An overview of Difference-in-Differences and Synthetic Control Methods: Classical and Novel Approaches

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SER 58th Annual Meeting Workshop

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AGENDA FOR TODAY

- Logistics and introductions
- Part I Tarik ~ 80 min
- Q&A
- Break (~10min)
- Part II Roch ~ 90-120 min
- Q&A
- End

OUTLINE – PART 1

- Causal inference, natural experiments and quasi-experimental methods
- Difference-in-differences methods
- Interrupted Time Series
- Synthetic Control Methods
- Focus on staggered interventions
- Other topics

WORKSHOP OBJECTIVES

1. Understand the conceptual foundations of quasi-experimental methods based on the timing of a natural experiment
2. Understanding how Difference-in-Differences (DID), Interrupted Time Series (ITS) and Synthetic Control Methods (SCM) work and their specific identification assumptions.
3. Being able to implement (in *R*) DID, ITS and SCM in different settings, interpret estimands of interest and check/visualize possible assumptions' violations ➔ Part II

RANDOMIZATION AS A SOLUTION TO DEAL WITH CONFOUNDING

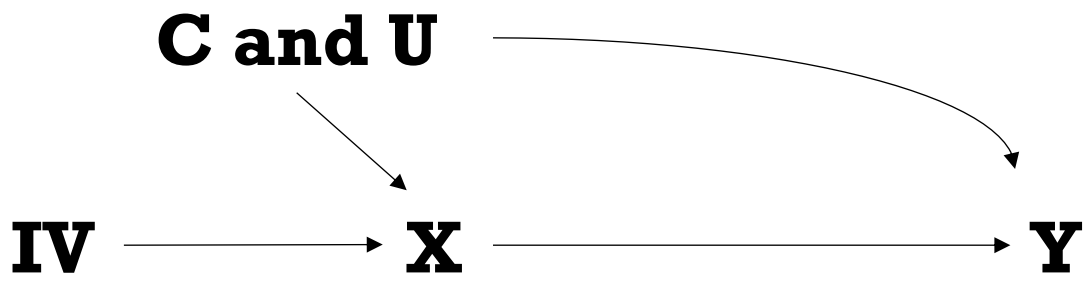
- Randomization has been proposed as a solution to deal with confounding
  - Complying with exchangeability between exposed and non-exposed to the policy/treatment
  - For both **measured & unmeasured** confounding

IDEAL RANDOMIZED EXPERIMENTS

- What makes an ideal randomized experiment:
  - No loss to follow-up,
  - Full adherence to the assigned treatment over the duration of the study,
  - A single version of treatment, and double-blind assignment
- Ideal randomized experiments are unrealistic **but useful to introduce some key concepts for causal inference**

THE IDEA BEHIND RANDOMIZATION

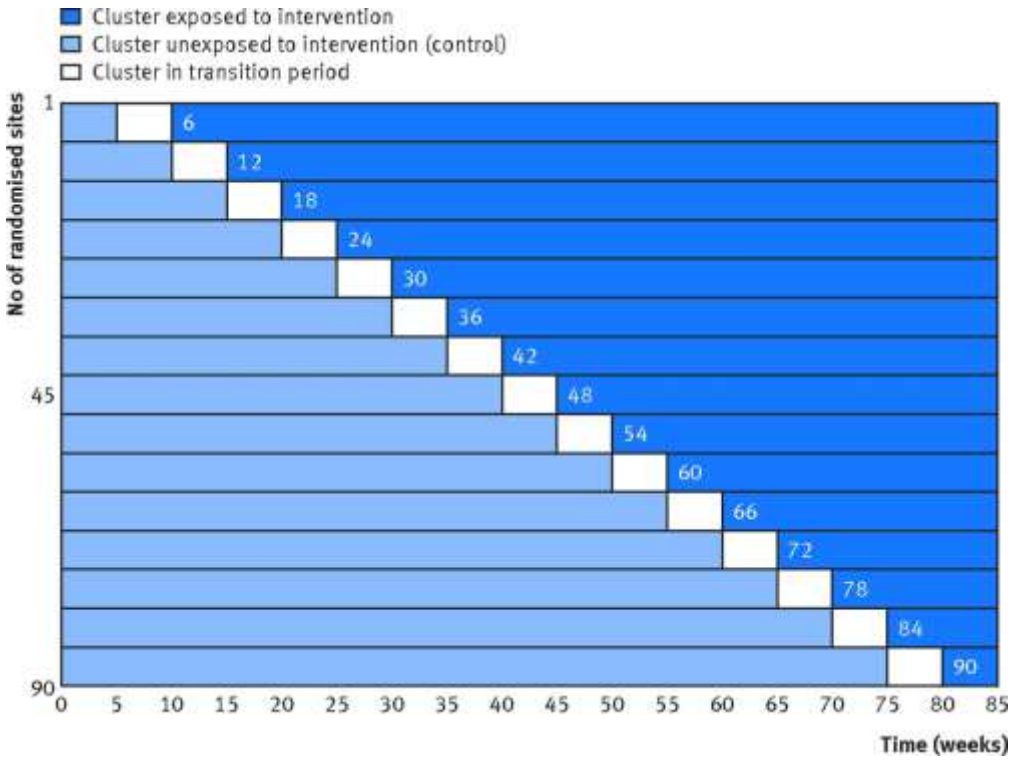
- How do RCT work …
- Randomization can be analyzed as an "**Instrumental Variable**"
- The overall aim is to deal with <u>both measured and unmeasured</u> confounding



- **The problem:** in many cases RCT are not feasible due costs, scale or ethical objections
- Or because it is simply too late ..

DIFFERENT TYPES OF RCTS

- Two-arm, parallel design
- Planned cross-over design
- Factorial design
- Cluster randomized trials
- **Stepped Wedge Designs**
  - **Based on the timing of the intervention**



Hemming, Karla, et al. "The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting." Bmj 350 (2015): h391.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

USING NATURAL EXPERIMENTS

- By capitalizing on natural experiments, Quasi-experimental methods (QEM) can be used as alternatives to experimental methods to provide causal estimates from observational studies.
- The term quasi-experiment refers to:
  - "*experiments that have treatments, outcome measures, and experimental units, but do not use random assignment to create the comparisons from which treatment-caused change is inferred*" (Cook et al. 1979)
- Different QEM, different configurations, different assumptions to draw causal inference
- To <u>partially</u> deal with <u>both measured and unmeasured confounding</u>

EXAMPLES OF NATURAL EXPERIMENTS
NOT ONLY FOR POLICY EVALUATION

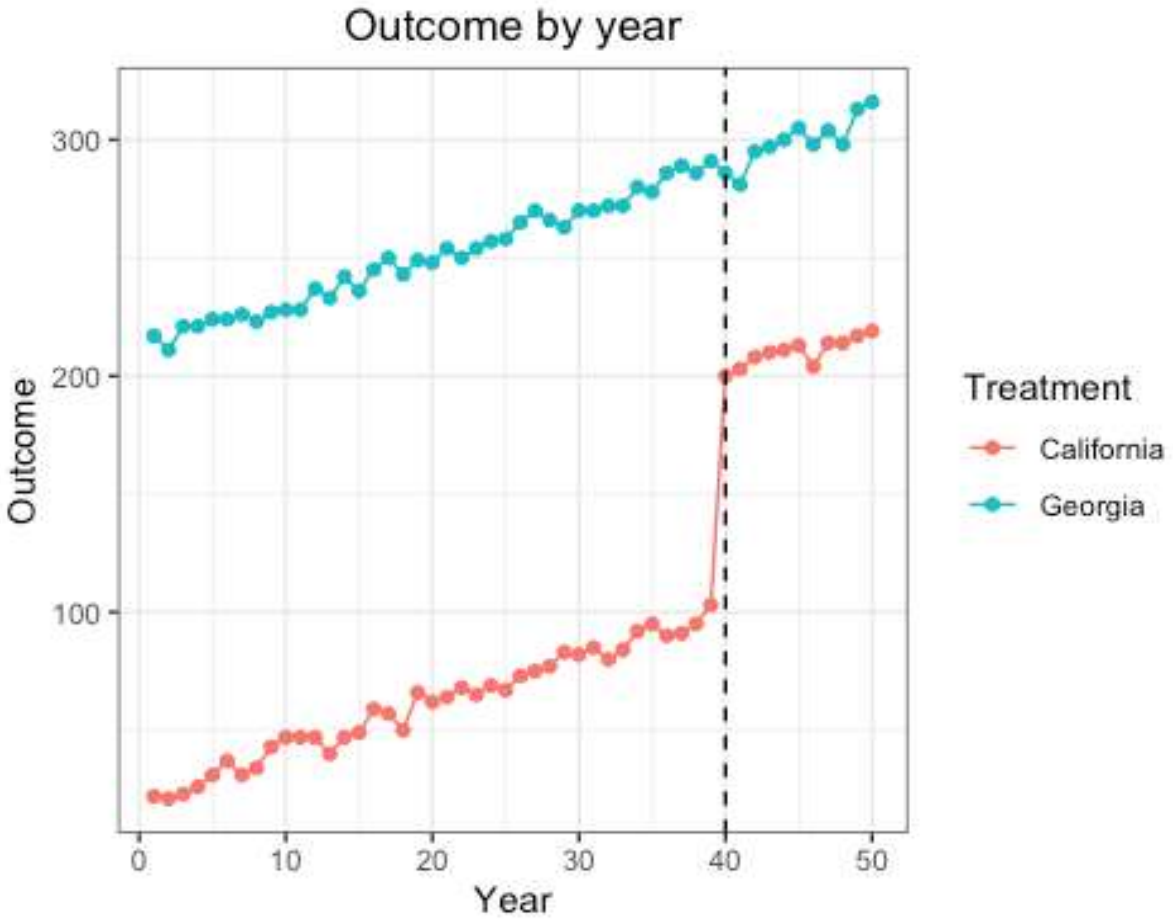
- Public policies:
  - Smoking ban
  - Legalization of marijuana
- Clinical Treatments, Vaccination
- Conditional Cash Transfers
- Natural Hazards
  - Earthquakes
  - Wildfires

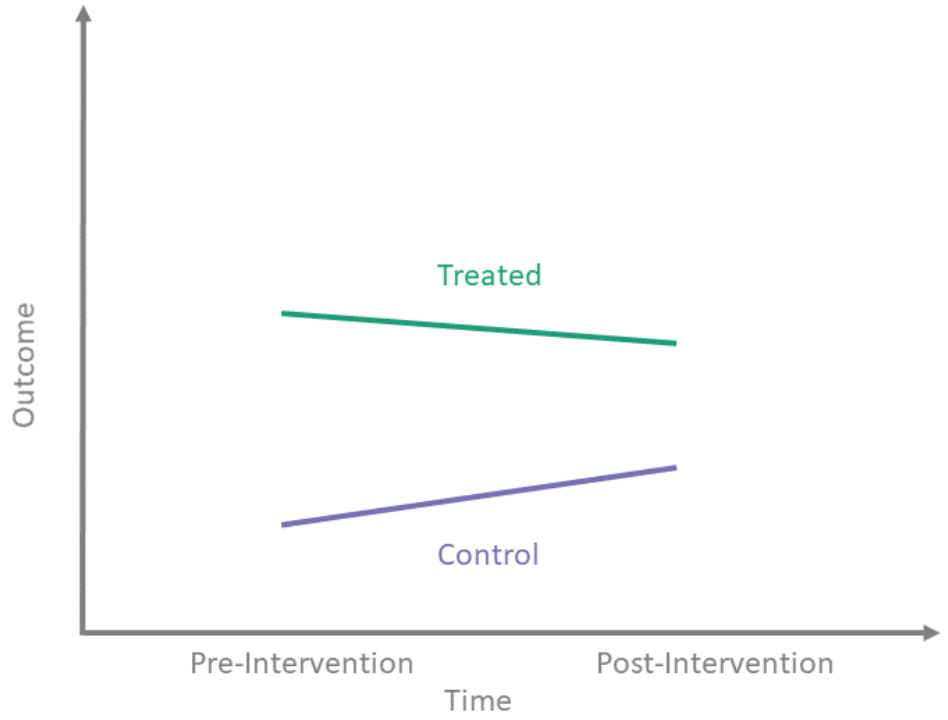
2 main types of natural experiments

- **<u>Timing of the intervention</u>**
- Eligibility to a specific policy (e.g. age for vaccination) and other IV strategies

DIFFERENCE-IN-DIFFERENCES

The difference-in-differences idea





By Bret Zeldow and Laura Hatfield

DIFFERENCE-IN-DIFFERENCES
THE STANDARD APPROACH

- To estimate the effect of interest

$$(\mu_{11} - \mu_{10}) - (\mu_{01} - \mu_{00})$$

$i = 0$ is control group, $i = 1$ is treatment.

$t = 0$ is pre-period, $t = 1$ is post-period.

- Simple Regression modeling approach (with 2 groups)
  - $E[Y \mid a, t, did] = \beta_0 + \beta_1 a + \beta_2 t + \beta_3 did$
  - Where:
    - a represents the group with the policy
    - t represents the period after the policy implementation
    - DID is the interaction between a and t

HOW DOES IT WORK?

	T=0	T=1
A=0	β_0	$\beta_0 + \beta_1$
A=1	$B'_0 + \beta_2$	$B'_0 + \beta'_1 + \beta'_2 + \beta_3$

$$E[Y \mid a, t, did] = \beta_0 + \beta_1 t + \beta_2 a + \beta_3 [a*t]$$

0 0
1 0
0 1
1 1

Like a double or 2-way fixed effect

You can also include more complex time trends

A NOTE ON THE 2-WAY FIXED EFFECTS TERMINOLOGY

- In this workshop (and in epidemiology applications more generally), we used the term 2-way fixed effect to describe the previous setting:
  - One fixed effect for before/after the policy
  - One fixed effect for the intervention/control units
  - And then an interaction term (DID term) between these 2 fixed effects
- In other disciplines (e.g. education), this term can be used in a different way:
  - Mostly in settings in which all units eventually receive the treatment by the end of the study period
  - Similarly, a fixed effect for the treated unit and a fixed effect for before and after
  - But a weighting procedure will be applied to consider the timing of the intervention to obtain an overall treatment effect (ATT)

DID ASSUMPTIONS

- The key assumptions of the DiD analysis are:
  1. The trend in the control group represents a good approximation for the counterfactual trend of the treated group in the absence of the treatment.
  2. Common Shock Assumption
  3. No spillover

MANY APPLICATIONS

Removing user fees for facility-based delivery services: a difference-in-differences evaluation from ten sub-Saharan African countries

Britt McKinnon,[1]* Sam Harper,[1] Jay S Kaufman[1] and Yves Bergevin[2]

Gotta catch'em all! Pokémon GO and physical activity among young adults: difference in differences study

Katherine B Howe,[1,2] Christian Suharlim,[3] Peter Ueda,[4,5] Daniel Howe, Ichiro Kawachi,[2] Eric B Rimm[1,6,7]

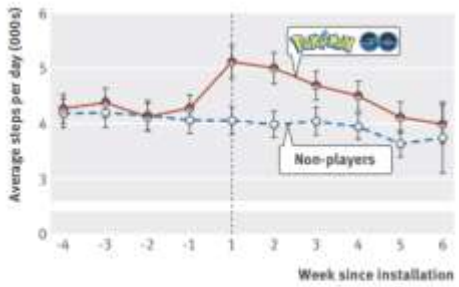


Fig 1 | Average number of daily steps and 95% confidence intervals by week before and after installation of Pokémon GO (median 8 July 2016)

JAMA Pediatrics | Original Investigation

Difference-in-Differences Analysis of the Association Between State Same-Sex Marriage Policies and Adolescent Suicide Attempts

Texting Bans and Fatal Accidents on Roadways: Do They Work? Or Do Drivers Just React to Announcements of Bans?†

By Rahi Abouk and Scott Adams*

Evaluating the effect of hierarchical medical system on health seeking behavior: A difference-in-differences analysis in China

Zhongliang Zhou [a], Yaxin Zhao [b,*], Chi Shen [a], Sha Lai [a], Rashed Nawaz [a], Jianmin Gao [a]

DID COUPLED WITH PROPENSITY SCORE METHODS

- When multiple control groups are available, it is possible to use available information on time-varying and time-fixed confounders
- We can use propensity score matching and IPTW for example
- By doing so, we aim at identifying similar observations at each time point in the control groups

Using propensity scores in difference-in-differences models to estimate the effects of a policy change

Elizabeth A. Stuart · Haiden A. Huskamp · Kenneth Duckworth · Jeffrey Simmons · Zirui Song · Michael E. Chernew · Colleen L. Barry

LETTER

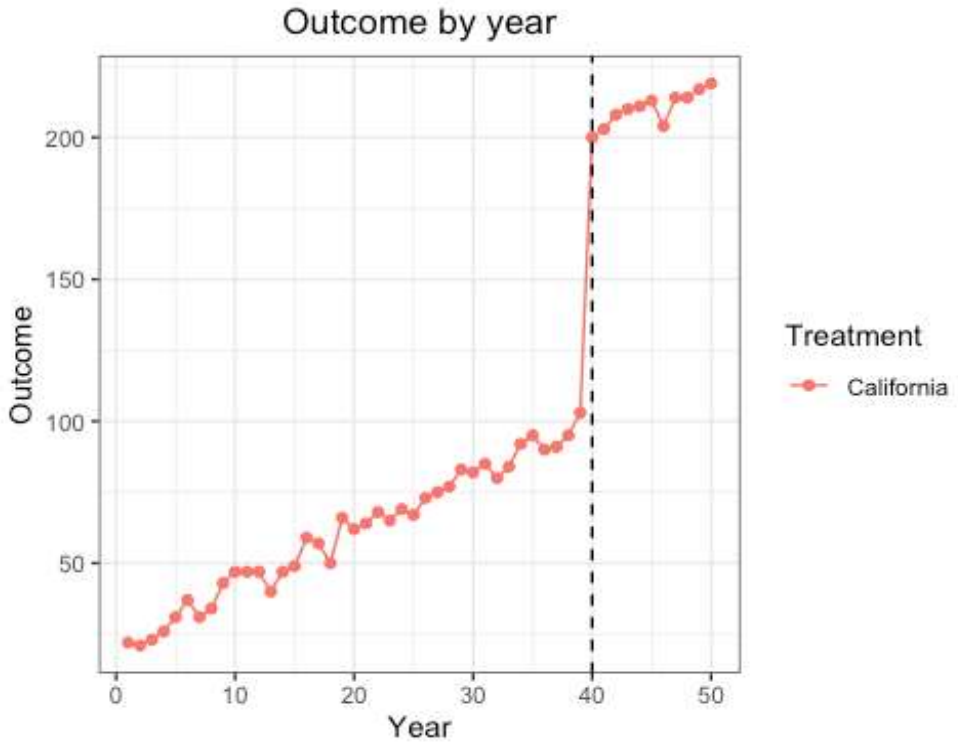
Quantifying the impact of changing the threshold of New York City heat emergency plan in reducing heat-related illnesses

Tarik Benmarhnia[1,3], Lara Schwarz[1], Amruta Nori-Sarma[2] and Michelle L Bell[2]

Evaluating the potential public health impacts of the Toronto cold weather program☆

Tarik Benmarhnia[a,*], Xu Zhao[b], John Wang[b], Melissa Macdonald[c], Hong Chen[b,d,e]

INTERRUPTED TIME SERIES: DID WITHOUT CONTROL GROUPS



Estimation

The traditional approach:

The following model can be used to estimate the effect of the policy on the outcome y

$$y = \alpha + \beta_1(\text{year}) + \beta_2(\text{post}) + \beta_3(\text{xi}) + \beta_4(\text{xt}) + \beta_5(\text{xit}) + \beta_6(\text{year} \times \text{post}) + \epsilon$$

Can be also done through a 2-stage approach:

1. Building and optimizing a predictive model for Y in the pre-treatment period
2. Predicting *Y* in the post-treatment period using the model developed in stage 1 and compare with observed outcomes

Various approaches can be used for stage 1 (ARIMA, random forest, and other ML algorithms)

TWO-STAGE TIME SERIES ANALYSIS COUPLED WITH MACHINE LEARNING: EVALUATING THE HEALTH EFFECTS OF THE 2018 WILDFIRE SMOKE EVENT IN SAN FRANCISCO COUNTY AS A CASE STUDY

- We compared multiple algorithms in a 2-stage ITS approach
  - Autoregressive Integrated Moving Average (ARIMA)
  - NNETAR (Neural Network)
  - Prophet-XGBoost

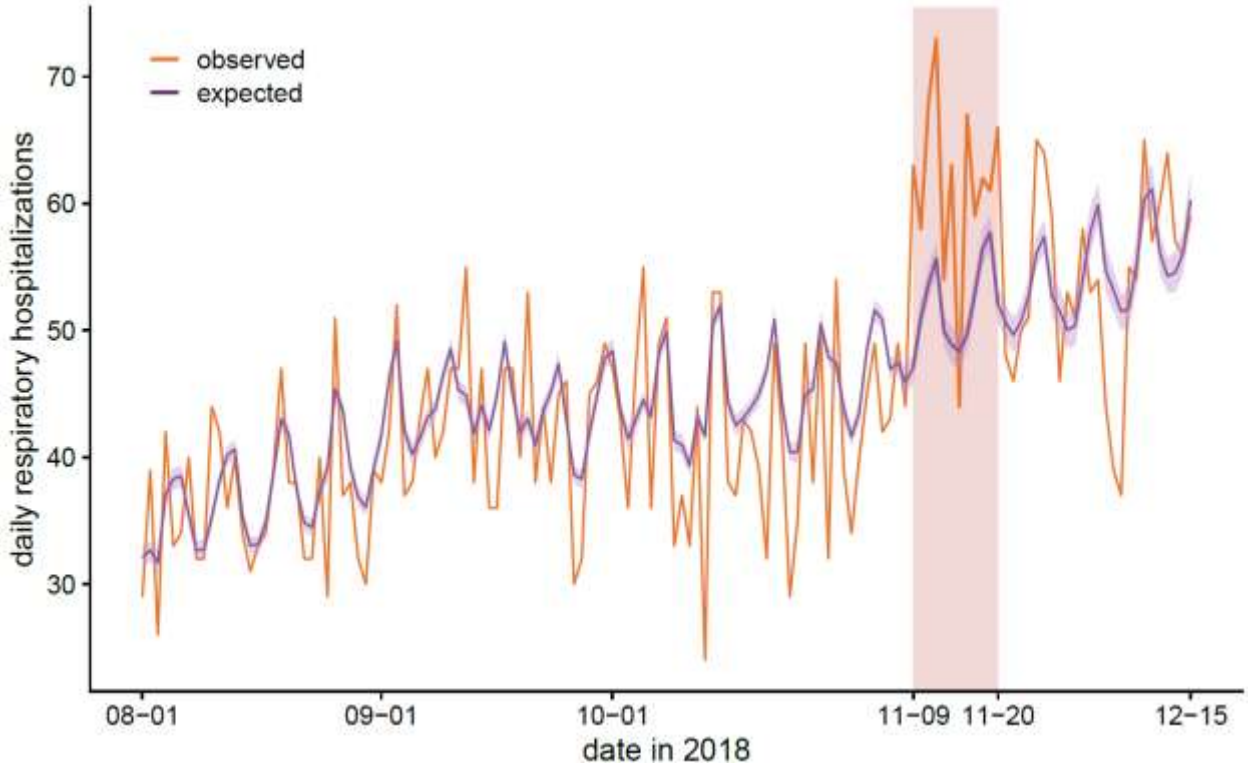


Table 1. Performance metrics of the ARIMA, NNETAR, and Prophet-XGBoost model

	Training (2009-01-01 to 2016-11-07)			Testing (2016-11-08 to 2018-11-07)		
	ARIMA	NNETAR	Prophet-XGBoost	ARIMA	NNETAR	Prophet-XGBoost
R^2	0.71	0.83	0.83	0.65	0.58	0.71
MAE	7.08	5.52	5.33	8.67	9.36	8.11
RMSE	9.19	7.12	7.02	11.84	13.00	10.85
MAPE	0.14	0.11	0.11	0.16	0.16	0.15
SMAPE	0.13	0.11	0.10	0.16	0.17	0.15

R^2: coefficient of determination
MAE: mean absolute error
RMSE: root mean square error
MAPE: mean absolute percentage error
SMAPE: symmetric mean absolute percentage error

OTHER ITS TOPICS NOT DISCUSSED TODAY

- Using Bayesian ITS
- Staggered Interventions

Florida's Opioid Crackdown and Mortality From Drug Overdose, Motor Vehicle Crashes, and Suicide: A Bayesian Interrupted Time-Series Analysis

Kenneth A. Feder, Ramin Mojtabai, Elizabeth A. Stuart*, Rashelle Musci, and Elizabeth J. Letourneau

Education Corner

Staggered interventions with no control groups

Brice Batomen [1,*] and Tarik Benmarhnia[2,3]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [2]Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA and [3]Irset Institut de Recherche en Santé, Environnement et Travail, Inserm, University of Rennes, EHESP, Rennes, France

*Corresponding author. Department of Epidemiology, Dalla Lana School of Public Health, University of Toronto, 155 College Street, Room 688, Toronto, ON M5T 3M7, Canada. E-mail: brice.kuimi@utoronto.ca

Key Messages

- In staggered intervention scenarios without control groups, common model specification for impact evaluations may yield biased estimates due to ill-defined post-intervention periods.
- Alternative model specifications that are drawn from the difference-in-differences literature for staggered interventions can be easily adopted when no control group is available.
- The adoption of these alternative models improves the validity of impact evaluations, especially if heterogeneity is expected across treated groups and across post-intervention time periods.

CONTROLLED ITS OR DID?

- When using one (or more) control group.s, there is no fundamental distinction between Controlled ITS and DID models
- They yield the same counterfactuals and identify the same treatment effects.
- The terminology simply varies across disciplines

Fry, C. E., & Hatfield, L. A. Birds of a feather flock together: Comparing controlled pre–post designs. *Health Services Research*. https://onlinelibrary.wiley.com/doi/epdf/10.1111/1475-6773.13697

ALTERNATIVE OPTIONS FOR SELECTING CONTROL GROUPS

- Besides geographical units that did not receive the treatment/policy, it is possible to consider different types of control groups
- It is possible to use different outcomes or population subgroups to contrast the change in the outcome over time
  - For example, if a given policy only targets individuals above 65 years, it will be possible to use the 64 years of age and below subgroup as a reference group

Research

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/EHP203.

A Difference-in-Differences Approach to Assess the Effect of a Heat Action Plan on Heat-Related Mortality, and Differences in Effectiveness According to Sex, Age, and Socioeconomic Status (Montreal, Quebec)

Tarik Benmarhnia,[1] Zinzi Bailey,[1] David Kaiser,[2] Nathalie Auger,[3] Nicholas King,[4,5] and Jay S. Kaufman[1,5]

- The Montreal heat warning system
  - Implemented in 2004
  - 'active watch' alert level, when daily max temperatures **<u>exceed 30°C</u>**
  - Focus on vulnerable populations
    - Age
    - SES
    - Gender as a placebo

THE ANALYTICAL APPROACH:

- Assigning days (the unit of analysis) to two groups: an "intervention" group that meets an eligibility criterion and a "non-intervention" group that does not.
- the "intervention" group: if 'active watch' alert level is present (heat wave days)
- The non-intervention group: non heat wave days
- The **counterfactual quantity** being estimated is:
  - The difference in the daily number of deaths between intervention (heat wave) and non-intervention (non-heat wave) days in the post-2004 period, had the heat warning system not been implemented

ANALYSES

- Quasi-Poisson Model to estimate a number of 'prevented' daily deaths during heat waves after the policy implementation.
- $\log\big(E(Y_{ct})\big) = \beta_0 + \beta_1 E_{ct} + \beta_2 I_t + \boldsymbol{\beta_3} E_{ct} I_t + f(confounders_{ct}) + offset_{ct}$.
  - E_{ct} to be an indicator variable taking the value of 1 if day t in community c (here Montreal) is an eligible day (i.e., exceeds the community's threshold for activating its HAP)
  - I_t to be an indicator variable taking the value of 1 if day t is post-HAP implementation and the value 0 otherwise
  - β_3 represents our coefficient of interest (DID estimate), capturing whether the HAP affected daily mortality after its implementation
- Cumulative heat effect (lag 0-5) and harvesting effect
- **Sensitivity analysis: Defining the policy implementation at arbitrary ('fake') policy implementation periods (2000 and 2002)**
- **Equity in the causal effect**
  - **To assess heterogeneity in the policy causal effect, we calculated differences-in-differences-in-differences (DIDID) estimates**

DID ASSUMPTIONS

- No time trends in daily mortality among non-eligible days
- Among non-eligible days (less than 30°C), daily mortality did not change before and after 2004
- Short interval of time (4 years before and 4 years after the initiation of the HAP intervention), to limit confounding due to population adaptation and urban changes

RESULTS

- Main effect: 2.52 deaths per day (95% CI: –0.34, 5.38)
- Represents ~50% of deaths attributable to HWs (using the same definition)

Table 2. Estimated effect of the heat action plan program on equity.

Potential modifiers of the program benefits	Heterogeneity in the program effect[a] estimate	95% CI	*p*-Value[b]
Sex (men vs. women)	1.38	(–1.60, 4.36)	0.36
Age (≥ 65 vs. < 65 years)	2.44	(0.27, 4.59)	0.03
Neighborhood SES (lowest SES tercile vs. highest SES tercile)	2.48	(0.69, 4.27)	< 0.01

[a]From DIDID (differences-in-differences-in-differences) estimates (Poisson model adjusted for temporal trends); 95% CIs were obtained by bootstrapping (1,000 samples).
[b]*p*-Values are obtained from a Wald test on the interaction term (i.e., DID estimate considering as health outcome the daily difference between two groups).

SENSITIVITY ANALYSES

Table 3. Sensitivity analyses for the estimated effects of the heat action plan program.

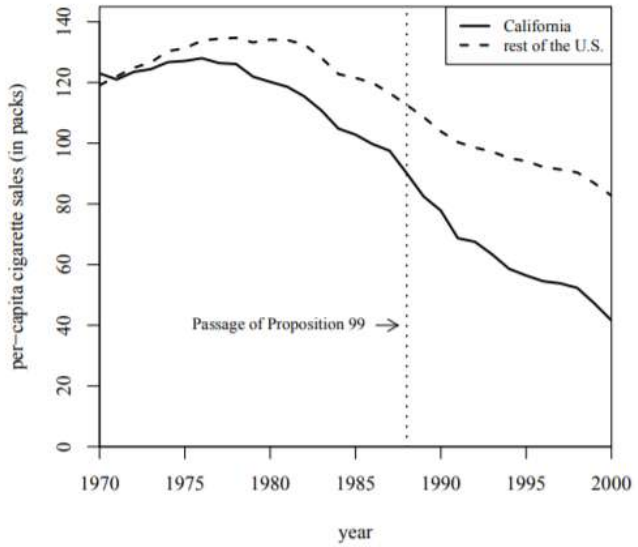
Sensitivity analyses	DID estimate	95% CI	*p*-Value[a]
Arbitrary programs			
Program implemented in 2000[b]	0.94	(–2.08, 3.96)	0.54
Program implemented in 2002[c]	0.42	(–3.62, 2.77)	0.80
Other hot days definitions			
When maximum temperature is above 28°C	0.58	(–1.77, 2.93)	0.63
When maximum temperature is above 32°C	2.79	(–2.65, 8.23)	0.32
Cumulative heat[d]	4.87	(0.67, 8.20)	0.03
Accounting for displacement ratio[e]	1.87	(0.29, 3.47)	0.02
Restriction to non-eligible days above 25°C	2.23	(–0.80, 5.27)	0.15

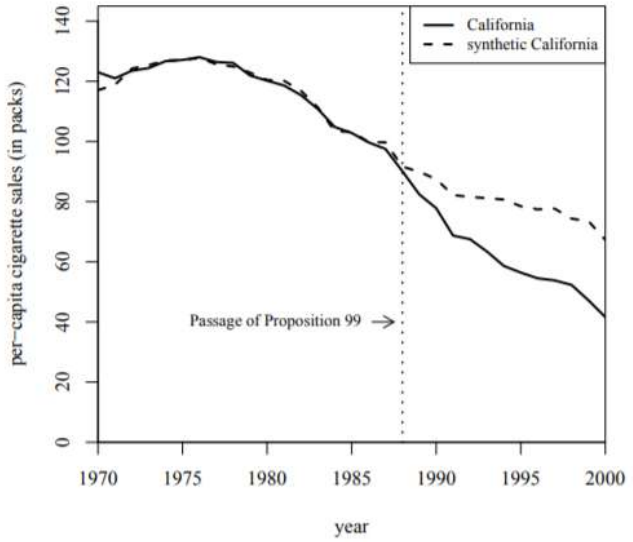
[a]*p*-Values are obtained from a Wald test on the interaction term (i.e., DID estimate).
[b]Using mortality and temperature data for periods 1996–1999 vs. 2000–2003.
[c]Using mortality and temperature data for periods 1998–2001 vs. 2002–2005.
[d]Considering a cumulative heat effect up to 5 consecutive hot days (lag 0–5).
[e]The displacement ratio (Saha et al. 2014) was 0.65.

SYNTHETIC CONTROL METHODS

THE INTUITION

- When using a DID, it is '*sometimes*' difficult to establish whether the parallel trends assumption is met and whether the control group is a sufficiently accurate representation of what would have happened in the treated area without the intervention
- Synthetic control methodology (SCM) allows the construction of a counterfactual by selecting a **weighted average** of the outcome variable from a group of units similar to the treated unit
- The intuition behind this method using the original paper by Abadie et al. 2010





HOW DOES IT WORK?

- The synthetic control is based on the vector of weights **W** that minimizes the imbalance between the treated unit and a weighted average of the controls across a set of variables **X** (e.g. pre-intervention outcomes and/or covariates), $(\boldsymbol{X_1 - X_0 W})' \boldsymbol{V} (\boldsymbol{X_1 - X_0 W})$
  - X_1 and X_0 contain the pre-treatment outcomes and covariates for the treated unit and control units respectively, and ***V*** captures the relative importance of these variables as predictors of the outcome of interest.
- In this setting, we assume the weights W to be positive and summing to 1 to avoid extrapolations issues (Abadie et al 2010). More recent approaches relaxed this assumption
- The treatment effect for the treated unit ($i = 1$), τ_{1t}, can then be estimated by $(Y_{1t} - \hat{Y}_{1t}^{0})$ for each post-intervention period separately, and these can be averaged over time to obtain an ATT over the post-intervention period
- This is a non-parametric approach, but statistical inference can be obtained via permutation tests
- What happens when we have multiple treated units?
  - Discussed later …

STEPS IN CONDUCTING A SYNTHETIC CONTROL STUDY

1. Ensure the theory behind the intervention is well understood. Develop or present a conceptual model to make the theory transparent.
   - To ensure areas that have also been exposed to a similar intervention are excluded from the pool of potential controls
2. Identify potential control units that are plausibly eligible
3. Develop the synthetic control.
   - An optimization procedure using the outcome variables from the potential control areas to select the best weighting of units from the donor pool to create a synthetic control
4. Run outcome analysis and present results
5. Run robustness checks (discussed later)

KEY ASSUMPTIONS

Synthetic control methodology as a tool for evaluating population-level health interventions

Janet Bouttell,[1] Peter Craig,[2] James Lewsey,[1] Mark Robinson,[3] Frank Popham[2]

Table 2 Key assumptions of synthetic control methodology

Assumption	Assessment
1. Treated units and potential control units in the donor pool are similar.	Similar levels in variables known to influence outcome variable (see box 1 for objective and subjective elements of this assessment).
2. There is no contamination – spillover of effects of intervention into potential control units.	Based on background knowledge of researchers.
3. No external shocks in potential control units.	Based on background knowledge of researchers informed by review of trends in outcome variable.

EXAMPLES

SEX WORK REGULATION AND SEXUALLY TRANSMITTED INFECTIONS IN TIJUANA, MEXICO

TROY QUAST[a,*] and FIDEL GONZALEZ[b]

[a]Health Policy and Management, College of Public Health, University of South Florida, Tampa, FL, USA
[b]Economics and International Business, Sam Houston State University, Huntsville, TX, USA

A New Tool for Case Studies in Epidemiology—the Synthetic Control Method

David H. Rehkopf,[a] and Sanjay Basu[b]

Original Contribution

Health Behaviors, Mental Health, and Health Care Utilization Among Single Mothers After Welfare Reforms in the 1990s

Sanjay Basu*, David H. Rehkopf, Arjumand Siddiqi, M. Maria Glymour, and Ichiro Kawachi

Do medical marijuana laws reduce addictions and deaths related to pain killers?☆

David Powell[a,*], Rosalie Liccardo Pacula[a,b], Mireille Jacobson[b,c]

[a] RAND, Santa Monica, United States
[b] NBER, Cambridge, MA, United States
[c] University of California, Irvine, United States

Effects of changes in permit-to-purchase handgun laws in Connecticut and Missouri on suicide rates

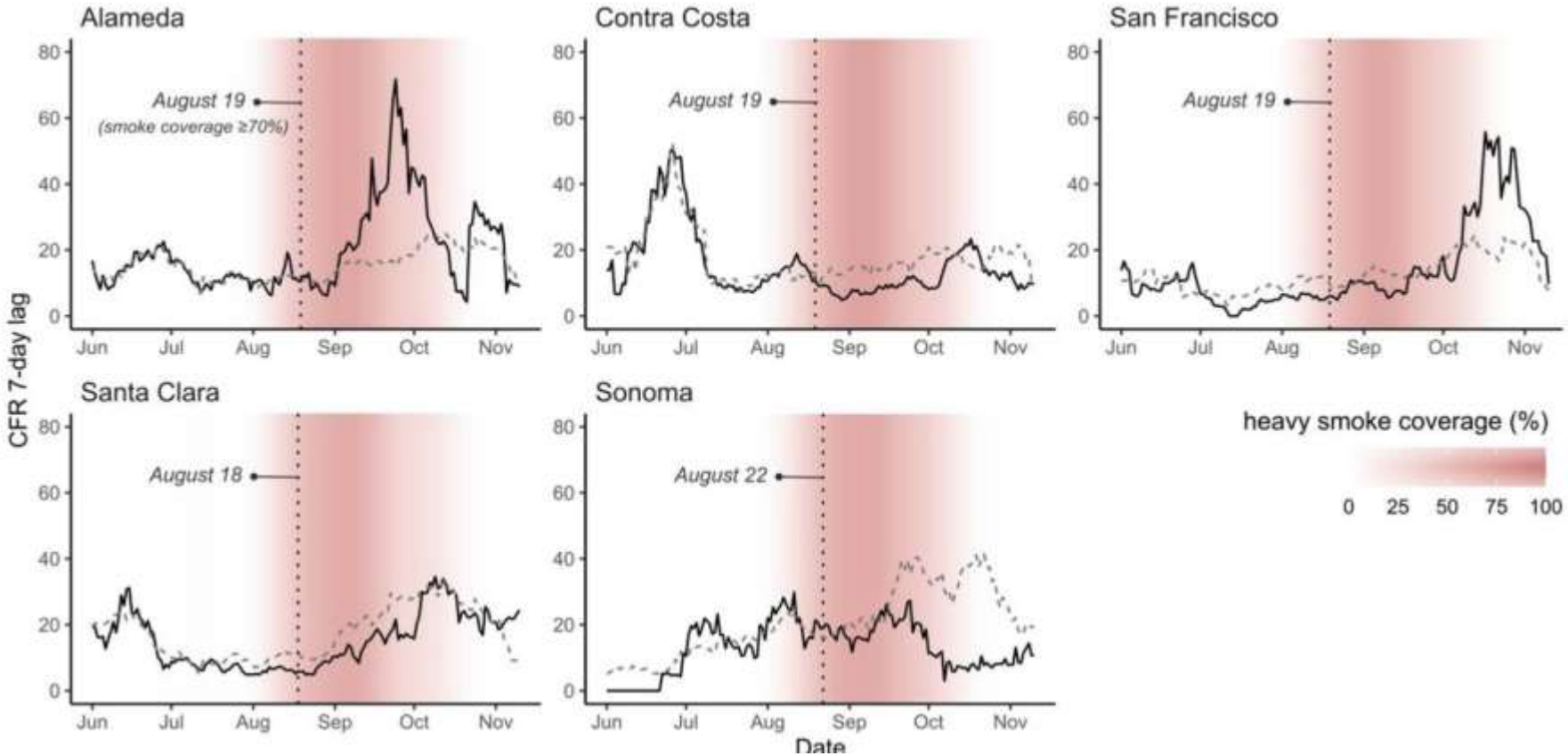
Cassandra K. Crifasi *, John Speed Meyers, Jon S. Vernick, Daniel W. Webster

Johns Hopkins Center for Gun Policy and Research, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

LETTER

Smoke and COVID-19 case fatality ratios during California wildfires

Lara Schwarz[1,2,*], Anna Dimitrova[3], Rosana Aguilera[3], Rupa Basu[4], Alexander Gershunov[3] and Tarik Benmarhnia[2,3]



MULTIPLE TREATED GROUPS

- When dealing with multiple treated units, there are two distinct settings:
  - All treated units received the intervention of interest at the same time
    - Covered today
  - Treated units received the intervention at different times
    - Discussed later
- When multiple units receive the intervention at the same time:
  - A simple approach is to estimate a separate ATT for each treated unit and then conduct a meta-analysis to get a pooled estimate (and also information about heterogeneity across units)
  - Or aggregate the treated units and form a synthetic control for the aggregated treated unit (Acemoglu et al. 2013; Dube and Zipperer, 2015)

EXTENSIONS OF TRADITIONAL SC: GENERALIZED SYNTHETIC CONTROL (GSC)

Xu et al. 2017 proposed generalized synthetic control (**GSC**): estimates the average treatment effect on the treated using time-series cross sectional data

Improves efficiency and interpretability from SC, and can be used with multiple treated units and time varying confounders

GSC overcomes limitations in SC:

- Only unbiased when weights yield exact balance on lagged outcomes (and unidirectional weights)
- Only handles one treated unit at a time
- No formal measures of variance in traditional SC

HOW DOES GSC WORK?

- Generalized synthetic control (**GSC**) methods estimate the average treatment effect on the treated (ATT) using time-series cross sectional data
- Well suited for:
  - Time varying confounding: temperature, other weather events
  - Widespread exposure - multiple exposed units
- **The intuition behind this approach**

$$Y_{it} = \delta_{it} D_{it} + x'_{it}\beta + \lambda'_i f_t + e_{it}$$

- D_{it} treatment indicator
- x_{it} observed covariates
- f_t latent factors
- λ_i factor loadings

$$Y^0_{it} = x'_{it}\beta + \lambda'_i f_t + e_{it}$$

$$Y^1_{it} = \delta_{it} + x'_{it}\beta + \lambda'_i f_t + e_{it}$$

$$\widehat{\Delta}_{it} = Y^1_{it} - \widehat{Y}^0_{it}$$

CASE STUDY: 2007 SOUTHERN CALIFORNIA WILDFIRES ON RESPIRATORY HOSPITALIZATIONS [SHERIDAN ET AL.]

As the climate changes, wildfires are expected to increase in frequency, intensity and duration (especially in California)

In this case study we use:

- Satellite based smoke plume data and burn area data to classify wildfire exposure
- OSHPD respiratory hospitalization data by zip code for outcome

EPIDEMIOLOGY

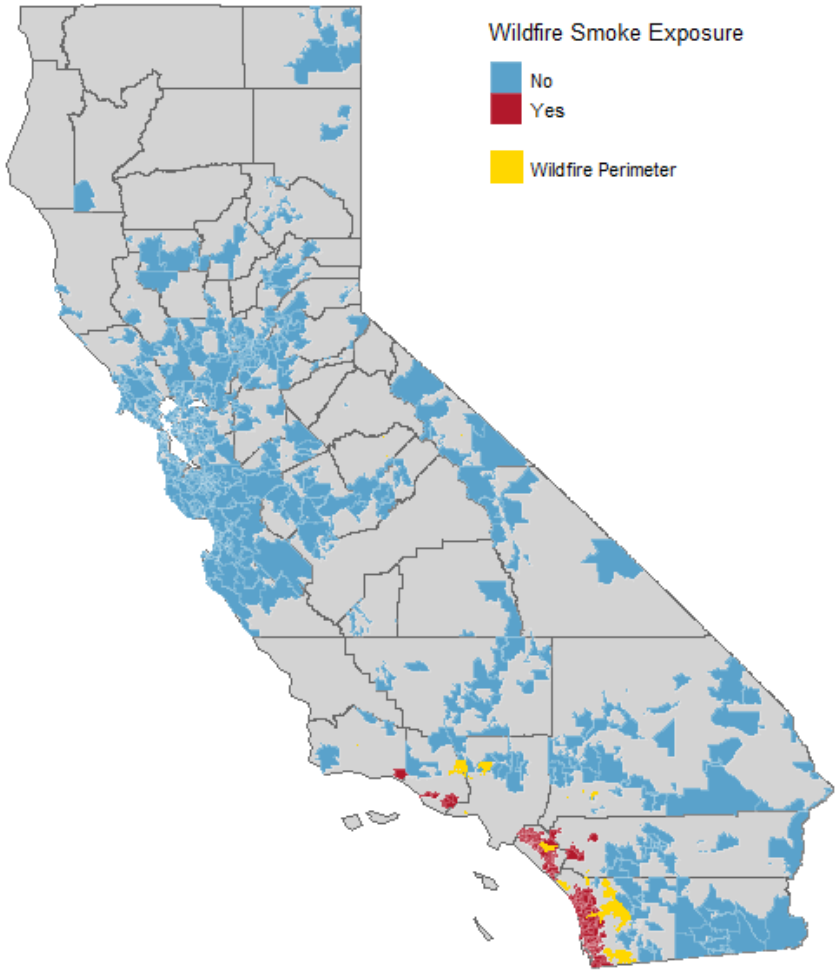
Sheridan P, McElroy S, Casey J, Benmarhnia T. Using generalized synthetic control to estimate the impact of extreme weather events on population health. Epidemiology [In Press]

RESULTS

Out of 1779 zip code tabulation areas in California

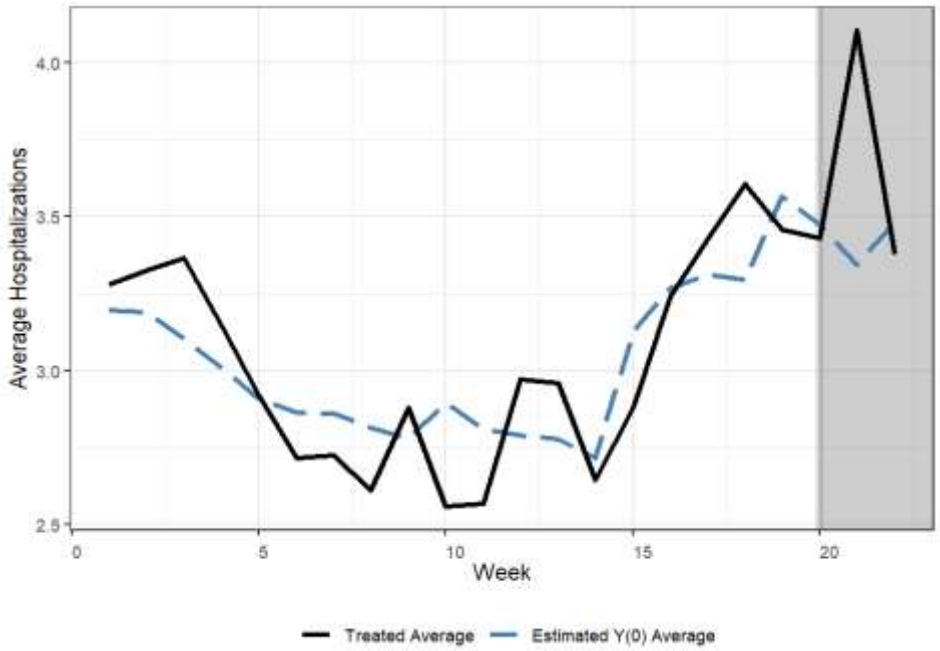
685 were included:

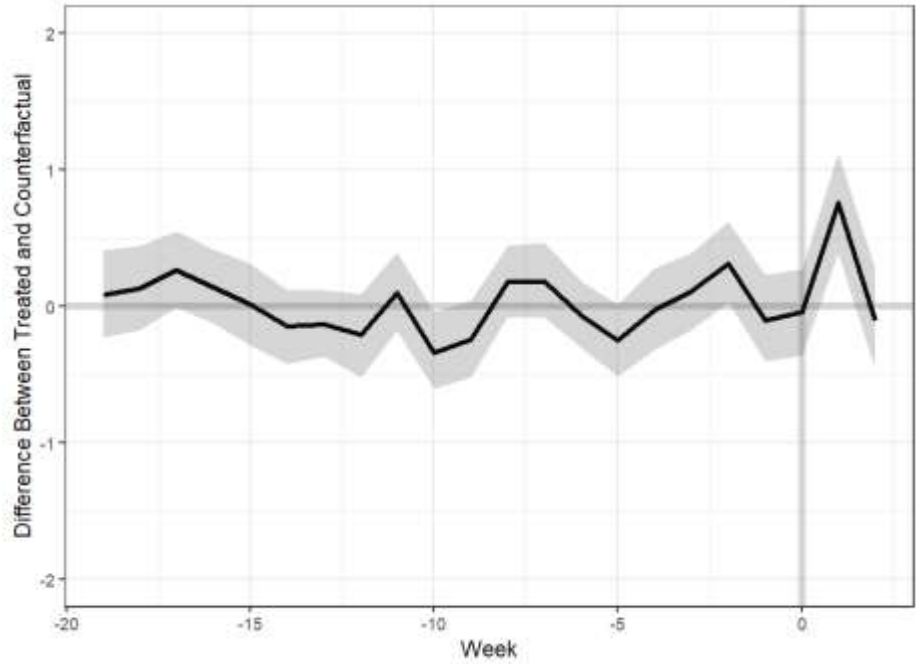
- 130 exposed
- 555 unexposed



Map of California zip codes exposed to wildfire smoke week of October 20th 2007.

RESULTS





We found an **18% (95%CI: 10%-29%)** average increase in respiratory hospitalizations as a result of the wildfire storm

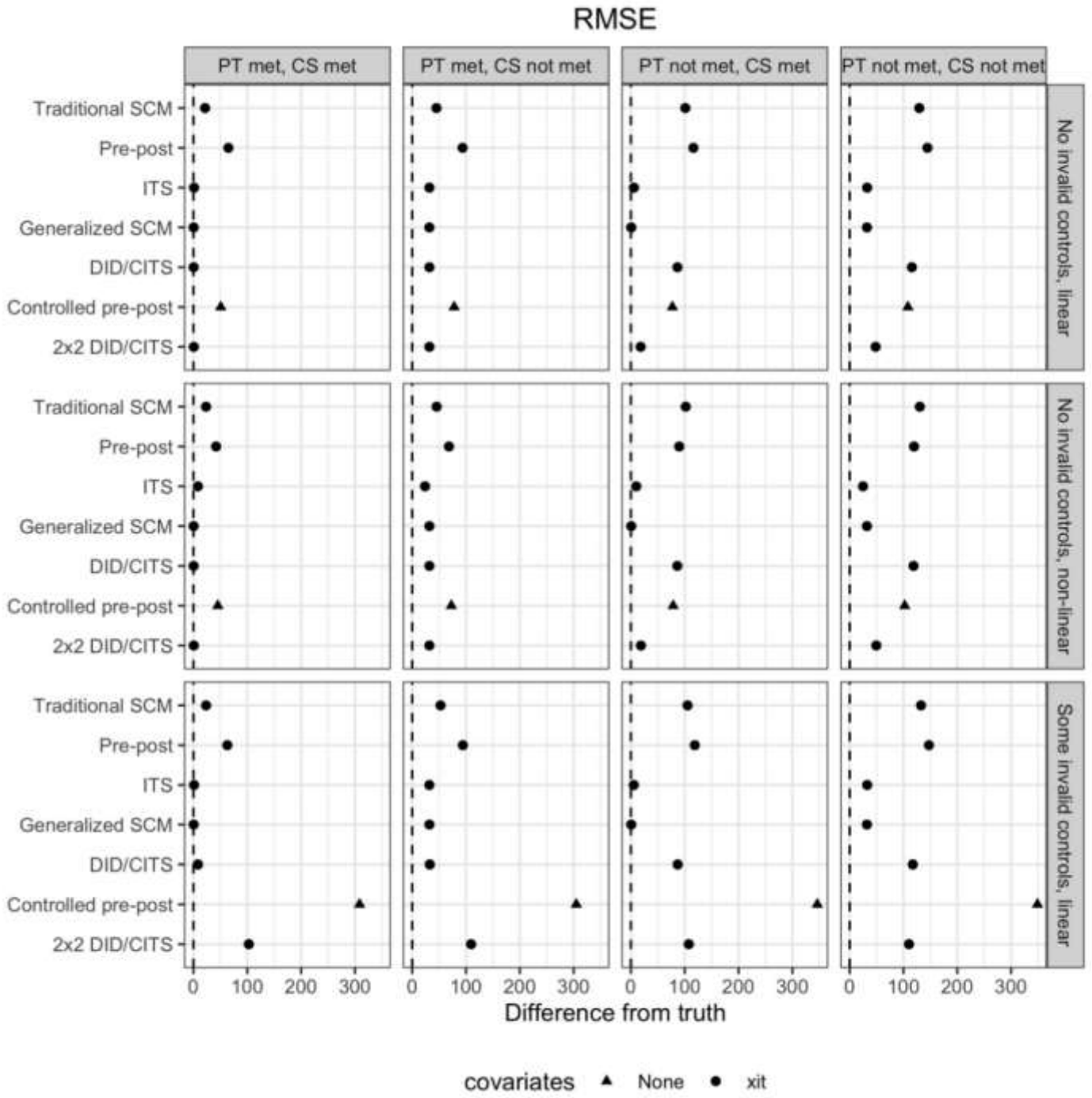
A COMPARISON OF THE DIFFERENT APPROACHES DISCUSSED TODAY

- We compared several quasi-experimental methods that use data before and after an intervention and contrast their performance within a simulation framework
  - Root mean squared error as our metric of interest
- We conducted a comprehensive simulation to assess:
  - The parallel trend assumption
  - The common shock assumption
  - Different sets of control groups
  - Different types of time trends
  - Time-varying confounding

A comparison of quasi-experimental methods with data before and after an intervention: an introduction for epidemiologists and a simulation study

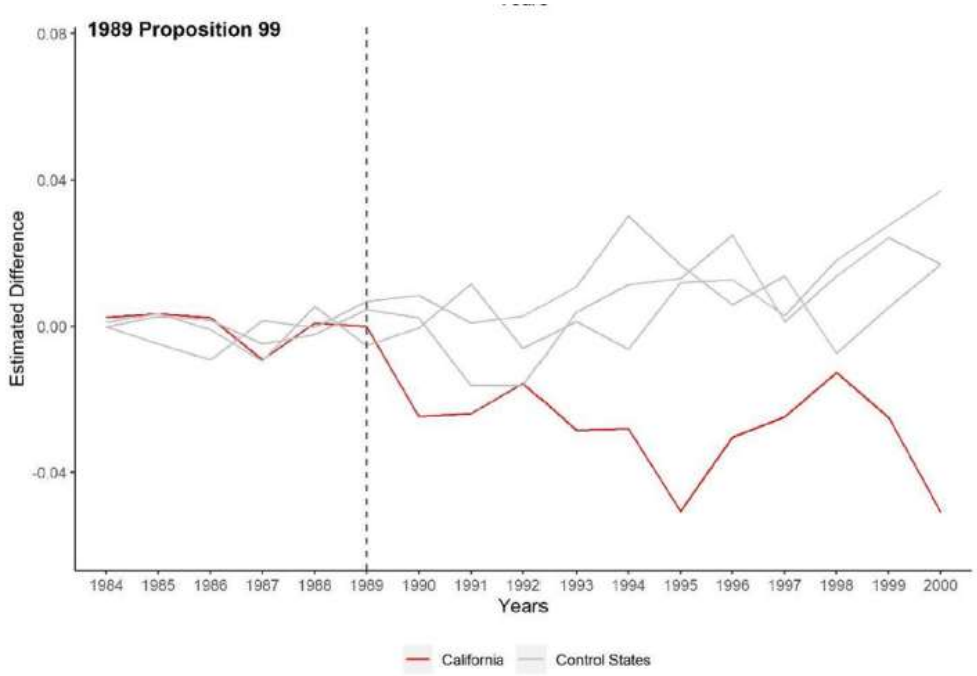
Roch A Nianogo ,[1,2]* Tarik Benmarhnia[3] and Stephen O'Neill[4]

International Journal of Epidemiology, dyad032.


RMSE
PT met, CS met
PT met, CS not met
PT not met, CS met
PT not met, CS not met
No invalid controls, linear
No invalid controls, non-linear
Some invalid controls, linear
Traditional SCM
Pre-post
ITS
Generalized SCM
DID/CITS
Controlled pre-post
2x2 DID/CITS
0
100
200
300
Difference from truth
covariates
None
xit

THE IMPORTANCE OF FALSIFICATION TESTS

- <u>Permutation tests</u>
- Many assumptions cannot be checked empirically
  - It is therefore important to design a set of falsification/placebo tests to improve the inference of interest
- Negative control approaches
  - Lipsitch M et al. (2012): Negative controls: a tool for detecting confounding and bias in observational studies.



Sheridan et al. "Evaluating the impact of the California 1995 smoke-free workplace law on population smoking prevalence using a synthetic control method." Preventive medicine reports 19 (2020): 101164.

MULTIPLE TREATED UNITS AT DIFFERENT TIMES

- A very active area of research
  - Goodman-Bacon (2018) proposed a solution based on a weighted average of all possible DID estimators (using some groups multiple times) in the sample of interest. This approach requires an additional identifying assumption of time-invariant treatment effects.
  - Callaway and Sant'Anna (2020) proposed an analytical solution for such case where there are more than two time periods and units that can become treated at different points in time while relaxing the time-invariant treatment effects assumption

WHAT DO WE MEAN BY STAGGERED INTERVENTIONS?

- When a given policy/treatment is affecting multiple units <u>but at different times points</u>

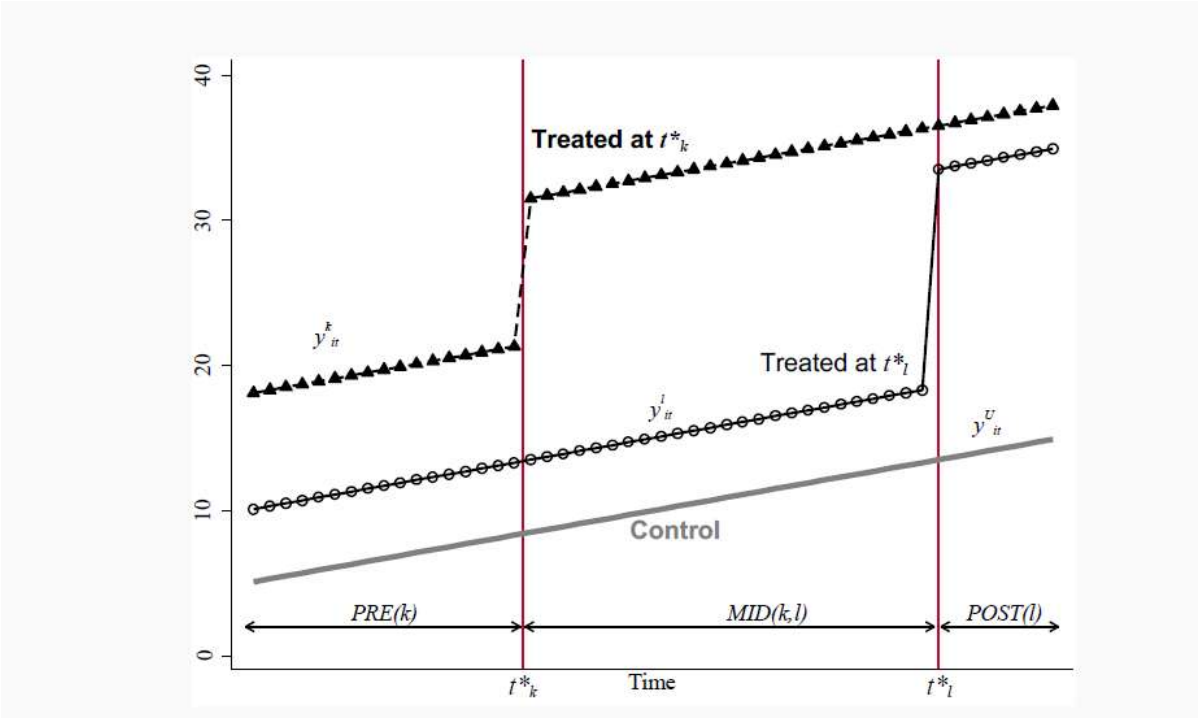


Figure from Goodman-Bacon, 2021

WHY DO TRADITIONAL METHODS FAIL IN SUCH SETTINGS?

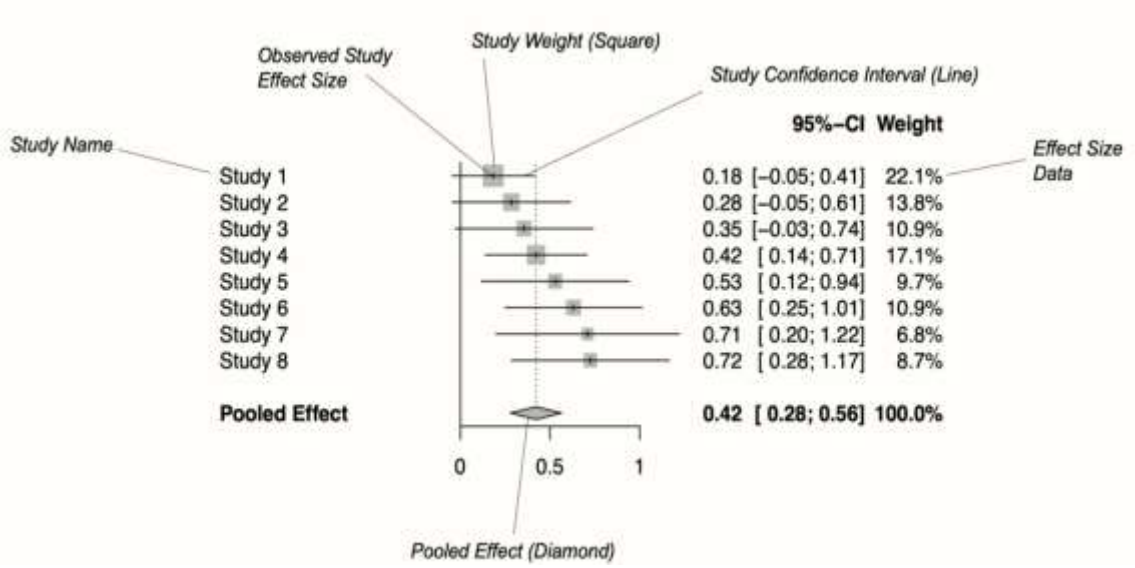
- Simple settings for DID and SCM do not apply here for a few reasons:
  - Each treated unit requires a suitable control group specific the timing of the policy/treatment
  - Units that receive the policy/treatment later may be used as control unit earlier in the study period
    - Some potential statistical dependence issues
  - **We do not want to assume that a given policy/treatment has the same effect across units and over time**

ANALYTICAL APPROACHES TO DEAL WITH STAGGERED INTERVENTIONS

- Multiple approaches have been proposed in the past few years
  - A very active area: De Chaisemartin, C., & d'Haultfoeuille, X. (2022)
- We follow the 2-stage approach proposed by Callaway and Sant'Anna (2020)
- This approach requires:
  - To have –enough- never treated units
  - To assume independence regarding the timing of the implementation over treated units
  - Similar assumptions as traditional settings

A QUICK NOTE ON META-ANALYSES AND META-REGRESSIONS

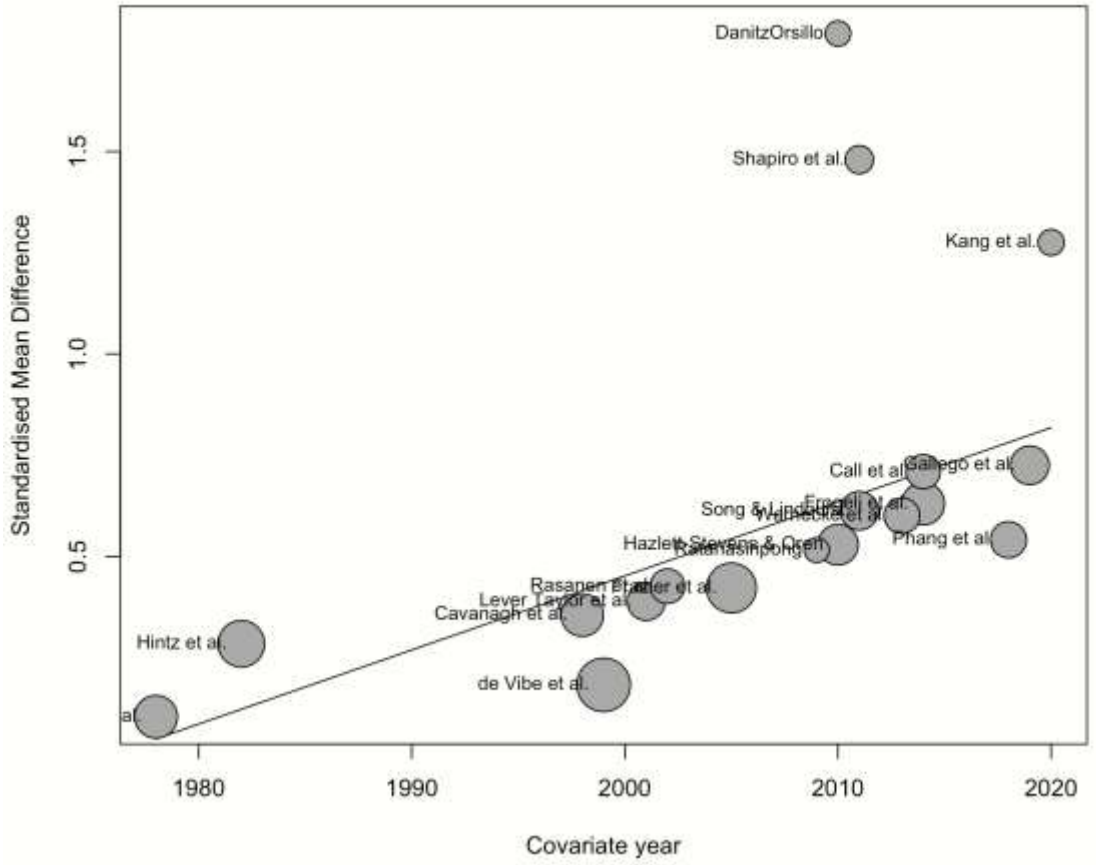
- Meta-analyses are typically used to pool effect estimates from multiple studies
- This is a form of multilevel model, in which participants are nested within studies
- We obtain a pooled effect estimate by applying a weighting procedure (usually based on the inverse of the standard error)
- We can also quantify the level of heterogeneity across studies
- If there is some heterogeneity, we then can conduct a meta-regression in which the dependent variable is the study-specific effect estimate and independent variables study-specific characteristics (e.g. study period, population composition etc…)



https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/forest.html

HOW DO META-REGRESSION WORK?

- An intuitive way to describe meta-regression is a weighted regression based on the study-specific variance
  - If all studies have the same variance: meta-regression = simple regression
- We then obtain a slope for each independent variable, and we can understand the drivers of effect estimates heterogeneity

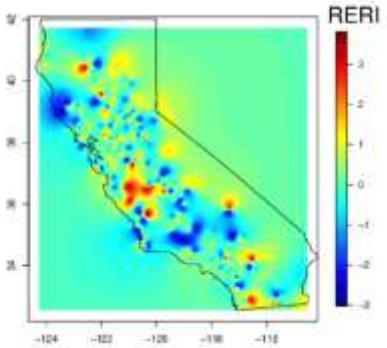


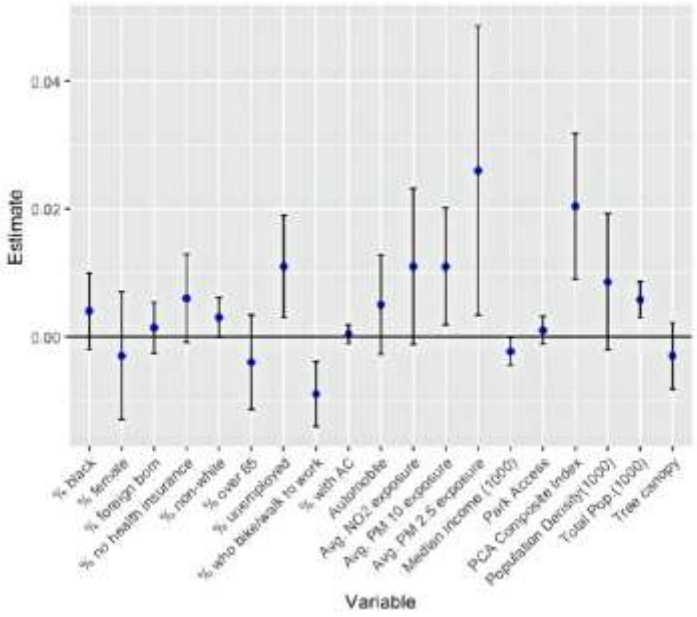
https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/metareg.html

SOME EXAMPLES

Spatial variation in the joint effect of extreme heat events and ozone on respiratory hospitalizations in California

Lara Schwarz[a,b,1,2], Kristen Hansen[b,1,2], Anna Alari[c], Sindana D. Ilango[d], Nelson Bernal[e], Rupa Basu[f], Alexander Gershunov[g], and Tarik Benmarhnia[b,g]





Epidemiology of *Chlamydia trachomatis* in the Middle East and north Africa: a systematic review, meta-analysis, and meta-regression

Alex Smolak, Hiam Chemaitelly*, Joumana G Hermez, Nicola Low, Laith J Abu-Raddad*

Sex differences in injury rates in team-sport athletes: A systematic review and meta-regression analysis

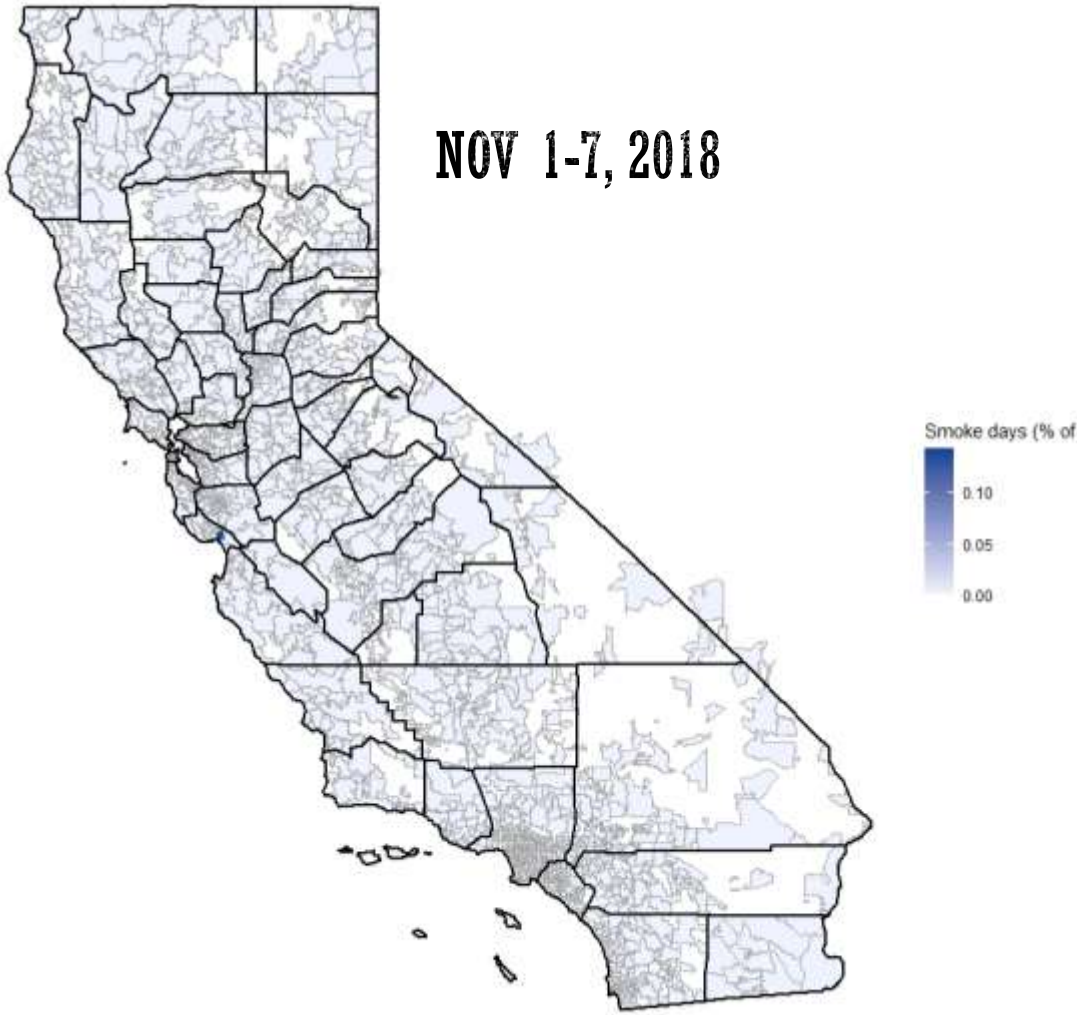
Astrid Zech [a,*], Karsten Hollander [b], Astrid Junge [b,c], Simon Steib [d], Andreas Groll [e], Jonas Heiner [e], Florian Nowak [a], Daniel Pfeiffer [a], Anna Lina Rahlf [f]

A CASE STUDY: WILDFIRE SMOKE AND COMPOUNDED RISKS FROM RESPIRATORY INFECTIOUS DISEASES

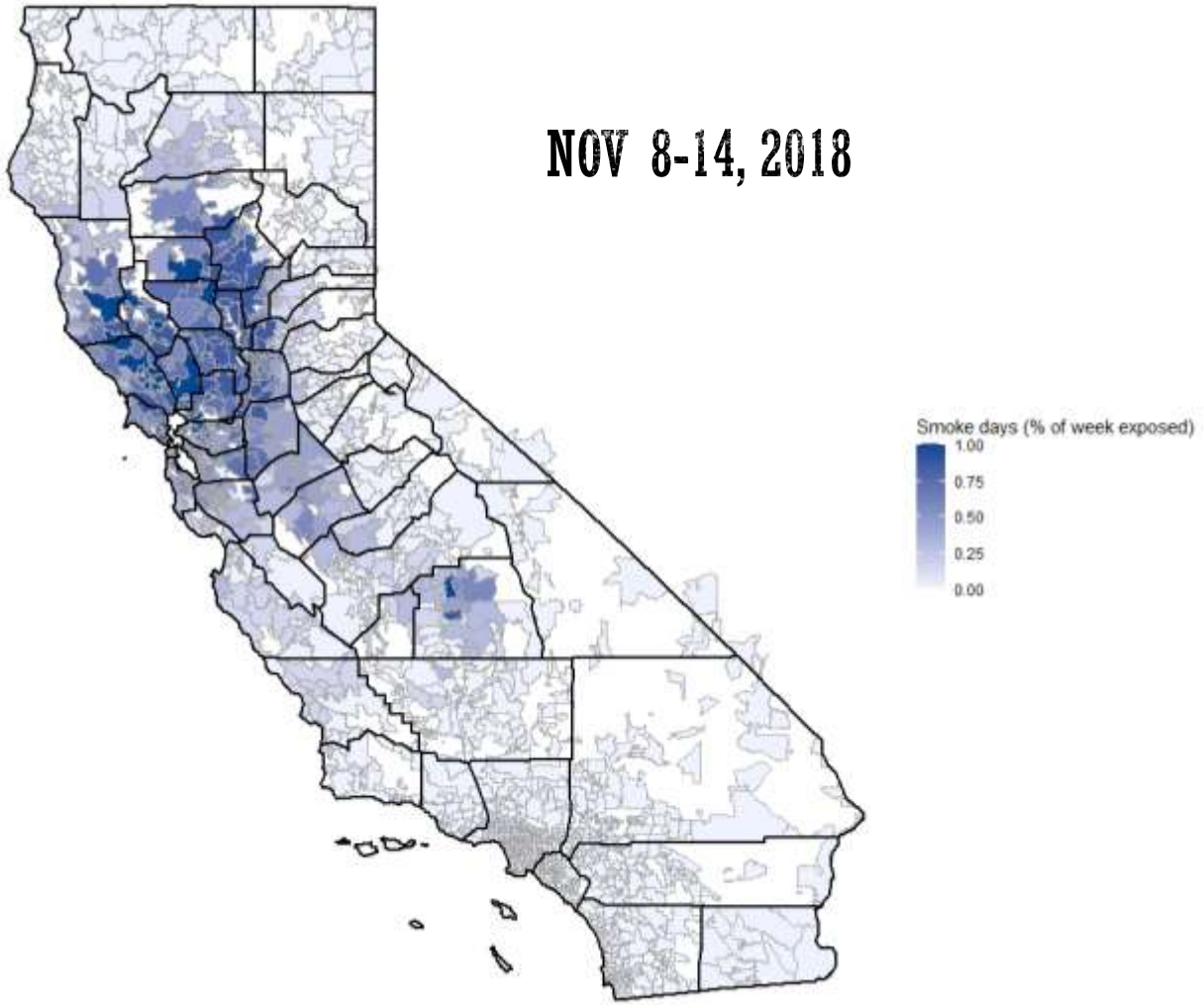
- Objectives:
  - Assess the county-specific effects of wildfire smoke on all respiratory hospitalizations using a large wildfire event in November 2018 as a case study
    - Using generalized synthetic control methods
  - Evaluate how population-level influenza frailty modifies such effects
    - Using a random effect meta-regression

TREATED ZIP CODES WITH SMOKE PM2.5>0

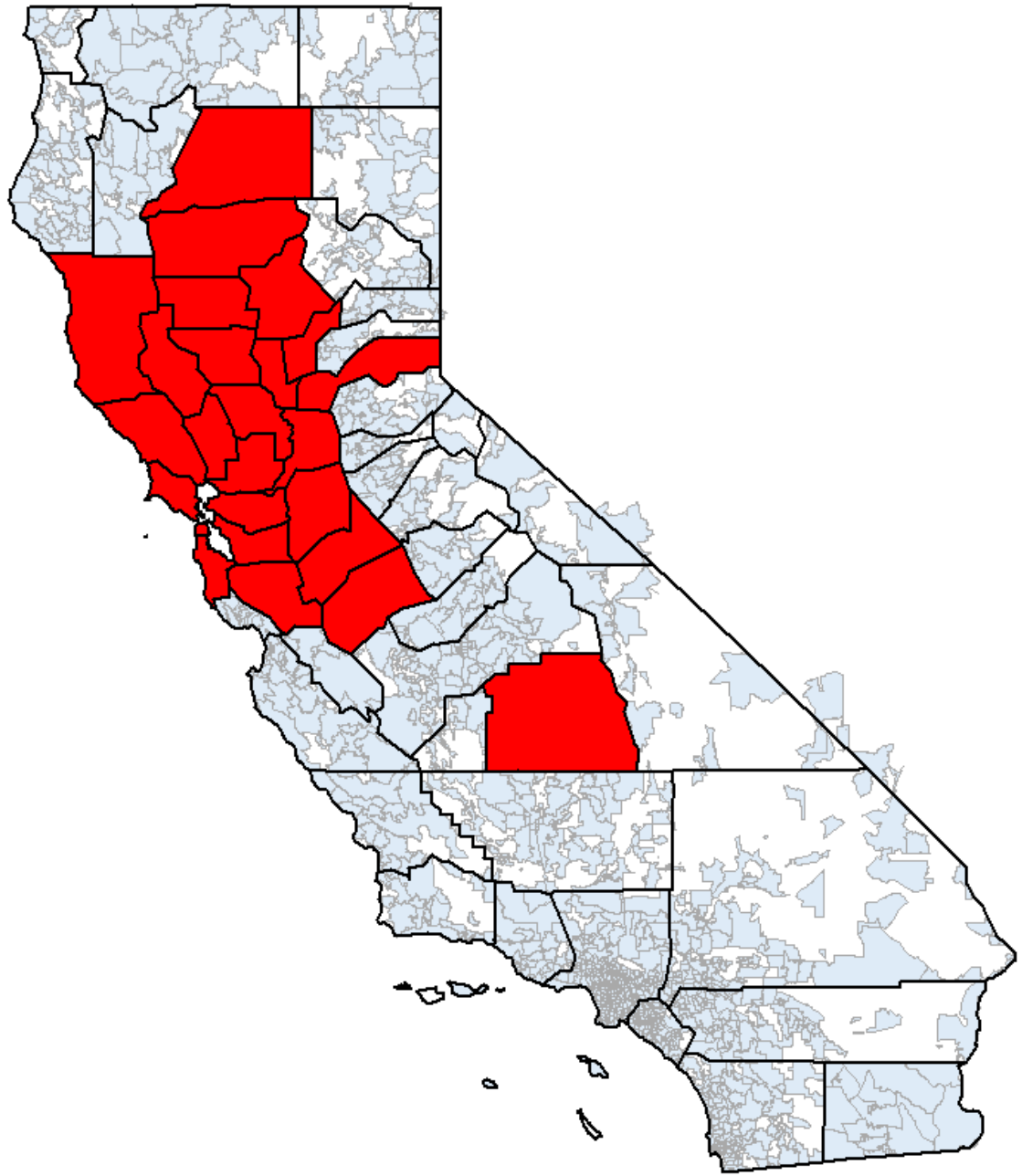
NOV 1-7, 2018



NOV 8-14, 2018



25 COUNTIES EXPOSED DURING NOV 8-14 WEEK



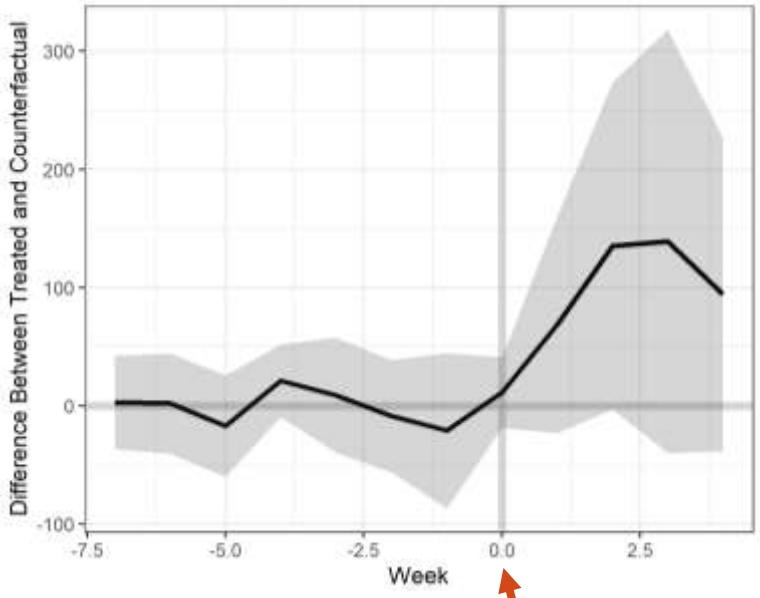
ESTIMATING INFLUENZA BURDEN Z-SCORE

- OSHPD flu data was processed at the daily zip code level
  - ICD-9 codes: 487, 488 ICD-10 codes: J09, J10, J11
- Weekly counts were summarized at the County level
- Weekly z-score computed for every County
  - Restricted to 2010-2019, flu season based on CDC (October to May)
- Average flu z-score for weeks 42-44 (**3 weeks prior** to wildfire smoke start) for each County

*OSHPD: Office of Statewide Health Planning and Development Patient Discharge Data

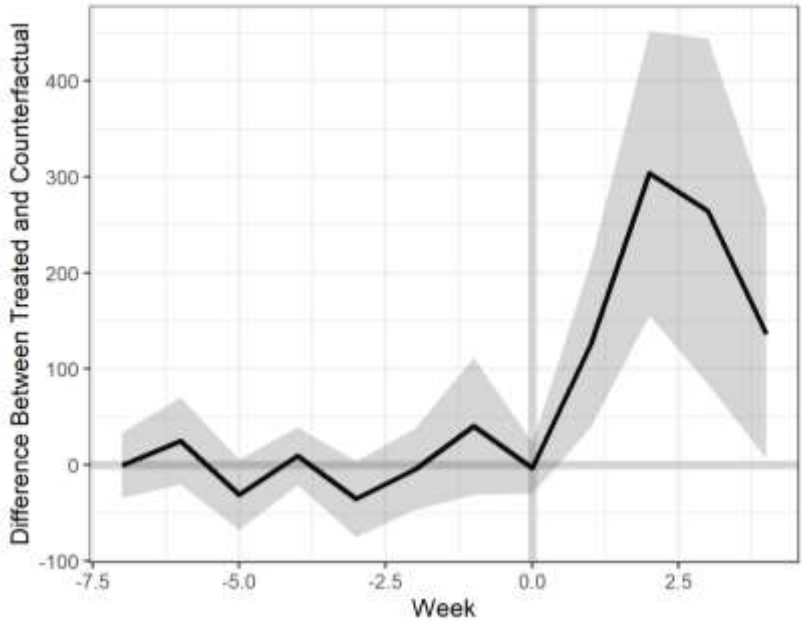
RESULTS (1/2)

SAN JOAQUIN COUNTY

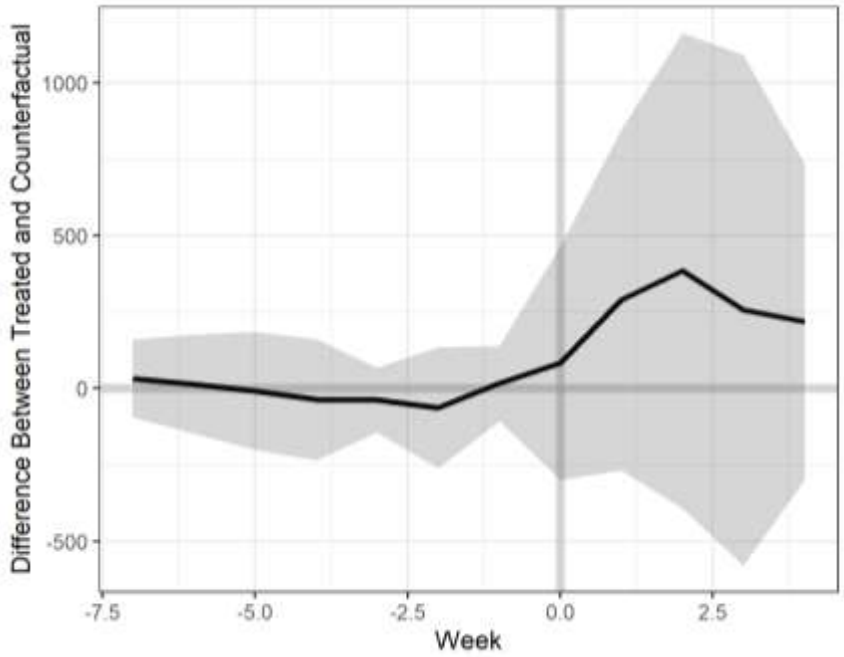


WILDFIRE START

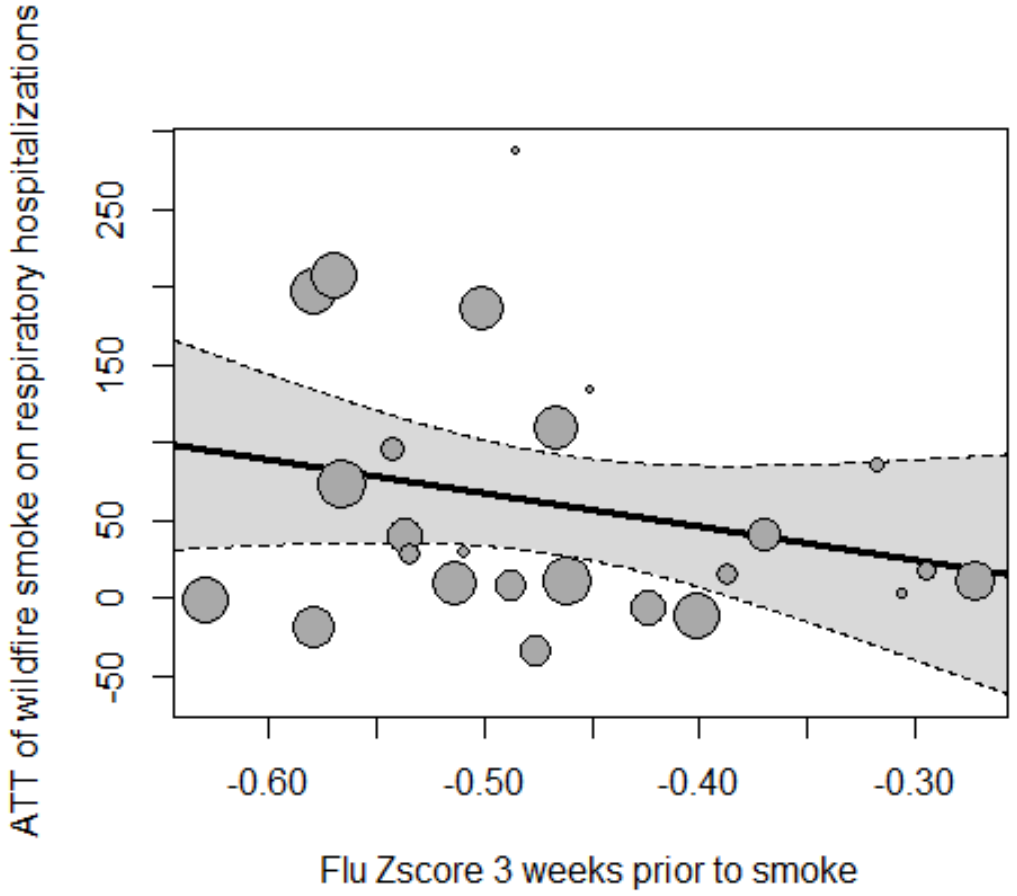
SANTA CLARA COUNTY



ALAMEDA COUNTY



RESULTS (2/2)



RESULTS FROM THE RANDOM-EFFECT META-REGRESSION MODEL

β = -215.42 (95% CI:, -550.72, -119.88)

TOPICS NOT DISCUSSED TODAY

- Alternative approaches
  - E.g. Augmented Synthetic Control
- Multi-stage interventions
- The Scale of interest
  - Important to think about the scale of the interaction term
    - When Is Parallel Trends Sensitive to Functional Form? (Roth and Sant'Anna, 2021)
- Lagged/delayed effects
  - Many available tools

IN SUMMARY
DESIGNING A STUDY CAPITALIZING ON THE TIMING OF AN INTERVENTION

When designing a study in which the timing of an intervention is capitalized on, we recommend to undertake the three following steps

1. Define a **clear research question**, ideally with a well-defined intervention with specific implementation time and targeted population;
   - ✓ The target trial framework which considers the design of an ideal randomized experiment, can be helpful in framing the study and the target causal estimand of interest.
2. Propose an **identification strategy** about how we can exploit the setting of the intervention implementation of interest to estimate the targeted causal quantity of interest (estimand) and identify possible falsifications tests
3. Propose an **estimation strategy** which often relates to the statistical or modelling approach (i.e. estimator) that we will use to obtain a given estimate (e.g. regression coefficient) to quantitatively represent the targeted estimand of interest (i.e. ATT).

REVISITING THE WORKSHOP OBJECTIVES

1. Understand the conceptual foundations of quasi-experimental methods based on the timing of a natural experiment
2. Understanding how Difference-in-Differences (DID), Interrupted Time Series (ITS) and Synthetic Control Methods (SCM) work and their specific identification assumptions.
3. Being able to implement (in *R*) DID, ITS and SCM in different settings, interpret estimands of interest and check/visualize possible assumptions' violations
   - ✓ **Coming next**

REFERENCES

- Nianogo, R. A., Benmarhnia, T., & O'Neill, S. (2023). A comparison of quasi-experimental methods with data before and after an intervention: an introduction for epidemiologists and a simulation study. International Journal of Epidemiology, dyad032.
- Craig, P., Katikireddi, S. V., Leyland, A., & Popham, F. (2017). Natural experiments: an overview of methods, approaches, and contributions to public health intervention research. Annual review of public health, 38, 39-56.
- De Chaisemartin, C., & d'Haultfoeuille, X. (2022). Two-way fixed effects and differences-in-differences with heterogeneous treatment effects: A survey (No. w29734). National Bureau of Economic Research.
- Abadie, A., Diamond, A., & Hainmueller, J. (2010). Synthetic control methods for comparative case studies: Estimating the effect of California's tobacco control program. Journal of the American statistical Association, 105(490), 493-505.
- Xu, Y. (2017). Generalized synthetic control method: Causal inference with interactive fixed effects models. Political Analysis, 25(1), 57-76.
- Acemoglu, D., Johnson, S., Kermani, A., Kwak, J. and Mitton, T., 2016. The value of connections in turbulent times: Evidence from the United States. Journal of Financial Economics, 121(2), pp.368-391.
- Dube A, Zipperer B. Pooled synthetic control estimates for recurring treatment: an application to minimum wage studies, University of Massachusetts. Amherst Working Paper.2013
- Kreif, N., Grieve, R., Hangartner, D., Turner, A.J., Nikolova, S. and Sutton, M., 2016. Examination of the synthetic control method for evaluating health policies with multiple treated units. Health economics, 25(12), pp.1514-1528.
- Goodman-Bacon, A. (2021). Difference-in-differences with variation in treatment timing. Journal of Econometrics.
- Callaway, B., & Sant'Anna, P. H. (2020). Difference-in-differences with multiple time periods. Journal of Econometrics.
- Roth, J., & Sant'Anna, P. H. (2020). When Is Parallel Trends Sensitive to Functional Form?. arXiv preprint arXiv:2010.04814.
- Lipsitch, M., Tchetgen, E. T., & Cohen, T. (2010). Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology (Cambridge, Mass.), 21(3), 383.

THANK YOU

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