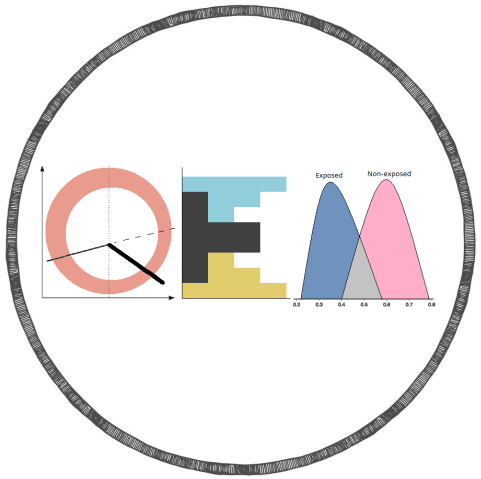


Your badge?

Within patient, case-only designs: The self-controlled case series and the case-crossover study

Revision: ever/never designs

- Lots of rubbish studies suggesting that medicines are associated with various outcomes among people with diabetes (eg. insulin & lung cancer[1]; metformin & lower risk of brain tumors[2]), comparing 'ever-users' and 'never-users' of the medicines
- This is wrong: 'ever-users' of insulin and 'never-users' of metformin are more unwell for multiple reasons [also there is immortal time bias!]
- Adjusting for comorbidity at baseline is likely insufficient to fix this – residual confounding
- Ever/never variables can be used together with a time-varying measure of cumulative exposure. The ever/never term distinguishes between different types of participant (as a confounder), and the effect-of-interest is the cumulative exposure
- The ever/never term must also be time-varying to avoid immortal time bias

1. Tseng C-H (2019) Human Insulin Therapy Is Associated With an Increased Risk of Lung Cancer: A Population-Based Retrospective Cohort Study. *Front. Endocrinol.* 10:443. doi: 10.3389/fendo.2019.00443
2. Tseng, C.-H. Metformin Is Associated with a Lower Incidence of Benign Brain Tumors: A Retrospective Cohort Study in Patients with Type 2 Diabetes Mellitus. Biomolecules 2021, 11, 1405. https://doi.org/10.3390/biom11101405

Some research questions ...

- Does the MMR vaccine cause idiopathic thrombocytopenic purpura?
- Do influenza vaccines cause asthma exacerbations?
- Do mobile phone calls cause car crashes?
- Does drinking alcohol cause heart attacks?
- Do influenza infections cause strokes?
- Do hospital admissions cause people to take overdoses of illegal drugs?
- Do heatwaves cause acute mental health crises?
- Does long-haul air travel cause thromboembolisms?

Common features of these questions …

- Focus on causal triggers
- Sudden onset of outcomes
- Exposures vary over time within individuals
- We are focused on the timing of outcomes and exposures – ‘when?’ rather than ‘who?’

Imagine if 300 children in Bradford were reported to have had a seizure in the past month …

Some of the children watched Cocomelon in the 30 minutes before the seizure. Would you be worried about Cocomelon if this was:

- 1 child?

Imagine if 300 children in Bradford were reported to have had a seizure in the past month …

Some of the children watched Cocomelon in the 30 minutes before the seizure. Would you be worried about Cocomelon if this was:

- 1 child?

- 5 children?

Imagine if 300 children in Bradford were reported to have had a seizure in the past month …

Some of the children watched Cocomelon in the 30 minutes before the seizure. Would you be worried about Cocomelon if this was:

- 1 child?
- 5 children?
- 25 children?

Imagine if 300 children in Bradford were reported to have had a seizure in the past month …

Some of the children watched Cocomelon in the 30 minutes before the seizure. Would you be worried about Cocomelon if this was:

- 1 child?
- 5 children?
- 25 children?
- 100 children?

Imagine if 300 children in Bradford were reported to have had a seizure in the past month …

Some of the children watched Cocomelon in the 30 minutes before the seizure. Would you be worried about Cocomelon if this was:

- 1 child?
- 5 children?
- 25 children?
- 100 children?
- 225 children?

Self-controlled case series

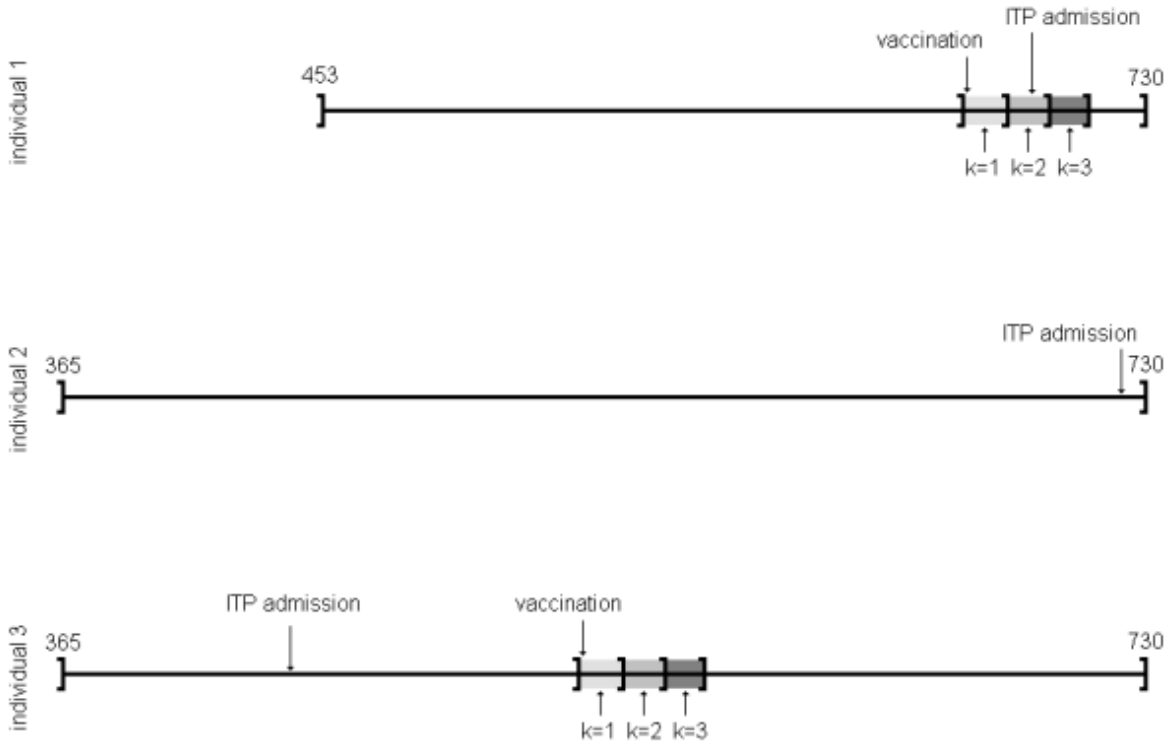


Figure 1: Observation periods for the first 3 individuals in the ITP and MMR data set.

Whitaker, Heather J.; Hocine, Mounia N. and Farrington, C. Paddy (2009). The methodology of self-controlled case series studies. Statistical Methods in Medical Research, 18(1) pp. 7–26.

Self-controlled case series

Individual	Risk period	Start age	End age	Duration	IPT
1	Unexposed	453	599	146	0
1	MMR1	600	609	9	0
1	MMR2	610	619	9	1
1	MMR3	620	629	9	0
1	Unexposed	630	730	100	0
2	Unexposed	365	730	365	1
3	Unexposed	365	499	134	1
3	MMR1	500	509	9	0
3	MMR2	510	519	9	0
3	MMR3	520	529	9	0
3	Unexposed	530	730	200	0

```
clogit(IPT ~ risk_period + offset(log(duration)) + strata(individual), data = df)
```

- ✓You might only have data on cases
- ✓Even if you can find controls, they might be biased
- ✓Eliminates time-invariant confounding
- ✓Great for sudden events

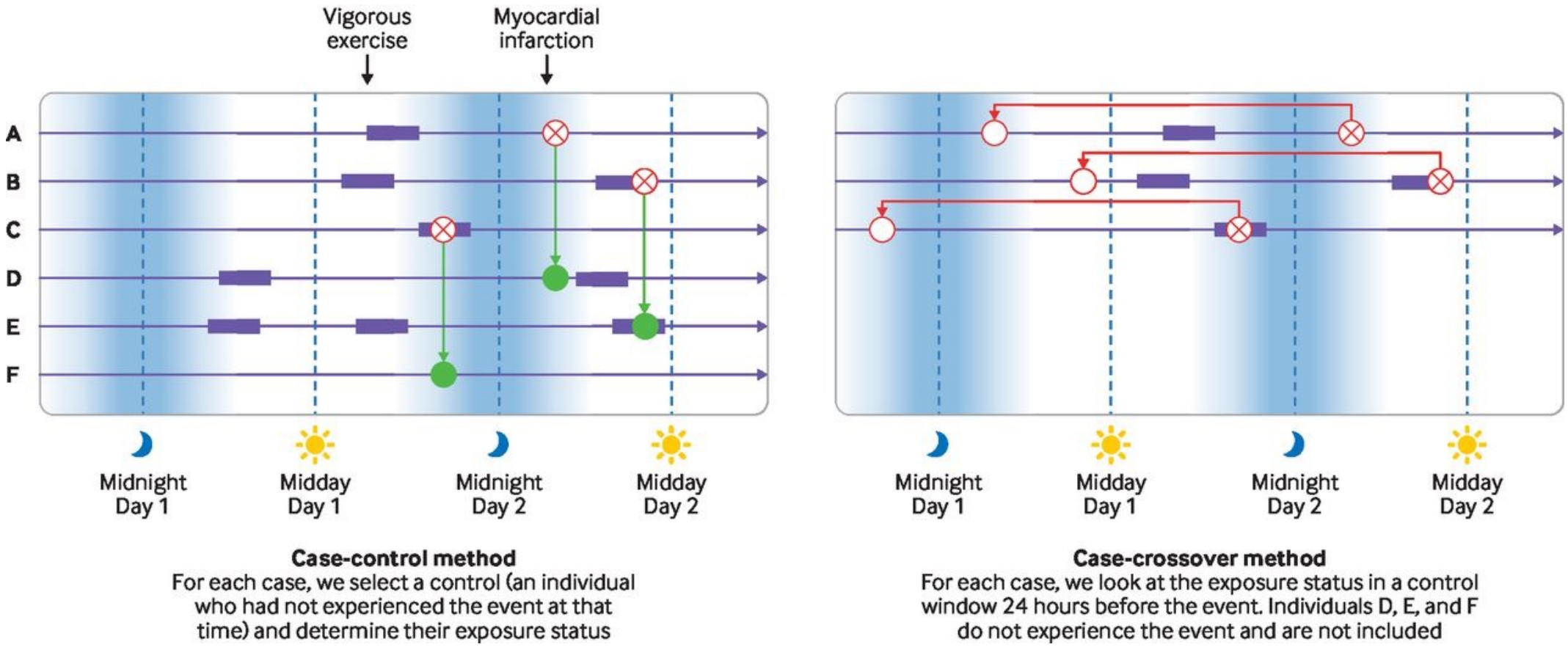
- ✗Only estimates relative effects
- ✗Event should not affect subsequent exposures
- ✗Usually not much use for chronic diseases
- ✗Can be difficult if you don't have the precise timing of onset

Self-controlled case series

Individual	Risk period	Start	End	IPT	Immune disorder
1	Unexposed	453	599	0	Yes
1	MMR1	600	609	0	Yes
1	MMR2	610	619	1	Yes
1	MMR3	620	629	0	Yes
1	Unexposed	630	730	0	Yes
2	Unexposed	365	730	1	No
3	Unexposed	365	499	1	No
3	MMR1	500	509	0	No
3	MMR2	510	519	0	No
3	MMR3	520	529	0	No
3	Unexposed	530	730	0	No

$$\text{clogit}(\text{IPT} \sim \text{risk\_period} + \text{offset}(\log(\text{duration})) + \text{strata}(\text{individual}), \text{data} = \text{df})$$

The case-crossover design



Case-control method
For each case, we select a control (an individual who had not experienced the event at that time) and determine their exposure status

Case-crossover method
For each case, we look at the exposure status in a control window 24 hours before the event. Individuals D, E, and F do not experience the event and are not included

Lewer D, Petersen I, Maclure M. The case-crossover design for studying sudden events. BMJ Medicine 2022;1:e000214. doi: 10.1136/bmjmed-2022-000214

The case-crossover design

Individual	MI	Exercise
1	Case	Yes
1	Control	Yes
2	Case	No
2	Control	Yes
3	Case	Yes
3	Control	No
4	Case	No
4	Control	Yes

```
clogit(MI ~ exercise + strata(individual), data = df)
```

Acute and long-term effects can be in the opposite direction.

Exercise might increase the risk of MI in the subsequent 30 minutes, but decrease the underlying risk each time you do it.

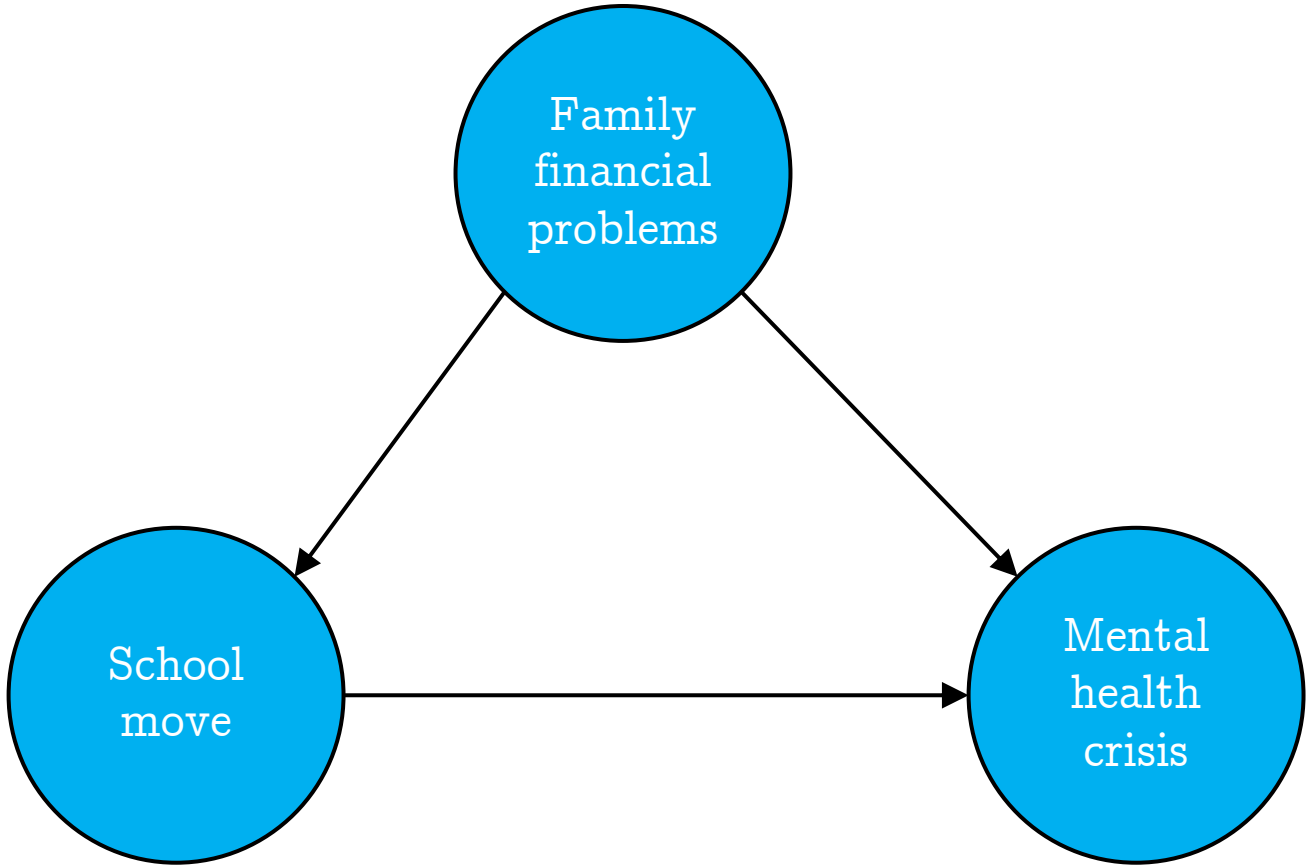
A case-crossover study or self-controlled case series would only capture the acute component of risk.

Imagine we're doing a case-control study

Individual	MI	Exercise	History of CVD
1	Case	No	Yes
2	Control	Yes	No
3	Case	No	Yes
4	Control	Yes	No
5	Case	No	Yes
6	Control	Yes	No
7	Case	No	Yes
8	Control	Yes	No

```
glm(MI ~ exercise + cvd, data = df, family = 'binomial')
```

Time varying confounding



Why choose one or the other design?

- Case-crossover studies focus on causes of an outcome (eg. triggers of a heart attack)
- SCCS focus on effects of an exposure (eg. vaccine side effects)
- SCCS may be more statistically powerful
- SCCS requires that exposures are not dependent on the event. This is not a requirement of the case-crossover design [eg. Mobile phones and car crashes]

Uses in Bradford?

- What is the benefit of peri-natal mental health support? (Focusing on parents with multiple children and varying support each time)
- Can moving house (or school) trigger a mental health crises?
- Do housing problems affect school attendance? (And does this differ according to the support provided by the local authority?)