The value of negative controls for the self-controlled case series design

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The purpose of OHDSI

- To generate **reliable evidence** for the benefit of patients, providers, researchers, health care systems, industry, and government agencies
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**RESULTS**

We identified 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20.0 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute myocardial infarction during the risk interval as compared with the control interval was 6.05 (95% confidence interval [CI], 3.86 to 9.50). No increased incidence was observed after day 7. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B, influenza A, respiratory syncytial virus, and other viruses were 10.11 (95% CI, 4.37 to 23.38), 5.17 (95% CI, 3.02 to 8.84), 3.51 (95% CI, 1.11 to 11.12), and 2.77 (95% CI, 1.23 to 6.24), respectively.
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**ORIGINAL ARTICLE**

**Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection**

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**IRR: 6.05 (95% CI 3.86, 9.50)**
Population-level effect estimation

- Methods for identifying causal relationships
  - Attempts to estimate unbiased, average effect of an exposure on an outcome

- Compares outcome occurrence between comparable populations

- Causal effect identification criteria
  - Consistency
  - Positivity
  - Exchangeability
Self-controlled case series design (SCCS)

• Compares outcomes *within* persons during time periods of differing exposure status

• Consistency:
  • Time-stamped risk intervals and outcome events

• Positivity:
  • Patients must have both exposed time and unexposed time

• Exchangeability:
  • Unexposed time = counterfactual approximation
Replication study specification

- **Exposure (influenza)**
  - Dx code, +lab result
  - OP, any visit
  - No influenza past 60 days, no outcome during visit

- **Risk interval**
  - Influenza visit end date +1 day to visit start date +7 days

- **Outcomes (first MI + 31 negative control outcomes)**
  - IP, any visit
  - Primary position

- **Analytic variants**
  - Simple SCCS
  - Pre-exposure window
  - Age and seasonality adjustment
  - Event-dependent observation period correction
## Negative control outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>Inflammatory disorder of digestive system</td>
</tr>
<tr>
<td>HIV</td>
<td>Infectious disease of genitourinary system</td>
</tr>
<tr>
<td>Depression</td>
<td>Infectious disease of abdomen</td>
</tr>
<tr>
<td>Ingrowing nail</td>
<td>Functional finding of gastrointestinal tract</td>
</tr>
<tr>
<td>Soft tissue lesion</td>
<td>Edema</td>
</tr>
<tr>
<td>Skin or mucosa lesion</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Organic mental disorder</td>
<td>Chronic inflammatory disorder</td>
</tr>
<tr>
<td>Observation of colon</td>
<td>Chronic disease of genitourinary system</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorder</td>
<td>Acute genitourinary disorder</td>
</tr>
<tr>
<td>Mass of trunk</td>
<td>Abscess</td>
</tr>
<tr>
<td>Mass of respiratory structure</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Mass of lymphoreticular structure</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Lymphoproliferative disorder</td>
<td>Substance abuse</td>
</tr>
<tr>
<td>Lesion of brain</td>
<td>Traumatic injury</td>
</tr>
<tr>
<td>Inflammatory disorder of extremity</td>
<td></td>
</tr>
</tbody>
</table>
Acute myocardial infarction
IRR: 6.05 (95% CI 3.86, 9.50)

Diabetes mellitus
IRR: 1.35 (95% CI 0.50, 3.62)
Replication results

Influenza diagnosis code (any visit), outcome (IP)

Acute myocardial infarction
IRR: 4.85 (95% CI 4.06, 5.74)
Replication results

Influenza diagnosis code (any visit), outcome (any visit)

Acute myocardial infarction

IRR: 4.15 (95% CI 3.57, 4.79)
Replication results

Influenza + lab result (any visit)

Outcome (IP)

Outcome (any visit)
Discussion

• **Negative controls are an important diagnostic to understand the validity of study findings**

• Negative controls **CAN:**
  • Identify problems, quantify error, test hypotheses, and compare alternative methods

• Negative controls **CANNOT:**
  • Solve the problem they help identify, generate hypotheses
Thank you!

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