Self-controlled Case Series (SCCS)

Irene Petersen, Professor of Epidemiology and Health Informatics

Primary Care and Population Health

Acknowledgements

Thanks to ALL the people I have worked with on SCCS in the last 15 years

Special thanks to:

Paddy Farrington

Heather Whitaker

Ian Douglas

Today

- Overview of SCCS method
- Example
- Basic assumptions/features of SCCS
- Indication bias

Observational studies

Cohort studies

- Compare risks of events between exposed and non exposed individuals
- Event random, exposure fixed
- Poisson regression
  - Condition on time

Case control studies

- Compare exposure between cases and controls
- Exposure random, event fixed
- Logistic regression

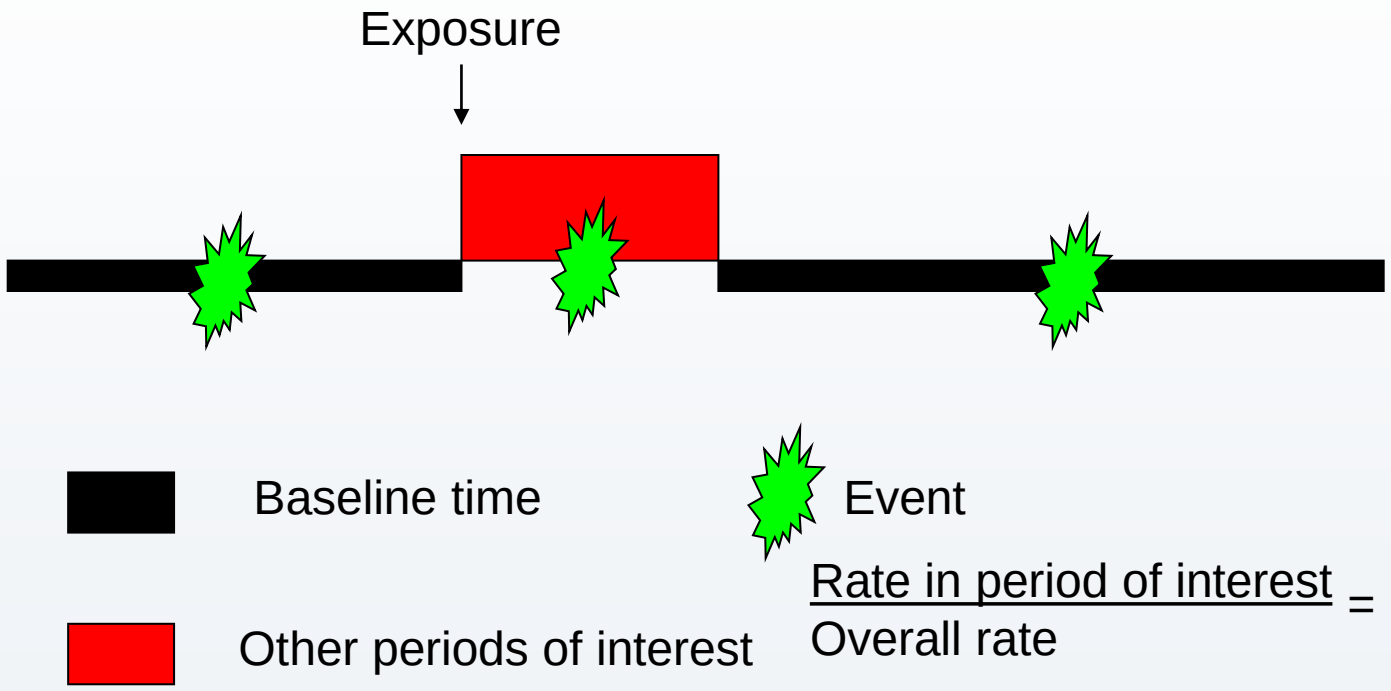
What if….

- We *only* have people who have the event, but we don't know the exact denominator
  - Hospital data
  - Long-haul flights and thromboembolism (VTE)
- There is a substantial difference between exposed and unexposed individuals
  - Ethnicity
  - Deprivation
  - Indication bias (severe asthma and influenza vaccine)

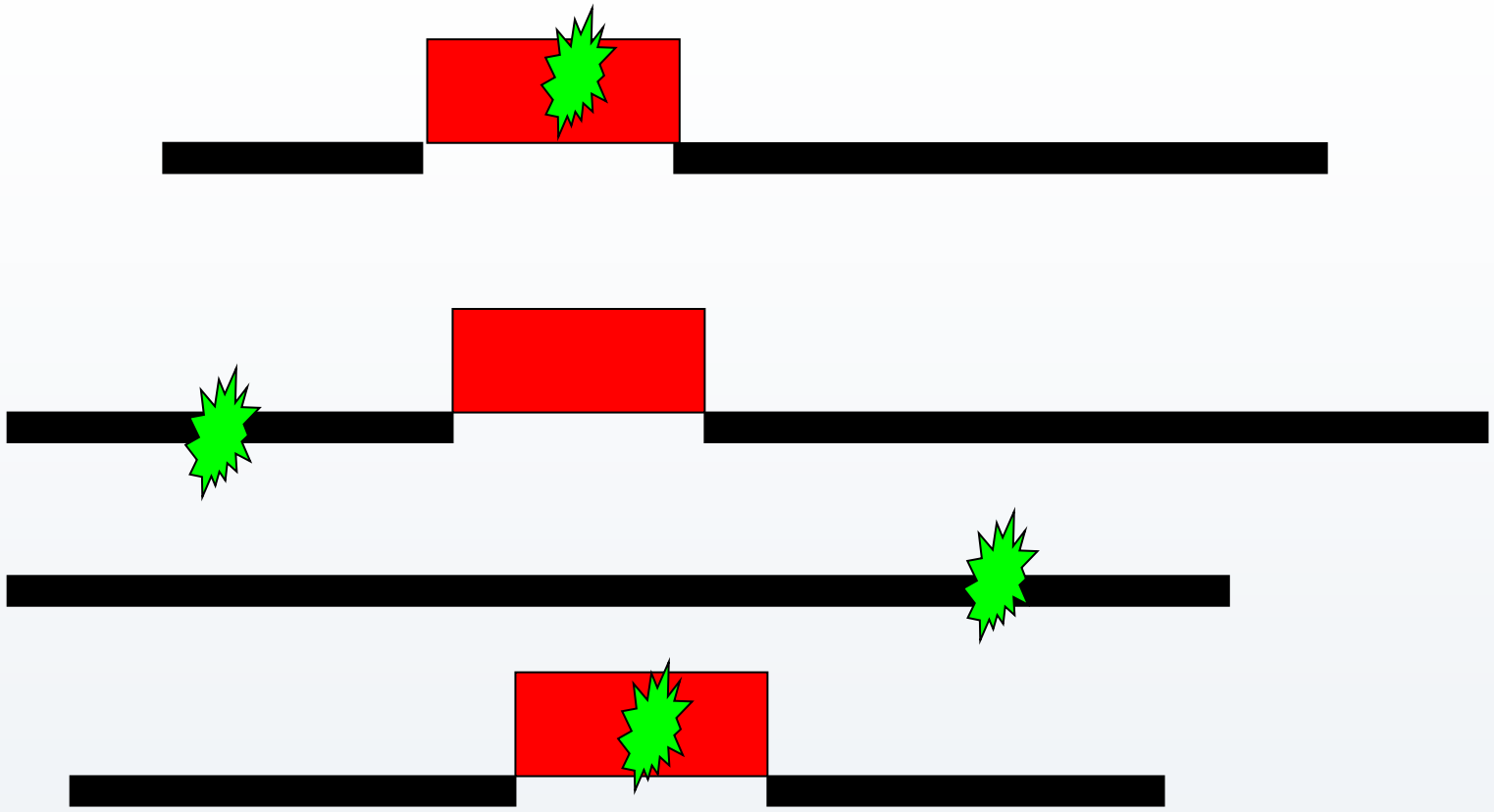
Self-controlled case series may be the answer?

- Case series analysis – *only* cases are sampled
- Estimation is within individuals rather than between individuals

It is a conditional cohort method: exposures are regarded as fixed, event times as random



Farrington CP. Biometrics 1995;51:228-235



Other key features of case series method

- Follow-up is *not* censored at event
- Can be used with:
  - *independent* recurrent events
  - *uncommon* non-recurrent events
- The analysis is *self-matched*, thus eliminating the effect of fixed confounders

Fitting the case series model

Conditional Poisson model

A: exp(Φi) = Baseline incidence of condition

B: exp(α1) = Relative incidence exposure group k

We want an estimate of B ☺

We can't measure A with SCCS

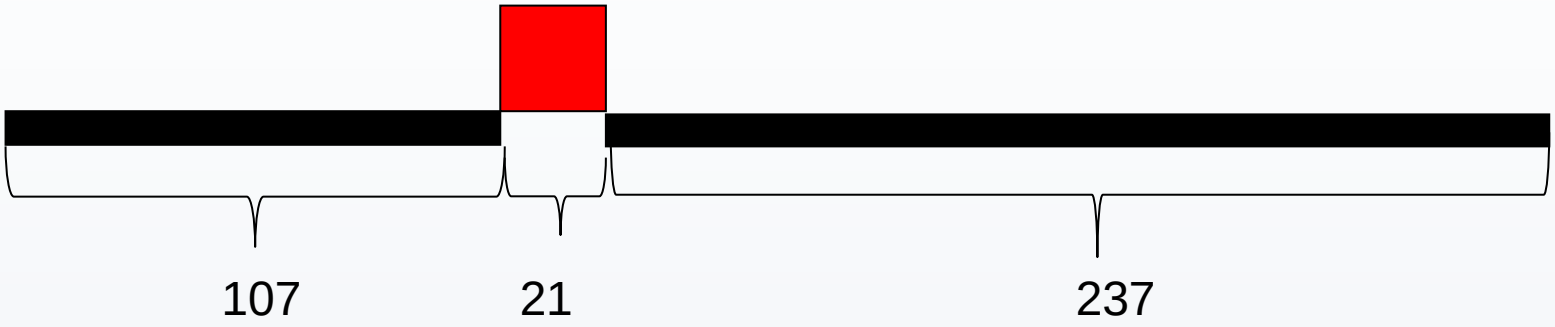
Case series

- We know that all had the event
- Overall Poisson Rate = 1
- Estimate conditional likelihood that event happened in specific period

Example: MMR vaccine and Viral meningitis example

- Meningitis in second year of life
- 1 Oct 1988 and 31 December 1991
- 10 children with viral meningitis
- Don’t know how many were vaccinated

MMR vaccine and viral meningitis



Three exposure periods:

1: 107 days 2: 21 days 3: 237 days

Estimate likelihood of event in each of those periods:

$\lambda 1 = 107A \quad \lambda 2 = 21AB \quad \lambda 3 = 237A$

Overall Poisson rate for child 1:

$\Lambda = 107A + 21AB + 237A$

MMR vaccine and viral meningitis

Child 1 had event in first period - estimate conditional likelihood of event in this period:

$\lambda 1/\Lambda = 107A/(107A + 21AB + 237A)$

A is cancelled out = self-controlled

$\lambda 1/\Lambda = 107/(344 + 21B)$

$\log(\lambda 1/\Lambda) = \log(107/(344 + 21B))$ and repeat for other children

Baseline risk of event may change over time

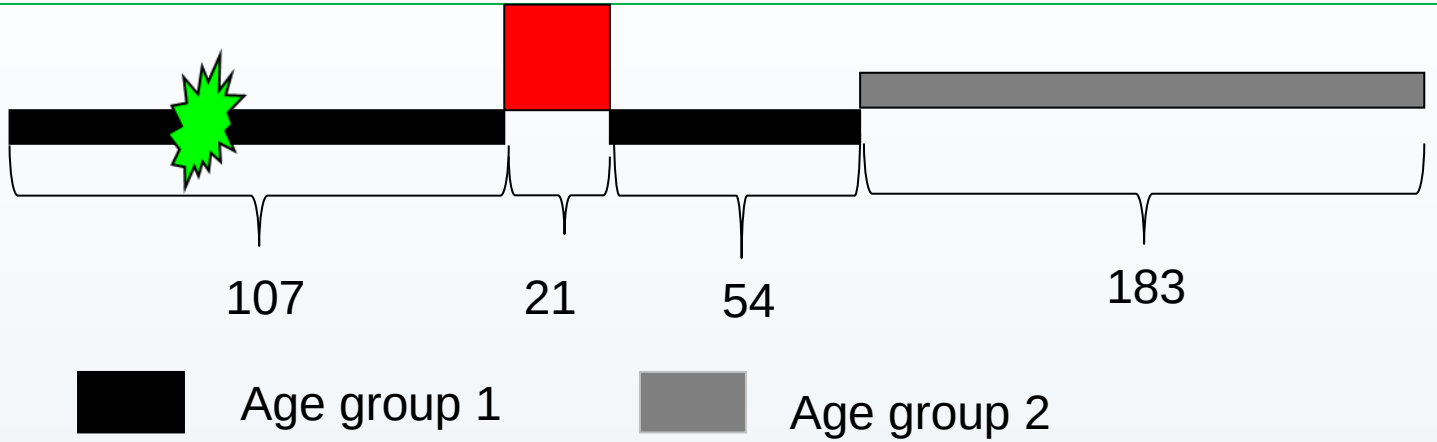
- Risk of event may change with age
- Introduce different risk periods

A: $\exp(\Phi i)$ = baseline incidence of viral meningitis

B: $\exp(\alpha 1)$ = relative incidence exposure group k

C: $\exp(\beta 1)$ = relative incidence age group j

MMR vaccine and viral meningitis



- Four exposure periods:
- 1: 107 days 2: 21 days 3: 54 days 4: 183 days
- Estimate likelihood of event in those periods
- λ1 = 107A, λ2 = 21AB, λ3 = 54A, λ4 = 183AC

Multinormial likelihood for *all* children

- Repeat for other children as for child 1
- log and estimate log-likelihood
- β1: -1.491 α1: 2.488

B: exp(α1) = relative incidence exposure group k: 12.037

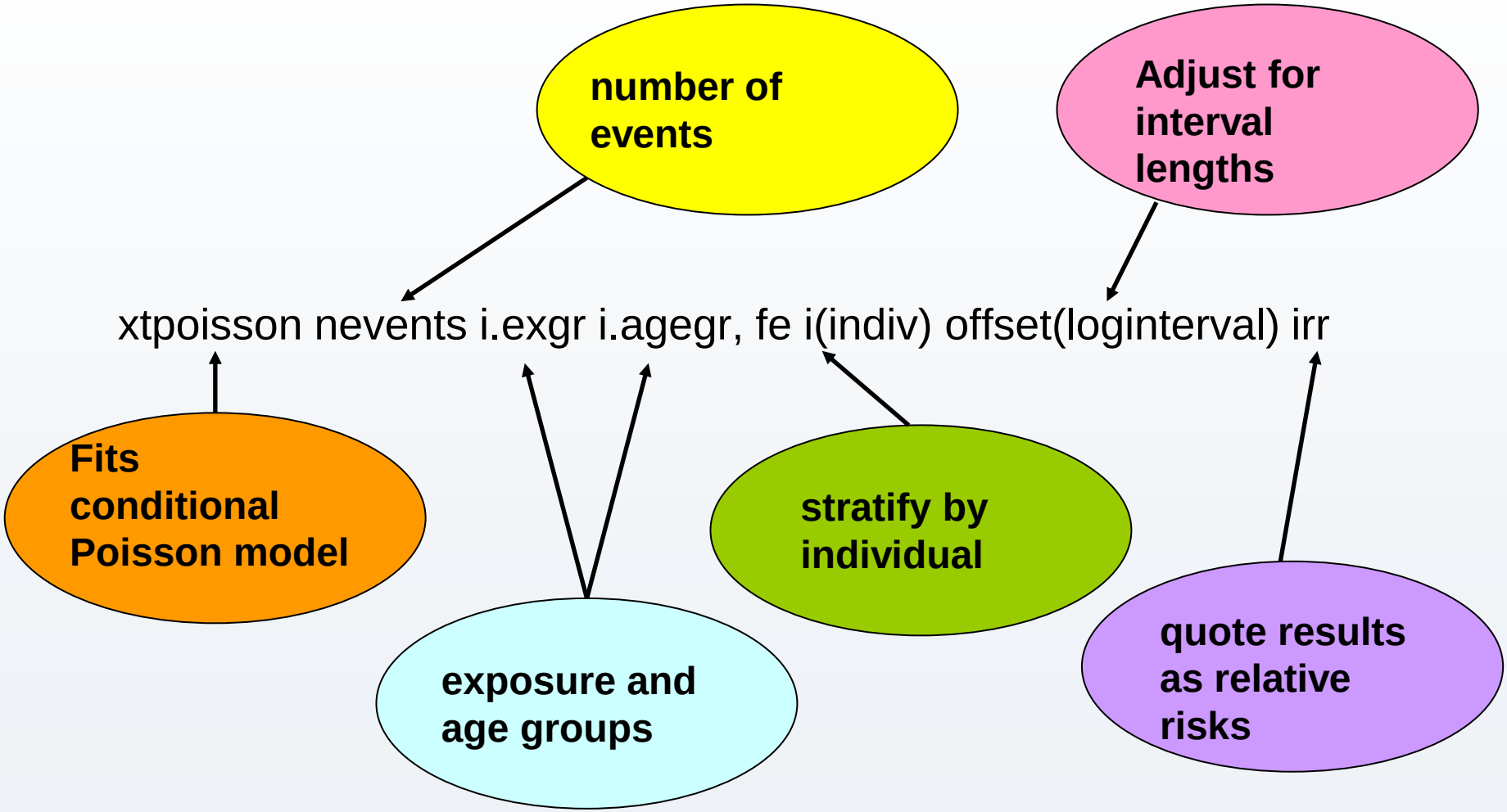
C: exp(β1) = relative incidence age group j: 0.225

OBS OBS

A: exp(Φi) = Baseline incidence of condition – eliminated!

Whitaker et al., *Statist. Med.* 2006, 25: 1768 – 1797

Statistical analysis in STATA



http://statistics.open.ac.uk/sccs

The assumptions and features of SCCS

1. Events must be:
   - Independently recurrent
   - Rare

2. Occurrence of an event should *not* (appreciably) affect subsequent exposures
   - Occurrence of an event should *not* (appreciably) increase mortality

3. Events cannot happened at exact same time or age

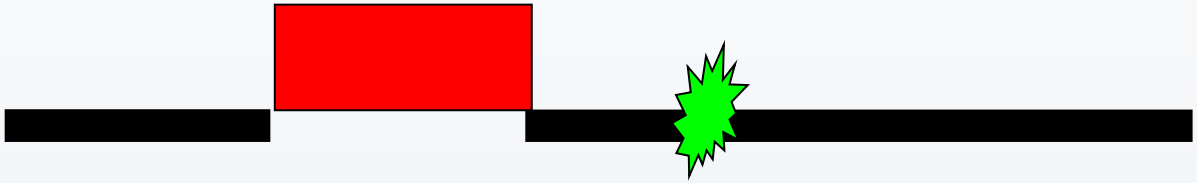
4. Does not produce estimates of absolute incidence

Assumption 1 - Events must be independently recurrent or rare

- The method was developed for *independent* recurrent events
- Bias is ignorable if the method is used with non-recurrent events with risk of occurrence < 10% over the observation period
- A test for independence has been developed (Farrington & Hocine, *Applied Statistics* 2010 59: 457 – 475)
- If events dependent – you can use just *first* event
  - fractures
  - MI

Assumption 2 - Occurrence of an event should not affect subsequent exposures

- Conditioning on full exposure histories is only valid provided events do not affect subsequent exposures



- In other words, exposure must be an exogenous variable (coming from outside a system)

Direction of bias

- The direction of bias is predictable:
  - If the event reduces the chance of exposure, the *Relative Incidence* will be biased upwards
  - If the event increases the chance of exposure, the *Relative Incidence* will be biased downwards
- This may be helpful to know

Assumption 2 - cont.

Occurrence of an event should not (appreciably) increase mortality

- The observation period is assumed to be independent of the event
- Failure of the assumption can cause bias, in an unpredictable direction
- However, see Farrington *et al*, *JASA* 2011, 106: 417 – 426

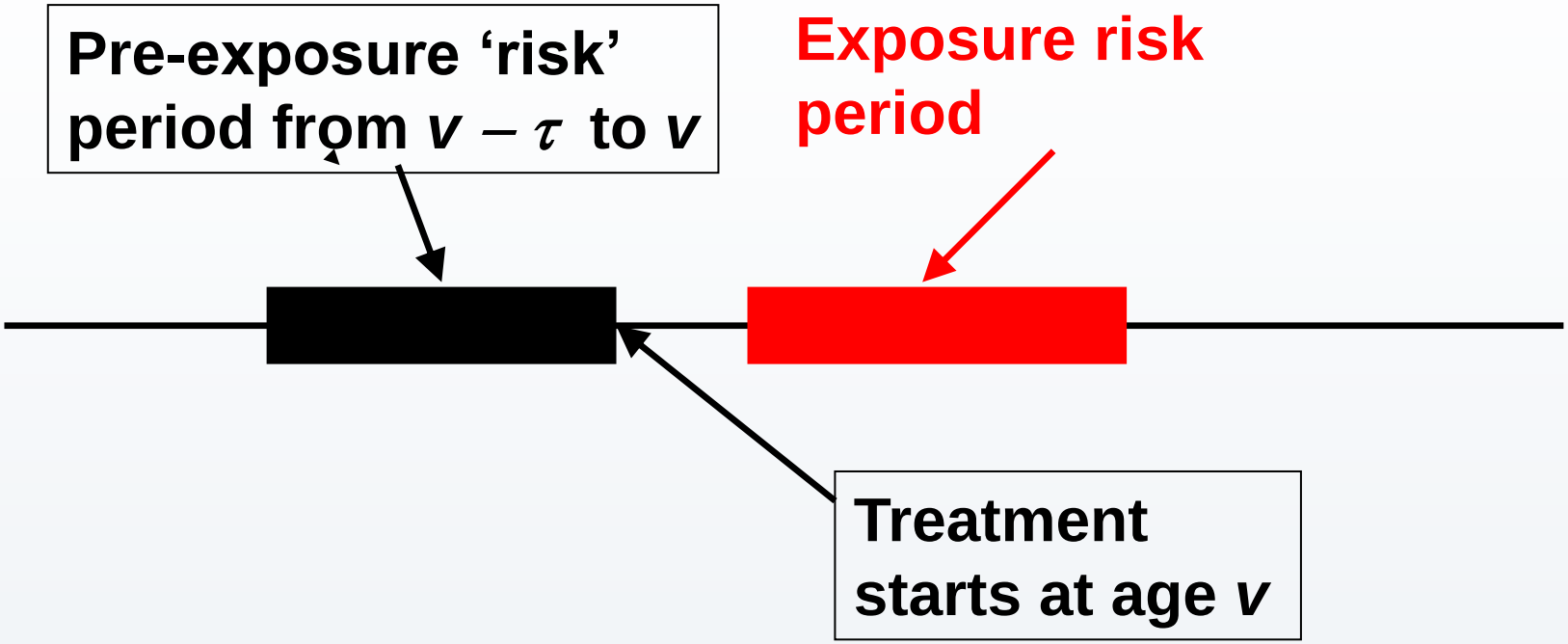
When can events influence subsequent exposures?

- Occurrence of an event may delay exposure:
  - Treatment (eg vaccination) may be deferred until recovery
- The event may be a contra-indication for treatment:
  - For example, intussusception and rotavirus vaccine
- If the event is death:
  - No subsequent observation can occur

Short-term impact

- The event may only temporarily delay exposure
- This will result in a deficit of events in that period
- The *RI* will be biased upwards
- This can be corrected by including a pre-exposure ‘risk’ period

Including a pre-exposure 'risk' period



Under suitable conditions, the trick of including a pre-exposure 'risk' window will correct the bias in the *RI*

Farrington & Whitaker 2006, *Applied Statistics*

Longer term dependence

- The pre-exposure ‘risk’ window trick only works if *t* is relatively short

- If it is not - then only post-treatment time can be used

Indication bias - Asthma exacerbation and flu vaccine

- Cohort and case series studies in asthmatic children
- Aged 1 – 6 years in 1995/6
- Risk period: 2 weeks after flu vaccine.

- Kramarz *et al, Arch. Fam. Med*. 2000, 9: 617 – 623

Asthma exacerbation and flu vaccine

Method	Sample size	*RI*	95% *CI*
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)

The cohort results are subject to indication bias? Children with severe asthma more likely to have flu vaccine?

Kramarz *et al, Arch. Fam. Med*. 2000, 9: 617 – 623

Asthma exacerbation and flu vaccine

Method	Sample size	*RI*	95% *CI*
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)
Case series	2075 cases	0.98	(0.76, 1.27)

The cohort results are subject to indication bias - The case series results are unaffected by this bias.

Summary

- SCCS builds on the cohort methodology
  - Event is random, exposure is fixed
- Ultimate matching (within individuals)
  - Cancel out all fixed characteristics
- Statistical powerful
- Beware of the assumptions

Self controlled case series methods: an alternative to standard epidemiological study designs

Irene Petersen,[1,2] Ian Douglas,[3] Heather Whitaker[4]

[1]Department of Primary Care and Population Health, University College London, London NW3 2PF, UK

[2]Department of Clinical Epidemiology, Aarhus University, Aarhus N, Denmark

[3]London School of Hygiene and Tropical Medicine, London, UK

[4]Department of Mathematics and Statistics, Open University, Milton Keynes, UK

Correspondence to:
I Petersen i.petersen@ucl.ac.uk

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2016;354:i4515
http://dx.doi.org/10.1136/bmj.i4515

Accepted: 24 July 2016

The self controlled case series (SCCS) method is an epidemiological study design for which individuals act as their own control—ie, comparisons are made within individuals. Hence, only individuals who have experienced an event are included and all time invariant confounding is eliminated. The temporal association between a transient exposure and an event is estimated. SCCS was originally developed for evaluation of vaccine safety, but has since been applied in a range of settings where exact information on the size of the population at risk is lacking or

such as cohort and case-control studies, have been widely applied in medical research (see supplementary web table w1). There are several situations, however, where standard epidemiological study designs fall short. For example, in the research of adverse effects of vaccines it can be difficult to identify suitable comparison groups (eg, if most of the population receives the vaccine). Likewise, studies on hospital data may not have information on the exact catchment areas and hence it is a struggle to find suitable controls for cases of a particular event. In these situations the self controlled case series (SCCS) method provides an alternative epidemiological study design to investigate the association between a transient exposure and an outcome event. The SCCS method is a case only method; it has the advantages that no separate controls are required and any fixed confounder is automatically controlled for.[2 3]

In this paper we provide an overview of SCCS methodology and some examples of how the method has been applied, in order to give an idea of the potentials

References

- Farrington, CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 51, 228 – 235, 1995
- Whitaker, HJ. *et al*. Tutorial in biostatistics: The self-controlled case series method. Statistics in medicine. *Stats in medicine* 2006, 25: 1768 – 1797
- Farrington, CP. & Hocine MN. Within-individual dependence in self-controlled case series models for recurrent events. Journal of the Royal Statistical Society Series C 2010: 59: 457-475
- Farrington, CP. *et al.* Self-controlled case series analysis with event-dependent observation periods. *Journal of the American Statistical Association* 2011;106: 417-426
- Kramarz et al. Does influenza vaccination exacerbate asthma. *Arch Fam Med* 2000; 9: 617-623
- Petersen et al. Self controlled case series methods: an alternative to standard epidemiological study designs BMJ 2016

Case-crossover approach

- Based on case-control methods
- Exposures in the period immediately preceding the event are compared to exposures at earlier ‘control’ times

- Assumptions – exposure distribution in successive time periods is exchangeable – i.e. cannot account for change in effects of age.

- Maclure M. The case-crossover design: A method for studying transient effects on the risk of acute events AJE 1991: 133(2):144-153
- Greenland S. A unified approach to the analysis if case-distribution (case-only) studies. Statistics in Medicine 1996: 18:1-15.