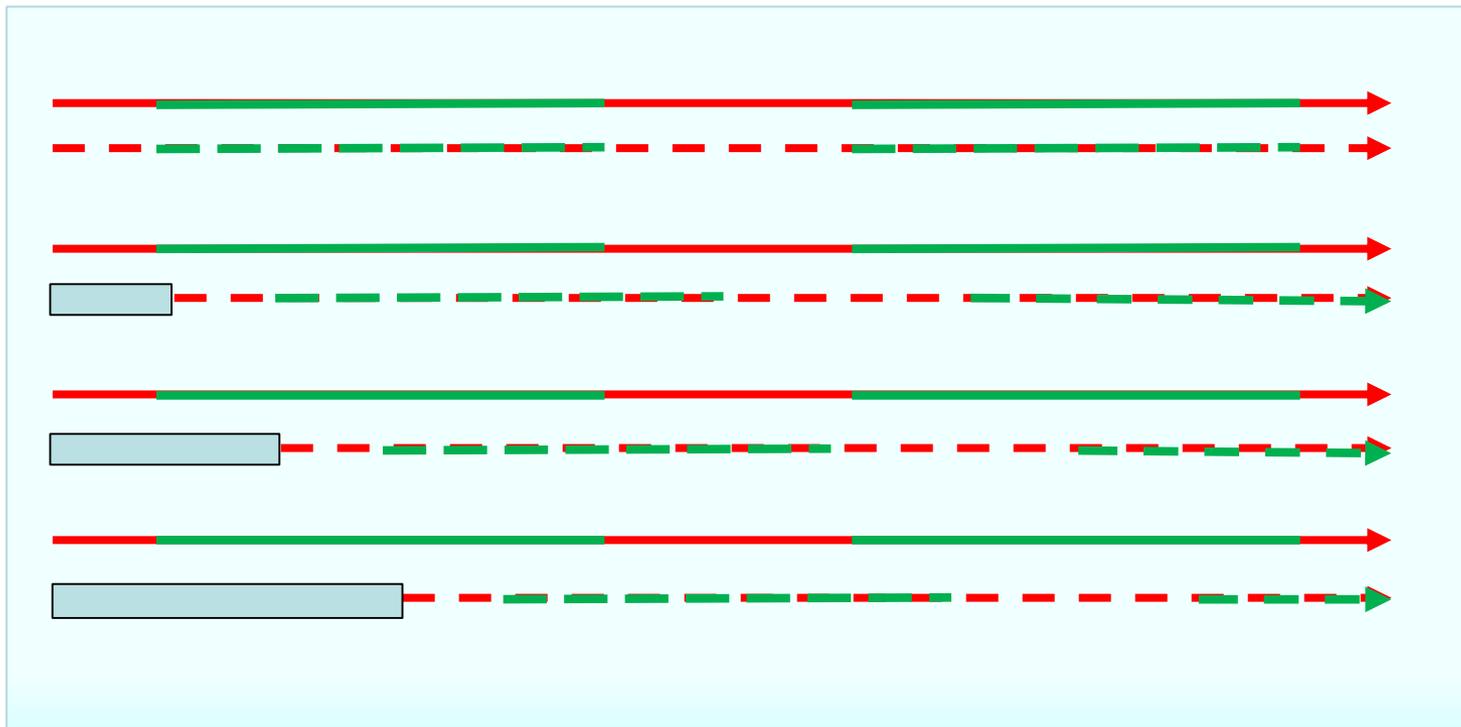


Reasons for stopping aspirin



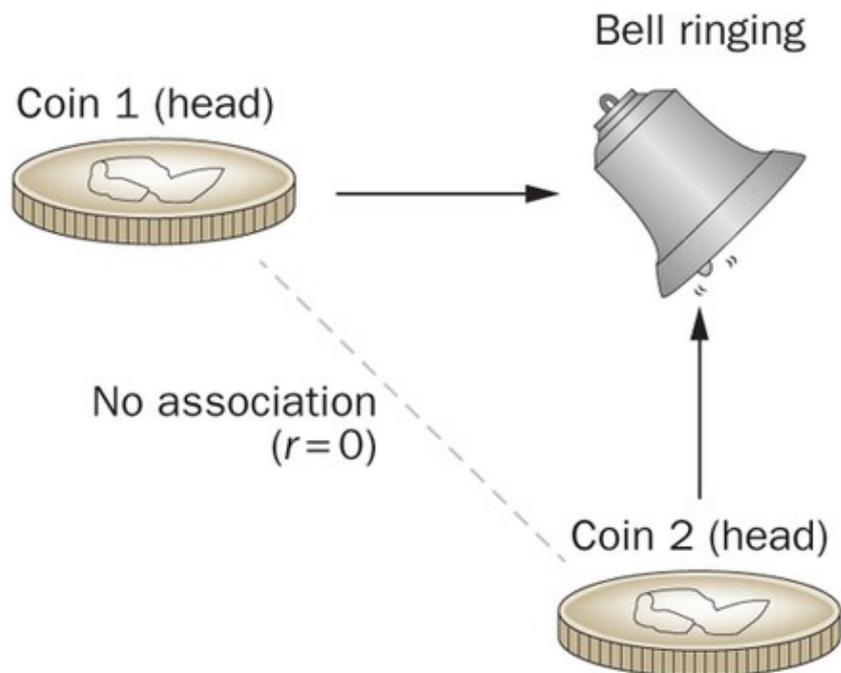
Time-varying covariates

- Lagging start/stop for analysis can influence exposure at event time

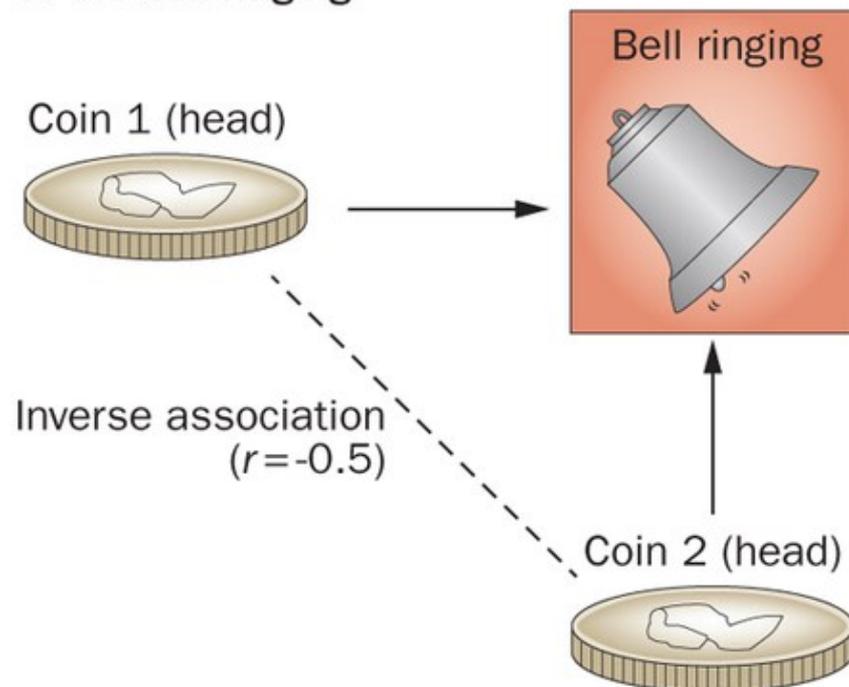


Collider stratification bias

No conditioning



Conditioning on the outcome of the bell ringing



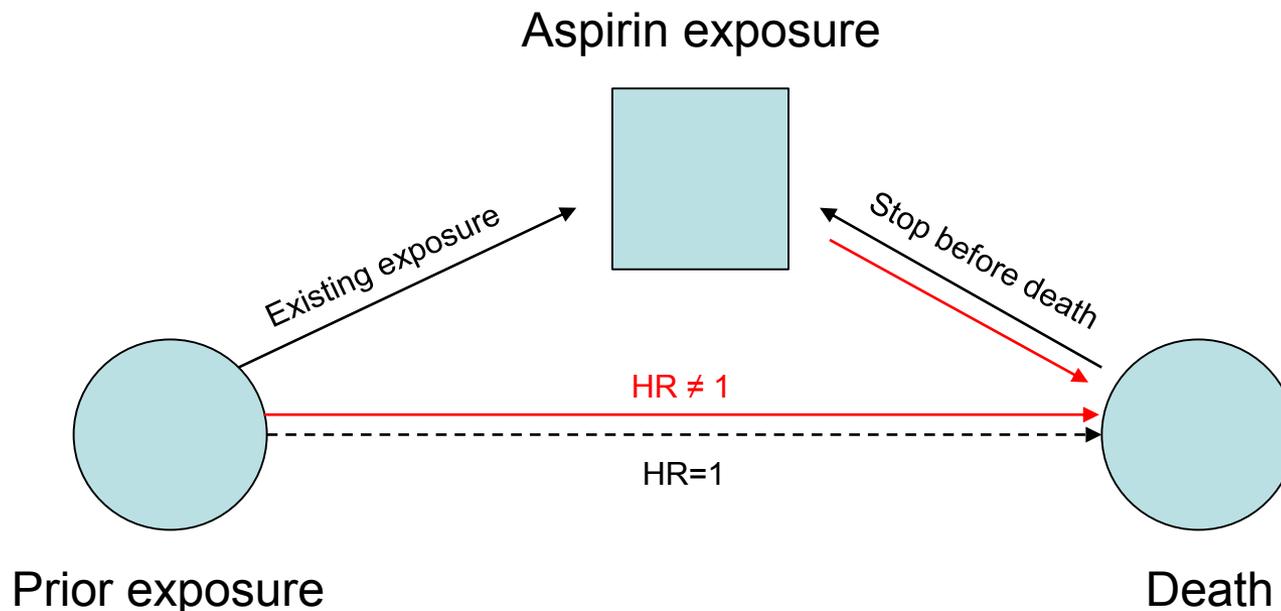
[Selection bias in rheumatic disease research](#)

[Hyon K. Choi](#), [Uyen-Sa Nguyen](#), [Jingbo Niu](#), [Goodarz Danaei](#) & [Yuqing Zhang](#)

Nature Reviews Rheumatology **10**, 403–412 (2014) doi:10.1038/nrrheum.2014.36

Collider stratification bias

- If changes in prognosis (e.g. recurrence, period pre-death) influence post-diagnostic exposure, this may introduce collider stratification bias.



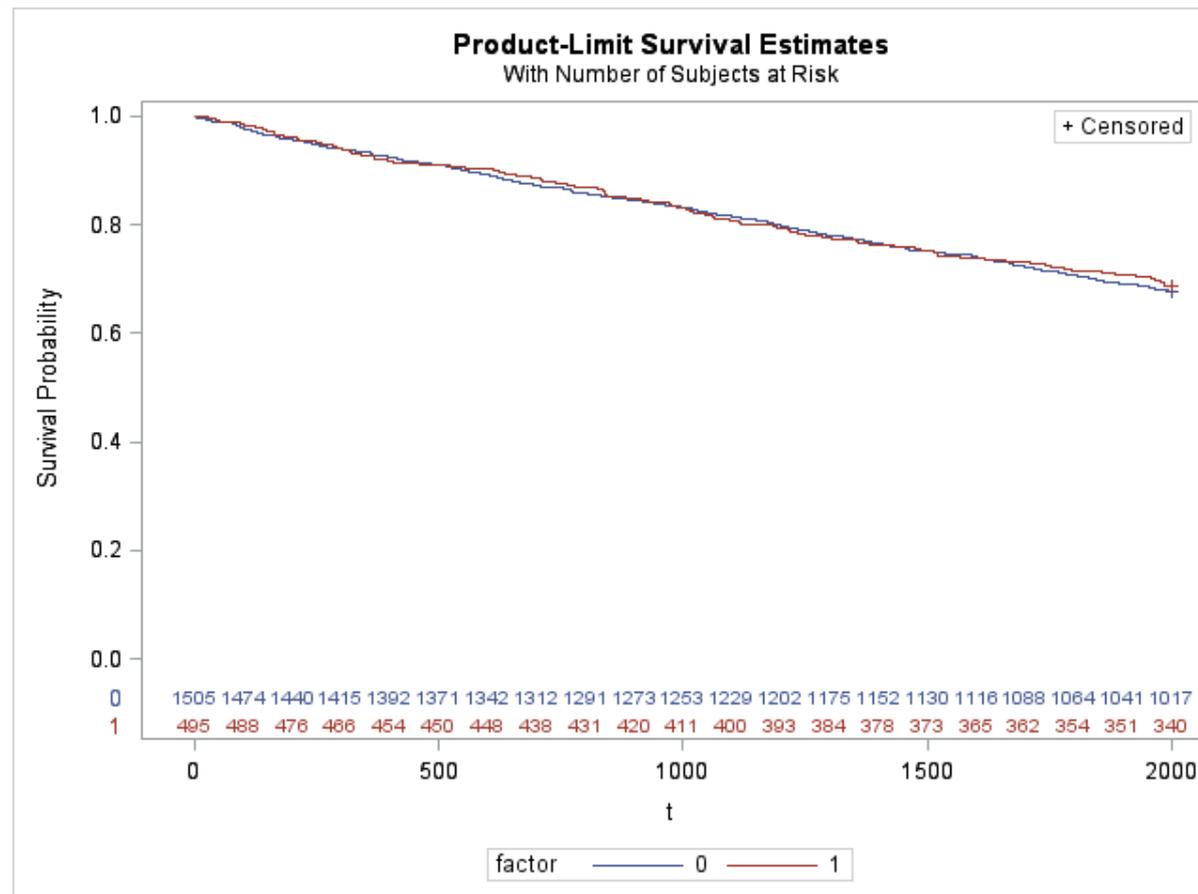
1. Simulate events

2000 cases, 5 years data, event rate 0.02%/day

Pre-diagnostic exposure:

Binomial $p=0.25$

Hazard Ratio = 1



2. Simulate TVC

Generated time-varying continuation of
post-diagnostic exposure with fixed
start/stop probabilities

Start = 10% / year

Stop = 3% / year

% Exposed over time (one dataset)



3. Introduce collider bias

- To illustrate CSB we modified stop probabilities in the year prior to death by a pre-death probability factor (PDPF) 1x-5x.



4. Fit time-varying Cox model

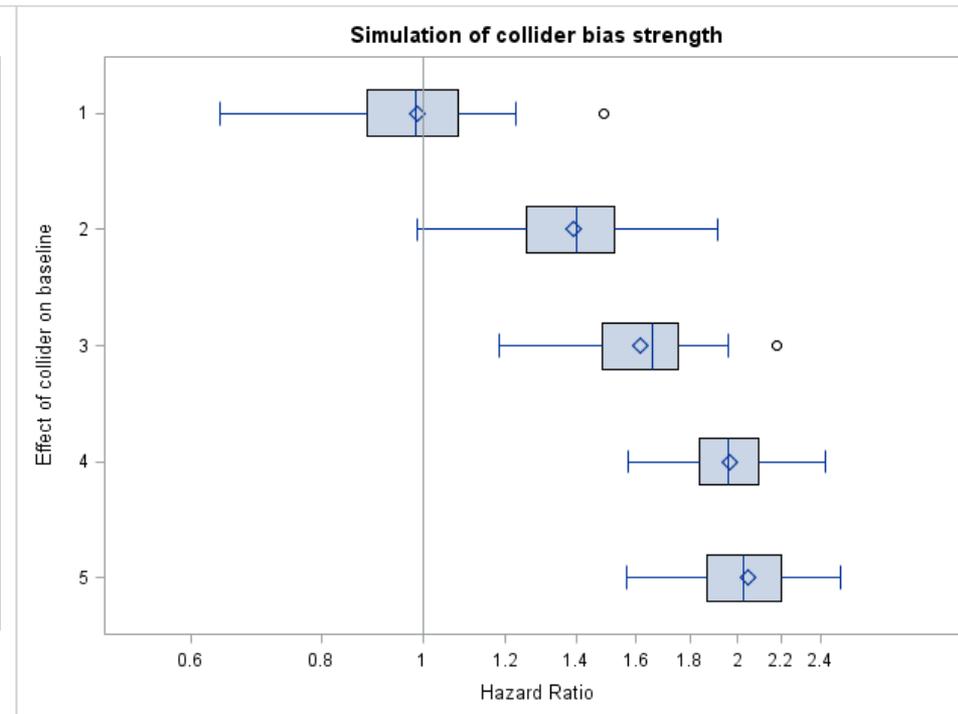
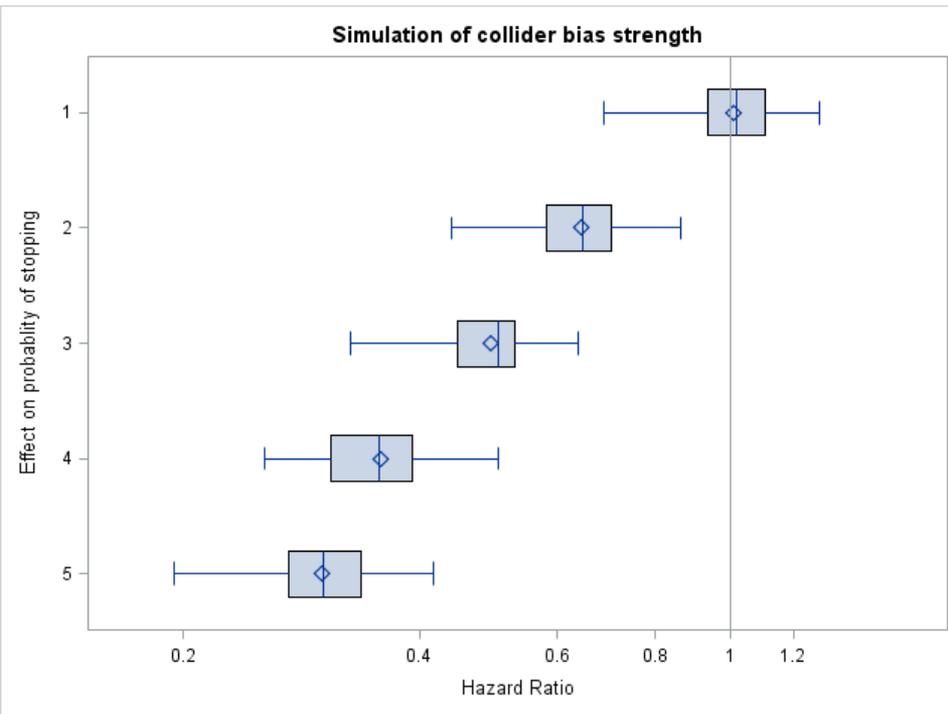
- Cox regression
 - HR for pre-diagnostic (Pre-HR)
 - HR post-diagnostic (Post-HR) exposures

$$\ln\left(\frac{H(t)}{H_0(t)}\right) = b_{pre}X_{pre} + b_{post}X_t$$

Pre-event state modifies HR

Effect of TimeVarying

Effect of Baseline



Conclusion

- In scenarios where post-diagnostic exposure is modified by changes in prognosis, naïve adjustment leads to spurious effect observations for pre-/post-diagnostic exposures.
- **Is there a solution?**
 - Don't adjust for colliders (i.e. exclude post-exp)
 - **Lag exposure stop times**
 - Analysis of 'any' exposure

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Further information:

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