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
## 1. Introduction

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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](https://www.bmj.com/content/354/bmj.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

  • 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

• 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

  • 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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Kwong et al. IRR</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
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### IV. Results

- **CCAE**

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Lung cancer
Ingrowing nail
Renal impairment
Acute liver injury
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Anemia
Depression
### IV. Results

- **CCAE**

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<td>1.22</td>
<td>1.05</td>
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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 replicate 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 reduced 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/pmc/articles/PMC5856503/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5856503/)

• **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](https://github.com/OHDSI/StudyProtocolSandbox/tree/master/FluAmiSccs)
V. Discussion

• Questions
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