MONASH University

Self-controlled case-series method

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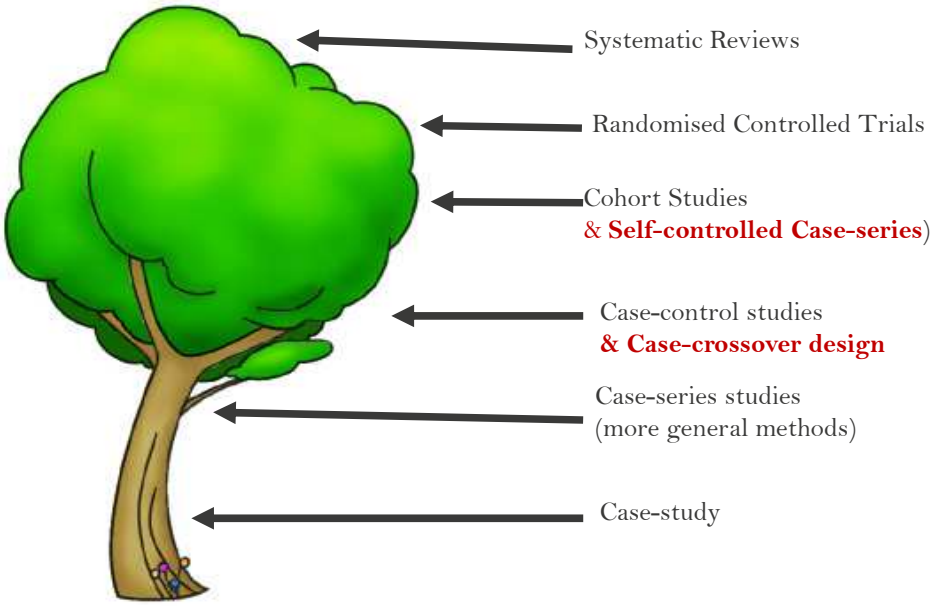
Objectives

- To describe the self-controlled case-series method
- Highlight possible uses of SCCS within registry based research
- Demonstrate use of SCCS using examples
- Describe the difference between SCCS & case-crossover design
- Name some extensions of the SCCS method

Hierarchy of research Evidence *(effectiveness)*



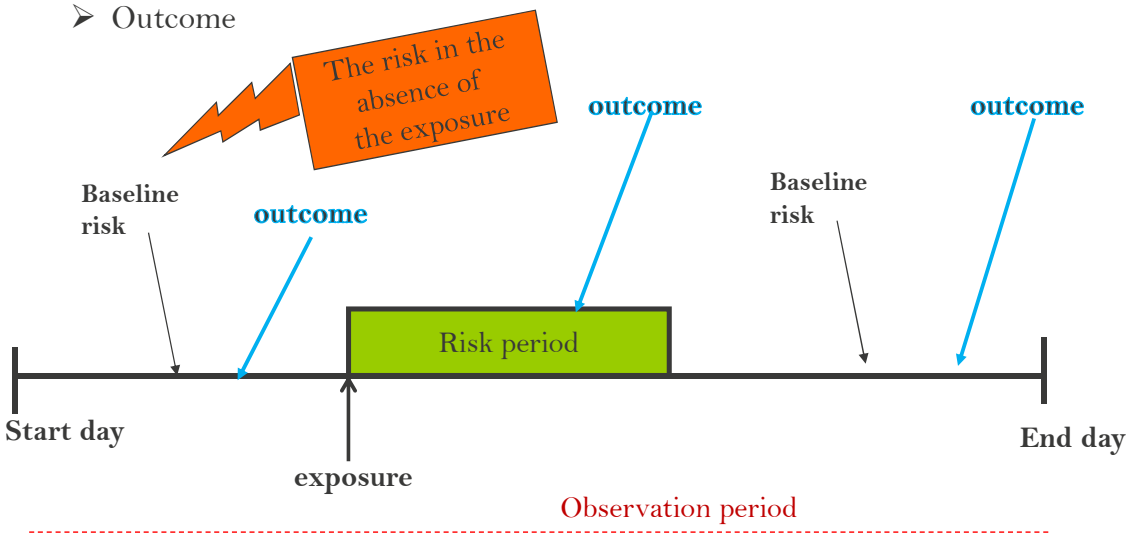
WHAT IS SCCS?

- When? **Time-varying exposure** ⟷ **Acute/non-acute outcomes**

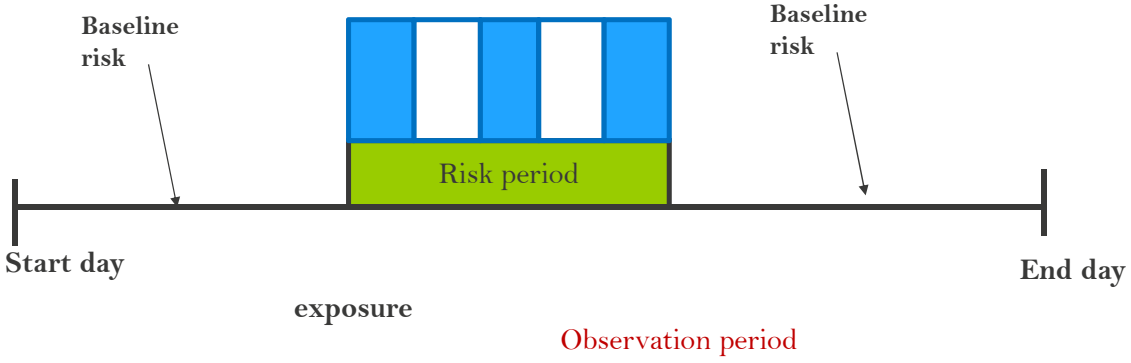
- Cases only
- Case acts as its own control
- Can include only exposed cases
- Analysis time can be age or calendar time

3 important phases

- Baseline risk period
- Exposure period
- Outcome



- An advantage is that the risk period can be cut into smaller intervals



Assumptions of the method

- Outcomes are either recurrent and independent or non-recurrent and rare.
  - If unsatisfied, can consider only the 1st occurrence if it is rare
  - If events cluster into episodes and episodes can be assumed independent, then the first event in each episode can be considered.
- The occurrence of an event does not affect subsequent exposures.
  - Can use the method only if the event affects exposure for a short time

Assumptions of the method (cont'd)

- The occurrence of an event should not censor or affect the rest of the observation period.
  - Alternative analysis methods if outcome censors observation period e.g. death
- Effect of the exposure is confined to a finite risk period.
  - Method can be used as long as there are sufficient unexposed cases

Why use SCCS?

- Control of fixed confounders (e.g. sex, genetic make up), hence reduces residual confounding.
- Can include other covariates in the analysis
- Good power, quick and relatively easy

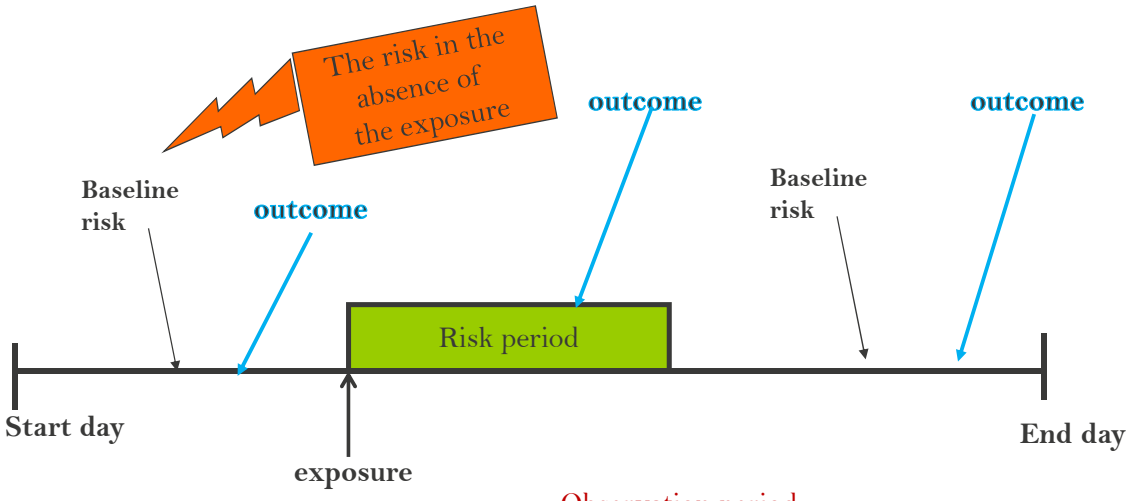
Usefulness within registries

- Registries contain only cases and can have challenges of finding controls for registry research can be overcome as cases act as own controls
- When important, fixed confounders are not recorded
  - E.g. Danish National Prescription Registry when cardiovascular outcomes were assessed among patients prescribed ephedrine–caffeine for weight loss but data on BMI and lifestyle habits such as smoking were not recorded in the registry *(Hallas 2008)*
- Requires small sample sizes
  - Might not be a big problem in registries
  - Useful for rare side-effects or secondary outcomes

Common uses of SCCS

- Pharmocoepidemiology post-approval stage
- Vaccine safety studies
- Exploration of drug side-effects or triggers of acute outcomes
- Examples from recent years:
  - Acute infections and cardiovascular diseases *(Corrales-Medina et al, 2009)*
  - Use of Prescription Medications and the Risk of Motor Vehicle Crashes *(Gibson et al, 2009)*
  - myocardial infarction and stroke following exacerbation of COPD *(Donaldson et al, 2010)*
  - hospitalization for stroke after antipsychotic use in the elderly *(Pratt et al, 2010)*

Analysis using SCCS



- Sample size calculation
  - Number of events required *(Musonda et al, 2006)*
  - Need: power of study, significance level, proportion exposed (total population), ratio of risk period to the observation period, log relative incidence associated with exposure
- Outcome measure
  - Relative incidence or Relative hazard
- Method of analysis
  - Conditional Poisson regression
- Can include covariates that are age or time dependent such as seasonality and time-invariant covariates interactions with time

EXAMPLE 1

Source: Gwini et al. The effect of influenza vaccination on risk of acute myocardial infarction: Self-controlled case-series study. Vaccine 29 (2011) 1145–1149

- **Objective:** to establish the incidence of acute myocardial infarction after influenza vaccination

Outcome

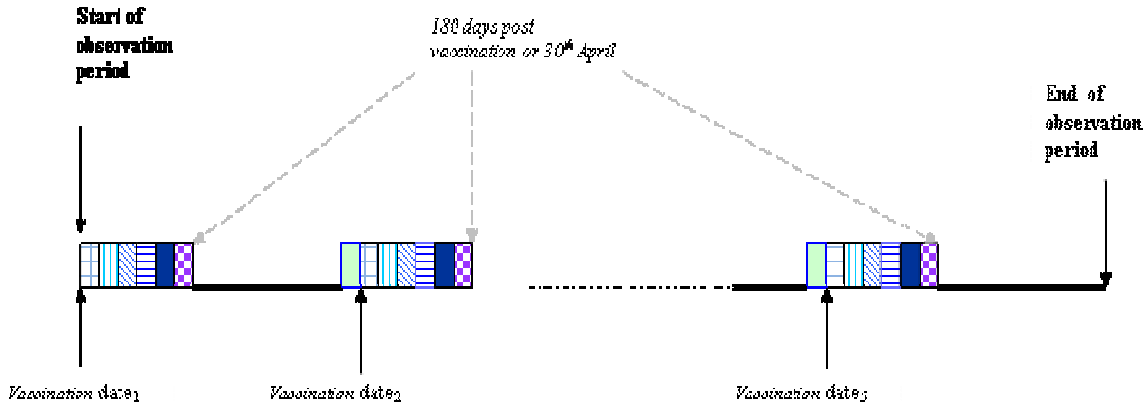
Exposure

- **Source of data:** UK General Practice Research Database
- **Observation period:** From 1st vaccination on/after 01/09/2002 to 31/05/2007 (i.e. only vaccinated cases)

- **Time-line:** Calendar time (dates)

- **Risk periods:** Post vaccination 15-28 days; 29-59 days; 60-90 days; 91 – 120 days; 121 -180 days

- **Baseline period:** time between 180 days after vaccination or the following 30th of April (whichever came first) and 14 days before next vaccination



- **Adjusted** for seasonality (September to November; December to February; March to May and June to August), gender, age at baseline (≤ 49 years, 50–64 years and ≥ 65 years)
  - Also conducted separate analysis for late and early vaccination (results not presented)
- **Study group**: aged 40 years and above at AMI diagnosis, registered with that same general practice for at least 5yrs before AMI diagnosis

Risk period (days)	Number of cases		Time at risk (person years)	Adjusted	
	N	(%)	N	IRR[2]	95% CI
Baseline	3913	47.8	16898	1.00	--
15-28 days	289	3.5	1410	0.75	(0.66 to 0.86)
29 – 59 days	703	8.6	3106	0.82	(0.75 to 0.90)
60 – 90 days	826	10.1	3073	0.96	(0.87 to 1.07)
91 – 120 days	762	9.3	2926	0.98	(0.89 to 1.09)
121 – 180 days	1273	15.6	5290	1.02	(0.95 to 1.10)

EXAMPLE 2

Source: Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza Infection and Risk of Acute Myocardial Infarction in England and Wales: A CALIBER Self-Controlled Case Series Study. *J Infect Dis*, 2012; **206**(11):1652-1659.

- **Objective:** To investigate whether acute respiratory infections likely to be caused by influenza were more liable than other infections to trigger AMI
- **Source of data:** UK GPRD (e.g. demographic and lifestyle factors, illness consultations) and a cardiac disease registry, the Myocardial Ischaemia National Audit Project (MINAP) (identification of cases)
- **Outcome:** 1st AMI recorded on the MINAP over the observation period.

- **Observation period:** 1 January 2003 through 31 July 2009
- **Risk periods:** 1–3, 4–7, 8–14, 15–28, and 29–91 days following an acute respiratory consultation
- **Baseline periods:** All other time excluding 14days before consultation
- **Variables adjusted for**: age and for season in 3-month blocks (ie, January–March, April–June, July–September, and October–December)

Table 2.
Age- and Season-Adjusted Incidence Ratios for Acute Myocardial Infarction (AMI) Occurring After Acute Respiratory Infection (ARI) Overall and by Sex, Age, Infarction Type, and History of Vascular Disease

Model	Adjusted Incidence Ratio (95% Confidence Interval), by Period of Infection Risk in Days[a]						
	1–3 (n = 52)	P[b]	4–7 (n = 44)	8–14 (n = 48)	15–28 (n = 80)	29–91 (n = 262)	Baseline (n = 3441)
Overall	4.19 (3.18–5.53)		2.69 (1.99–3.63)	1.66 (1.24–2.23)	1.41 (1.12–1.77)	1.05 (.92–1.21)	1.00
Sex							
Men	4.32 (3.02–6.19)	.82	2.01 (1.28–3.16)	1.28 (.83–1.97)	1.39 (1.03–1.89)	0.99 (.82–1.19)	1.00
Women	4.05 (2.62–6.27)		3.66 (2.45–5.46)	2.22 (1.50–3.29)	1.44 (1.01–2.06)	1.16 (.94–1.43)	1.00
Age, y							
<60 y	1.46 (.47–4.55)		1.46 (.54–3.91)	1.88 (.97–3.65)	1.50 (.88–2.56)	0.84 (.59–1.21)	1.00
60–69 y	3.93 (2.15–7.18)	.13[c]	1.89 (.89–4.00)	1.09 (.51–2.30)	0.96 (.54–1.71)	1.03 (.77–1.38)	1.00
70–79 y	4.14 (2.47–6.95)	.1[c]	3.55 (2.18–5.78)	2.31 (1.45–3.66)	1.81 (1.23–2.65)	0.96 (.73–1.26)	1.00
≥80 y	5.94 (3.90–9.04)	.023[c]	3.18 (1.93–5.25)	1.40 (.79–2.48)	1.35 (.88–2.07)	1.31 (1.04–1.66)	1.00
Infarction type							
STEMI	4.66 (3.04–7.15)	.53	1.76 (.97–3.21)	1.77 (1.12–2.80)	1.13 (.74–1.71)	0.98 (.78–1.23)	1.00
NSTEMI	3.89 (2.71–5.60)		3.25 (2.30–4.60)	1.60 (1.10–2.33)	1.58 (1.20–2.09)	1.10 (.93–1.31)	1.00
History of vascular disease							
No	4.32 (3.10–6.02)	.73	3.00 (2.12–4.25)	1.68 (1.18–2.39)	1.37 (1.03–1.82)	0.99 (.83–1.17)	1.00
Yes	3.89 (2.35–6.42)		2.03 (1.11–3.69)	1.62 (.97–2.72)	1.49 (1.00–2.21)	1.19 (.95–1.51)	1.00

SCCS vs. CASE-CROSSOVER DESIGN

CSSC

- Identify exposure and compare the likelihood of outcome in 'at risk' and 'control' periods.
- Mirrors cohort design
- Compare all the risk periods in the observation period i.e. include both before & after outcome

Case cross-over

- Identify outcome and compare probability of exposure in hazard and control periods just before outcome
- Mirrors case-control design
- Compare only risk periods immediately before outcome, usually hours or days

CSSC	Case cross-over
▪ Can allow for indefinite exposure	▪ Does not allow for indefinite exposures
▪ Allows for recurrent events in the model	▪ Require modified analysis for recurrent events *(Luo, 2007)*
▪ Allows for changes in risk over time	▪ Not amenable if probability of exposure is time dependant

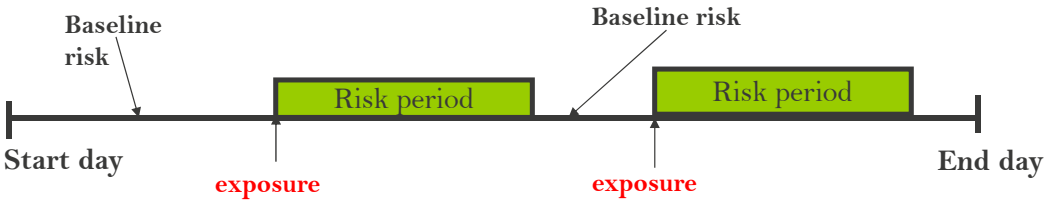
Smeeth L, et al. The use of primary care databases: case–control and case-only designs. Family Practice 2006; 23: 597–604.
Luo & Sorock. Analysis of recurrent event data under the case-crossover design with applications to elderly falls. Statist. Med. 2007; 00:1–22

Variations of the method

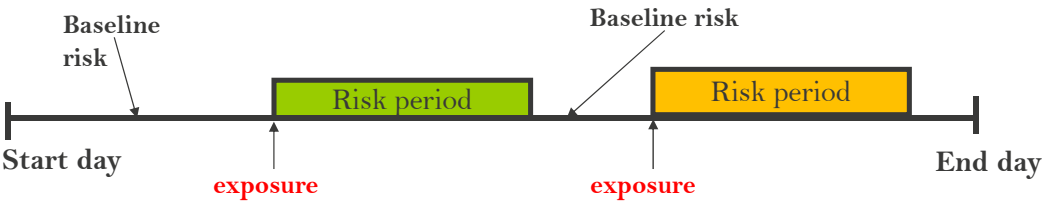
- **Multiple risk periods**
  - Useful when the effect of exposure varies significantly over time
- **Multiple events/outcomes**
  - Recurring events
  - Importantly: the occurrence of one event should not affect the occurrence of subsequent events

➢ Can include repeat exposures e.g. repeat vaccinations, repeat prescriptions

1. *Can either assume that the risk after each exposure is equal and hence give them same levels e.g. Gwini et al.*



2. *Or assume that the risk after every exposure is different and give separate levels*



➢ Multiple exposures

- Can be used to establish the association between outcome and two or more exposures e.g. multiple vaccines
- E.g. in the study by Warren-Gash, they assessed risk of AMI following influenza-like infections and other infections.

➢ Event affects post-event exposure

- Use modified CSSC method (Farrington, 2009)

Refer to http://statistics.open.ac.uk/sccs/papers.htm for more variations

Limitations of the method

- The probability of exposure need not be affected by occurrence of outcome/event
- If the outcome is non-recurrent, then the event risk has to be small over the observation period
- The method fails if time and age do not vary

Bibliography

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THANK YOU !!!