Time Series and Case Crossover Designs

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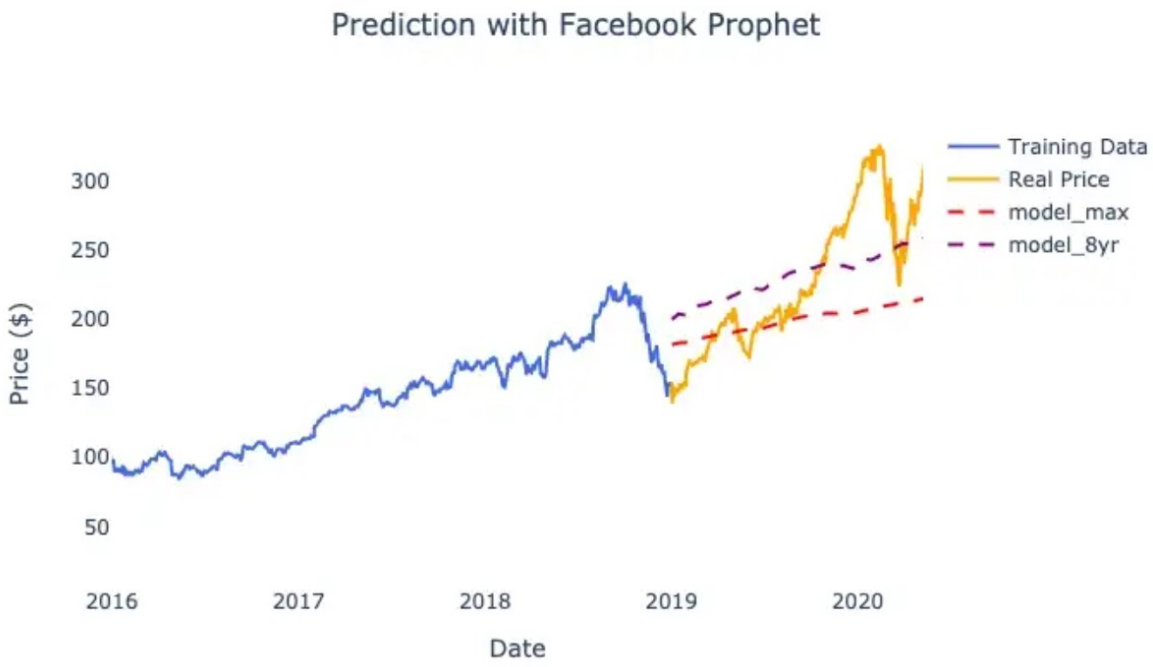
Objectives

- Understand the peculiarities of time series and case crossover study designs

1. What is the unit of analysis?
2. What are possible confounders and how to control for them?
3. What are the assumptions required to estimate a causal effect with these designs?
4. Similarities between the two designs
5. Triangulation
6. Extensions

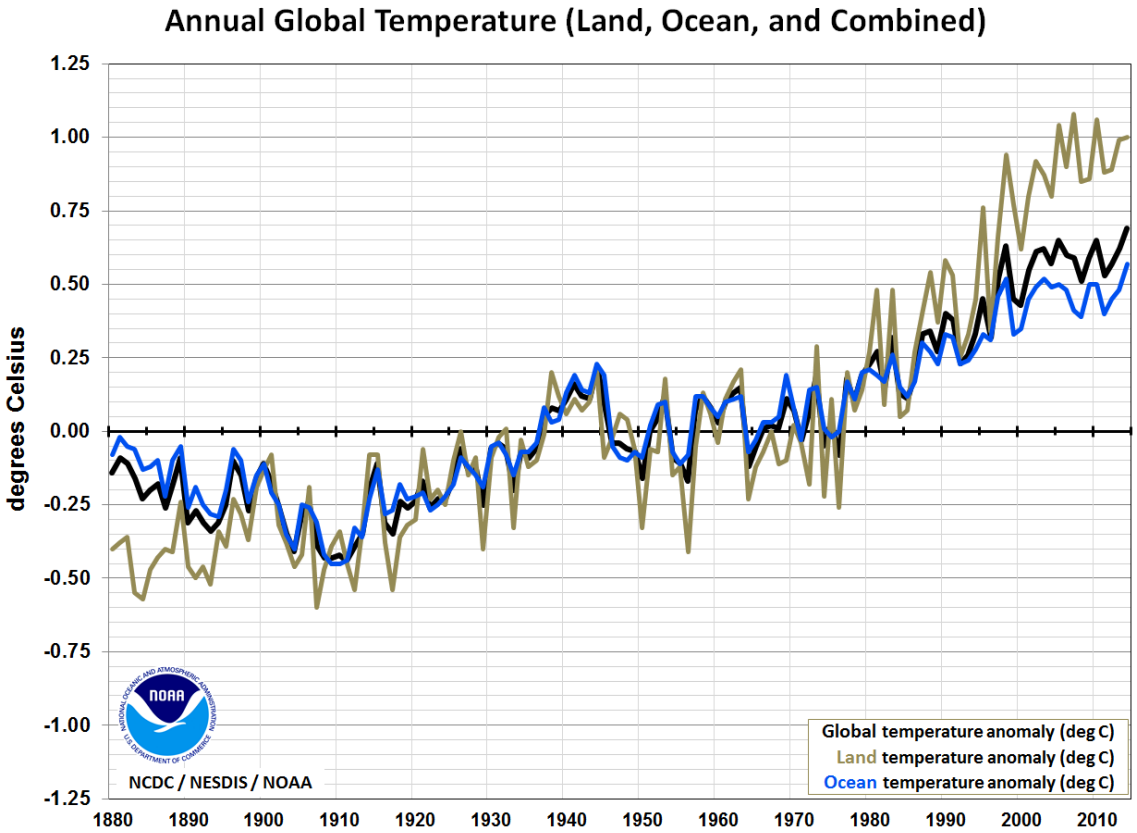
Introduction to time series

- A "time series" is simply a sequence of data points recorded at regular time intervals
- Time series design occur frequently in econometrics
  - E.g., forecast stock market price



Introduction to time series

- Used in environmental epidemiology to examine trends in environmental exposures



Introduction to time series

- Used in environmental epidemiology to quantify short-term associations of environmental exposures with health
  - E.g., Dominici et al. 2006: examine how day-to-day variation in $PM_{2.5}$ is associated with day-to-day variation in the number of deaths

Fine Particulate Air Pollution and Hospital Admission for Cardiovascular and Respiratory Diseases

Francesca Dominici, PhD
Roger D. Peng, PhD
Michelle L. Bell, PhD
Luu Pham, MS
Aidan McDermott, PhD
Scott L. Zeger, PhD
Jonathan M. Samet, MD

Context Evidence on the health risks associated with short-term exposure to fine particles (particulate matter ≤2.5 μm in aerodynamic diameter [$PM_{2.5}$]) is limited. Results from the new national monitoring network for $PM_{2.5}$ make possible systematic research on health risks at national and regional scales.

Objectives To estimate risks of cardiovascular and respiratory hospital admissions associated with short-term exposure to $PM_{2.5}$ for Medicare enrollees and to explore heterogeneity of the variation of risks across regions.

Design, Setting, and Participants A national database comprising daily time-series data daily for 1999 through 2002 on hospital admission rates (constructed from the Medicare National Claims History Files) for cardiovascular and respiratory outcomes and injuries, ambient $PM_{2.5}$ levels, and temperature and dew-point temperature for 204 US urban counties (population >200 000) with 11.5 million Medicare enrollees (aged >65 years) living an average of 5.9 miles from a $PM_{2.5}$ monitor.

Main Outcome Measures Daily counts of county-wide hospital admissions for primary diagnosis of cerebrovascular, peripheral, and ischemic heart diseases, heart rhythm, heart failure, chronic obstructive pulmonary disease, and respiratory infection, and injuries as a control outcome.

Results There was a short-term increase in hospital admission rates associated with $PM_{2.5}$ for all of the health outcomes except injuries. The largest association was for heart failure, which had a 1.28% (95% confidence interval, 0.78%-1.78%) increase in risk per 10-μg/m³ increase in same-day $PM_{2.5}$. Cardiovascular risks tended to be higher in counties located in the Eastern region of the United States, which included the Northeast, the Southeast, the Midwest, and the South.

Conclusion Short-term exposure to $PM_{2.5}$ increases the risk for hospital admission for cardiovascular and respiratory diseases.

JAMA. 2006;295:1127-1134 www.jama.com

NUMEROUS EPIDEMIOLOGICAL studies have shown associations of acute and chronic exposures to airborne particles with risk for adverse effects on morbidity and mortality.[1,2] The recent evidence on adverse effects of particulate air pollution on public health has led to more stringent standards for levels of particulate matter in outdoor air in the United States and in other countries. In 1997, the US National Ambient Air Quality Standard for airborne particulate matter was revised, maintaining the previous indicator of particulate matter of less than or equal to 10 μm in aerodynamic diameter (PM_{10}) and creating a new in-

Time-series

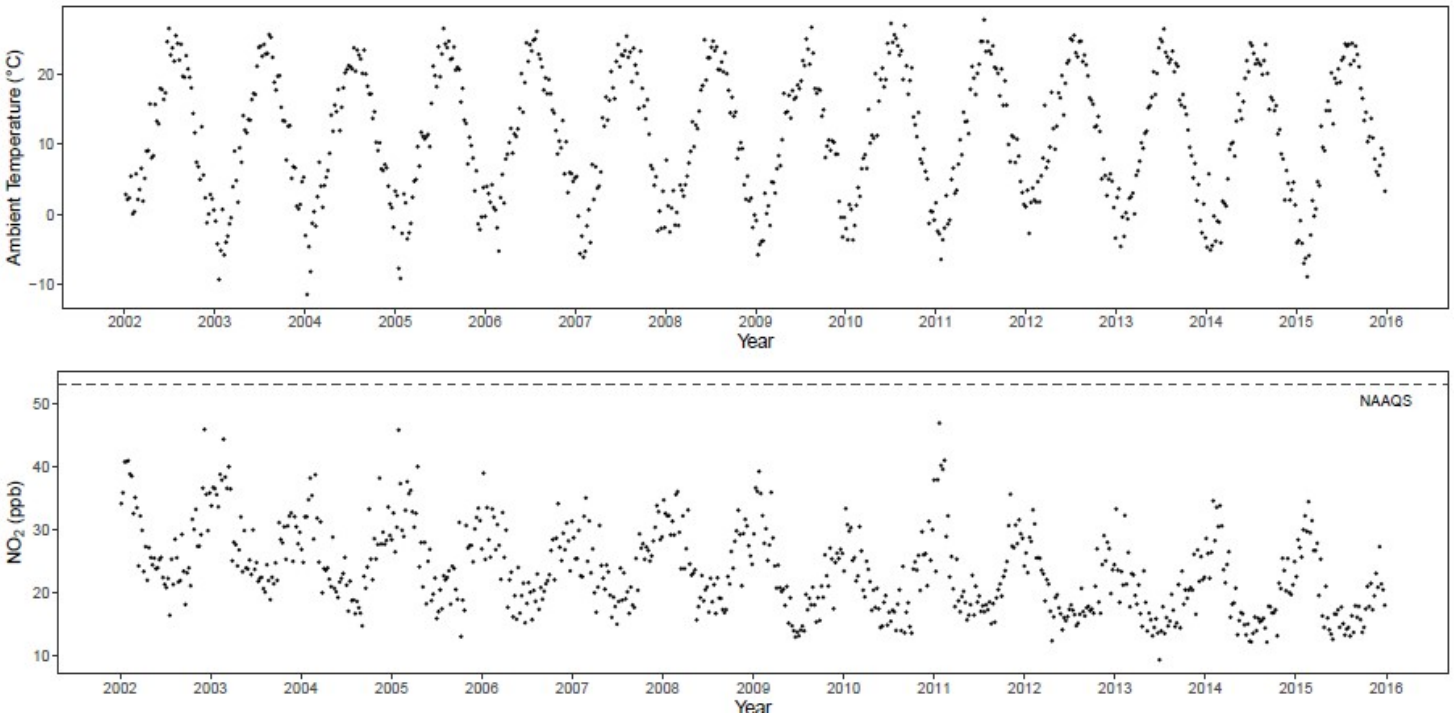
- Unit of analysis: unit of **time** not the individual person
  - E.g., hourly, daily, weekly, monthly etc.
  - Important point when it comes to consider potential confounders
    - More on this later!
- Outcome: Usually a count outcome per unit of time
  - Use administrative datasets (readily available, more power)
    - National Death Index (deaths per day)
    - Medicare (cause-specific admissions per day)
    - Babies delivered at Beth Israel Deaconess Medical Center (BIDMC)
- Exposure: Mean exposure per unit of time
  - Covers geographic area that gave rise to the counts of the outcome
  - For BIDMC data, average exposure for Boston Metropolitan area (e.g., city monitor)

Confounders

- If the unit of analysis is the **day**, what could be a confounder?
- Individual-level factors?
  - E.g., age, sex, race/ethnicity etc.
  - Now irrelevant $\longrightarrow$ *cannot* act as confounder
- Population characteristics in a city?
  - E.g., smoking rates, obesity rates, poverty etc.
  - Do not change day by day $\longrightarrow$ *cannot* act as confounder
- City characteristics?
  - E.g., city parks etc.
  - Do not change day by day $\longrightarrow$ *cannot* act as confounder

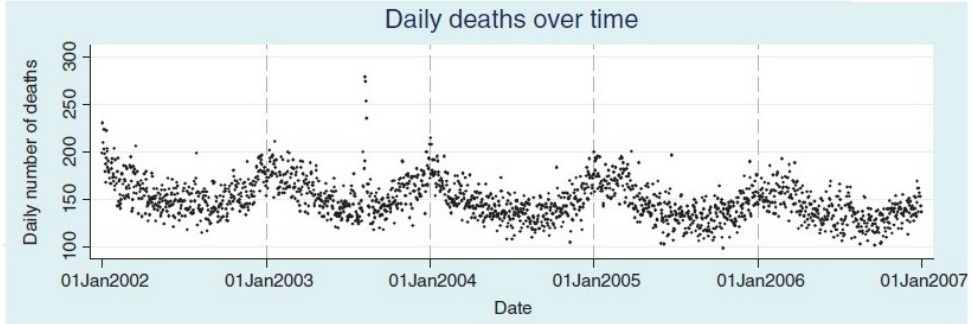
Confounders

- Confounders are things that vary day-by-day
  - Collection of factors that show seasonal variation (does not have to cause exposure)
    - E.g., weather, temperature, humidity, influenza, vitamin D etc.
  - Long-term trends in medical care, policy changes etc.
  - Many unmeasured, so most people control for time as a **proxy**

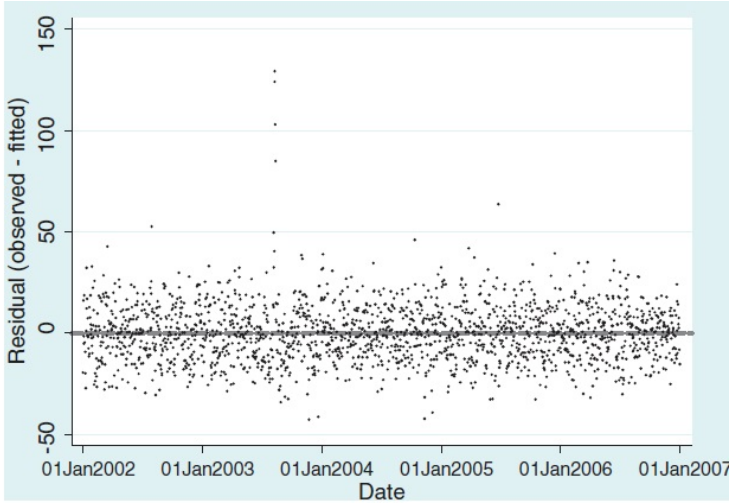


Confounders

- The aim is to remove the influence of time trends
  - E.g., below from Bhaskaran et al. 2013, de-trend daily deaths using spline for seasonality and long-term trends (but there are other ways to do this)
  - Does the exposure explain any of the remaining variability in the outcome?



De-trend



Model

- Poisson regression
  - Temperature directly included into model
  - Function of calendar time to remove long-term trend and seasonality

$$log(E[Death_i]) = \beta_0 + \beta_1 PM_{2.5i} + \beta_2 Temp_i + \beta Time$$

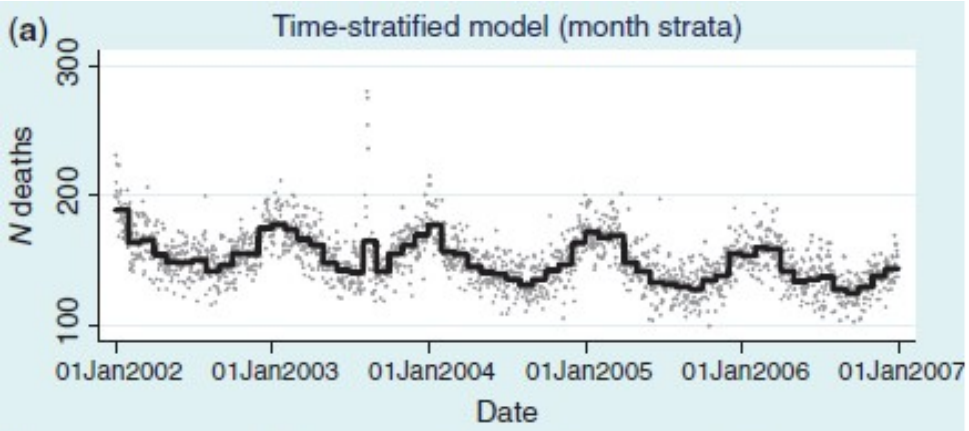
- Options to control for time:

1. Time stratified
2. Periodic functions (e.g., harmonics)
3. Flexible spline function

Model: controlling for seasonality

1. Time stratified model

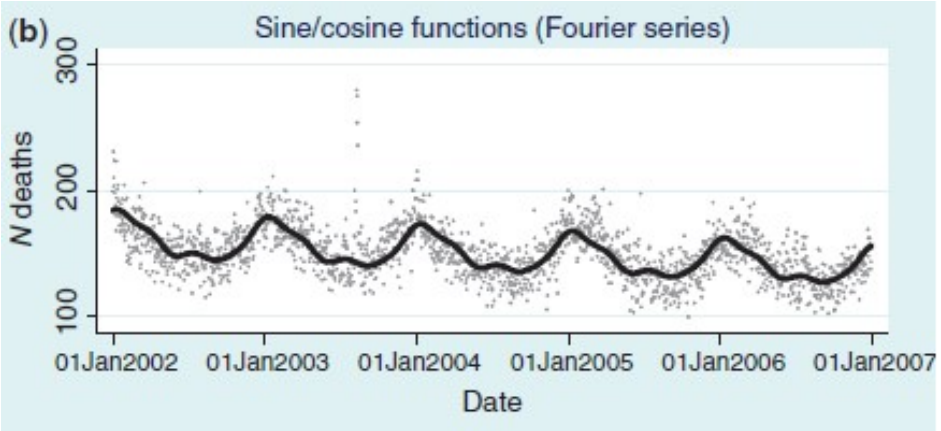
- Split study period into intervals (e.g., month) and estimate a different baseline mortality risk for each month
- E.g., for 5 years of data, there would be 12 x 5 = 60 strata
  - Pros: Easy to understand, often captures time trends quite well
  - Cons: Many model parameters; implicitly assumes jumps in risk between adjacent intervals



Model: controlling for seasonality

2. Periodic functions (e.g., harmonics)

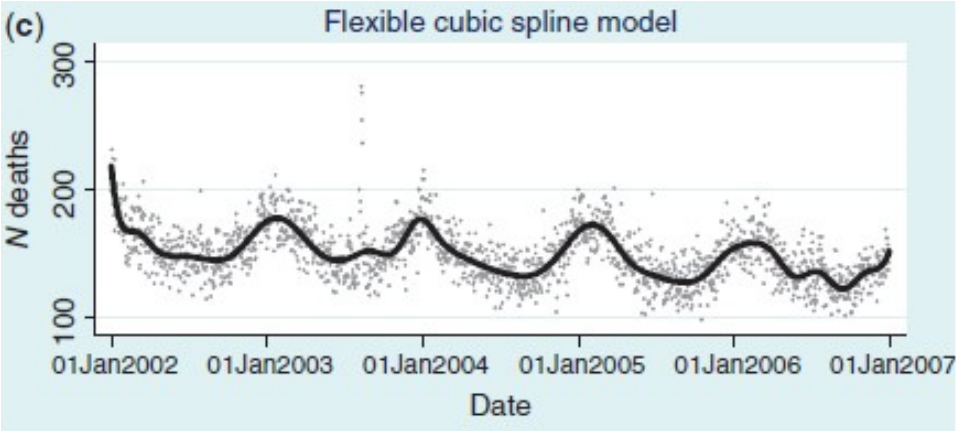
- Model time trends using smooth periodic functions
- A single harmonic (sine-cosine pair) will model seasonality as a regular wave per year
  - Pros: Models time trends smoothly, using few parameters
  - Cons: Forced to be a certain shape, may not reflect the data well (oversmoothing = residual confounding)



Model: controlling for seasonality

3. Flexible spline function

- Flexibility determine by number of knots (i.e., degrees of freedom)
- Too few may not capture time trends, too many will be too 'wobbly' and lead to wide confidence intervals
  - Pros: Models time trends smoothly and flexibly
  - Cons: More mathematically complex than other methods; need to assess trade-off between smoothness and residual confounding



Time Series Assumptions

- For valid causal effect:

1. Exchangeability
   - What exactly does this mean?
   - Control for seasonality and long-term trends

Time Series Assumptions

- For valid causal effect:

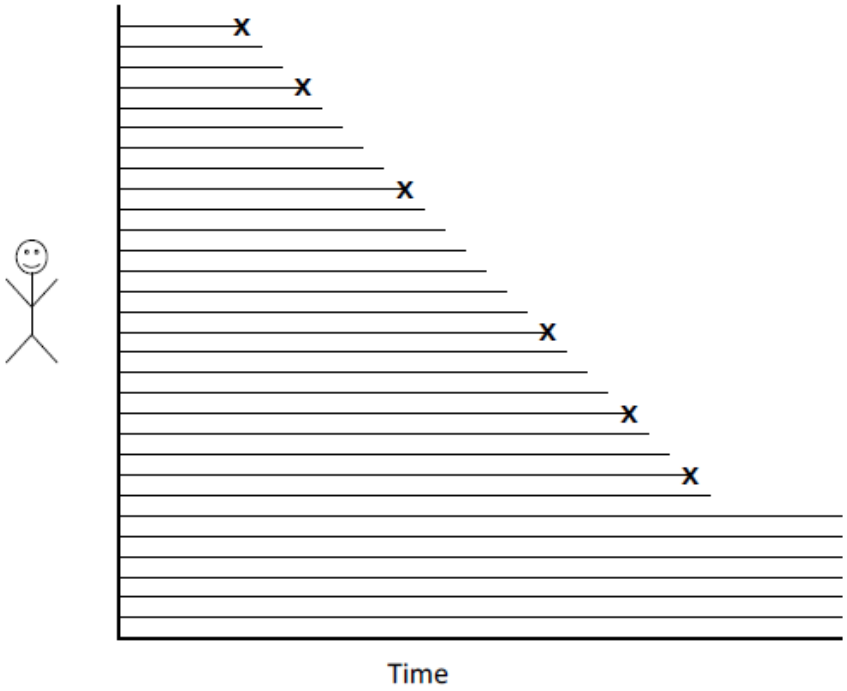
2. No selection bias
   - Study inclusion does not depend on exposure level/outcome
   - Any selection issues when using large administrative datasets (e.g., Medicare)?

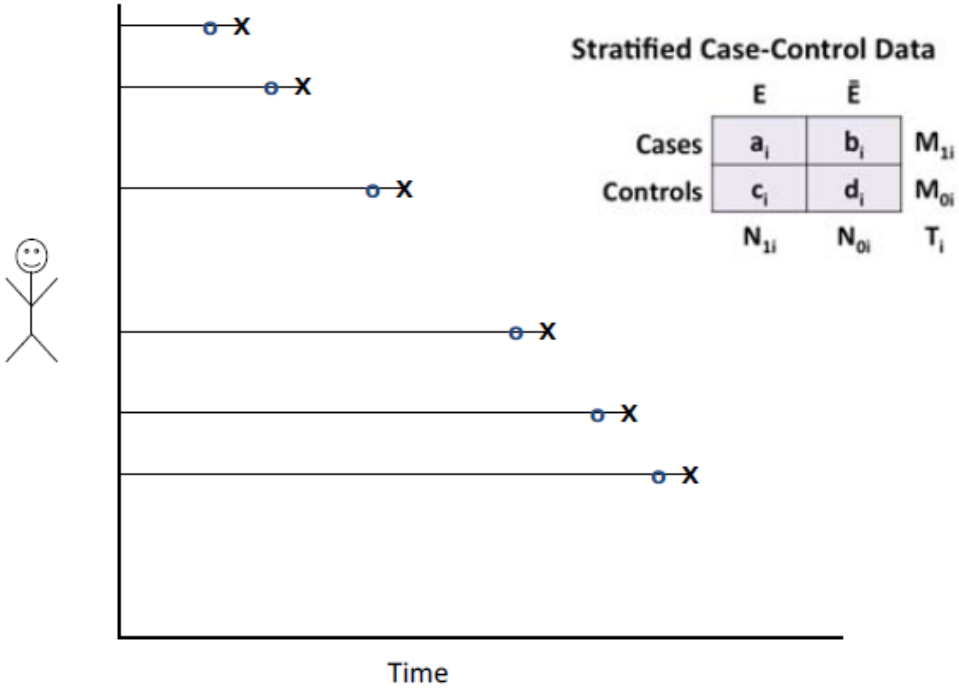
3. Correct model specification
   - Specification of seasonality and long-term trends
   - Dose-response of exposure
   - Outcome distribution (Poisson, Quasi-Poisson, Negative Binomial)

Questions on Time Series?

Case-crossover

- Case-only design
  - Each subject serves as their own control
  - No **between-individual** confounding





Adapted from EPI 201

Confounding control

- Case days: Select days that the events of my cases occurred
- Control days: Select days cases did not have an event
  - Control for Michael is still Michael on a day that Michael did not have the event

- Compare the exposure distribution between case and control days
  - Conditional logistic regression

$$log(\frac{p_{ij}}{1-p_{ij}}) = \alpha_i + \beta_1 A_{ij} + C_{ij}^T \beta_c$$

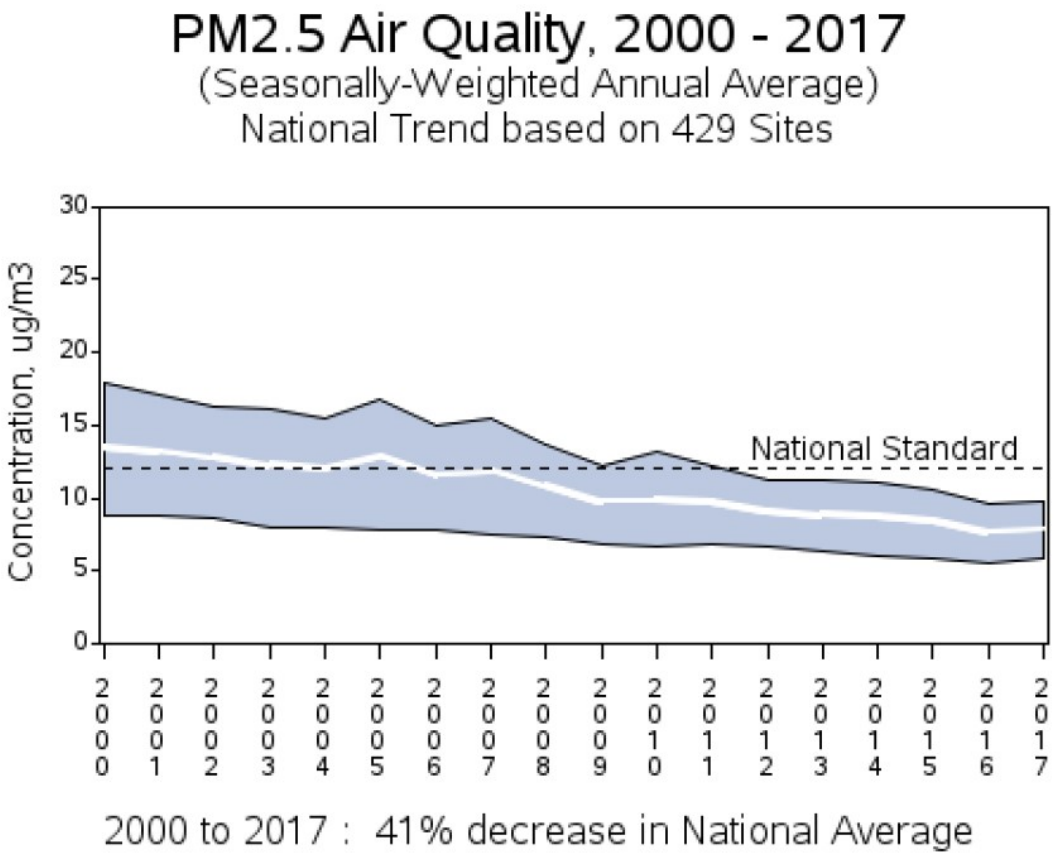
- Each subject is a stratum i (aka a matched set)
- $p_{ij} = P(Y_{ij} = 1 | A_{ij}, C_{ij})$ for a case ($j = 1$) or a control ($j = 0$) day

Confounding control

- How do you pick your control days?
- Need to consider
  1. Day of week patterns
     - E.g., Traffic on weekdays vs. weekends
     - Solution: Match on day of week!
  2. Seasonal trends
     - E.g., Temperature in the New England area shows strong seasonality
     - Solution: Match on season. Better yet, match on month!
  3. Long-term trends
     - E.g., Health care gets better over time (i.e., induces trend in outcome)
     - Solution: Match on year!

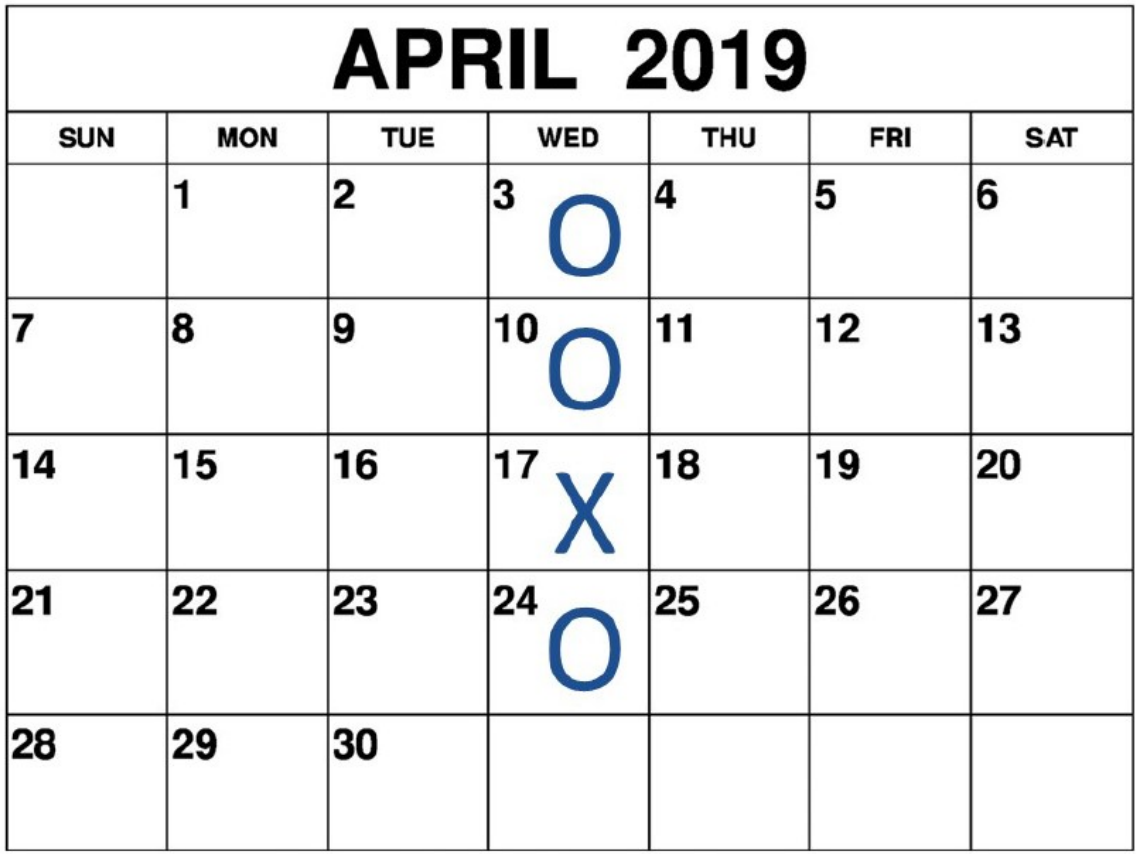
Confounding control

- What would happen if always picked control days before case days?
  - On average, control days would have higher exposure
  - What would this do?



Confounding control

- <u>Solution</u>: Also pick control days *after* the event!
  - Known as a **time stratified approach**



Example

Example

- Elser et al. 2023
  - Question: Does wildfire smoke exposure increase the risk of hospitalization for headaches?

RESEARCH SUBMISSIONS

Wildfire smoke exposure and emergency department visits for headache: A case-crossover analysis in California, 2006–2020

Holly Elser MD, PhD[1,2] | Sebastian T. Rowland PhD[3,4] | Maksym S. Marek MD, MS[1] | Mathew V. Kiang ScD[5] | Brittany Shea MA[3] | Vivian Do MPH[3] | Tarik Benmarhnia PhD[6] | Andrea L. C. Schneider MD, PhD[1,7] | Joan A. Casey PhD[3]

Example:

- Case crossover assumptions/conditions to estimate causal effect
  1. Variation in exposure over time
  2. No selection bias
  3. Exchangeability of risk of exposure
  4. Exposure assessment accuracy is independent of case status
  5. Transient effect

Example: case crossover assumptions/conditions

1. Variation in exposure over time

- What if exposure did not differ on case vs. control days?
- Violation of positivity

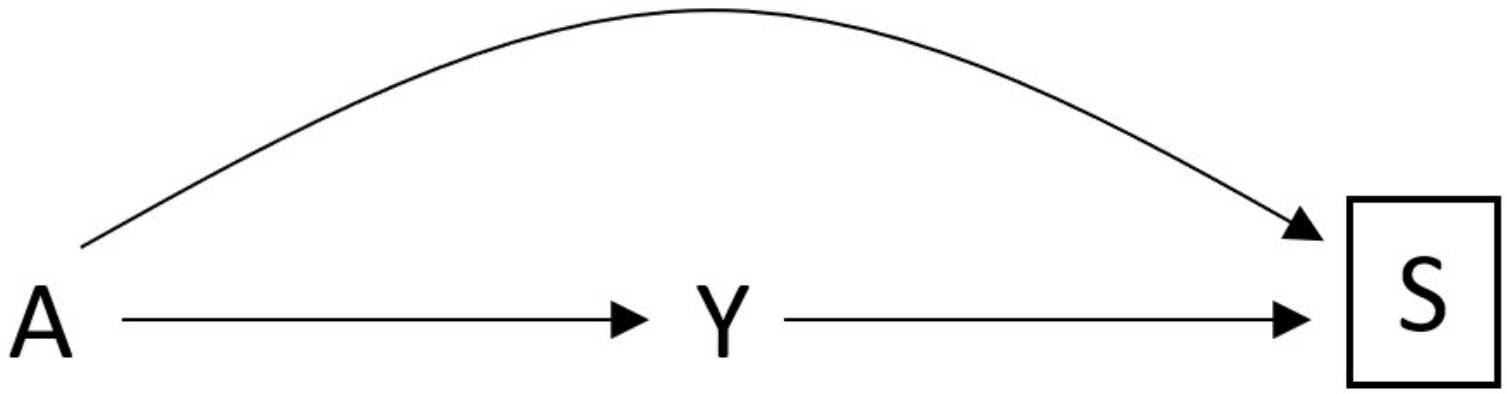
	Exposed	Unexposed
Cases	a_i	b_i
Controls	c_i	d_i

- What does this say about the exposure?

Example: case crossover assumptions/conditions

2. No selection bias

- What would happen if inclusion depended on air pollution levels?
  - They used Optum (large claims database)

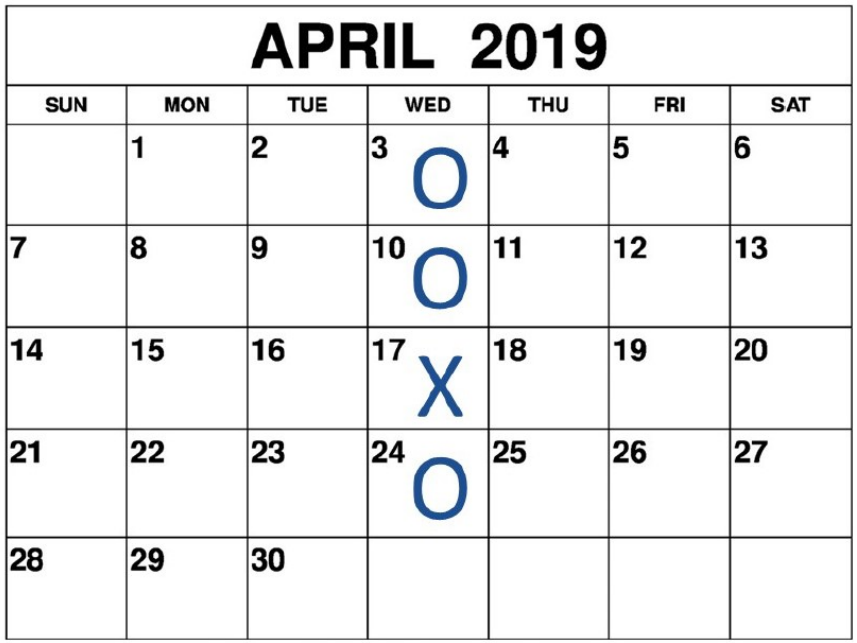


- Is selection bias an issue in this study?

Example: case crossover assumptions/conditions

3. Exchangeability

- We assume that control days represent the counterfactual exposure had the case not been a case (did not experience the event)
  - Self-matching and stratification by individual and year, month, day of week



Example: case crossover assumptions/conditions

4. Exposure assessment accuracy is independent of case status

- E.g., exposure is systematically higher in cases
- Use ambient measure such that individual-level covariates cannot affect it (Weisskopf and Webster 2017)

ORIGINAL ARTICLE

Trade-offs of Personal Versus More Proxy Exposure Measures in Environmental Epidemiology

Marc G. Weisskopf[a] *and Thomas F. Webster*[b]

Abstract: The technological ability to make personal measurements of toxicant exposures is growing rapidly. While this can decrease measurement error and therefore help reduce attenuation of effect estimates, we argue that as measures of exposure or dose become more personal, threats to validity of study findings can increase in ways that more proxy measures may avoid. We use directed acyclic graphs (DAGs) to describe conditions where confounding is introduced by use of more personal measures of exposure and avoided via more proxy measures of personal exposure or target tissue dose. As exposure or dose estimates are more removed from the individual, they become less susceptible to biases from confounding by personal factors that can often be hard to control, such as personal behaviors. Similarly, more proxy exposure estimates are less susceptible to reverse causation. We provide examples from the literature where adjustment for personal factors in analyses that use more proxy exposure estimates have little effect on study results. In conclusion, increased personalized exposure assessment has important advantages for measurement accuracy, but it can increase the possibility of biases from personal factors and reverse causation compared with more proxy exposure estimates. Understanding the relation between more and less proxy exposures, and variables that could introduce confounding are critical components to study design.

(*Epidemiology* 2017;28: 635–643)

to an explosion of environmental epidemiology research using these approaches as markers of exposure. It is clear why: these measures can provide accurate assessments of an individual's exposure to a given toxicant. In contrast, more proxy exposure estimates (i.e., further removed from the exposure of interest for the question being asked) can have a large amount of error in estimating an individual's actual exposure. Ideally the exposure of interest would be measured as precisely as possible, variables identified that can potentially introduce bias and those measured as precisely as possible, and then the appropriately adjusted analyses conducted. In practice, however, this ideal is often not possible. One issue is the choice of exposure metric to use, which can influence effect estimates in the absence of confounding, and can also affect what variables can introduce confounding. We argue here that while using more proxy exposure estimates has drawbacks, such exposure metrics can potentially provide some important advantages for causal inference in epidemiologic studies.

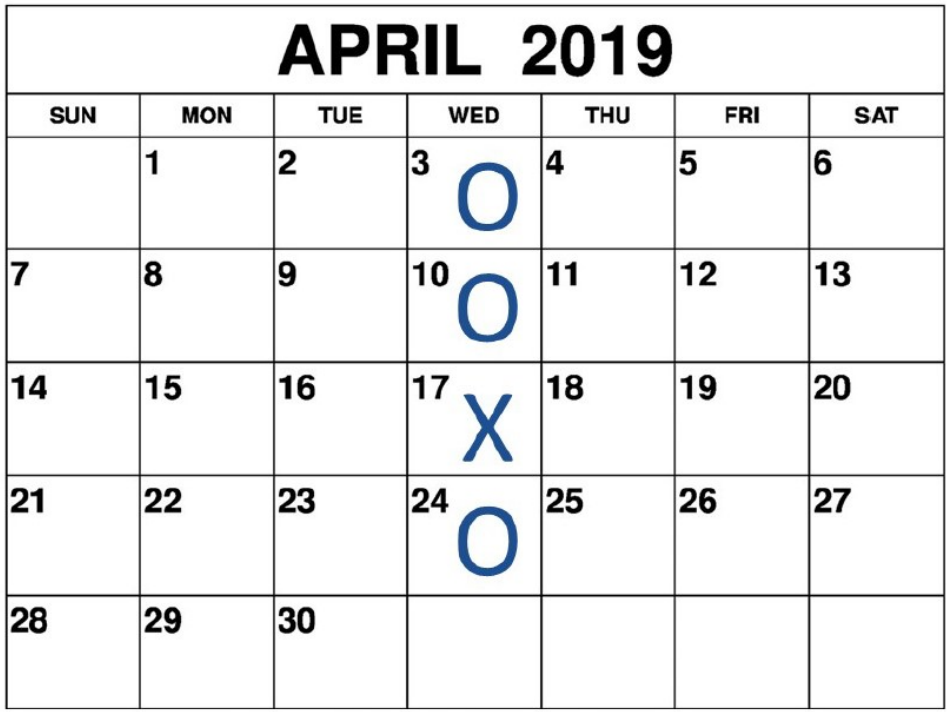
PROXY EXPOSURE MEASURES AND MEASUREMENT ERROR

From a toxicologist's perspective, if there is a question

Example: case crossover assumptions/conditions

5. Transient effect

- What would happen if it was not transient?
  - E.g., exposure on April 3 and 10 influenced risk of outcome?



Questions on case crossovers?

Objectives

- Understand the peculiarities of time series and case crossover study designs

1. What is the unit of analysis?
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4. **Similarities between the two designs**
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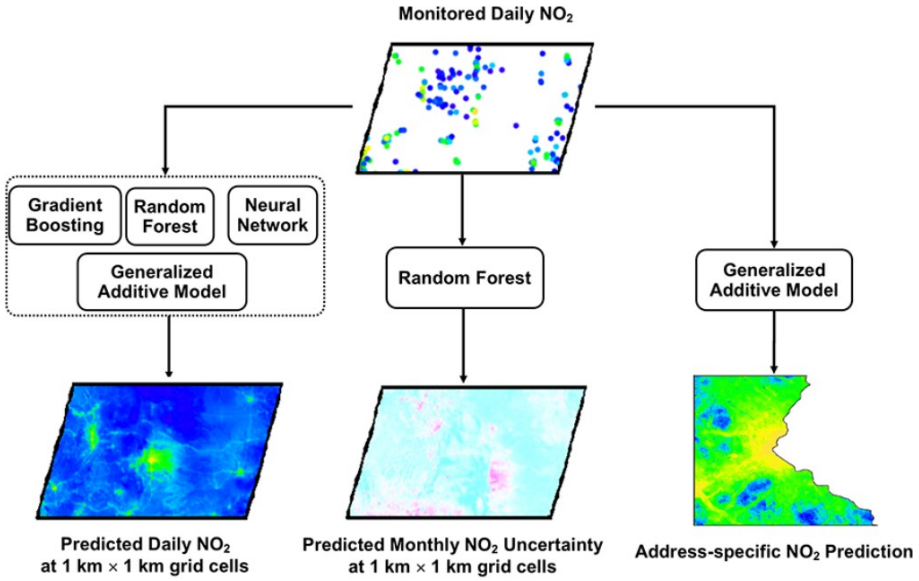
6. Extensions

Time Series Vs. Case Crossover: Exposure resolution

- Case crossover: Can use individual-level exposure data
  - E.g., predicted at their residences if known

- Time Series: Requires city-/county-level aggregate exposures
  - Usually concentrations at the monitor of that city (or average across monitors if >1)
  - Aggregate finer resolution, e.g., 1-km NO_2 (Di et al. 2020)



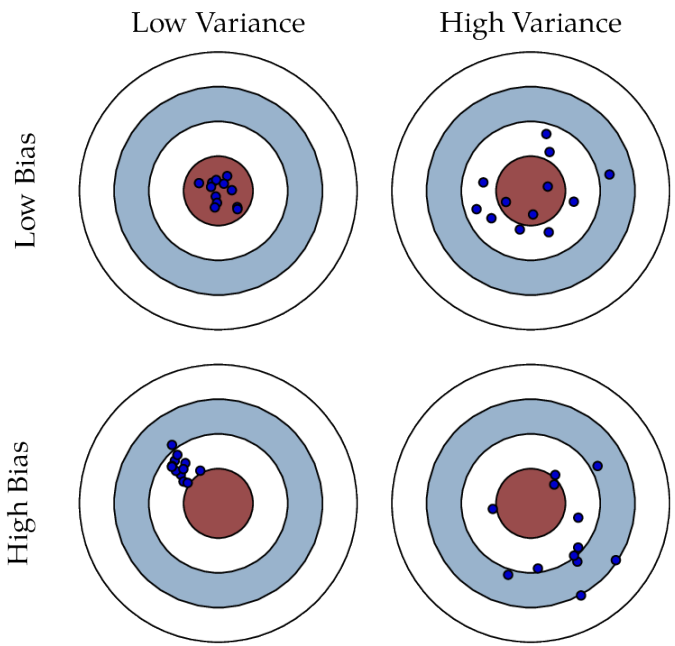
Time Series Vs. Case Crossover: Effect modification

- Case crossover: Can assess effect modification by individual-level data
  - E.g., smoking, BMI etc.

- Time series: Would need to stratify outcome by group to assess effect modification
  - E.g., Among $\geq$ 65 years old vs. $<$ 65 years old
  - Could result in small sample sizes

Time Series Vs. Case Crossover: Models

- Case crossover: Better control for confounding by matching
  - Less statistically efficient than time series
- Time series: Needs caution when building model
  - E.g., how are seasonality and long-term trends parameterized?



Equivalence of time series and case crossover

- Would time series and case crossover give the same (more or less) results?
- Under certain assumptions, yes
- Both methods estimate the <u>incidence rate ratio</u>, and will be asymptotically equivalent if:

1. City-level aggregated exposures are used in case crossover
2. The models are correctly specified (especially the time series)
   - Seasonality and long-term trend correctly modeled
   - No effect modification or correctly account for effect modification

Other Applications

- These methods are not only applicable in air pollution epidemiology. For example:
- Drinking water quality and gastrointestinal illness
  - Exposure: Average turbidity measured at distribution system and source water sites
  - Outcome: Number of emergency admissions for gastrointestinal illness (diarrhea)
- But also does not need to be restricted to environmental epidemiology

Other Applications

- Mittleman et al. 1993

The New England
Journal of Medicine

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Volume 329 DECEMBER 2, 1993 Number 23

TRIGGERING OF ACUTE MYOCARDIAL INFARCTION BY HEAVY PHYSICAL EXERTION

Protection against Triggering by Regular Exertion

MURRAY A. MITTLEMAN, M.D.C.M., M.P.H., MALCOLM MACLURE, SC.D., GEOFFREY H. TOFLER, M.B., JANE B. SHERWOOD, R.N., ROBERT J. GOLDBERG, PH.D., AND JAMES E. MULLER, M.D., FOR THE DETERMINANTS OF MYOCARDIAL INFARCTION ONSET STUDY INVESTIGATORS*

Abstract *Background.* Despite anecdotal evidence suggesting that heavy physical exertion can trigger the onset of acute myocardial infarction, there have been no controlled studies of the risk of myocardial infarction during and after heavy exertion, the length of time between heavy exertion and the onset of symptoms (induction time), and whether the risk can be modified by regular physical exertion. To address these questions, we collected data from patients with confirmed myocardial infarction on their activities one hour before the onset of myocardial infarction and during control periods.

Methods. Interviews with 1228 patients conducted an average of four days after myocardial infarction provided data on their usual annual frequency of physical activity and the time, type, and intensity of physical exertion in the 26 hours before the onset of myocardial infarction. We compared the observed frequency of heavy exertion (6 or more metabolic equivalents) with the expected values using two types of self-matched analyses based on a new case-crossover study design. The low frequency of heavy exertion during the control periods was validated by data from a population-based control group of 218 subjects.

Results. Of the patients, 4.4 percent reported heavy exertion within one hour before the onset of myocardial infarction. The estimated relative risk of myocardial infarction in the hour after heavy physical exertion, as compared with less strenuous physical exertion or none, was 5.9 (95 percent confidence interval, 4.6 to 7.7). Among people who usually exercised less than one, one to two, three to four, or five or more times per week, the respective relative risks were 107 (95 percent confidence interval, 67 to 171), 19.4 (9.9 to 38.1), 8.6 (3.6 to 20.5), and 2.4 (1.5 to 3.7). Thus, increasing levels of habitual physical activity were associated with progressively lower relative risks. The induction time from heavy exertion to the onset of myocardial infarction was less than one hour, and symptoms usually began during the activity.

Conclusions. Heavy physical exertion can trigger the onset of acute myocardial infarction, particularly in people who are habitually sedentary. Improved understanding of the mechanisms by which heavy physical exertion triggers the onset of myocardial infarction and the manner in which regular exertion protects against it would facilitate the design of new preventive approaches. (N Engl J Med 1993; 329:1677-83.)

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5. **Triangulation**
6. Extensions

Triangulation

- Hart et al. 2015
  - How does this type of analysis differ from a time-series analysis?

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women

Jaime E. Hart, ScD; Robin C. Puett, PhD; Kathryn M. Rexrode, MD, MPH; Christine M. Albert, MD, MPH; Francine Laden, ScD

Background—Ambient air pollution exposures have been frequently linked to cardiovascular disease (CVD) morbidity and mortality. However, less is known about the populations most susceptible to these adverse effects.

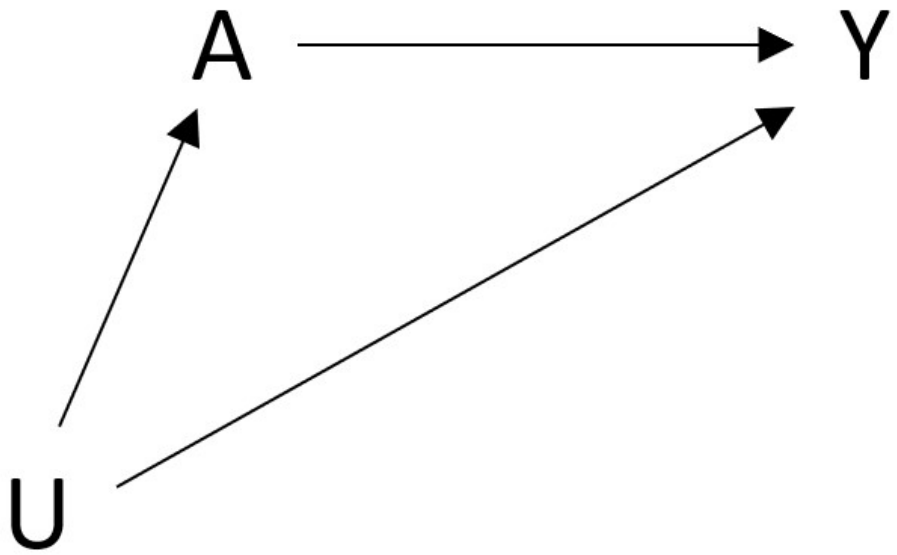
Methods and Results—We assessed the associations of long-term particulate matter (PM) exposures with incident CVD in a nationwide cohort of 114 537 women in the Nurses' Health Study, and performed analyses to identify subpopulations at the greatest risk. Residential address level time-varying monthly exposures to $PM_{2.5}$, PM_{10}, and $PM_{2.5\ to\ 10}$ microns in diameter were estimated from spatio-temporal prediction models. In multivariable models, increases in all size fractions of PM were associated with small, but not statistically significant, increased risks of total CVD, coronary heart disease, and stroke. PM-associated CVD risks were statistically significantly higher among women with diabetes as compared to those without (*P*-for-interaction <0.0001 for PM_{10} and $PM_{2.5}$ and 0.007 for $PM_{2.5\ to\ 10}$). For each 10 $\mu g/m^3$ increase in 12-month average $PM_{2.5}$, $PM_{2.5\ to\ 10}$, and PM_{10}, the multivariable adjusted hazard ratios were 1.44 (95% CI: 1.23 to 1.68), 1.17 (95% CI: 1.05 to 1.30), and 1.19 (95% CI: 1.10 to 1.28) among women with diabetes. There were also suggestions of higher risks among older (≥70 years) women, the obese, and those living in the Northeast and South. Smoking status and family history did not consistently modify the association between PM and CVD, and risks were most elevated with exposures in the previous 12 months.

Conclusions—In this nationwide cohort, women with diabetes were identified as the subpopulation most sensitive to the adverse cardiovascular health effects of PM. (*J Am Heart Assoc*. 2015;4:e002301 doi: 10.1161/JAHA.115.002301)

Key Words: air pollution • cardiovascular disease • effect modification • environment • myocardial infarction • stroke

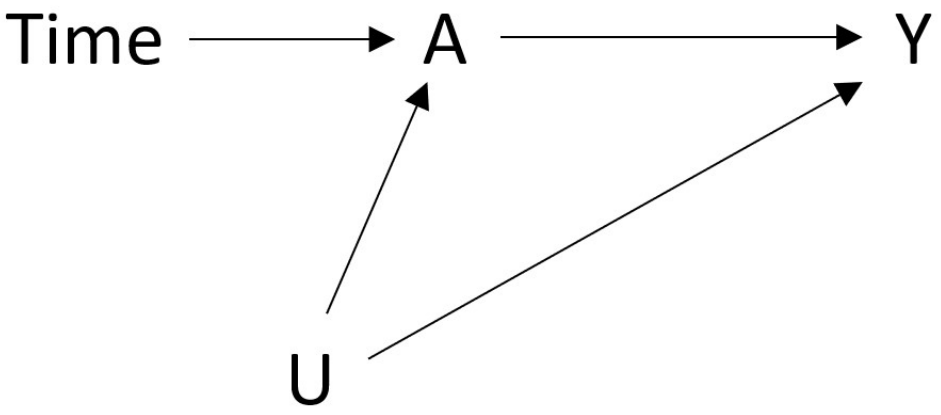
Triangulation

- Individual-level analysis (e.g., cohort/case-control)
  - Confounders in Hart et al. 2015: age, race, calendar year, season, body mass index, menopausal status, hormone use, comorbidities (hypertension, hypercholesterolemia, type II diabetes), family history of MI, smoking, marital status, employment status, and educational attainment, census tract level variables



Triangulation

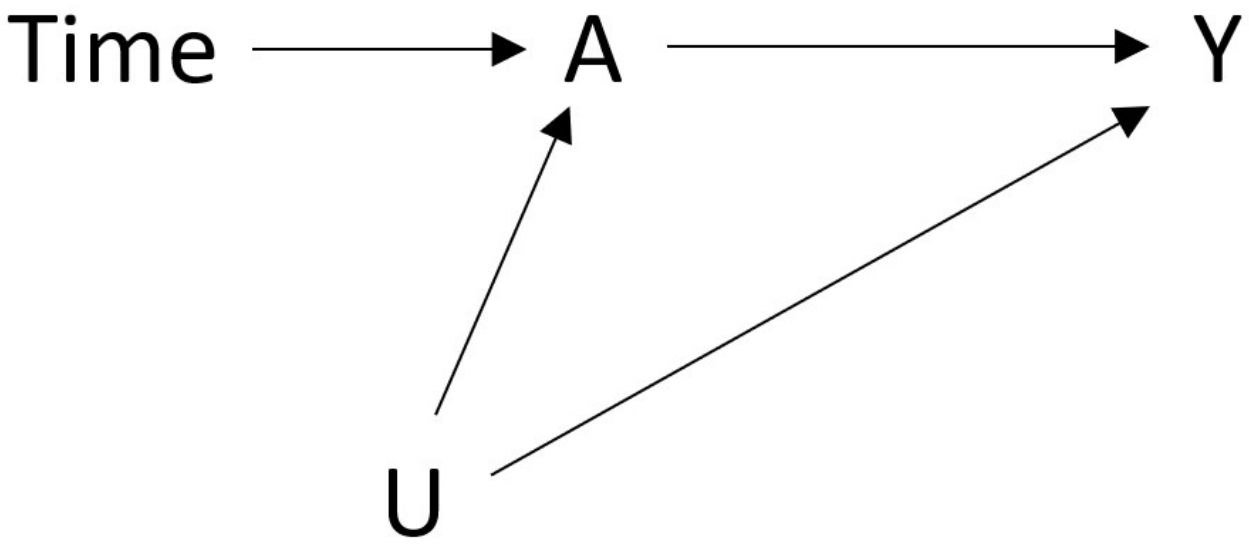
- Time series as an instrumental variable analysis (**EPI 289**)
  - Compare day-to-day variation in outcome with day-to-day variation in exposure



$$IV = \frac{E[Y|Time = t^*] - E[Y|Time = t]}{E[A|Time = t^*] - E[A|Time = t]}$$

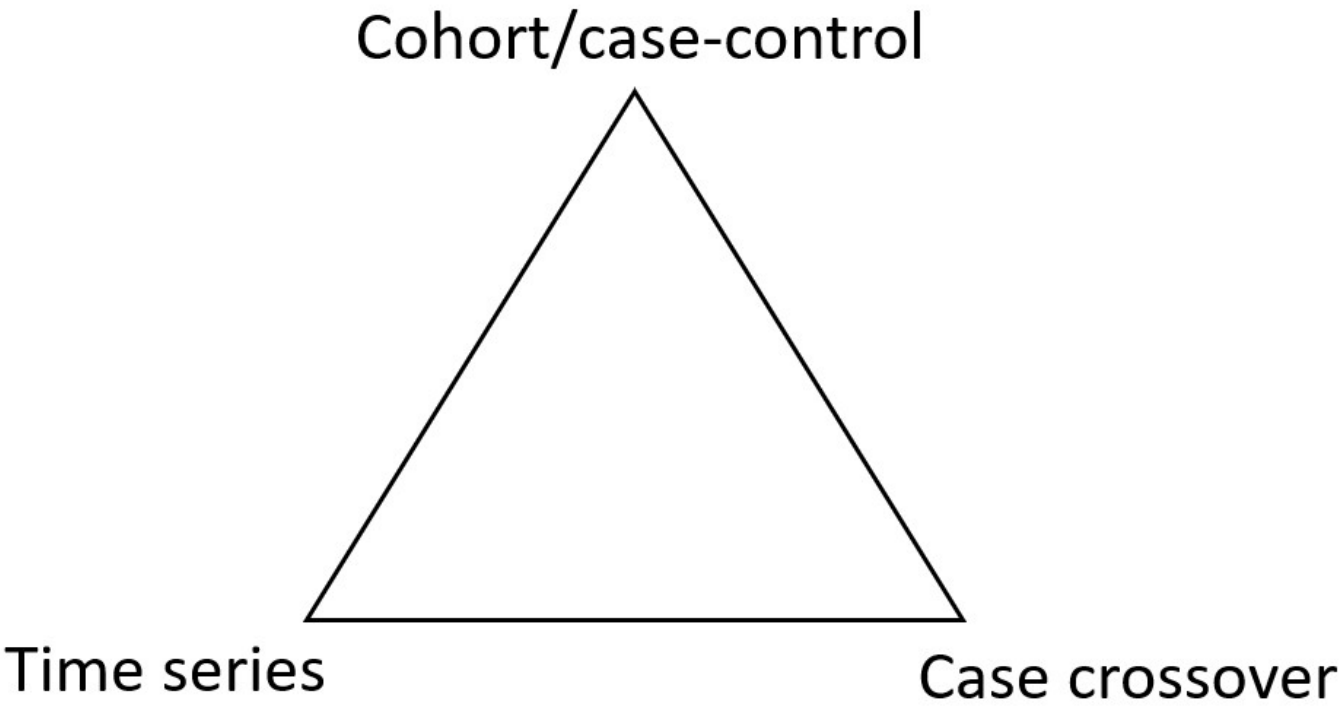
Triangulation

- Case crossover similar to time series
  - What happens to the DAG when we self-match?



Triangulation

- Alternative approaches to more traditional approaches
  - All have their own respective strengths, weaknesses and assumptions
  - Use multiple for triangulation effort



Objectives

- Understand the peculiarities of time series and case crossover study designs

1. What is the unit of analysis?
2. What are possible confounders and how to control for them?
3. What are the assumptions required to estimate a causal effect with these designs?
4. Similarities between the two designs
5. Triangulation
6. **Extensions**

Extensions

- Multiple locations
  - E.g., data from different cities/counties etc.
  - Meta-analysis methods (e.g., fixed effects, random effects, meta-regression)

SCIENCE ADVANCES | RESEARCH ARTICLE

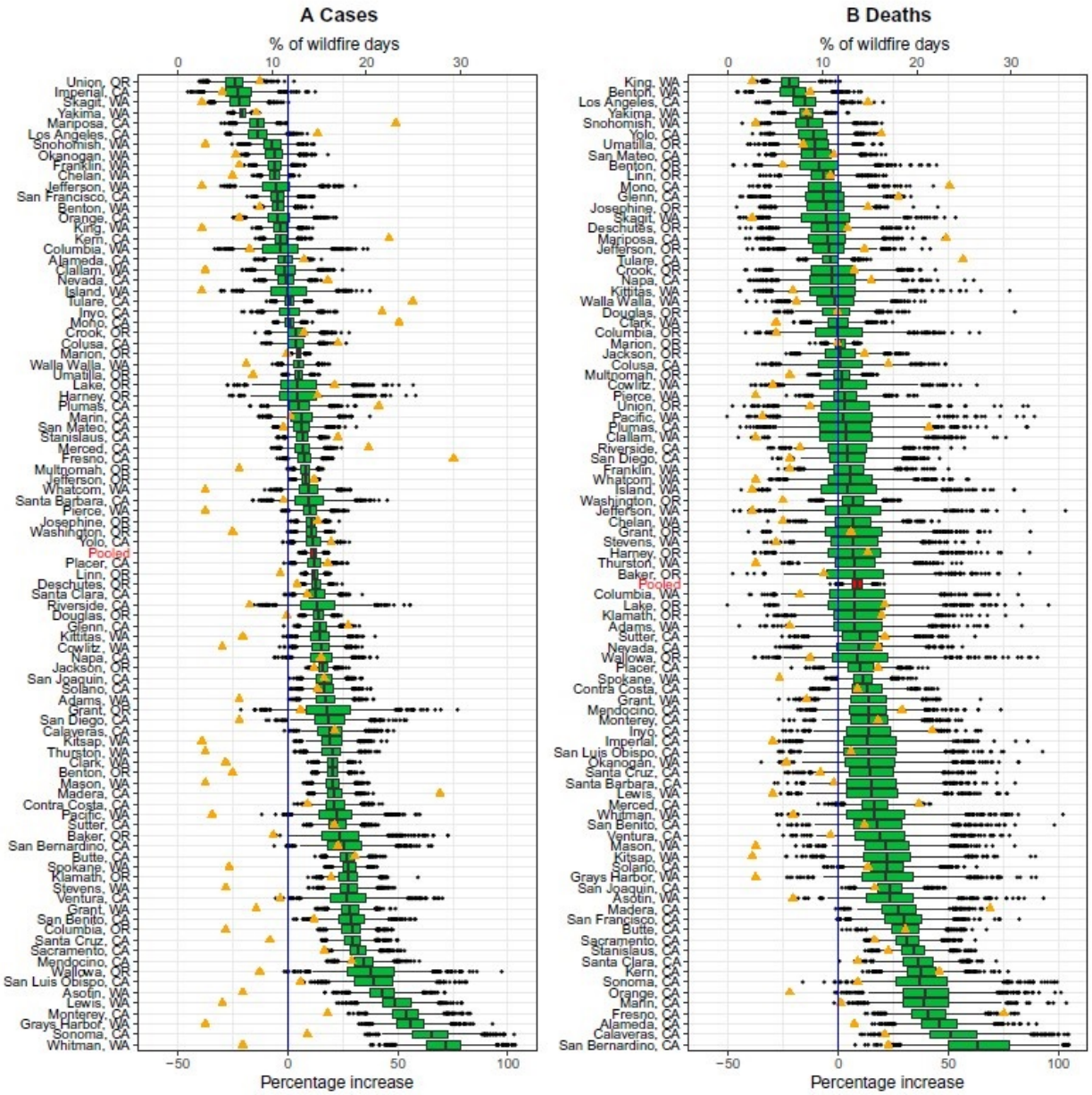
CORONAVIRUS

Excess of COVID-19 cases and deaths due to fine particulate matter exposure during the 2020 wildfires in the United States

Xiaodan Zhou[1†], Kevin Josey[2†], Leila Kamareddine[2], Miah C. Caine[3], Tianjia Liu[4], Loretta J. Mickley[3], Matthew Cooper[5], Francesca Dominici[2,6*]

The year 2020 brought unimaginable challenges in public health, with the confluence of the COVID-19 pandemic and wildfires across the western United States. Wildfires produce high levels of fine particulate matter ($PM_{2.5}$). Recent studies reported that short-term exposure to $PM_{2.5}$ is associated with increased risk of COVID-19 cases and deaths. We acquired and linked publicly available daily data on $PM_{2.5}$, the number of COVID-19 cases and deaths, and other confounders for 92 western U.S. counties that were affected by the 2020 wildfires. We estimated the association between short-term exposure to $PM_{2.5}$ during the wildfires and the epidemiological dynamics of COVID-19 cases and deaths. We adjusted for several time-varying confounding factors (e.g., weather, seasonality, long-term trends, mobility, and population size). We found strong evidence that wildfires amplified the effect of short-term exposure to $PM_{2.5}$ on COVID-19 cases and deaths, although with substantial heterogeneity across counties.

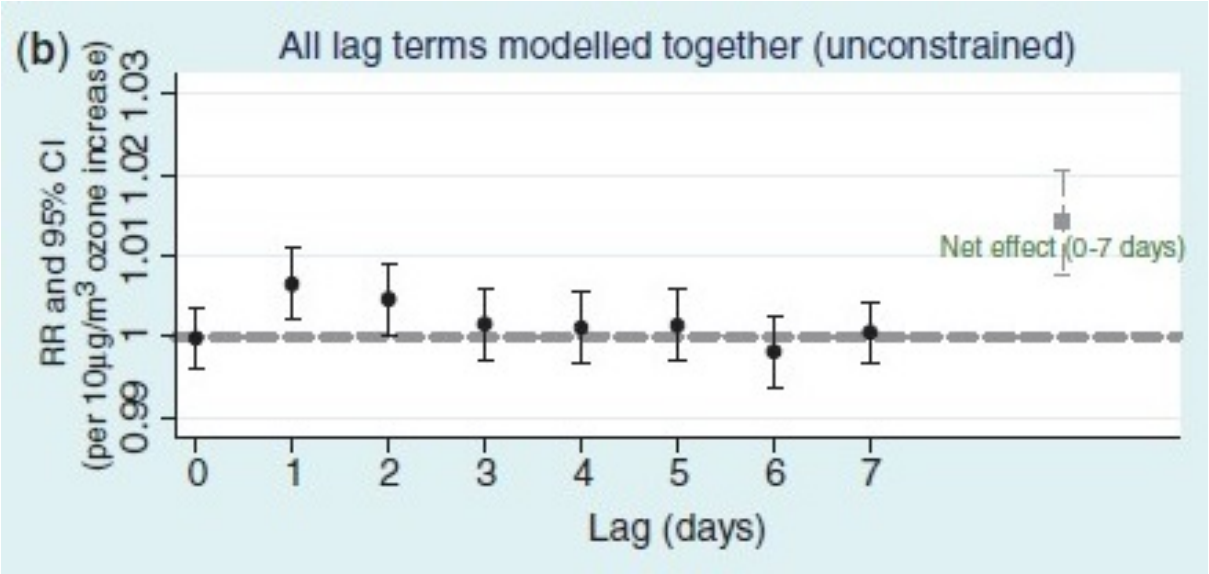
Extensions



Zhou et al. 2021

Extensions

- Lagged Effects
  - What happens if exposures take a while to have an effect?
  - E.g., $PM_{2.5}$ yesterday may be more relevant of today's outcome than $PM_{2.5}$ today?
  - "Distributed lag models" (see Gasparrini et al. 2010, or **ID 271**)



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References

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