Using negative control outcomes to identify biased study design: A self-controlled case series example

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Agenda

I. Introduction
II. Self-controlled case series for population-level effect estimation
III. Methods
IV. Results
V. Discussion

I. Introduction

	Methodological development	Open-source analytics development	Clinical applications
Observational data management			
Clinical characterization			
Population-level effect estimation			
Patient-level prediction			

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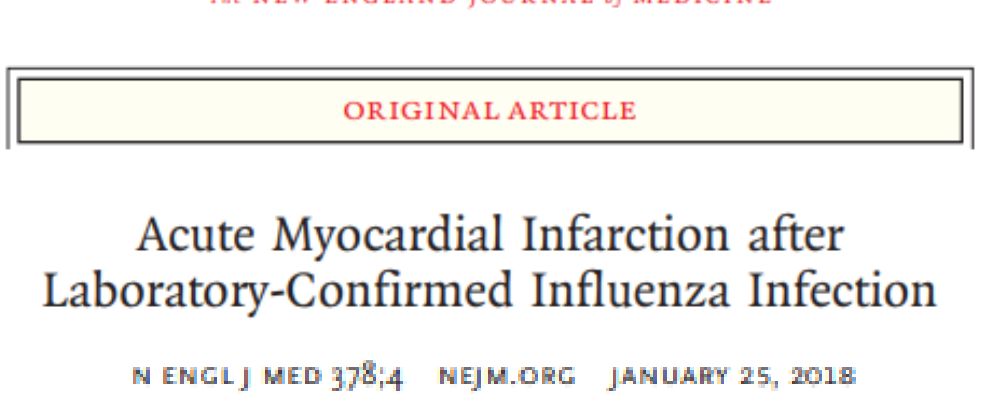
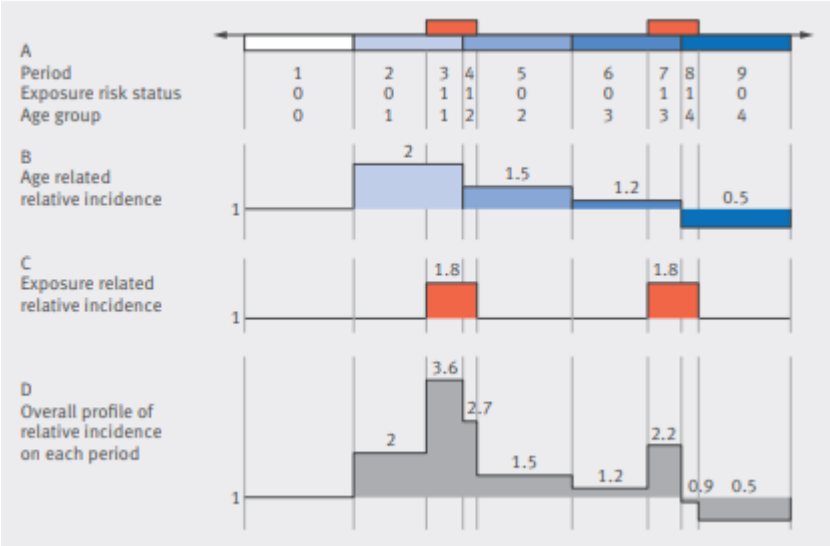
I. Introduction

- **Clinical application**
  - Does influenza cause acute myocardial infarction?
  - IRR = 6.05 (3.86 – 9.50)



- **Population-level effect estimation (PLE)**
  - Self-controlled case series (SCCS)
  - https://www.bmj.com/content/354/bmj.i4515

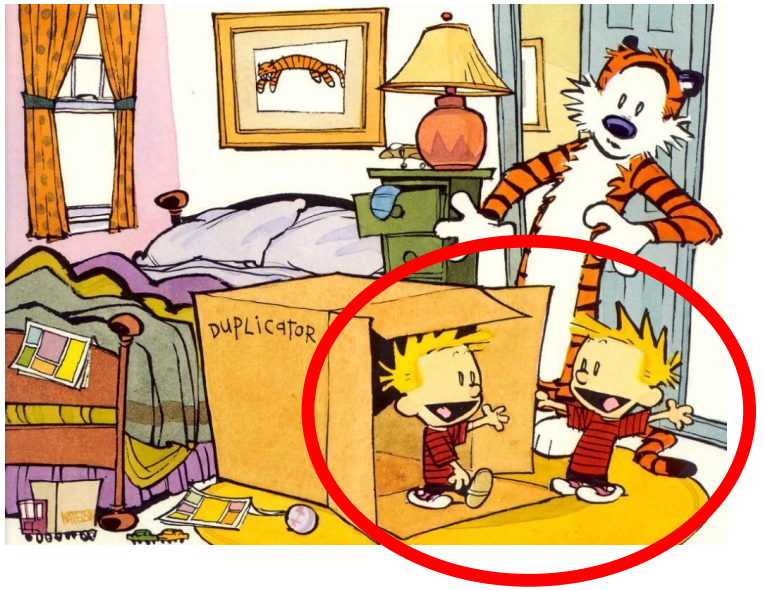


BMJ 2016;354:i4515

II. SCCS for PLE

- **Population-level effect estimation**
  - Epidemiologic methods for causal inference
  - Estimating unbiased, average treatment effect
  - Goal: compare outcomes between an exposed population and its counterfactual approximation

II. SCCS for PLEE



- **Population-level effect estimation**
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  - Goal: compare outcomes between an exposed population and its counterfactual approximation

II. SCCS for PLEE

- **Self-controlled case series**
  - Effect estimation: does T cause O?
  - Compares outcomes *within* persons during time periods of differing risk (e.g. exposed time vs unexposed time)
  - Unexposed time = counterfactual approximation of exposed population

II. SCCS for PLEE

- **Self-controlled case series**
  - Self-controlled: a patient is their own control
  - Cases only: intersection of exposed and outcome cohorts
  - Compares outcome incidence during a risk period (e.g. exposed time) to other time (e.g. unexposed time) during study window
  - When events occur relative to risk period *given that event(s) occurred*

III. Methods

- **Kwong et al., N Engl J Med 378;4:345-353.**
  - T: Highly specific, laboratory-confirmed influenza diagnosis
    - Flu and Other Respiratory Viruses Research Cohort
    - Specimens from routine clinical care, research, outbreak investigation
  - O: Primary, inpatient myocardial infarction (not same visit as flu dx)
    - Discharge Abstract Database, National Ambulatory Care Reporting System, Same-Day Surgery Database, Ontario Health Insurance Plan
  - Risk interval: 7 days following influenza diagnosis
  - Study period: 1 year before to 1 year after influenza diagnosis
  - Multiple sensitivity analyses

III. Methods

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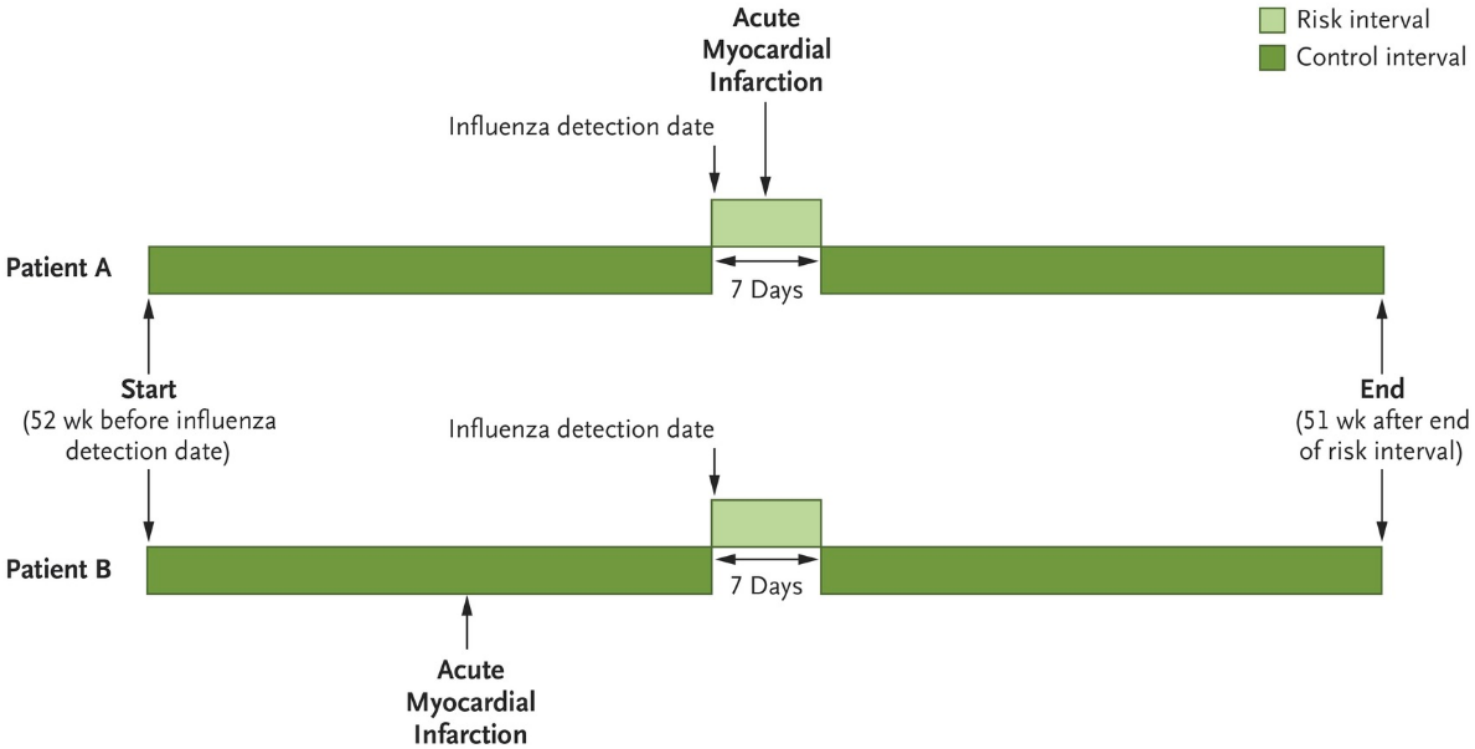

IV. Methods

- **Best faith replication**
  - T: Visit occurrence with influenza diagnosis, no outcome code, no influenza diagnoses in last 60 days
    - Truven Health MarketScan Commercial Claims and Encounters Database
    - Truven Health MarketScan Medicare Supplemental and Coordination of Benefits Database
  - O: Inpatient visit occurrence with primary, acute myocardial infarction (not same visit as flu dx)
  - Risk interval: start - influenza visit end, influenza visit start + 7 days
  - Study period: 1 year before to 1 year after influenza diagnosis
  - Multiple sensitivity analyses
  - **Negative control outcomes: lung cancer, ingrowing nail, T2DM, renal impairment, acute liver injury, HIV, anemia, depression**

IV. Results

- **CCAE**

	Kwong et al.			Replication		
Outcome	**IRR**	**95% CI lower**	**95% CI upper**	**IRR**	**95% CI lower**	**95% CI upper**
AMI	6.05	3.86	9.50			
T2DM	NULL	-	-			
Lung cancer						
Ingrowing nail						
Renal impairment						
Acute liver injury						
HIV						
Anemia						
Depression						

IV. Results

- **CCAE**

	Kwong et al.			Replication		
Outcome	**IRR**	**95% CI lower**	**95% CI upper**	**IRR**	**95% CI lower**	**95% CI upper**
AMI	6.05	3.86	9.50	3.76	3.16	4.43
T2DM	NULL	-	-	5.36	4.82	5.95
Lung cancer						
Ingrowing nail						
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IV. Results

- **CCAE**

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Outcome	**IRR**	**95% CI lower**	**95% CI upper**	**IRR**	**95% CI lower**	**95% CI upper**
AMI	6.05	3.86	9.50	3.76	3.16	4.43
T2DM	NULL	-	-	5.36	4.82	5.95
Lung cancer				4.02	3.07	5.16
Ingrowing nail				5.93	1.44	16.05
Renal impairment				9.45	8.74	10.20
Acute liver injury				15.94	12.69	19.76
HIV				8.91	6.42	12.03
Anemia				5.08	4.26	6.01
Depression				1.22	1.05	1.40

V. Discussion

- Replication showed similar acute myocardial infarction results across all analysis variants
  - Lesser magnitude of positive effect

- Replication showed conflicting T2DM results across all analysis variants
  - Strong positive effect rather than null

V. Discussion

- Replication unable to create highly specific, lab confirmed influenza exposure definition
- Ontario team re-executed T2DM analysis with influenza exposure definition using administrative data and found increased effect
  - Decreased specificity influenza definition
  - Influenza false positives responsible T2DM cases?
  - Inconsistent with replication findings of *lower* MI effect
- Berkon's bias – hospitalized patients at greater outcome risk
  - Test by restricting laboratory influenza definition to IP, OP

V. Discussion

- **What this work demonstrates:**
  - Value of negative controls as a diagnostic test
  - For assessing trust in main results
- Literature:
  - https://www.ncbi.nlm.nih.gov/pubmed/23900808
  - https://www.ncbi.nlm.nih.gov/pubmed/26970249
  - https://www.ncbi.nlm.nih.gov/pubmed/27592566
- **What this work does not demonstrate:**
  - The true effect of influenza on myocardial infarction

V. Discussion

- Next steps: find a design and specification that produces a null association between influenza and negative controls

- Executed cohort study assessing the hazards of first occurrence, primary inpatient AMI and negative controls among patients with influenza compared to 1:1 propensity scored matched patients with a cold during 7 days time-at-risk
  - Results roughly the same

V. Discussion

- **Challenge:**

- Can someone in the OHDSI community produce a design specification that estimates a null association between influenza and negative controls?

- https://github.com/OHDSI/StudyProtocolSandbox/tree/master/FluAmiSccs

V. Discussion

- Questions
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