6.3 Other controlled designs

Case-crossover design

- Introduced in 1991 (Maclure*)

(for studying ” transient effects on the risk of acute events”)

- compares the exposure of a case just before the episode or diagnosis of their disease to their exposure status at a previous comparable time interval

- design arose from difficulties with identifying a suitable control group!!

(Research question: why MI risk higher in the morning)

Maclure M, Am J Epidemiol, 133:144–53, 1991
Reprint with commentary: Am J Ep, 185:1174-1183, 2017.

Case-crossover design (continued)

Scientific way to answer the question "why now?" rather than the usual "why me?“

Initially widely used for vaccine studies (adverse events)

also traffic accidents, environmental pollution, extreme weather (snowfall & temperature Gan AJE 2020), …..

Case-crossover design (continued)

1.Advantage: adjusts for individual/genetic effects

2. Disadvantage: difficulty choosing ”reference period”

1. ➡ confounding by fixed covariates removed

2. ➡ many potential sources of selection, information and confounding bias (e.g. “recall bias” maybe still present)

Summary of strengths and weaknesses in *Redelmeier, JCE, 2013*

Analysis of case-crossover design

Paired data! We already have the tools

Paired OR, conditional logistic regression as for paired case-control study, likelihood:

$$\Pi_{i=1}^{N} \frac{exp^{\beta(X_{i1}-X_{i0})}}{1+exp^{\beta(X_{i1}-X_{i0})}}$$

X_1, X_0 now exposures of the case in the two periods

Case time-control design*
(to remove time trend)

$\rightarrow time \rightarrow$

Time	T_0	T_1
Exposure	X_0	X_1
Outcome:		
Case	0	1
Control	0	0

Analysis: conditional logistic regression (T=0, 1 as outcome!)
Interaction with time (for case pair)

* *Suissa, Epidemiology 1995*

Illustration: Case case-time-control*

beta-agonist use and asthma

	OR (95% C.I.) **controls**	**OR** (95% C.I.) **cases**
Dichotomous		
Case-crossover		3.2 (1.5 - 6.8)
Case-time-control	2.6 (1.6 - 4.1)	1.2 (0.5 - 3.0)
Continuous		
Case-crossover		2.8 (1.6 - 4.5)
Case-time-control	1.6 (1.2 - 2.2)	1.7 (0.9 - 3.0)

Analysis: conditional logistic regression (T=0, 1 as outcome!)

* *Suissa, Epidemiology 1995*

Case-case-time-control design*

Similar to case-time-control

but

Controls are chosen from ”future” cases

Reduces bias due to changes in exposure prior to disease

* *Wang et al,* Epidemiology, 22:568–74, 2019.

Self-Controlled Case-Series*

Like case-crossover, uses only cases

Unlike case-crossover, subjects can have more than one event

Developed to investigate if meningitis associated with MMR vaccine (difficulty in identifying suitable controls, but all vaccination records available)

Method highlighted risk of meningitis approximately 2-3 weeks after vaccination with a specific MMR vaccine, resulting in a change in the MMR vaccines used for young children in the UK

Whitaker et al. Tutorial in biostatistics: the self-controlled case series method. Stat Med, 25:1768–1797, 2006.

Includes STATA code

”Quasi Cohort” in pharmacoepidemiology
(for acute effects)

- select all events from a cohort, with their exposure at the moment/day of the event
- Random sample of ”person-moments” from whole cohort or from risk set defined by the event time
- Reweight sample to represent the whole cohort

Obtain: incidence rates

rate ratios

adjusted rate ratios

Suissa, Epidemiology, 2015.

”Quasi Cohort” (continued)

Reweighting (same idea as we saw in earlier lectures)

		Full Cohort Analysis	
Exposed	Outcome Events	Person-moments	Rate of Outcome per Person-moment
Yes	x_1	N_1	x_1 / N_1
No (reference)	x_0	N_0	x_0 / N_0
Total	x	N	x / N
		Quasi-cohort Analysis[a]	
Exposed	Outcome Events	Quasi Person-moments	Quasi-rate of Outcome per Person-Moment
Yes	x_1	n_1	$(n/N)\,(x_1 / n_1)$
No (reference)	x_0	n_0	$(n/N)\,(x_0 / n_0)$
Total	x	n	$(n/N)\,(x / n)$

Illustration from Suissa

To illustrate the quasi-cohort approach, I use a cohort of patients with COPD formed from the health insurance databases of the province of Quebec, Canada.[10] This cohort includes 163,514 patients newly treated during 1990–2005 and followed through 2007, with 20,344 who had the outcome event of hospitalization for pneumonia during the 5.4 years of follow-up (overall incidence rate 24.4/1000/year). The study question is whether inhaled corticosteroids increase the risk of serious pneumonia. Because the relevant risk under study is suspected to occur only under current use and disappear once exposure is halted, and given that inhaled corticosteroids are often used irregularly, it is crucial to measure exposure on a daily basis, making the day the time-unit of analysis. Because the cohort generates an incidence density of 304,646,593 person-days of follow-up and involves several time-varying variables, a quasi-cohort approach is inevitable. For the purpose of the illustration, I selected a four-fold quasi-cohort (size four times the number of outcome events) as a random sample of 81,376 person-moments from the cohort

Illustration (continued)

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Illustration continued (from Table 3 in Suissa)

	No. With Pneumonia	No. Quasi-cohort Person-days	Quasi-rates[a] (per 1000 Person-years)	Crude Quasi-rate Ratio
		Quasi-cohort size: one-fold		
Number	20,344	20,344		
Inhaled corticosteroid use				
No use[c]	9,453	12,201	18.9	1.00
Current use	7,636	4,559	40.9	2.16
Discontinued use	3,255	3,584	22.2	1.17
		Quasi-cohort size: four-fold		
Number	20,344	81,376		
Inhaled corticosteroid use				
No use[c]	9,453	49,267	18.7	1.00
Current use	7,636	18,082	41.2	2.20
Discontinued use	3,255	14,027	22.6	1.21

Adjusted estimates from logistic regression

”Test negative” designs for vaccine efficiency (e.g., measured as reduced patient visits/admissions)

Widely used for many years in studies of flu vaccines

Standard cohort study:

compare outpatient flu visits in vaccinated vs. unvaccinated

Standard case-control study:

compare vaccination rate in patients seeking care for flu to persons not seeking such care.

Biases/Problems?

”Test negative” design

By sampling only from those seeking care for an acute respiratory infection, the idea is to *estimate the OR of vaccination among those who would seek care for flu.*

VE represented by odds ratio of vaccination among subjects testing positive for influenza to subjects testing negative.

Analogy to the “indirect cohort design” (also for **VE**)
e.g. persons with pneumococcal disease classified according to whether they were infected with a pneumococcal serotype covered by the vaccine or with a serotype not covered by the vaccine.

Can be bias from severity of disease
(Ciocanea-Teodorescu et al AJE 2021)

Test-negative design important for studies of Covid vaccine efficiency

Comparison with other case-control designs:

Vandenbroucke&Pearce Epidemiology 2019

Studies of different vaccines, regimes (3 doses vs 2) different variants:

BMJ, NEJM, JAMA, Lancet (many articles 2021-2022)

Challenges:

Calendar time is an important confounder (*Dean et al AJE, 2020*)

Various sources of bias but good article in epi literature

”Negative controls” for detecting confounding and bias

Idea:

choose negative controls so effect of interest would be impossible by the hypothesized mechanism

Logic discussed in *Lipschitz et al, Epi, 2010*

Negative controls for exposure or for outcome:
Extensive DAGS in *Arnold et al. Epidemiol 2016.*

Selection Bias Structure

outcome

exposure

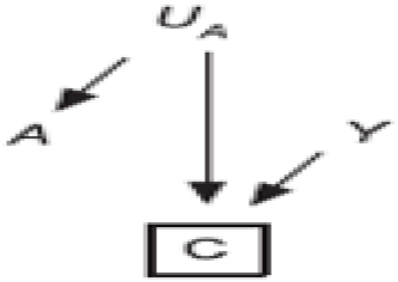
selection

A

Bias introduced by selection that depends on

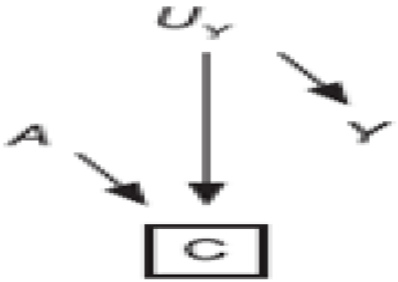
exposure and outcome

B



outcome and a cause of exposure

C



exposure and a cause of outcome

D

a cause of exposure and outcome

Choice of negative controls:

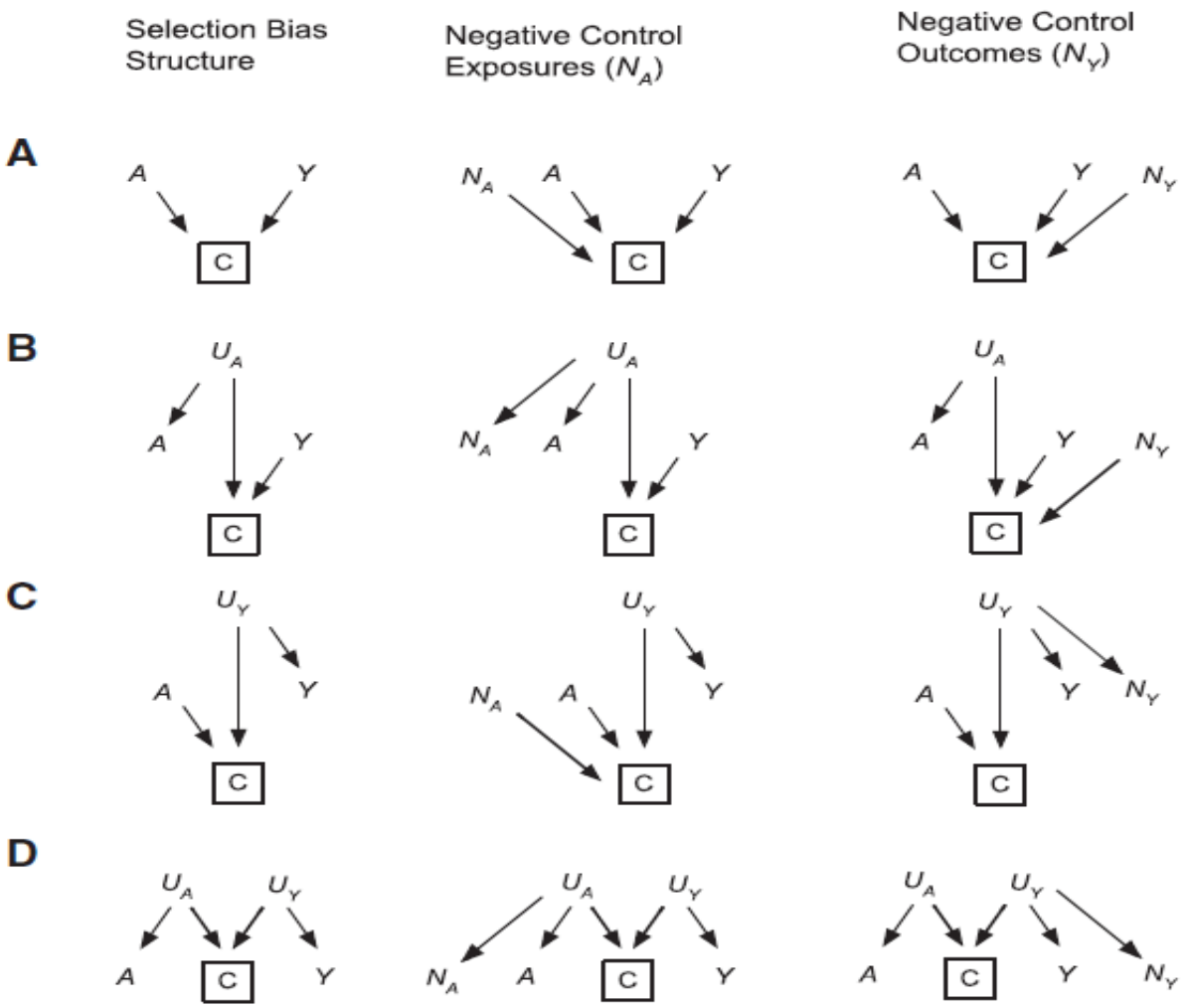


FIGURE 1. Simplified causal diagrams of selection bias for exposure *A* and outcome *Y* along with negative control exposures (N_A) and outcomes (N_Y). In all four structures, selection bias results from conditioning on *C*, a common descendant of (A) exposure *A* and outcome *Y*, (B) cause of exposure U_A and outcome *Y*, (C) exposure *A* and cause of outcome U_Y, or (D) cause of exposure U_A and cause of outcome U_Y.

Examples of published studies*

(type of bias on previous causal diagram)

Study	Exposure	Outcome	Potential bias	Negative control
Ivers et al. Lancet Glob Health, 2015	Oral cholera vaccine	Diarrhea stool positive for cholera	Selective enrollment cases vs. Controls (1A)	Noncholera diarrhea
De Groot et al Eur J Epi 2014	Use of ACE inhibitors, statins, PPI	Community acquired pneumonia	Selective enrollment among hospitalized patients (1B)	Selective serotonin reuptake inhibitors
Zaadstra et al. Mult Scler, 2008	Viral infections in early childhood	Multiple sclerosis	More accurate exposure recall among cases (2B)	Broken arm, concussion, tonsillectomy

** Arnold et al. Negative Controls to Detect Selection Bias and Measurement Bias in Epidemiologic Studies. Epi Sept 2016.*

Negative controls in perinatal epidemiology*

International Journal of Epidemiology, 2018, Vol. 47, No. 2

Table 1. Selected examples of studies which have used negative control exposure methods

Exposure	Negative control exposure	Outcome(s)
Maternal smoking	Paternal smoking	Offspring outcomes: Inattention/hyperactivity[15,20] Obesity/adiposity[16,22–24] Blood pressure[17] Gestational diabetes[21] ADHD symptoms[19] Cognitive development[18] Offspring psychotic symptoms[46]
Maternal psychosocial stress	Paternal psychosocial stress	Offspring vascular function[54]
Maternal smoking during pregnancy	Maternal smoking after pregnancy	Offspring respiratory outcomes[39] Offspring psychotic symptoms[46]
Maternal alcohol consumption during pregnancy	Maternal alcohol consumption before pregnancy	Offspring ADHD symptoms[40]
Maternal BMI/obesity	Paternal BMI	Offspring BMI/adiposity[26–33] Offspring cognitive and psychomotor development[55]
Length of pre-birth inter-pregnancy interval	Length of post-birth inter-pregnancy interval	Risk of schizophrenia in the offspring[56]
Folic acid supplements in pregnancy	Other supplements in pregnancy	Autism spectrum disorders[37]

** Sanderson et al Int J Epi 2018 Negative control exposure studies in the presence of measurement error.*

”Active comparators” in self-controlled designs*

Similar idea to negative controls,
but look for similar (as opposed to null) effect

case-crossover, case-time-control, self-controlled case series

Example in paper by Hallas et al*:

- study of association between penicillin and VTE
- Confounding by indication (UTI)
- Used roxithromycin, as “active comparator”
- Ratio of effects approx 1.

* *Hallas et al, AJE, 2021*