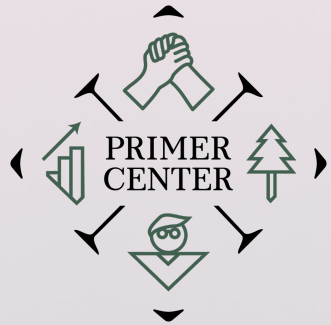


Evaluating Social Care Natural Experiments



Miguel Marino, PhD and Jorge Kaufmann, ND MS

Department of Family Medicine

Oregon Health & Science University

PRIMER Center

SIREN METHODS CONVERSATIONS



Outline of today's talk

- *Definitions relevant to Natural Experiments*
- *Overview of Common Methods w/ Examples*
- *Pragmatic Motivating Example: CRISP Study*
- *Recent Developments w/ Time-varying Start Times*
- *Future Potential in Natural Experiments*
- *Checklist when designing an analysis for a Natural Experiment*

Context

siren

Social Interventions Research
& Evaluation Network

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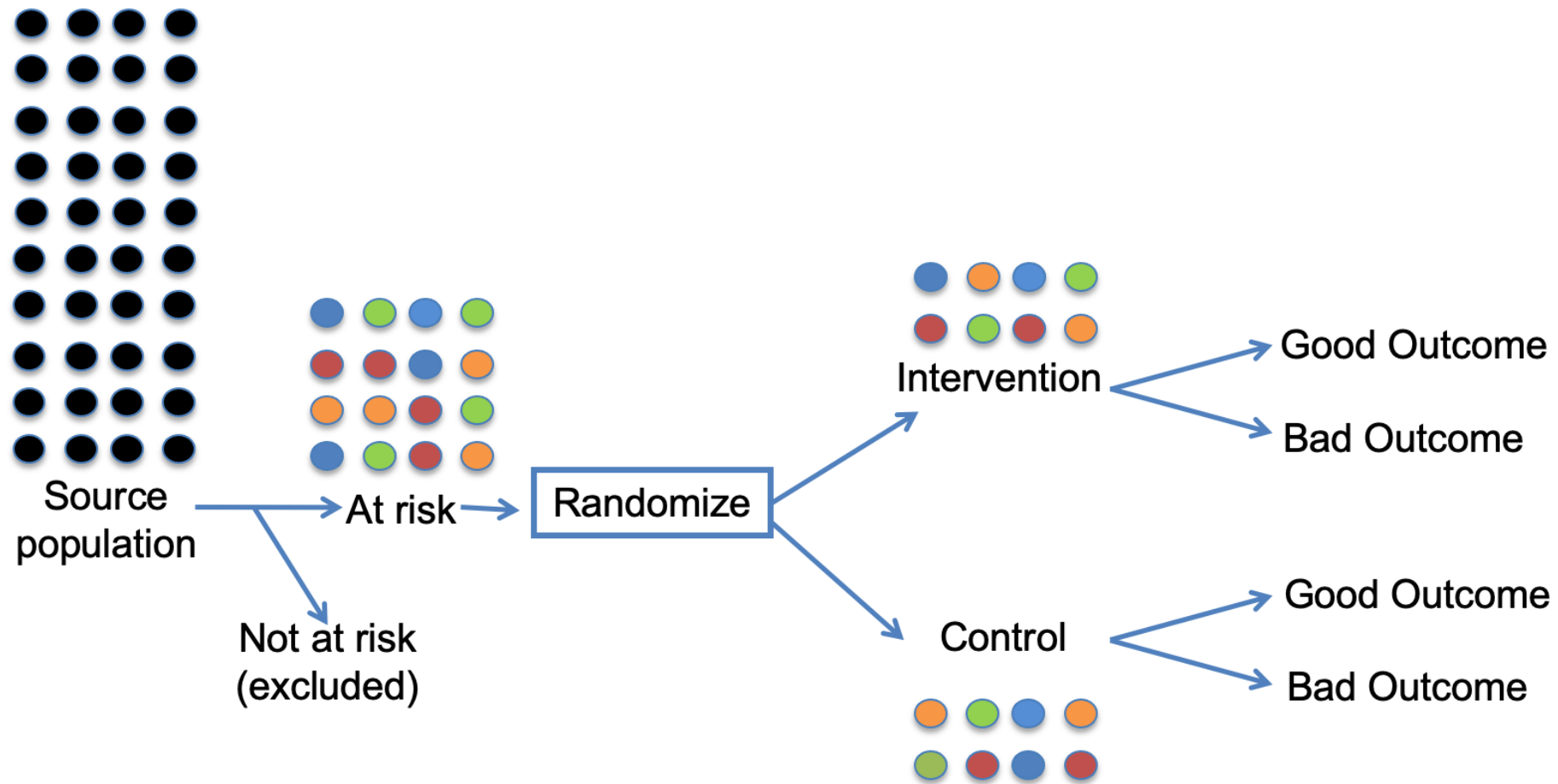
[Engagement Grants](#)



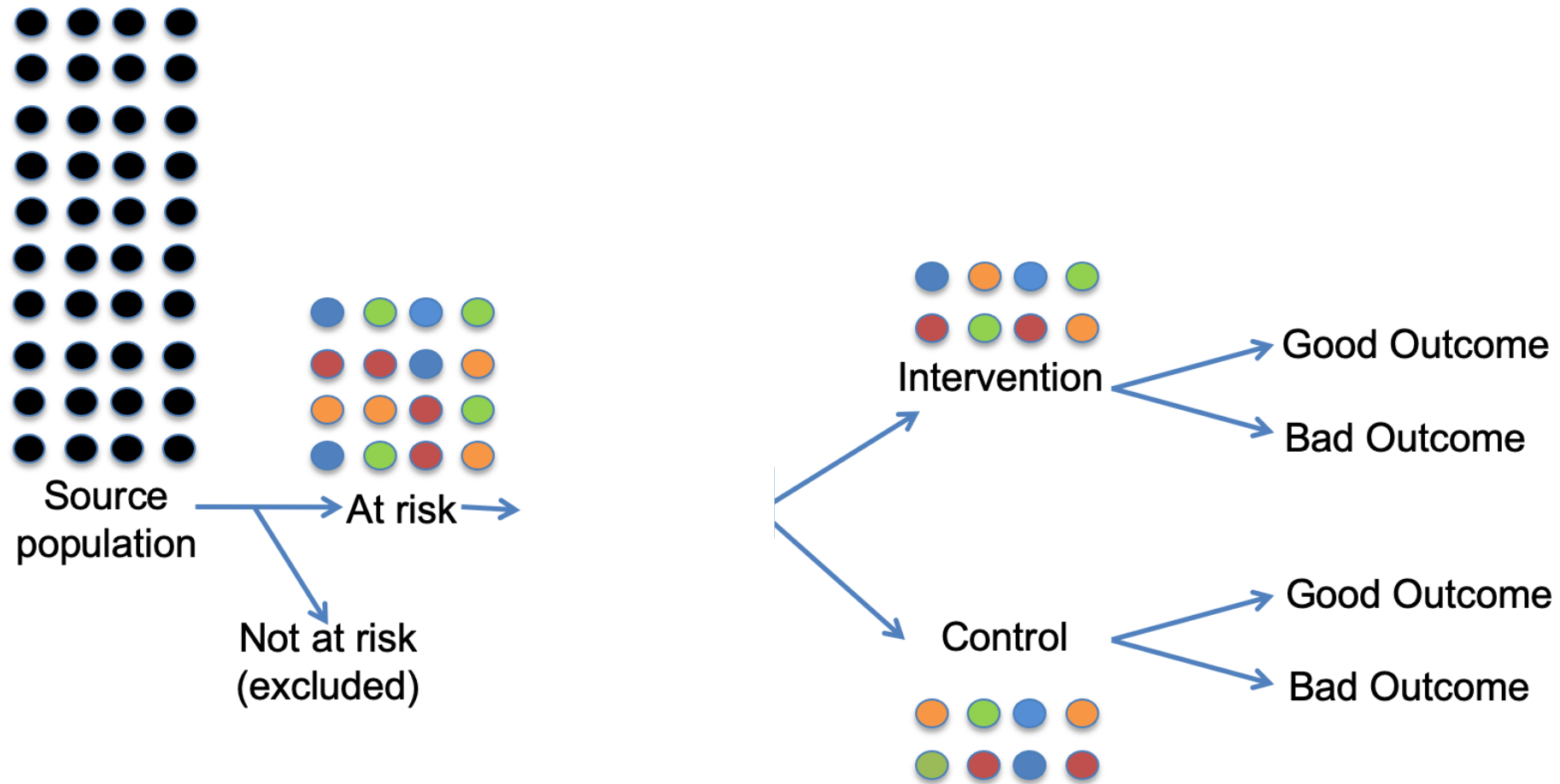
Our Mission

Our mission is to improve health and health equity by advancing high quality research on health care sector strategies to improve social conditions.

Randomized Trials

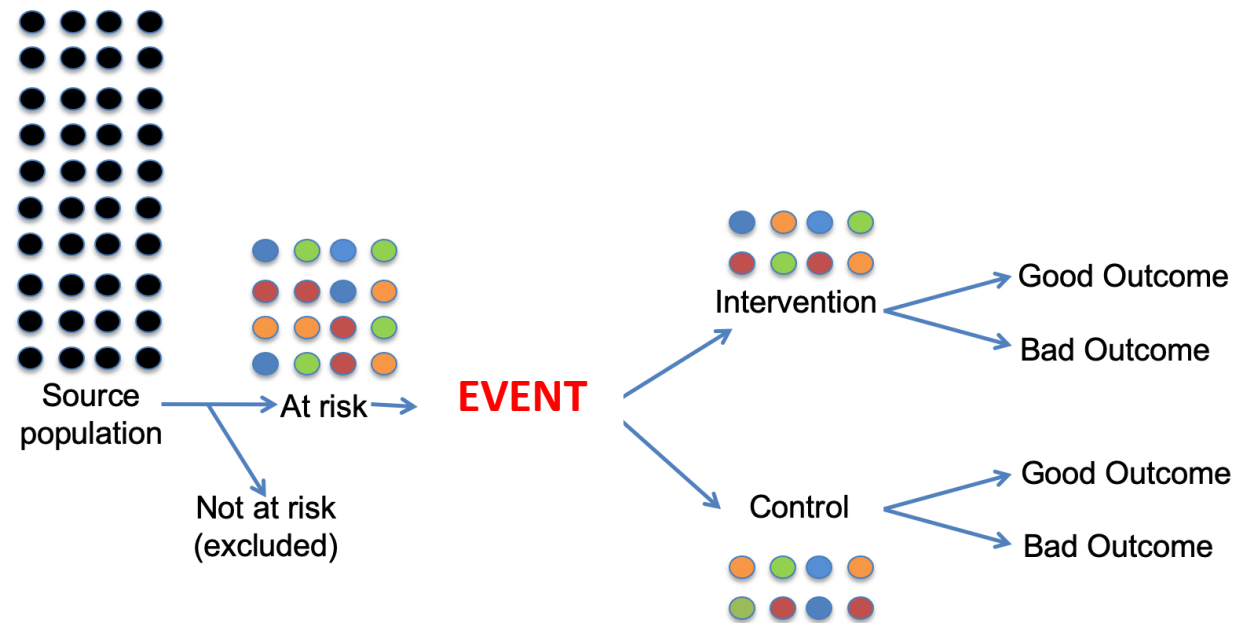


Realistic view of most scientific studies



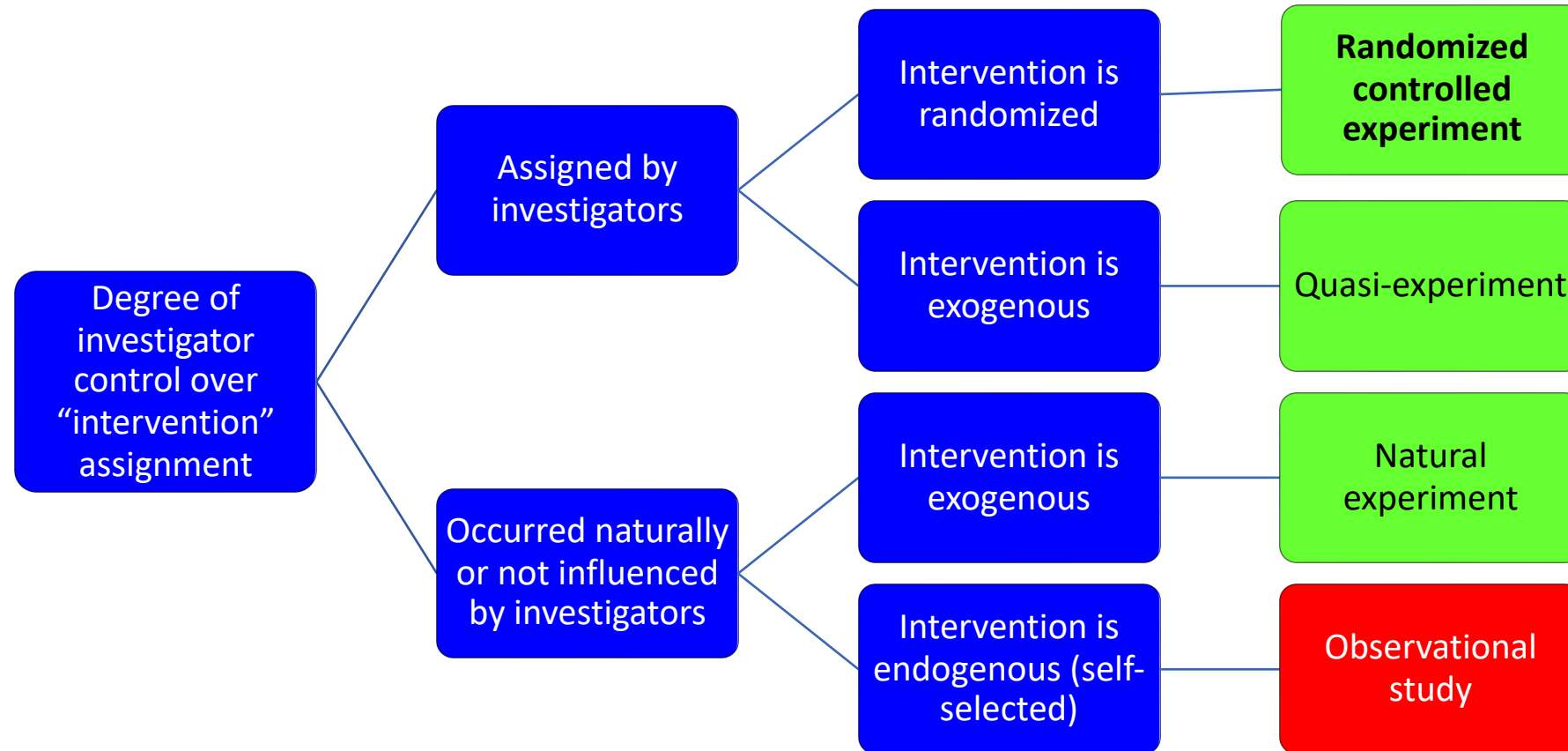
Definition of Natural Experiments

- Any **event** not under the control of a researcher that divides the population into exposed ("intervention") and unexposed ("control") groups.



Source: Craig, Peter, et al. "Using natural experiments to evaluate population health interventions: new Medical Research Council guidance." *J Epidemiol Community Health* 66.12 (2012): 1182-1186.

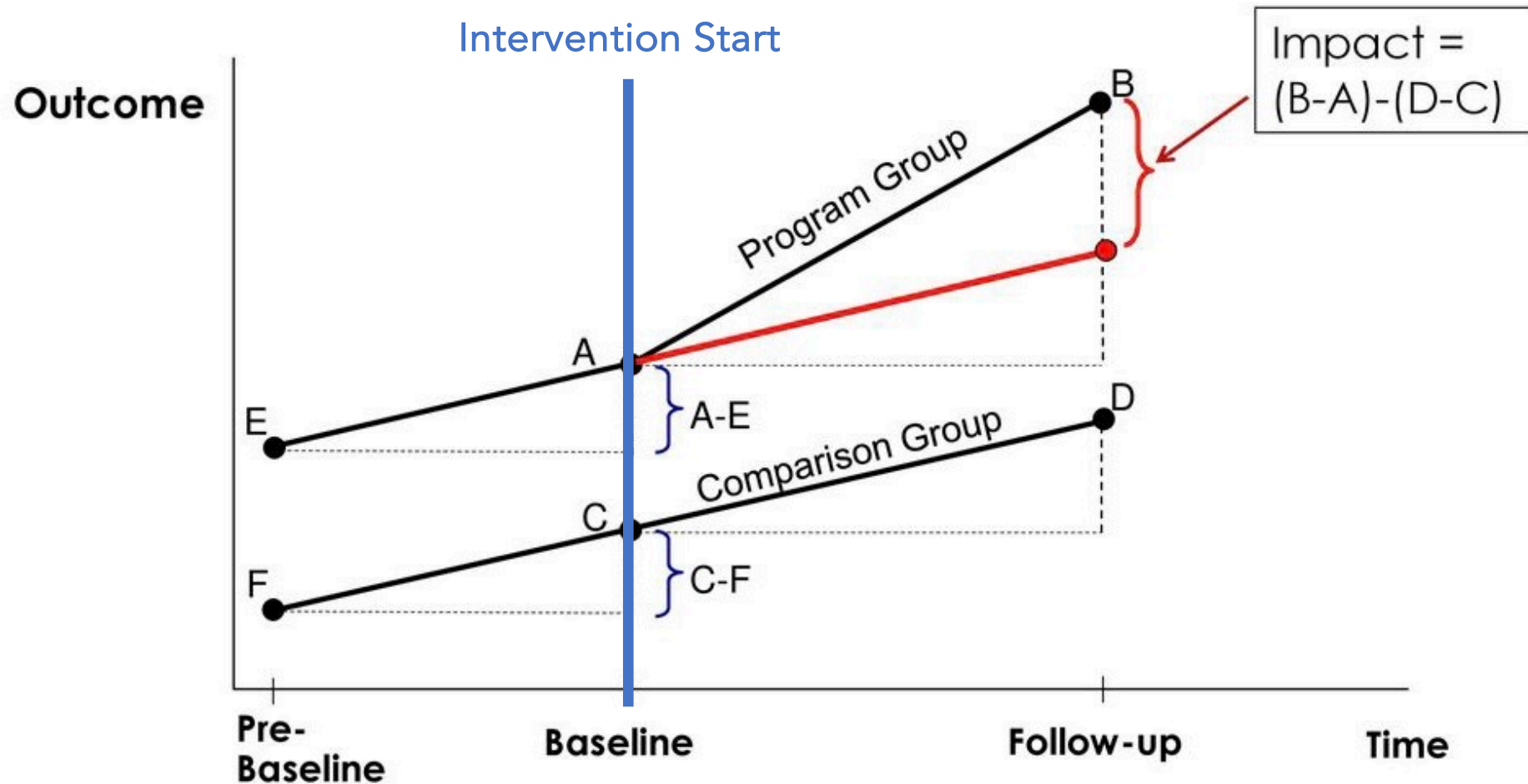
How to determine if it's a Natural Experiment?



Source: Wharam F. What are Natural Experiments and Why Should we Study Them?

<https://www.uclahealth.org/sites/default/files/documents/Final%20Frank%20Day%202%20slides.pptx>

Natural Experiments: Difference-in-differences



Difference-in-differences Examples

Research Letter

FREE

August 20, 2021

Association of Remote vs In-Person Benefit Delivery With WIC Participation During the COVID-19 Pandemic

Aditi Vasani, MD, MSHP¹; Chén C. Kenyon, MD, MSHP¹; Christina A. Roberto, PhD²; Alexander G. Fiks, MD, MSCE¹; Atheendar S. Venkataramani, MD, PhD²

» Author Affiliations | Article Information

JAMA. 2021;326(15):1531-1533. doi:10.1001/jama.2021.14356

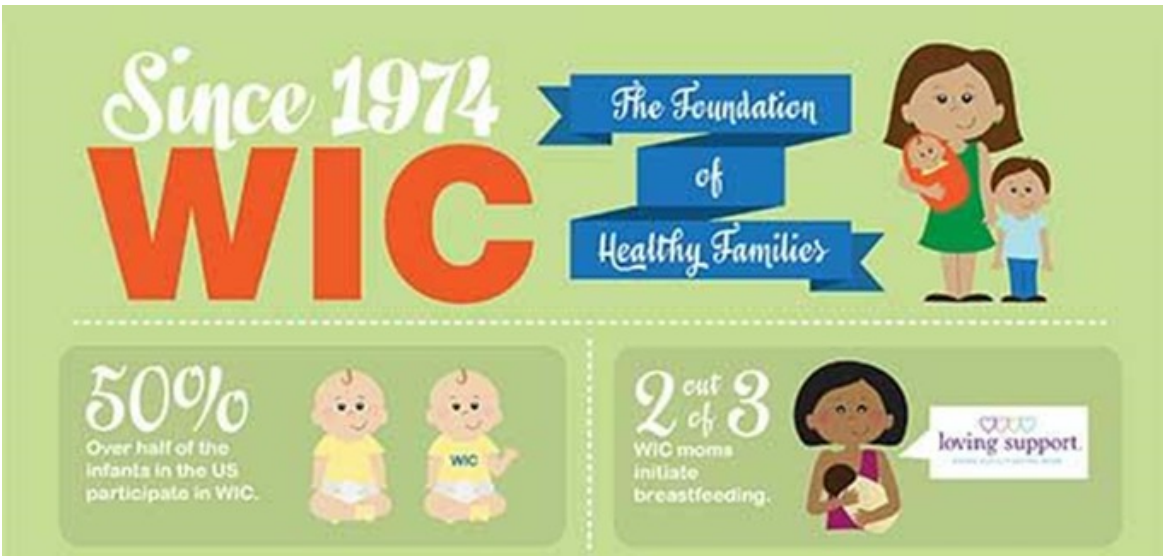
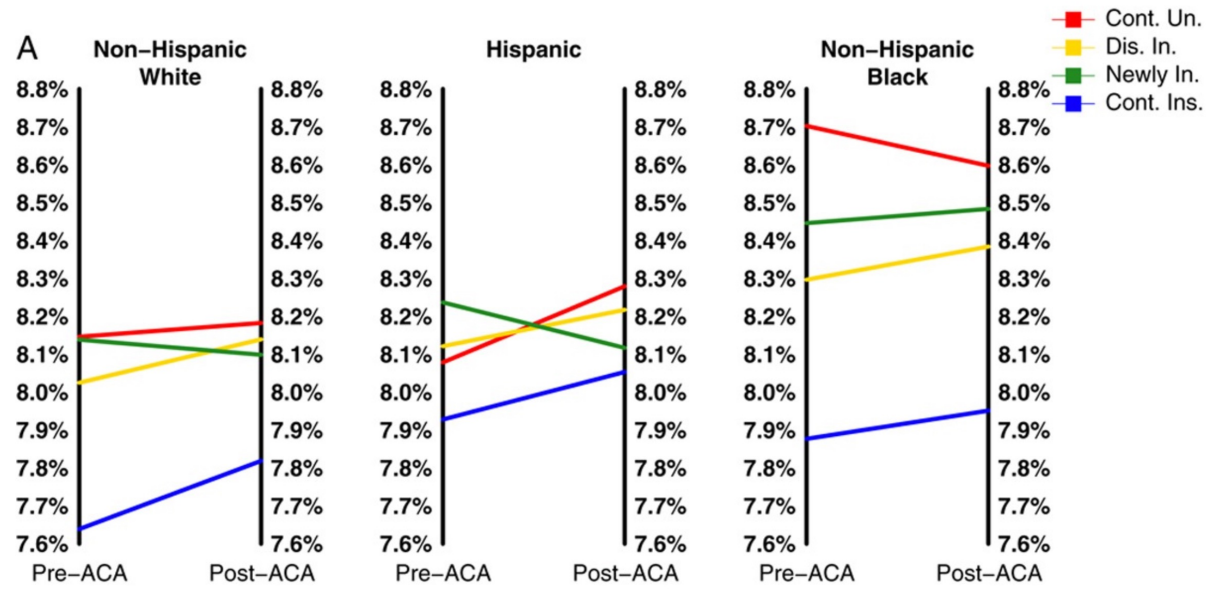
NATURAL EXPERIMENTS

Disparities in Biomarkers for Patients With Diabetes After the Affordable Care Act

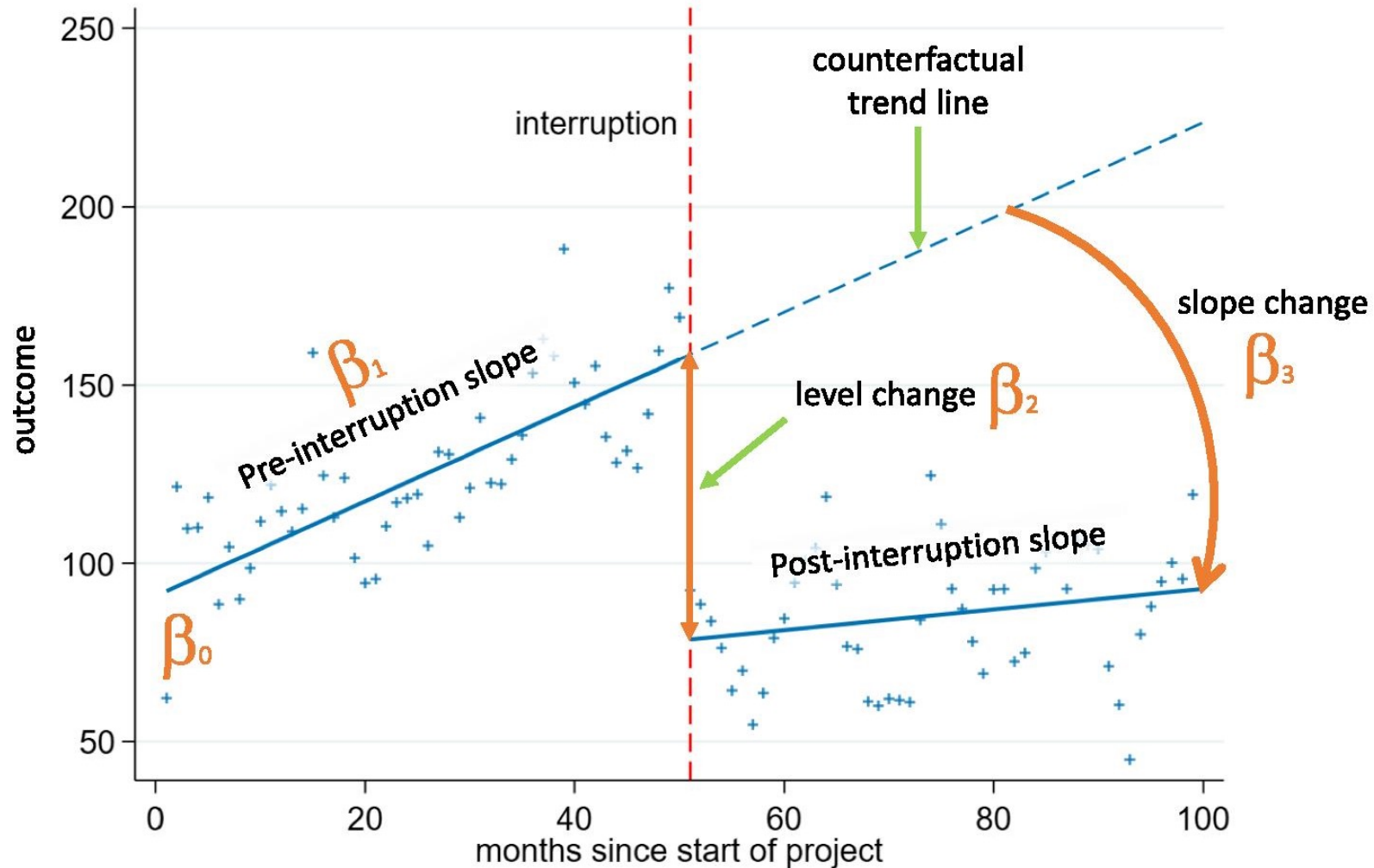
Marino, Miguel PhD^{*†}; Angier, Heather PhD, MPH^{*}; Fankhauser, Katie MPH^{*}; Valenzuela, Steele MS^{*}; Hoopes, Megan MPH[‡]; Heintzman, John MD, MPH^{*‡}; DeVoe, Jennifer MD, DPhil^{*‡}; Moreno, Laura MPH^{*}; Huguet, Nathalie PhD^{*}

Author Information

Medical Care 58():p S31-S39, June 2020. | DOI: 10.1097/MLR.0000000000001257



Natural Experiments: Interrupted time series



Source: Turner, S.L., et al. Comparison of six statistical methods for interrupted time series studies: empirical evaluation of 190 published series. BMC Med Res Methodol 21, 134 (2021).

Interrupted time series Examples

Original Investigation

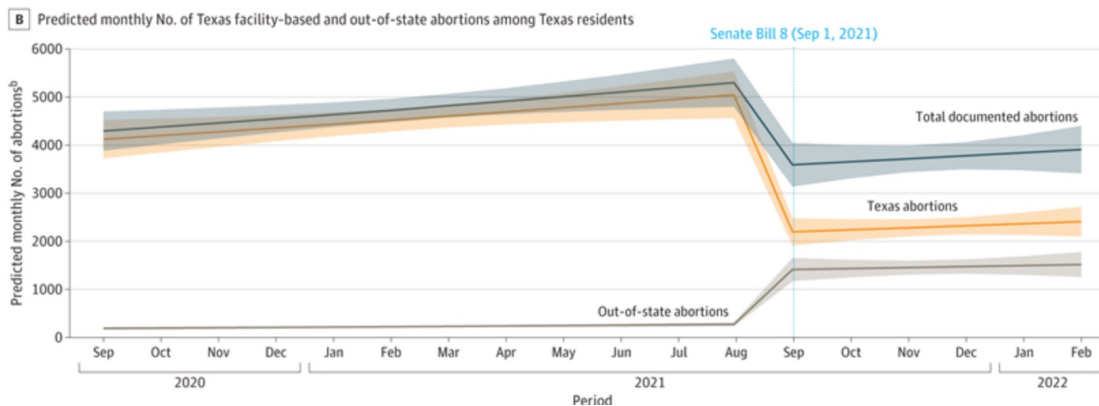
November 1, 2022

Association of Texas' 2021 Ban on Abortion in Early Pregnancy With the Number of Facility-Based Abortions in Texas and Surrounding States

Kari White, PhD, MPH^{1,2}; Gracia Sierra, PhD, MS^{2,3}; Klaira Lerma, MPH^{2,3}; [et al](#)

[» Author Affiliations](#) | [Article Information](#)

JAMA. 2022;328(20):2048-2055. doi:10.1001/jama.2022.20423



Original Investigation | Medical Education

January 19, 2021

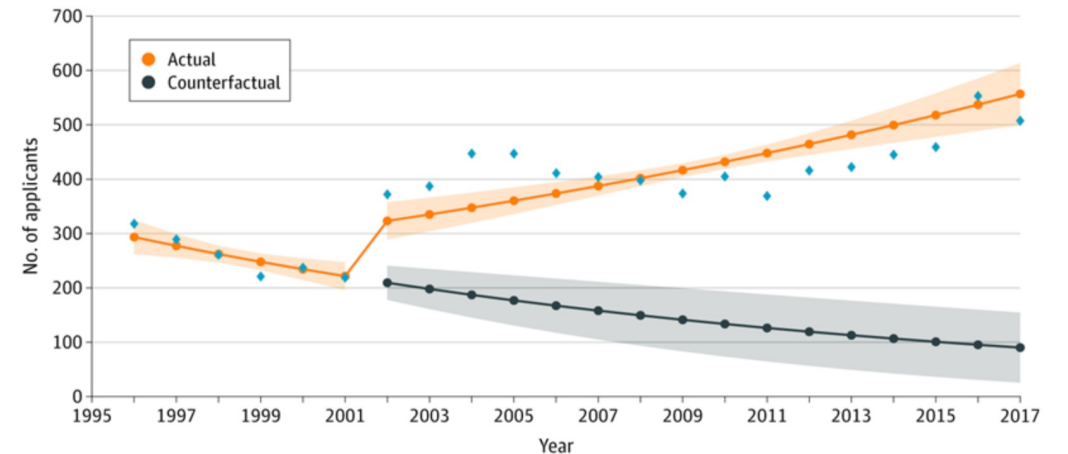
Measurement of American Indian and Alaska Native Racial Identity Among Medical School Applicants, Matriculants, and Graduates, 1996-2017

Erik Brodt, MD^{1,2}; Steele Valenzuela, MS^{3,4}; Allison Empey, MD^{5,6}; Amanda Bruegl, MD, MS^{7,8}; Dove Spector, BS^{9,10}; Miguel Marino, PhD^{1,11,12}; Patricia A. Carney, PhD, MS¹

[» Author Affiliations](#) | [Article Information](#)

JAMA Netw Open. 2021;4(1):e2032550. doi:10.1001/jamanetworkopen.2020.32550

Figure 1. Number of Applicants From 1996-2017



Blue diamonds indicate the observed raw counts for the respective years for applicants. The shading around the orange line indicates 95% CIs, and the shading around the blue line indicates 95% prediction intervals.

Natural Experiments: Synthetic controls

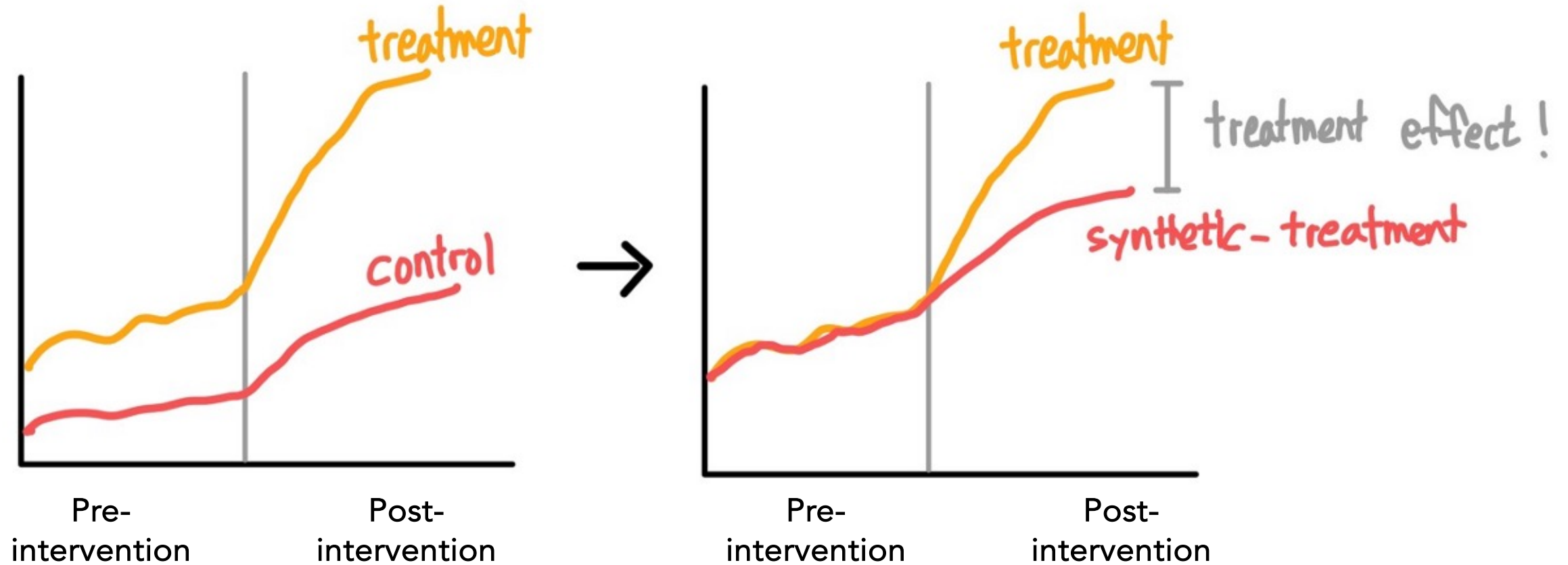


Figure Source: <https://medium.com/@chyun55555/synthetic-control-method-for-causal-inference-basics-with-simple-mathematics-c61fc42fd472>

Synthetic controls Examples

Synthetic Control Methods for Comparative Case Studies: Estimating the Effect of California's Tobacco Control Program

Alberto ABADIE, Alexis DIAMOND, and Jens HAINMUELLER

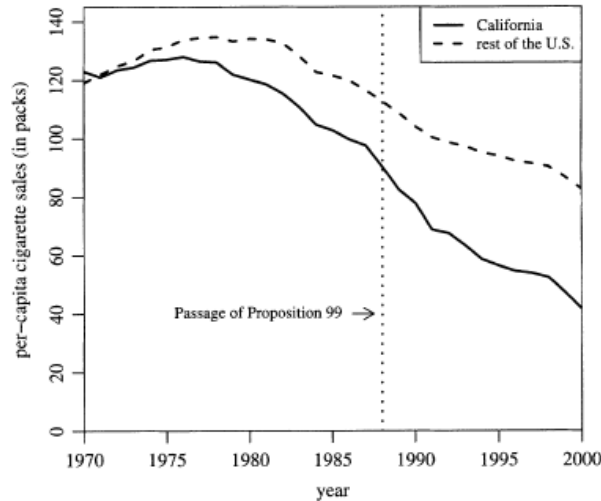


Figure 1. Trends in per-capita cigarette sales: California vs. the rest of the United States.

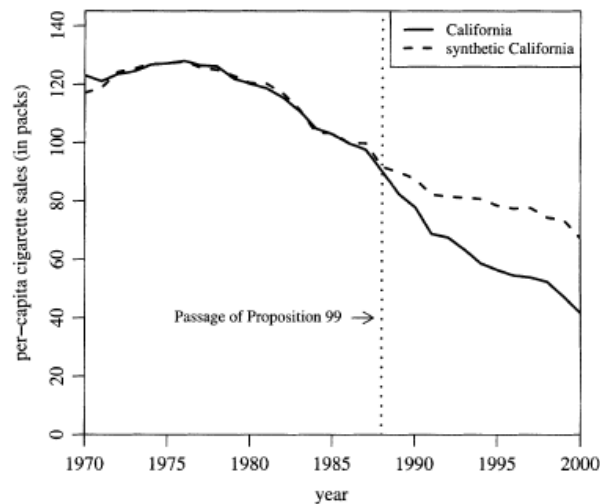


Figure 2. Trends in per-capita cigarette sales: California vs. synthetic California.

Original Investigation

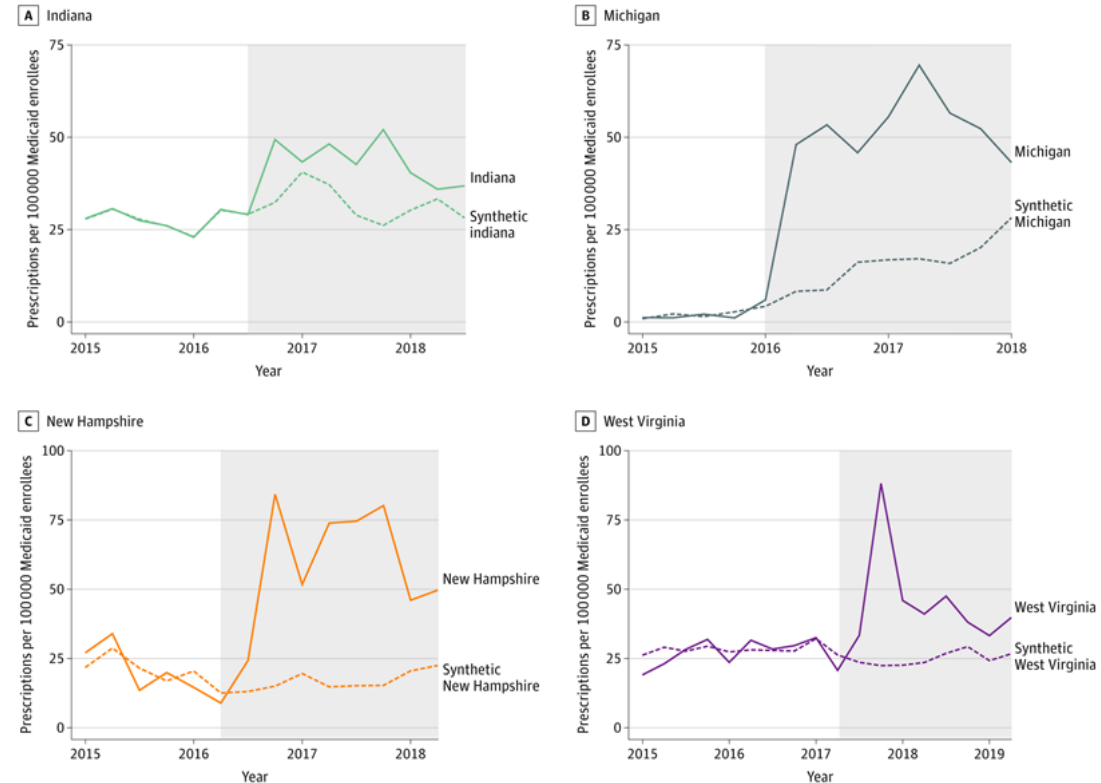
August 27, 2021

Association of Medicaid Managed Care Drug Carve Outs With Hepatitis C Virus Prescription Use

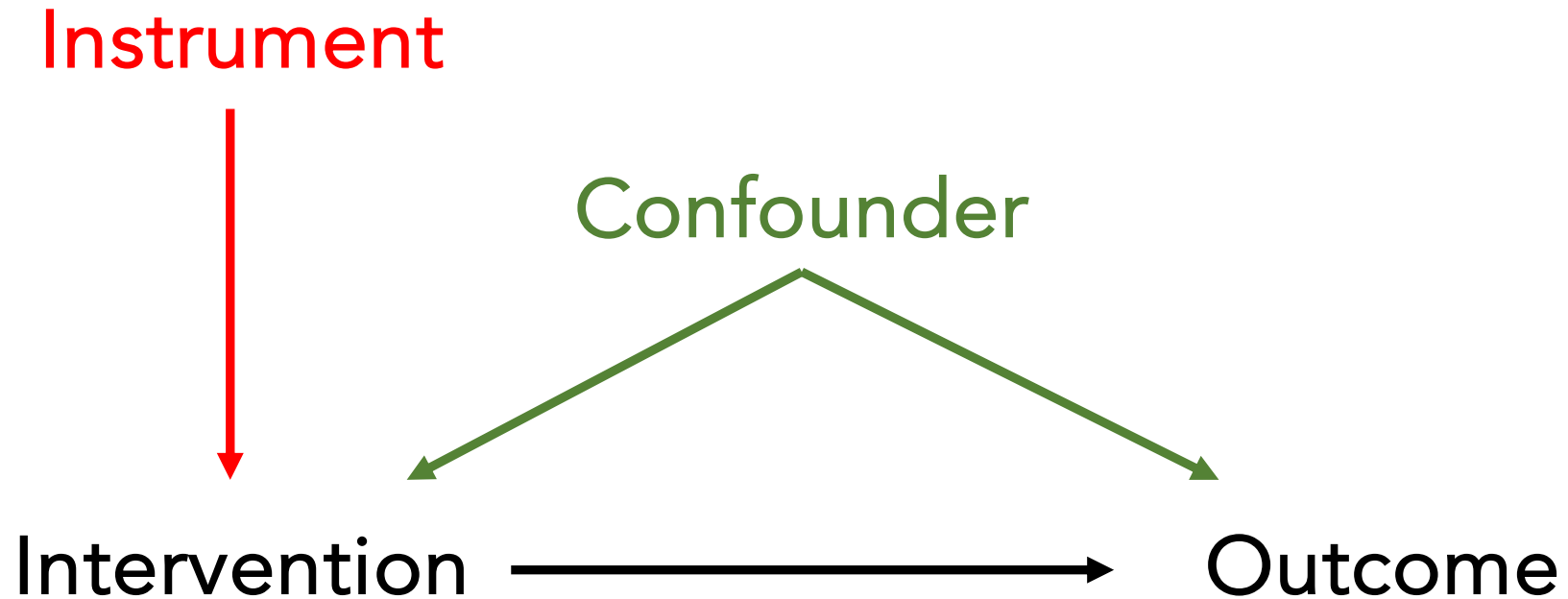
Samantha G. Auty, MS¹; Paul R. Shafer, PhD¹; Stacie B. Dusetzina, PhD²; et al

[» Author Affiliations](#) | [Article Information](#)

JAMA Health Forum. 2021;2(8):e212285. doi:10.1001/jamahealthforum.2021.2285



Natural Experiments: Instrumental Variables



Instrumental Variables Examples

Original Investigation

April 22, 2019

Association Between Receipt of a Medically Tailored Meal Program and Health Care Use

Seth A. Berkowitz, MD, MPH^{1,2,3,4}; Jean Terranova, JD⁵; Liisa Randall, PhD⁶; Kevin Cranston, MDiv⁶; David B. Waters, MA⁵; John Hsu, MD, MBA, MSCE^{7,8}

» [Author Affiliations](#) | [Article Information](#)

JAMA Intern Med. 2019;179(6):786-793. doi:10.1001/jamainternmed.2019.0198



American Journal of Preventive Medicine

Volume 50, Issue 2, February 2016, Pages 161-170

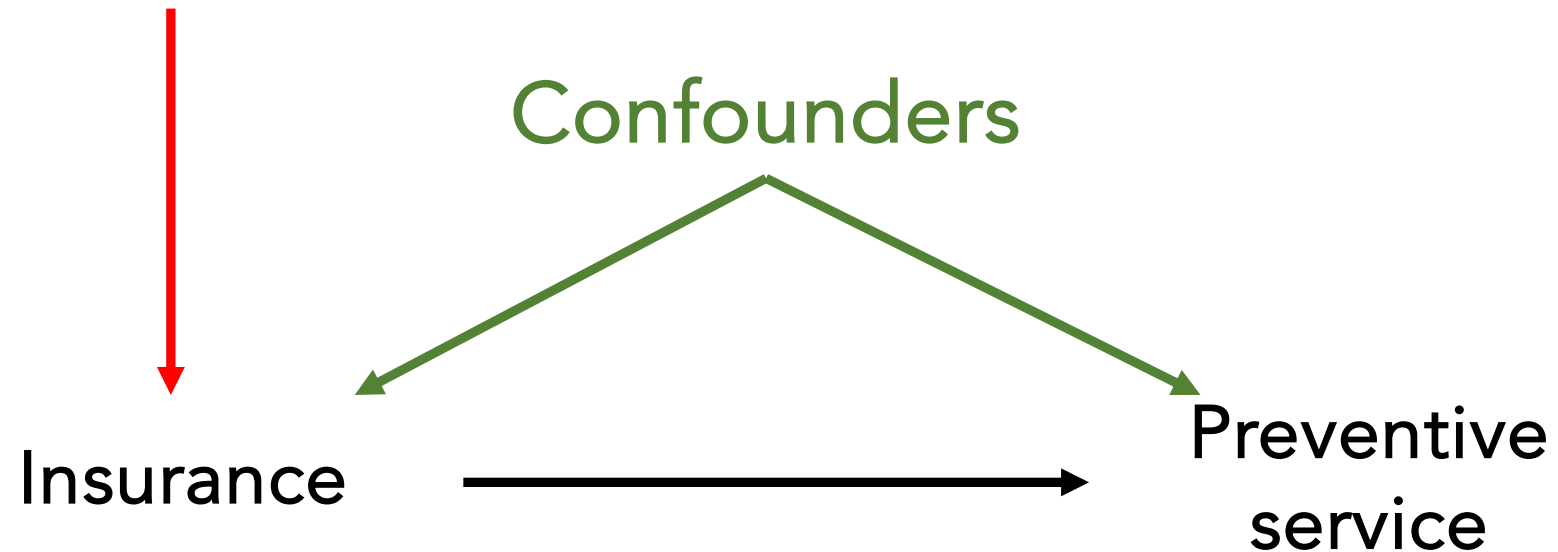


Research Article

Receipt of Preventive Services After Oregon's Randomized Medicaid Experiment

Miguel Marino PhD^{1,2} , Steffani R. Bailey PhD¹, Rachel Gold PhD, MPH^{3,4}, Megan J. Hoopes MPH³, Jean P. O'Malley MPH², Nathalie Huguet PhD¹, John Heintzman MD¹, Charles Gallia PhD⁵, K. John McConnell PhD⁶, Jennifer E. DeVoe MD, DPhil^{1,3}

Randomization



Just the tip of the iceberg...



Motivation

- Recognized impact of social risk on person health
 - Examples: food, housing, transportation insecurity
- Calls for health care based social needs assessment
- Screening tools incorporated into EHR platforms

Will the EHR tools be used?

Are there interventions to help promote tool adoption?

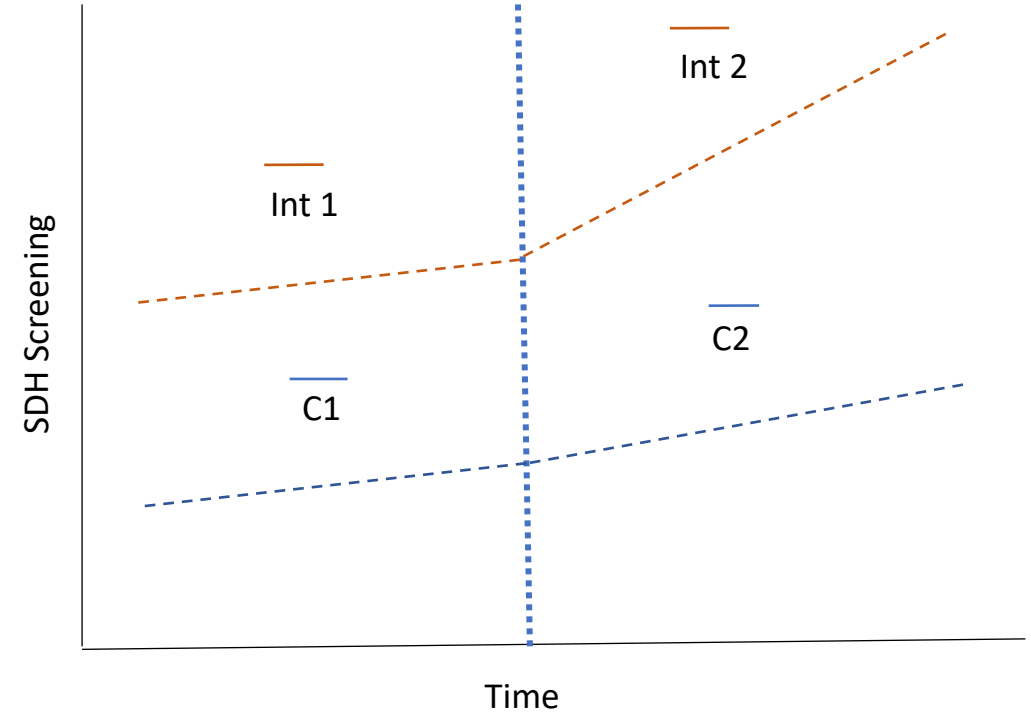
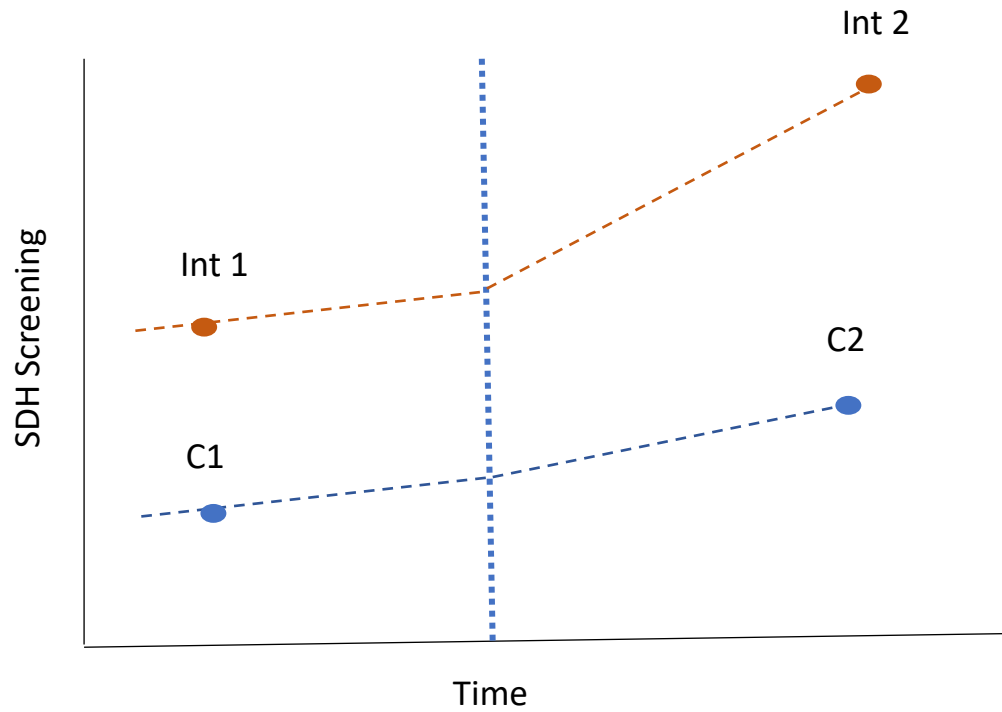
Simple Natural Experiment I

- 1 **clinic** receives support to increase SDH screening
- 1 **clinic** does not

- Support begins on a known date t
- SDH screening data before and after t for both clinics

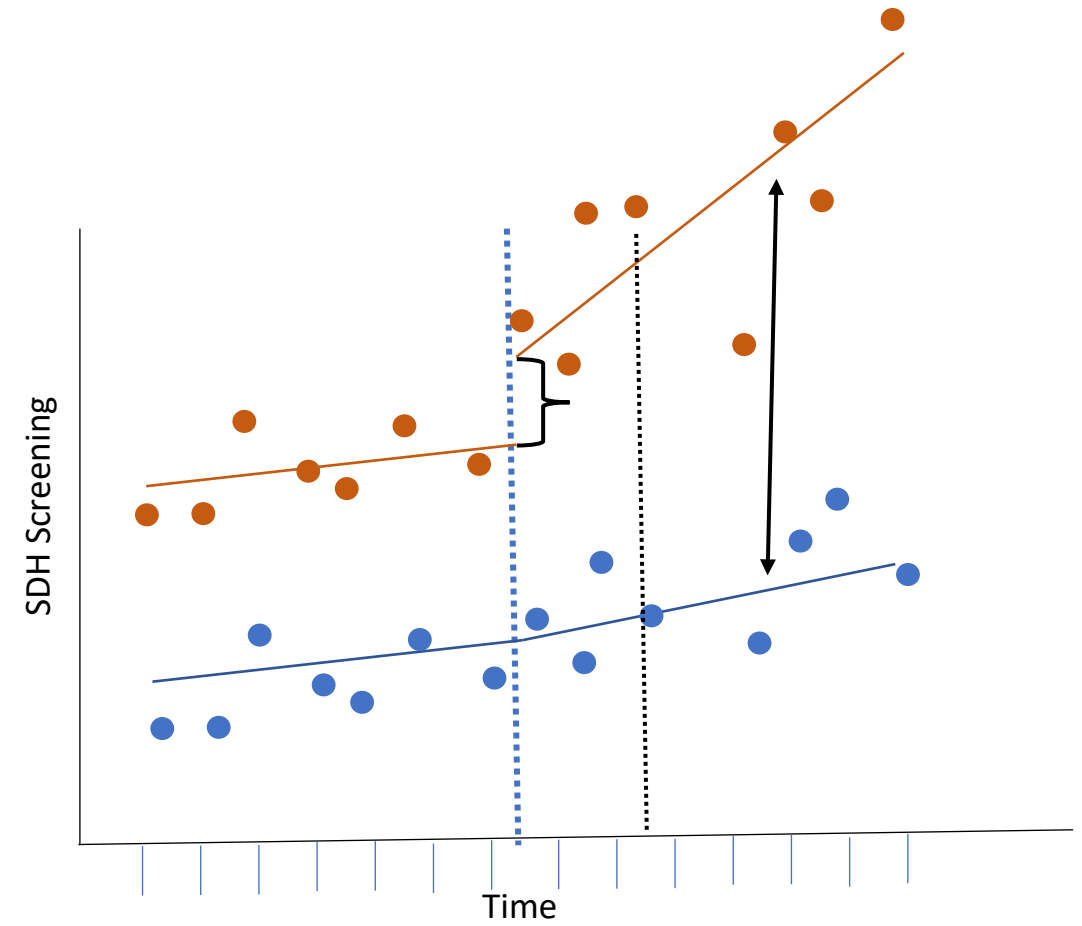
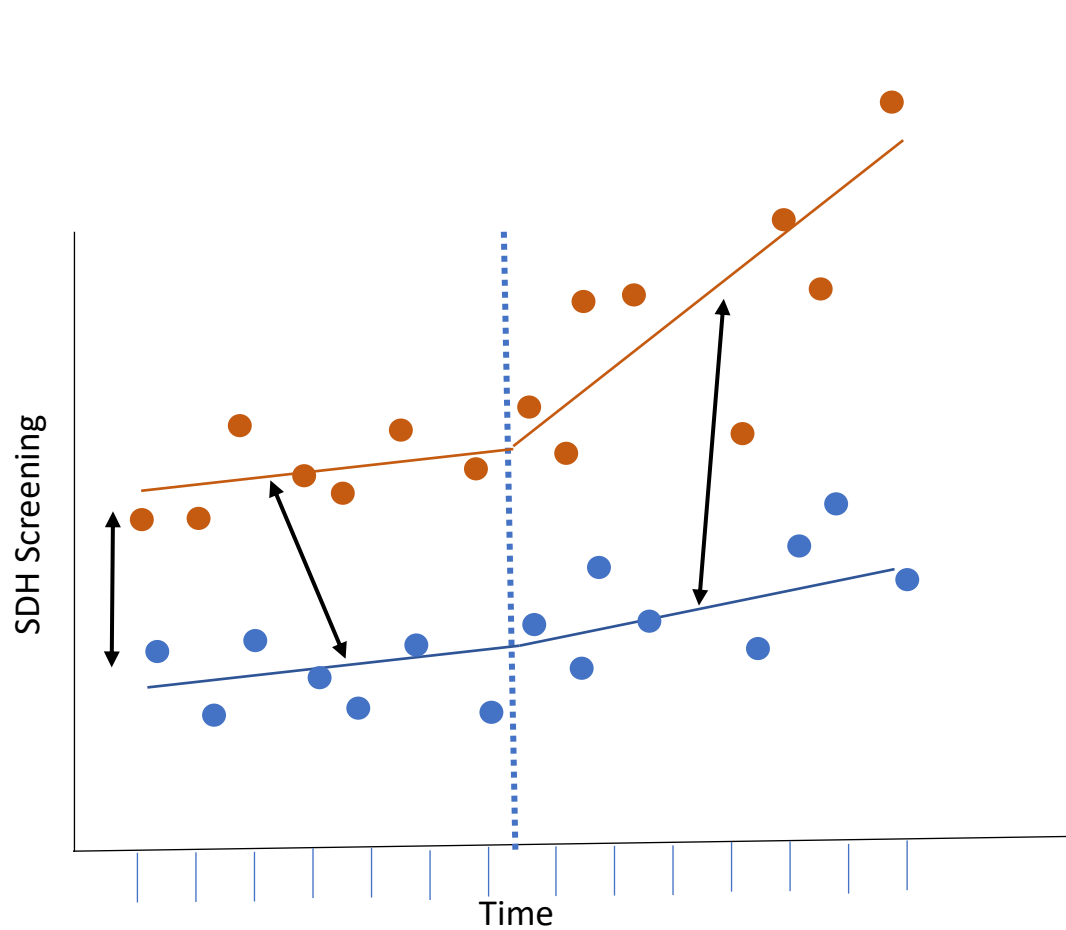
Does the support affect a change?

Controlled Pre/Post Design



$$\text{Difference in Differences} = (\text{Int 2} - \text{C2}) - (\text{Int 1} - \text{C1})$$

Comparative Interrupted Time Series



$$\text{Difference in Differences} = (\text{SlopeInt2} - \text{SlopeC2}) - (\text{SlopeInt1} - \text{SlopeC1})$$

Simple Natural Experiment II

- A new state program incentivizes SDH screening
- All clinics must enroll, have 18 months to do so
- Each clinic enrolls at different time
- Clinics **not yet** enrolled act as controls

Does the new state program increase SDH screening?

Multiple Baseline Comparison

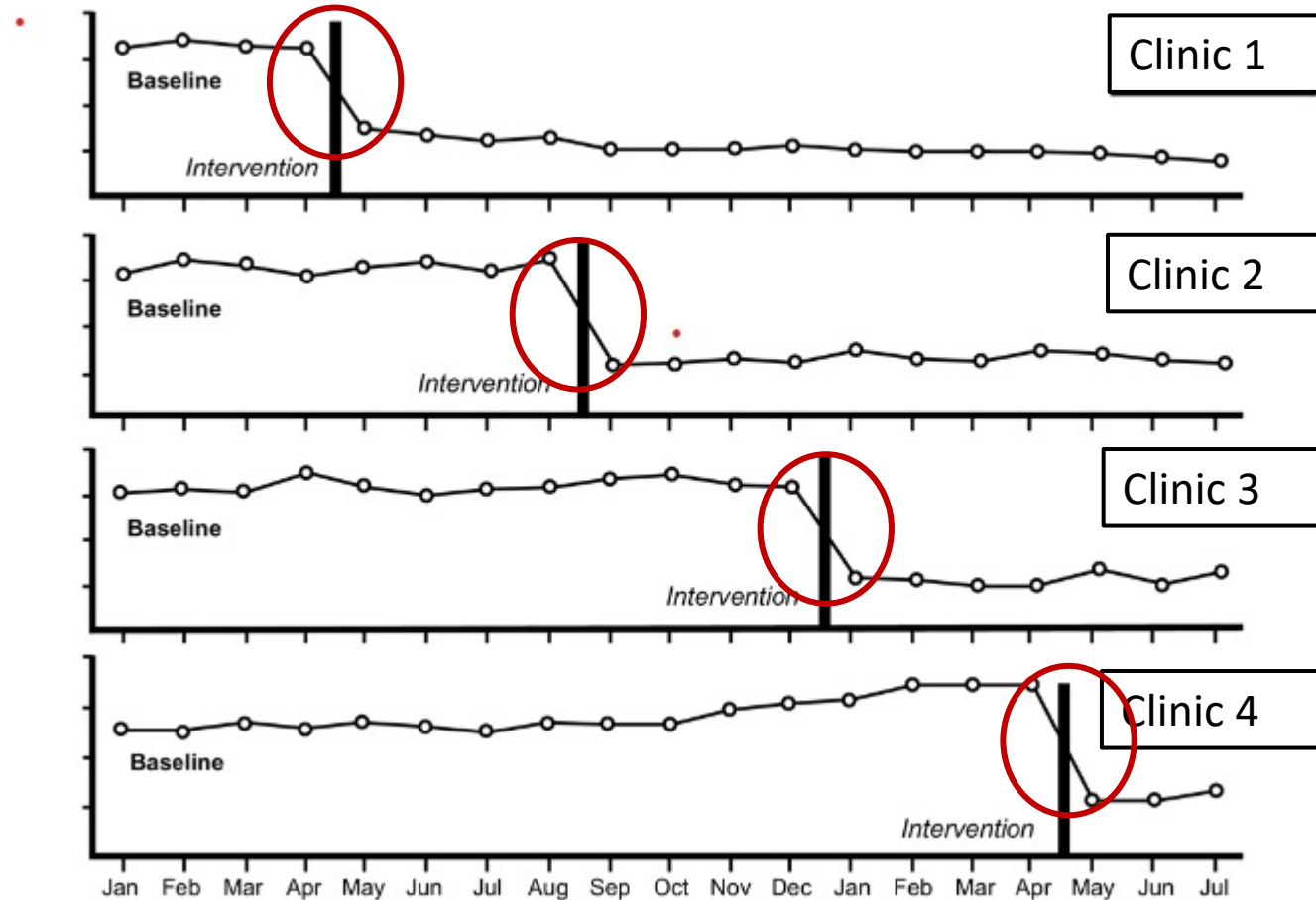


Image from: Hawkins et.al *The Multiple Baseline Design for Evaluating Population-based Research*. AJPM 2007.

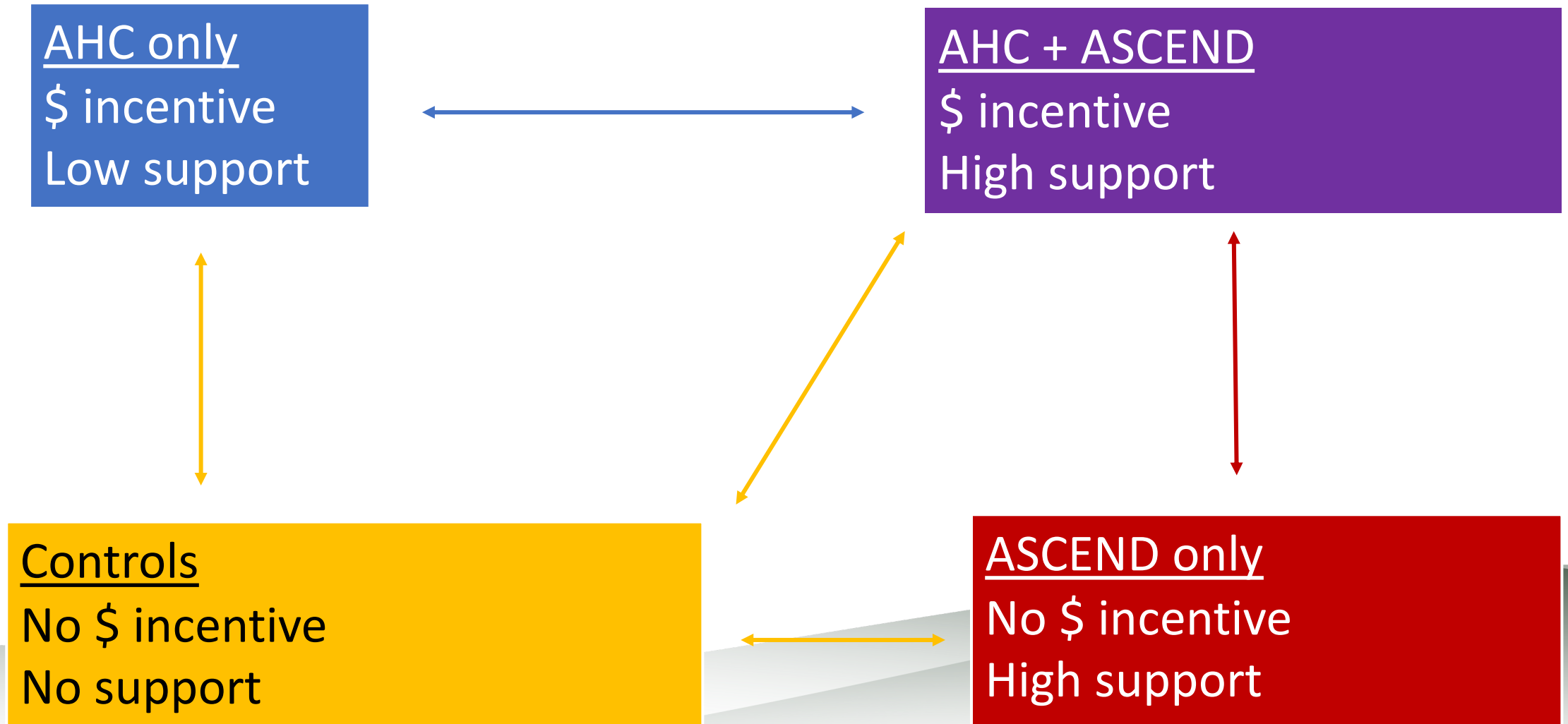
Free-range Organic All Natural Experiment

- 2 interventions aimed to improve clinical HD screening
- 26 clinics received implementation (ASCEND)
- 13 clinics received monetary incentives
- 7 of these clinics received both interventions
- Large pool of 100+ clinics

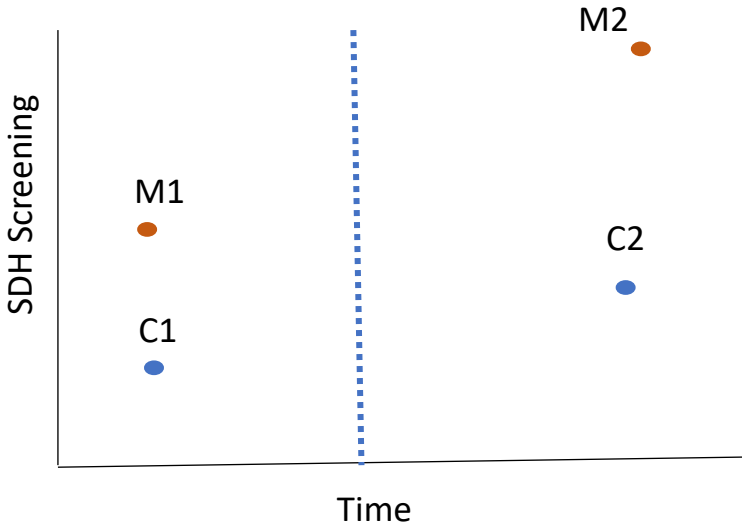
CRISP

Did either intervention work, independently or in combination?

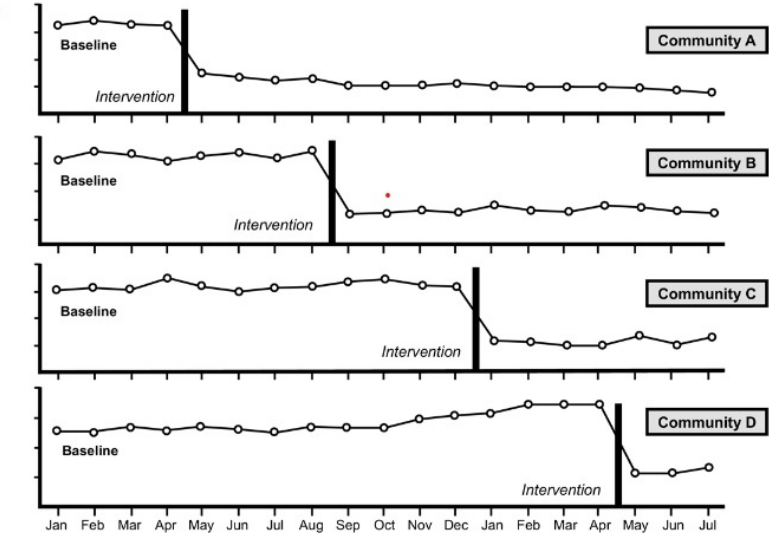
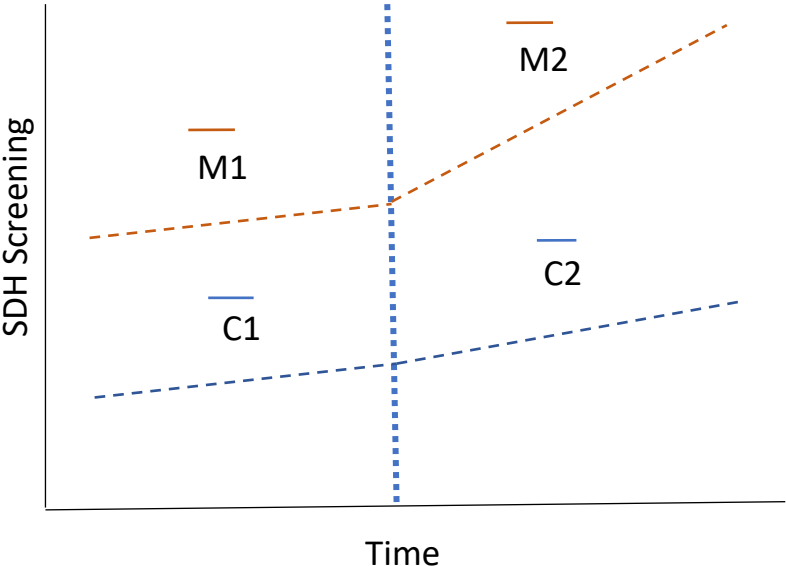
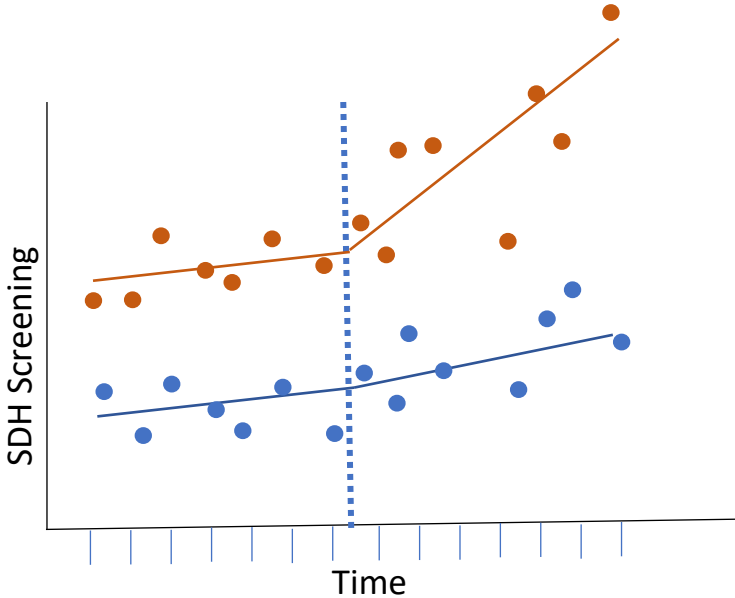
CRISP Aims



Controlled Pre/Post Design



CITS



Multiple Baseline Design

CRISP Additional Detail

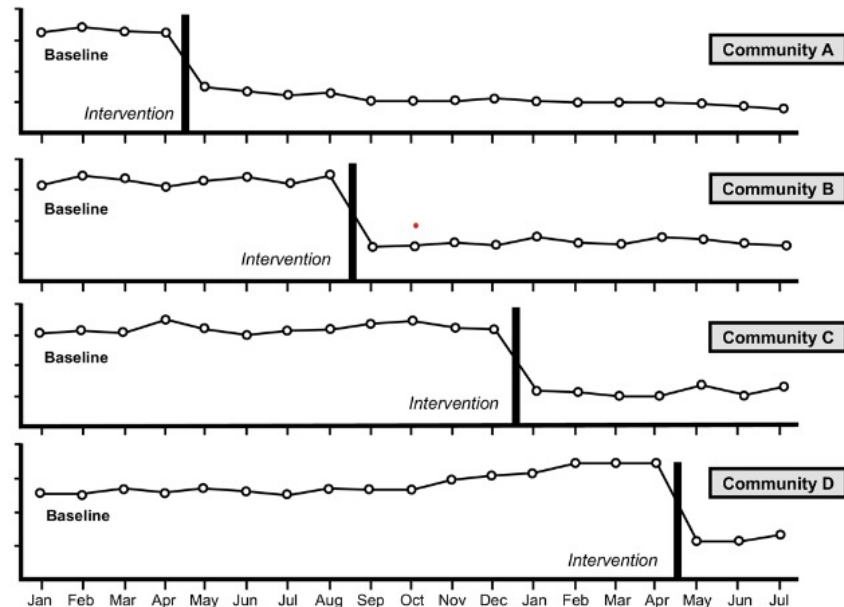
- Monthly data, March 2018- April 2023
- 1st intervention start date September 2018
- 13th (last) intervention start date February 2021

- The 7 dual clinics each have two distinct start dates
 - From 75 to 608 days apart
 - 3 began with AHC, 4 began with ASCEND

Did either intervention work, independently?

- Did implementation support yield effect? (ASCEND SW-CRT):
 - Gold R, et.al. Implementation Support for a Social Risk Screening and Referral Process in Community Health Centers. *New England Journal of Medicine Catalyst Innovations in Care Delivery*. 2023.
- Did monetary incentives yield effect? (AHC Natural Experiment):

Not yet treated
act as controls

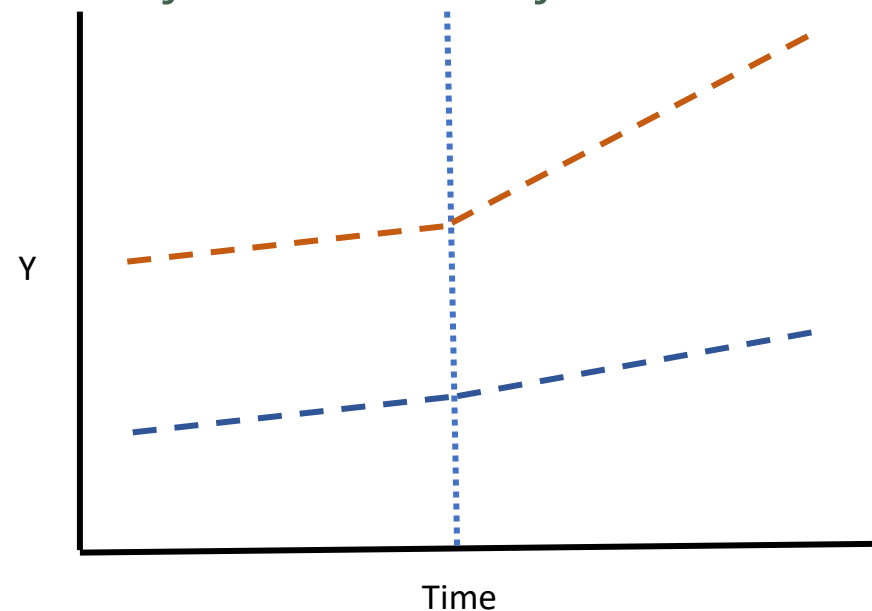


Multiple Baseline
Comparison

Was any *intervention* better than *none*?

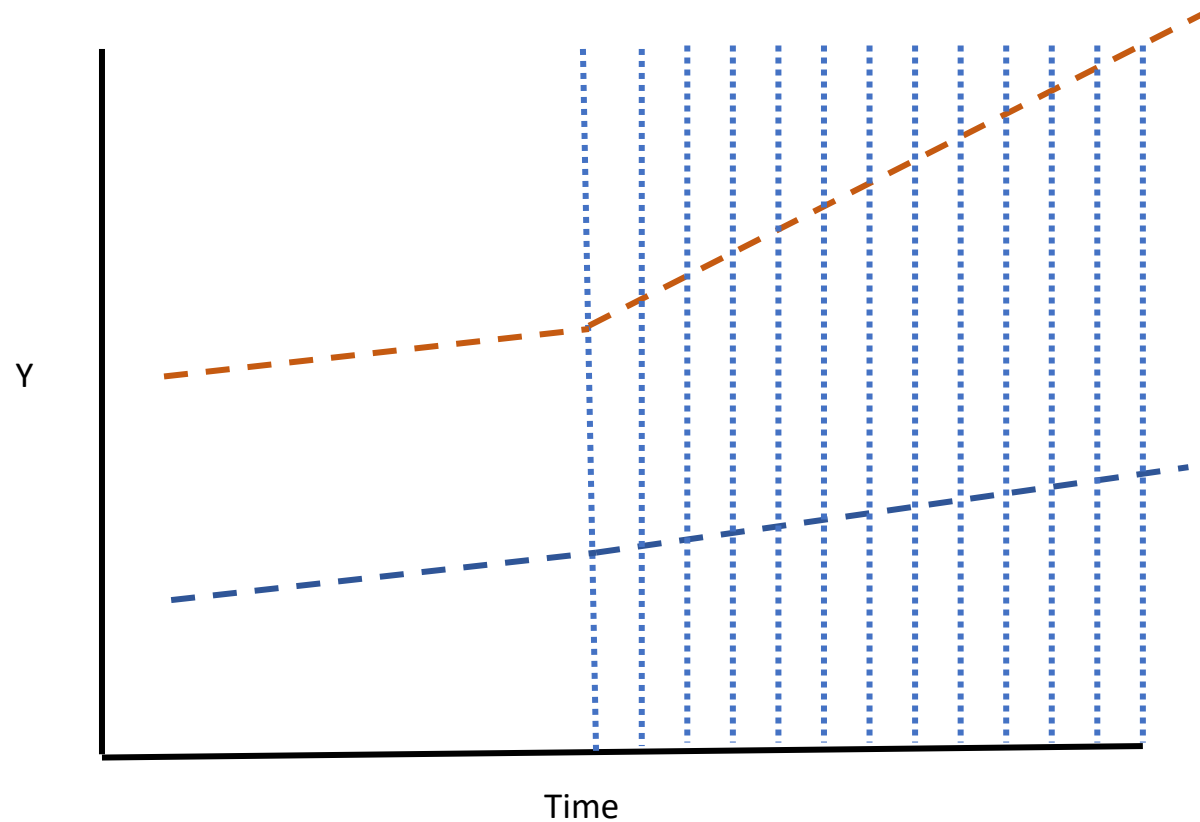
- Match control clinics using 6-month baseline summaries:
 - SDH screening rate
 - Total encounters, distinct patients
 - % age 18+, female, Hispanic, non-Hispanic Black, non-English preferring, public insurance, uninsured
 - Expansion state, FQHC, years active at study start, rurality, onsite social services, primary care

If all intervention clinics having same intervention start date



CRISP *it's free-range organic all natural!!!*

any intervention vs. none



Difference in Differences (DiD) = (Slope2 - Slope1) - (Slope2 - Slope1) ???

Callaway & Sant'Anna

Journal of Econometrics 225 (2021) 200–230



Contents lists available at [ScienceDirect](#)

Journal of Econometrics

journal homepage: www.elsevier.com/locate/jeconom



Difference-in-Differences with multiple time periods[☆]

Brantly Callaway^a, Pedro H.C. Sant'Anna^{b,*}

^a Department of Economics, University of Georgia, United States of America

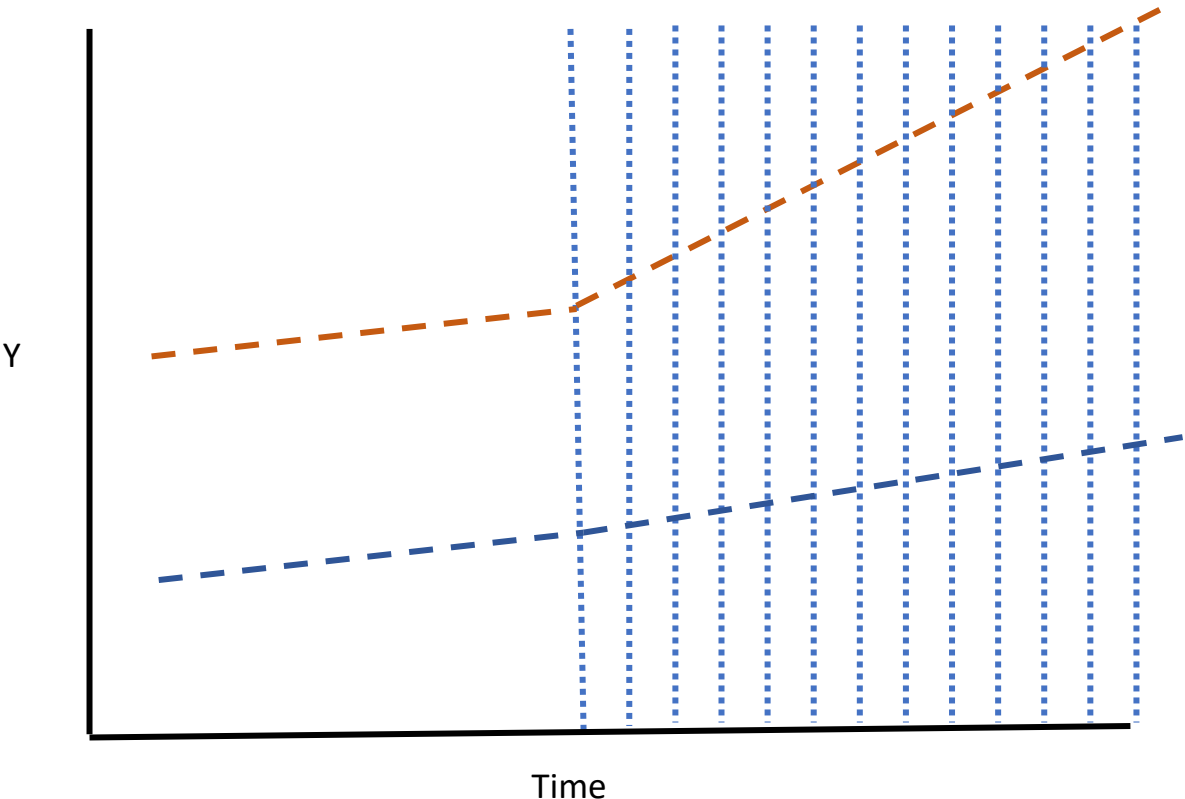
^b Department of Economics, Vanderbilt University, United States of America



Callaway & Sant'Anna DiD Estimator

A difference-in-differences will be estimated at each group-time combination (13 in CRISP).

These DiD can then be aggregated into a single average treatment effect.



Was *dual* intervention better than *single* intervention?

- **Duals** vs. **AHC-only**
 - Subset Duals to clinics receiving AHC first
 - Pre-period: monetary incentives
 - Post-period: additional implementation support
- **Duals** vs. **ASCEND-only**:
 - Subset Duals to clinics receiving ASCEND first
 - Pre-period: implementation support
 - Post-period: additional monetary incentives

Future Potential in Natural Experiments

- Natural experiments can be strengthened by the inclusion of additional features and data sources



Falsification
and Placebo
Tests

National Institute on Minority Health and Health Disparities Research Framework

		Levels of Influence*			
		Individual	Interpersonal	Community	Societal
Domains of Influence (Over the Lifecourse)	Biological	Biological Vulnerability and Mechanisms	Caregiver-Child Interaction Family Microbiome	Community Illness Exposure Herd Immunity	Sanitation Immunization Pathogen Exposure
	Behavioral	Health Behaviors Coping Strategies	Family Functioning School/Work Functioning	Community Functioning	Policies and Laws
	Physical/Built Environment	Personal Environment	Household Environment School/Work Environment	Community Environment Community Resources	Societal Structure
	Sociocultural Environment	Sociodemographics Limited English Cultural Identity Response to Discrimination	Social Networks Family/Peer Norms Interpersonal Discrimination	Community Norms Local Structural Discrimination	Social Norms Societal Structural Discrimination
	Health Care System	Insurance Coverage Health Literacy Treatment Preferences	Patient-Clinician Relationship Medical Decision-Making	Availability of Services Safety Net Services	Quality of Care Health Care Policies
Health Outcomes		Individual Health	Family/Organizational Health	Community Health	Population Health

Data Weighting Explained



Future Potential in Natural Experiments

- Increasing the role of qualitative approaches



Future Potential in Natural Experiments: Target Trials

*“The goal of target trial emulation is to **avoid making fundamental errors that can result in erroneous causal conclusions.**”*

- How would an observational study be conducted if it were an RCT?
- Recall: RCTs remain the gold standard study design for causal inference
 - **Pro:** By design, treatment and outcomes not confounded, through randomization of treatment
 - **Pro:** Time 0 for follow-up clearly defined by study protocols
 - **Con:** Not always practical/feasible/ethical
 - **Con:** Strict inclusion/exclusion criteria and intent-to-treat analysis may limit real-world generalizability
- Pragmatic trials focus on informing real-world practice, though at some potential costs to internal validity
- Target trial emulation helps to rigorously define goals of observational study
 - Necessarily emulating pragmatic rather than fully explanatory trials

Target Trial Emulation: Traction

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JAMA Guide to Statistics and Methods

December 12, 2022

Target Trial Emulation

A Framework for Causal Inference From Observational Data

JAMA | Original Investigation

Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses Results of 32 Clinical Trials

Shirley V. Wang, PhD, ScM; Sebastian Schneeweiss, MD, ScD; and the RCT-DUPLICATE Initiative

IMPORTANCE Nonrandomized studies using insurance claims databases can be analyzed to produce real-world evidence on the effectiveness of medical products. Given the lack of baseline randomization and measurement issues, concerns exist about whether such studies produce unbiased treatment effect estimates.

Research

Nirmatrelvir and risk of hospital admission or death in adults with covid-19: emulation of a randomized target trial using electronic health records

BMJ 2023 ; 381 doi: <https://doi.org/10.1136/bmj-2022-073312> (Published 11 April 2023)

Cite this as: *BMJ* 2023;381:e073312

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Yan Xie, senior clinical epidemiologist^{1 2 3}, Benjamin Bowe, senior biostatistician^{1 2}, Ziyad Al-Aly^{id}, director^{1 2 4 5 6}

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Original Investigation

October 20, 2020

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

Shruti Gupta, MD, MPH¹; Wei Wang, PhD²; Salim S. Hayek, MD³; et al

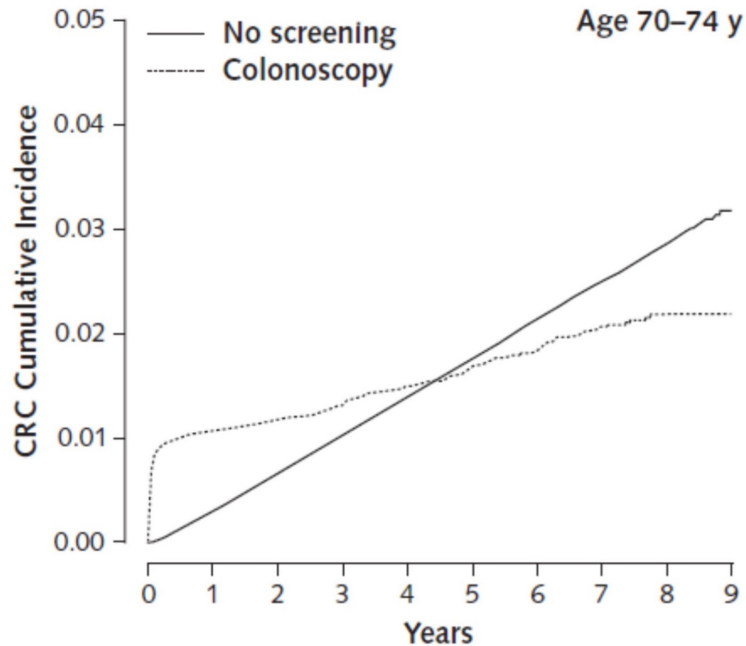
Target Trial Emulation: Example

Original Research | 3 January 2017

Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years

A Prospective Observational Study

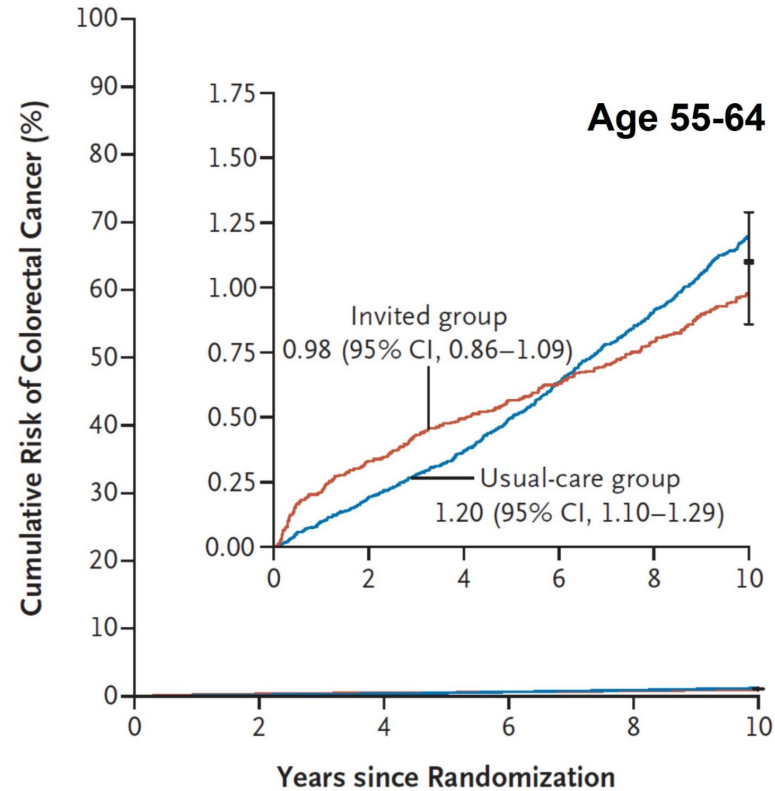
Xabier García-Albéniz, MD, PhD, John Hsu, MD, MBA, MSCE, Michael Bretthauer, MD, PhD, and Miguel A. Hernán, MD, DrPH [View fewer authors](#)



ORIGINAL ARTICLE

Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

Michael Bretthauer, M.D., Ph.D., Magnus Leberg, M.D., Ph.D., Paulina Wieszczy, Ph.D., Mette Kalager, M.D., Ph.D., Louise Emilsson, M.D., Ph.D., Kjetil Garborg, M.D., Ph.D., Maciej Rupinski, M.D., Ph.D., Evelien Dekker, M.D., Ph.D., Manon Spaander, M.D., Ph.D., Marek Bugajski, M.D., Ph.D., Øyvind Holme, M.D., Ph.D., Ann G. Zauber, Ph.D., et al., for the NordICC Study Group*



Target Trial Emulation: Steps

TTE as a 2-step process

- 1 Articulate causal question in form of protocol of a hypothetical randomized trial that would provide the answer**
 - Eligibility criteria
 - Treatment strategies
 - Treatment assignment
 - Start and end of follow-up
 - Outcomes
 - Causal contrasts
- 2 Explicitly emulate components of protocol using observational data**
 - Potential confounders for adjustment?
 - Take care with (mis)alignment of exposure, assignment, follow-up times
 - See: Hernán et al. (2016) – Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses

Steps for setting up Natural Experiment Analyses

1. Identify the event and conceptualize the potential causal pathway from the event to your health outcome of interest
2. Identify and define intervention and control groups
3. Identify your research design (e.g. Diff-in-diff, etc.)
4. Collect as many covariates as possible and check between group differences
5. Assess pre-intervention parallel trends (if applicable)
6. Perform a power analysis
7. Run your natural experiment method and interpret
8. Perform all your planned sensitivity analyses

Conclusion

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& Evaluation Network

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[Engagement Grants](#)



Our Mission

Our mission is to improve health and health equity by advancing high quality research on health care sector strategies to improve social conditions.

Thank you!!!

Miguel Marino : marinom@ohsu.edu Twitter: @MmMiguelmM

Jorge Kaufmann: kaufmjor@ohsu.edu

For more information, please visit: www.primerlab.org

