Guide to Statistics and Methods

Making Sense of the Difference-in-Difference Design

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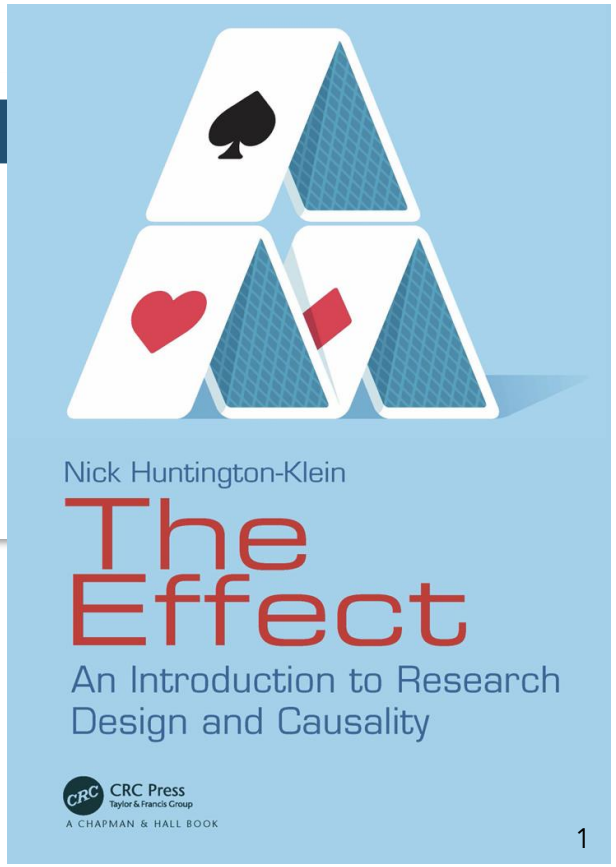
Research

JAMA Internal Medicine | Original Investigation

British Columbia's Safer Opioid Supply Policy and Opioid Outcomes

Hai V. Nguyen, PhD; Shweta Mital, PhD; Shawn Bugden, PharmD; Emma E. McGinty, PhD



Presented by Nantharat Apiwantanakul
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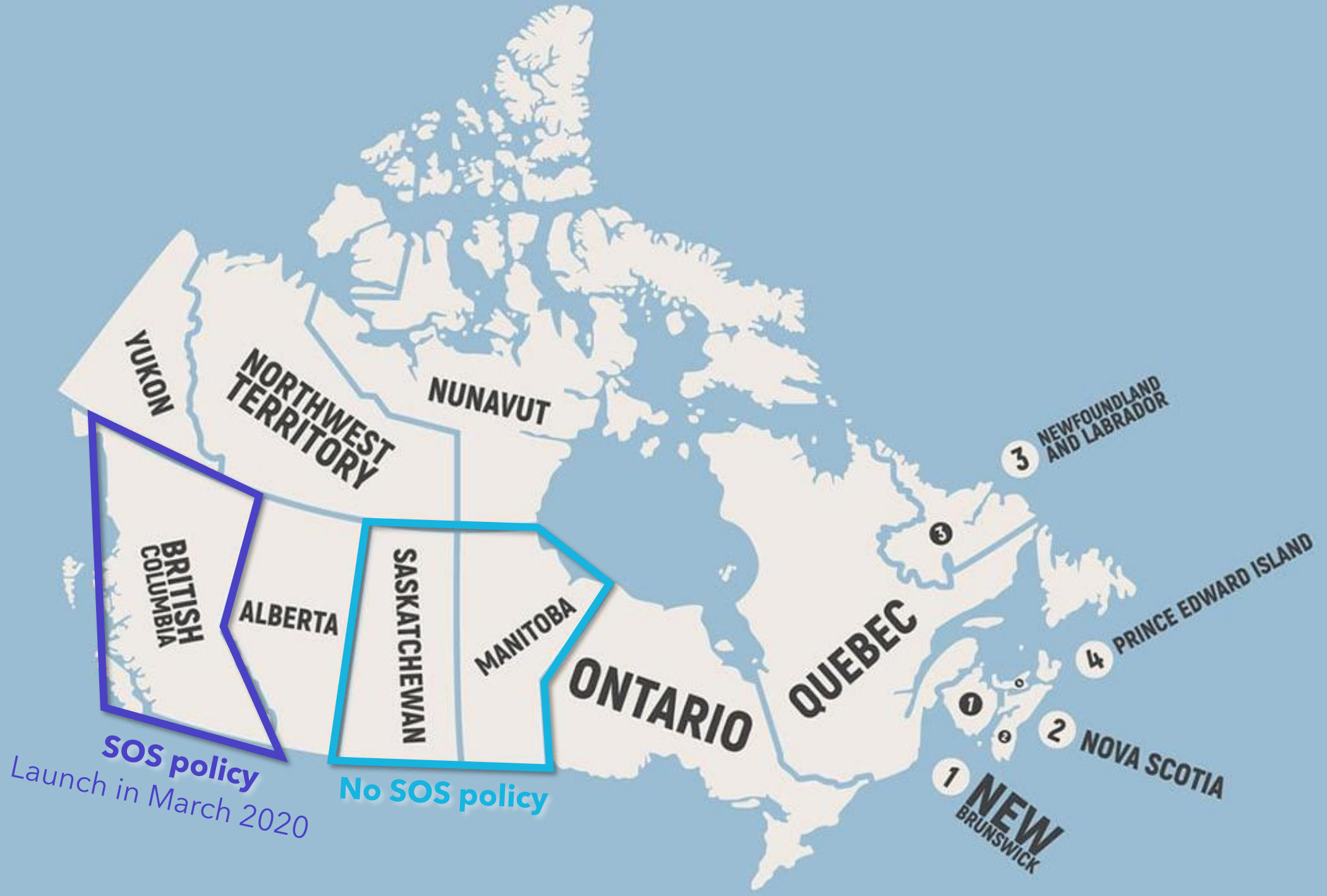
British Columbia's Safer Opioid Supply Policy and Opioid Outcomes

Hai V. Nguyen, PhD; Shweta Mital, PhD; Shawn Bugden, PharmD; Emma E. McGinty, PhD

- Canada's opioid crisis
  - 14 hospitalizations from opioid poisoning/day
  - 20 deaths of an opioid overdose/day
- **Hypothesis**: Potent synthetic opioids from the unregulated market are fueling the crisis.
- **Policy**: "Safer Opioid Supply (SOS) Policy"
  - Providing a safe supply of regulated and pharmaceutical-grade opioids to people who use drugs.
  - **Aims** : to reduce opioid overdose by inducing opioid users to switch from illegal to legal opioids


YUKON
NORTHWEST TERRITORY
NUNAVUT
BRITISH COLUMBIA
ALBERTA
SASKATCHEWAN
MANITOBA
ONTARIO
QUEBEC
3 NEWFOUNDLAND AND LABRADOR
4 PRINCE EDWARD ISLAND
2 NOVA SCOTIA
1 NEW BRUNSWICK
SOS policy
Launch in March 2020
No SOS policy

Research design

- **Objective**: To investigate the association of British Columbia's SOS policy with opioid prescribing and opioid-related health outcomes.

P	Individuals with opioid use disorder who are at high risk of overdose or poisoning
I	SOS policy (British Columbia)
C	No SOS policy (Manitoba and Saskatchewan)
O	Opioid prescribing outcomes • opioid prescription • opioid claimant (=number of people with at least 1 opioid prescription dispensed) • opioid prescriber Opioid-related health outcomes • hospitalization from opioid overdose poisoning • death from opioid toxicity

Research design

- Used deidentified and aggregate province-level data

P	Individuals with opioid use disorder who are at high risk of overdose or poisoning
I	SOS policy (British Columbia)
C	No SOS policy (Manitoba and Saskatchewan)
O	Opioid prescribing outcomes • opioid prescription • opioid claimant • opioid prescriber Opioid-related health outcomes • hospitalization from opioid overdose poisoning • death from opioid toxicity

Obtained from the Canadian National Prescription Drug Utilization Information System Database

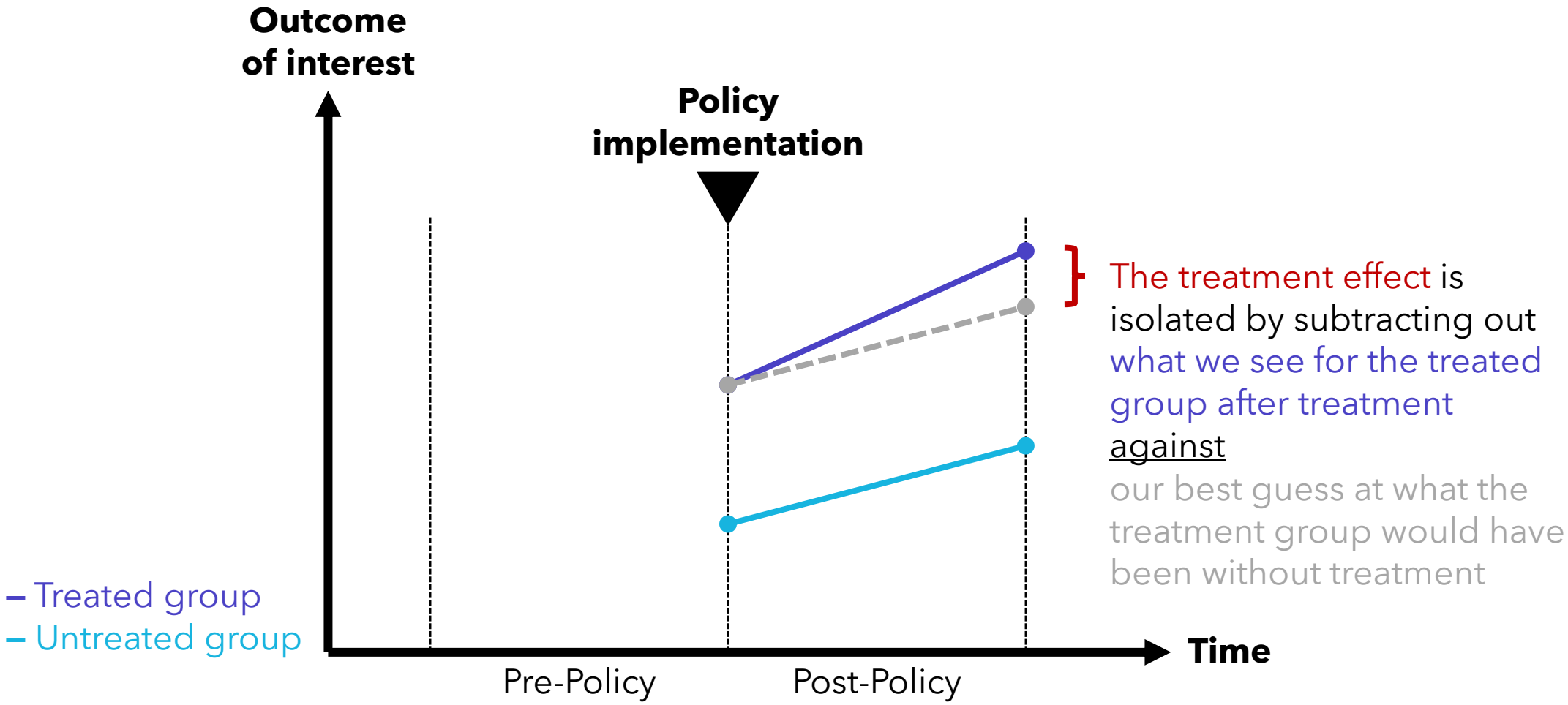
Identified using ICD-10 codes T40.0, T40.1, T40.2, T40.3, T40.4, T40.6

Available from the Public Health Agency of Canada

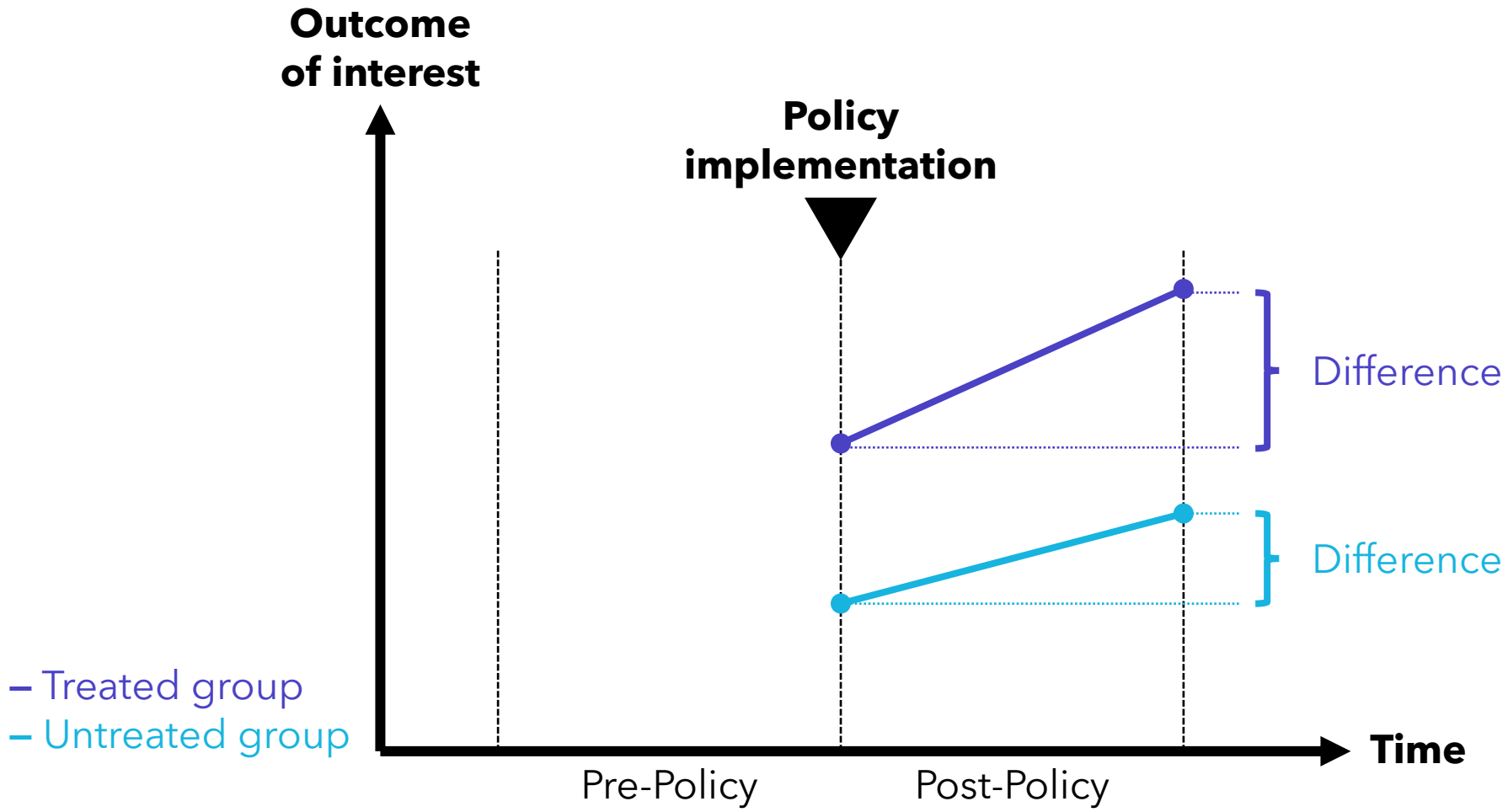
Research design

- Use quasi-experimental difference-in-difference (DID) design
- DID is often used to study interventions that have been adopted on a larger scale and under looser conditions.

Difference-in-Differences



Difference-in-Differences



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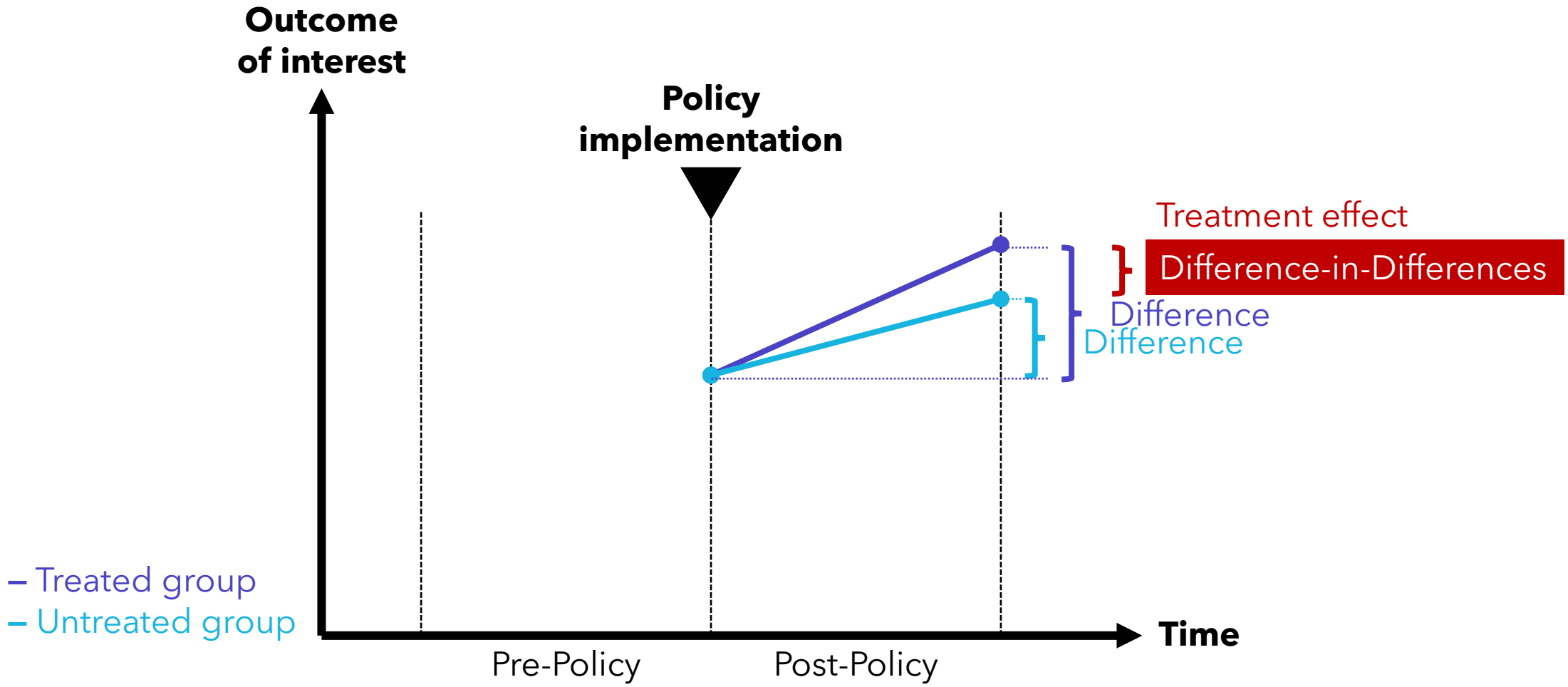
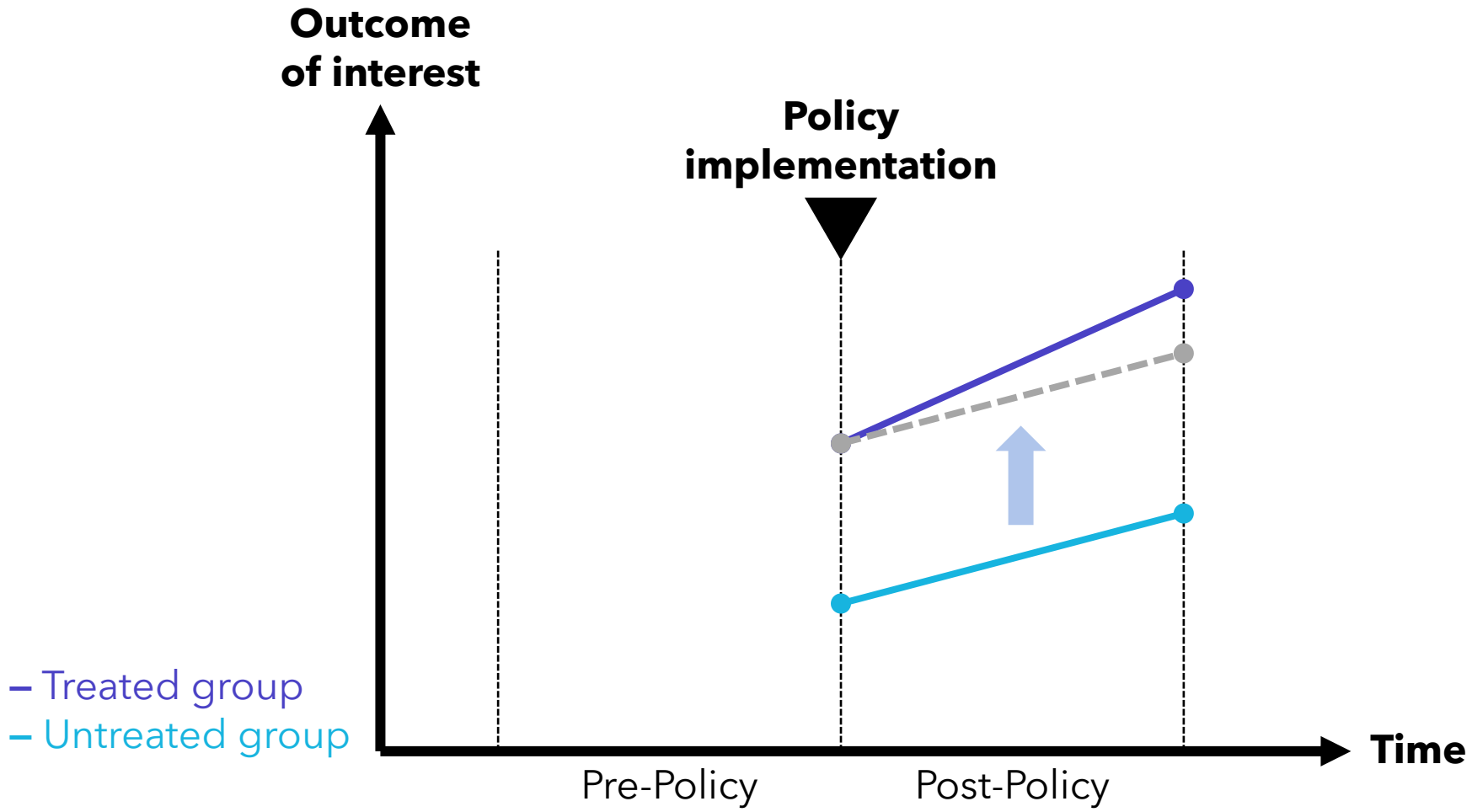


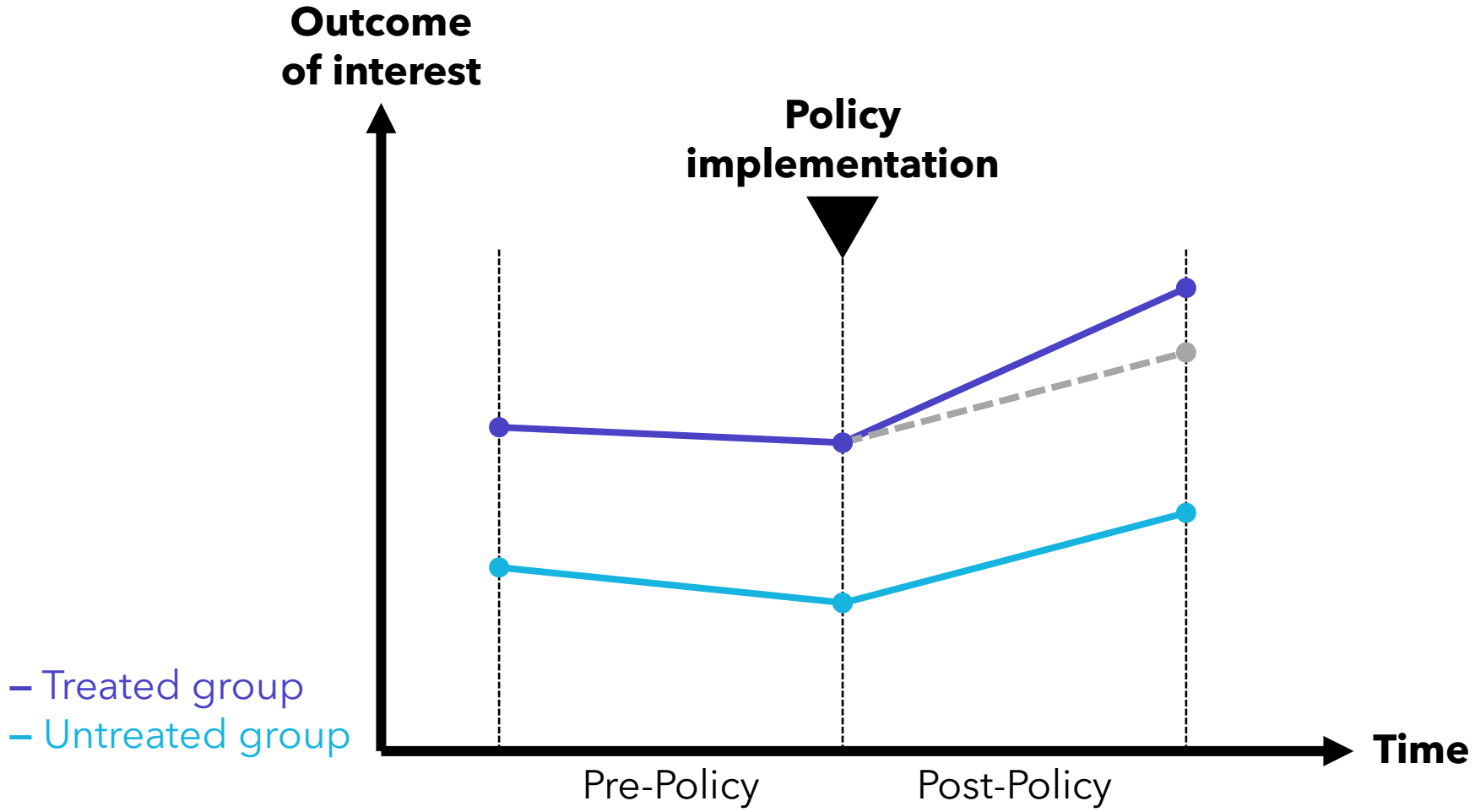
Difference-in-Differences

- Treated group
  - Difference = EffectofTreatment + OtherTreatedGroupChanges --------**(1)**
- Untreated group
  - Difference = OtherUntreatedGroupChanges -----**(2)**
- **DID = (1) - (2)**
- **DID = EffectofTreatment**; it has to be the case that OtherTreatedGroupChanges exactly cancels out with OtherUntreatedGroupChanges

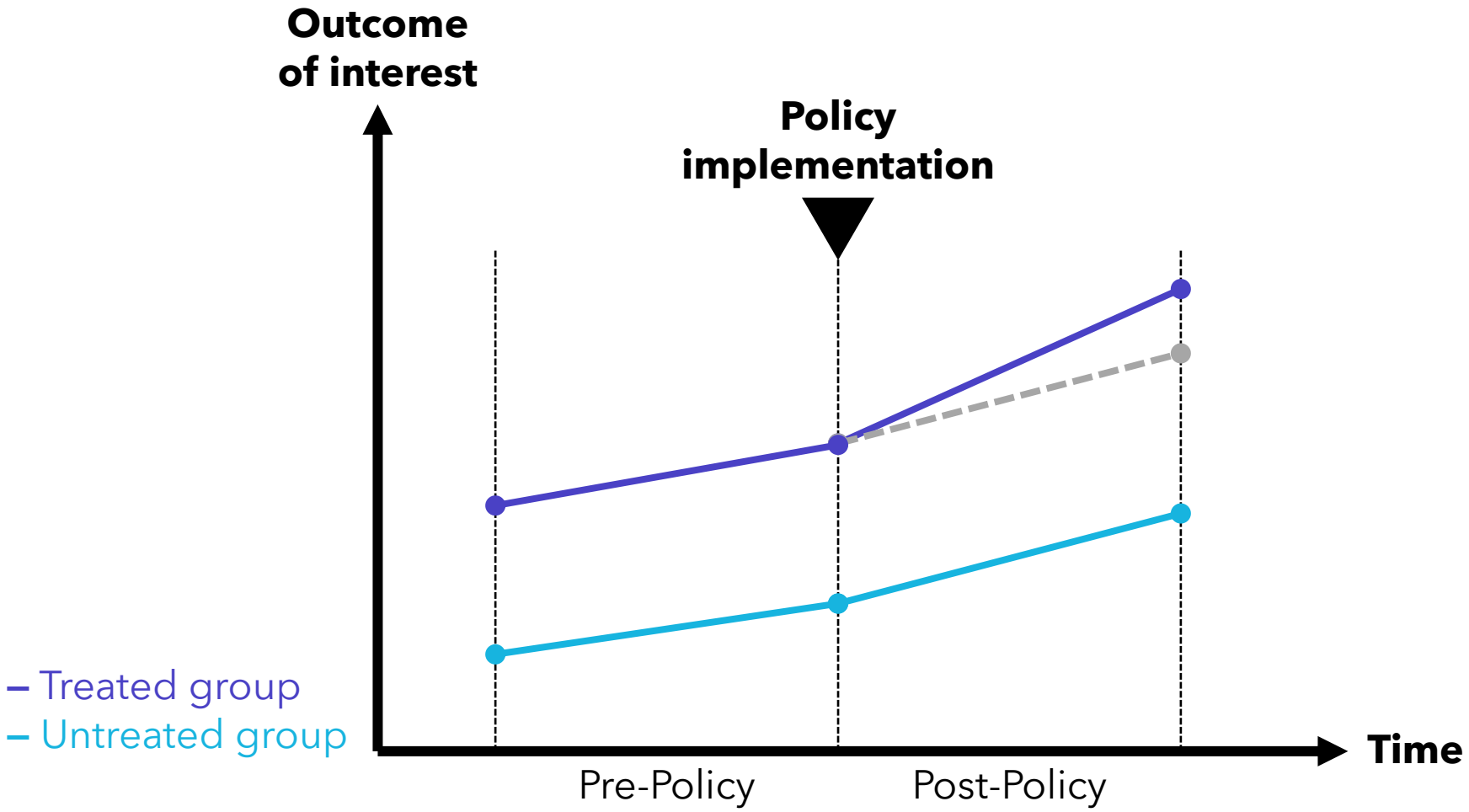
Parallel trend assumption



Parallel trend assumption



Parallel trend assumption

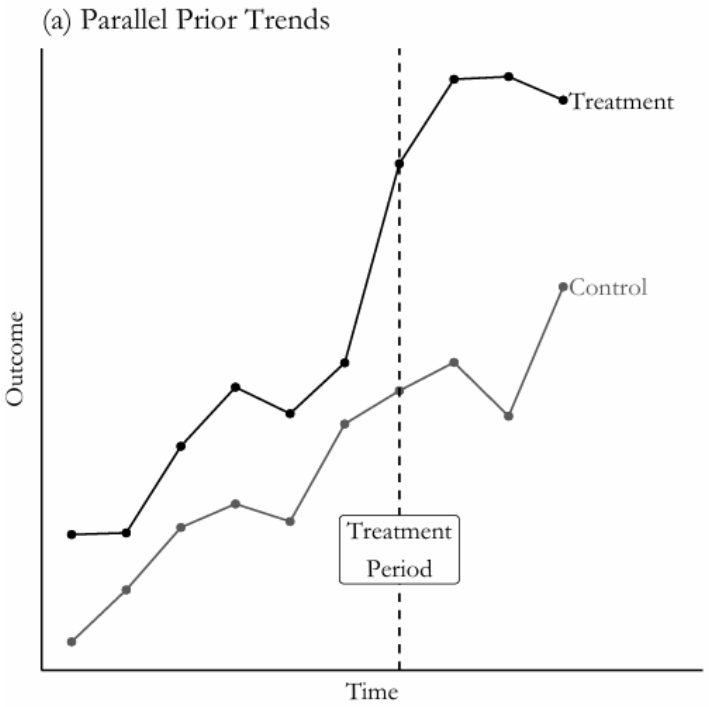


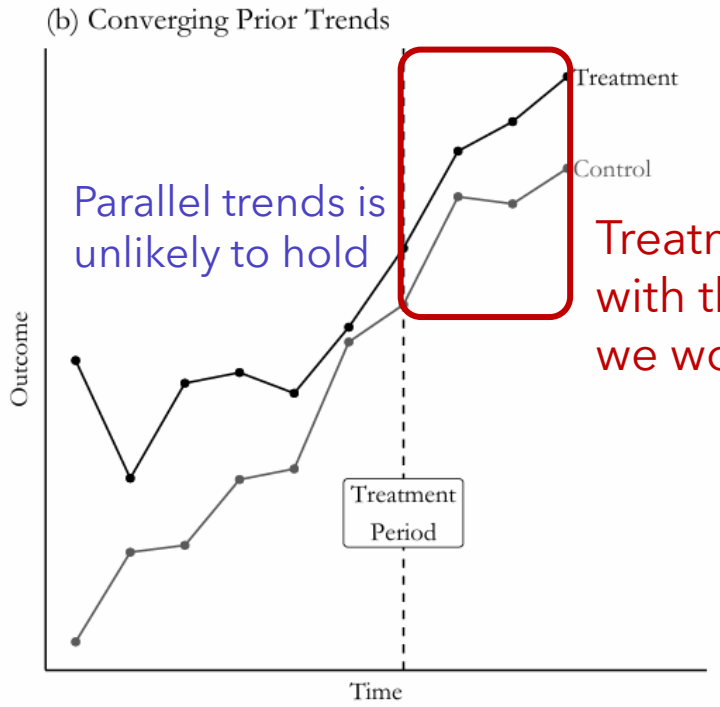
Parallel trend assumption

- The parallel trends assumption says that, if no treatment had occurred, the difference between the treated group and the untreated group would have stayed the same in the post-treatment period as it was in the pre-treatment period.
- No test of the data could possibly confirm or disprove the parallel trends assumption, since it's based on a counterfactual we can't see.
- The tests are more along the lines of suggestive evidence. If the tests fail, it makes the parallel trends assumption less plausible.

Parallel trend assumption

To **graph** the average outcomes over time in the pre-treatment period



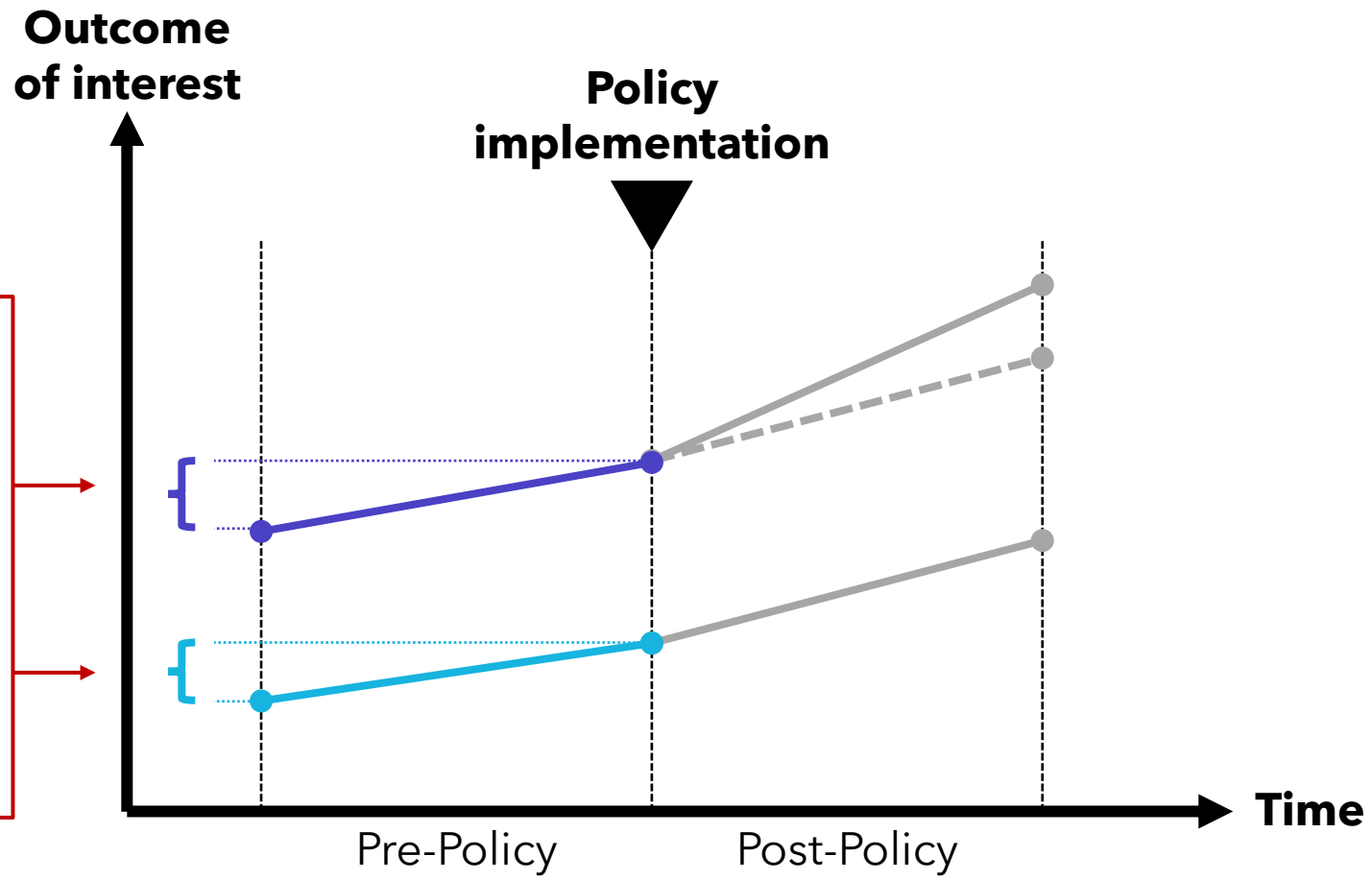


Treatment-related change will get mixed up with the nontreatment-related change, and we won't be able to tell them apart.

Parallel trend assumption

Placebo DID: Using the data from before a treatment was applied and pretend that the treatment was applied at that time, then estimate the DID

Nonzero DID during a period where there is no actual treatment tells us that there are differential trends, suggesting us a clue that something may be awry about the parallel trends assumption.



Key assumptions

- The validity of the of DID conclusion depends on the credibility of the assumptions.
  - Parallel trend assumption
  - No anticipation assumption

No anticipation assumption

- Treatment should not be induced by past outcomes.
- The current outcomes do not depend on future treatment exposure.

Statistical analysis

- DID analysis was used to compare changes in outcomes before and after policy implementation in British Columbia with those in the comparison provinces.


A Prescriptions
March 2020
July 2021
British Columbia
Saskatchewan
Manitoba
Total prescriptions per 100 000 population
14000
12000
10000
8000
6000
4000
2016 Q1
2017 Q3
2019 Q1
2020 Q3
2022 Q1
Time
B Claimants
March 2020
July 2021
Total claimants per 100 000 population
2500
2000
1500
1000
2016 Q1
2017 Q3
2019 Q1
2020 Q3
2022 Q1
Time
C Prescribers
March 2020
July 2021
Total prescribers per 100000 population
400
350
300
250
2016 Q1
2017 Q3
2019 Q1
2020 Q3
2022 Q1
Time
D Opioid overdose poisoning hospitalizations
March 2020
July 2021
Total cases per 100000 population
10
8
6
4
2
0
2016 Q1
2017 Q3
2019 Q1
2020 Q3
2022 Q1
Time
E Apparent deaths due to opioid toxicity
March 2020
July 2021
Total cases per 100000 population
15
10
5
0
2016 Q1
2017 Q3
2019 Q1
2020 Q3
2022 Q1
Time

No anticipation assumption

- Treatment should not be induced by past outcomes.
  - *Might fail* if British Columbia had adopted the new SOS policy because of a sudden, temporary rise in opioid overdoses that didn't occur in the comparison provinces.
- The current outcomes do not depend on future treatment exposure.
  - *Might fail* if the announcement of the SOS policy affected opioid utilization and enforcement before the policy came into effect.

Statistical analysis

- The difference-in-differences analyses were implemented using the regression model

DID estimate ATET
(Average treatment effect on the treated)

Province
To control for all time-invariant characteristics of provinces

Province-specific linear time trends
To control for possible differences in trends across provinces.

$$Y_{pt} = \alpha + \beta_1 (Safer\ Supply\ Policy)_{pt} + \beta_2 Z_{pt} + \beta_3 Province_p + \beta_4 Time_t + \beta_5\ Province_p\ x\ Time\ Trend_t + errors$$

Covariate of interest

Time-varying province-level covariates

- Proportion of individuals aged 0 to 17 years
- Proportion of males
- Consumer Price Index
- Unemployment rate
- Public health COVID-19 restrictions

Quarter-year indicators
To control for secular changes in outcomes that are common to British Columbia and the comparison provinces

Results

Table 1. Outcome Changes Associated With the Safer Opioid Supply Policy[a]

Outcome (province-quarter data points)	Difference-in-differences estimates, per 100 000 population (95% CI)	*P* value
Prescription rate (n = 75)	↑ 2619.6 (1322.1 to 3917.0)	<.001
Claimant rate (n = 75)	↑ 176.4 (33.5 to 319.4)	.02
Prescriber rate (n = 75)	15.7 (−0.2 to 31.6)	.053
Hospitalization rate (n = 75)	↑ 3.2 (0.9 to 5.6)	.01
Death rate (n = 75)	1.6 (−1.3 to 4.5)	.26

Opioid prescribing outcomes

Opioid-related health outcomes

[a] Data are from quarter 1 of 2016 to quarter 1 of 2022. Estimates are from difference-in-differences regressions estimated using ordinary least squares and controlled for proportion of individuals aged 0 to 17 years in the population, proportion of males, Consumer Price Index, unemployment rate, and COVID-19 restriction score in the province, province and quarter-year fixed effects, and province-specific linear time trend. Comparison provinces were Manitoba and Saskatchewan. Heteroskedasticity-consistent HC3 SEs were used.

What could explain the **higher hospitalization rate** after the policy's implementation?

- Diverted safer opioid supply for various reasons, including to purchase unregulated fentanyl
- A higher supply of prescription opioids led to an increase in prescription opioid misuse, which in turn, could increase hospitalization risks
- Availability of an unregulated drug supply increased more in British Columbia than in comparison provinces, leading to more hospitalizations in British Columbia.

Robustness of the results

- As the policy's launch coincided with the onset of the **COVID-19 pandemic**, we conducted additional analyses to rule out confounding effects of the pandemic.
  1) Re-ran the analysis excluding the 'COVID-19 washout period'
  2) Examined the policy effects separately during the first year (i.e., the policy's launch) and the second year (i.e., the policy's expansion).

Robustness of the results

1) Re-ran the analysis excluding the 'COVID-19 washout period'

- If any observed changes in hospitalizations and deaths were due to the pandemic, we would expect to see no or smaller changes in these outcomes after dropping the peak pandemic period.
- However, our analyses showed that the observed increases in hospitalizations and deaths were even greater after excluding the COVID-19 pandemic washout period

Table 2. Sensitivity Analyses[a]

Outcome	Difference-in-differences estimates, per 100 000 population (95% CI)	*P* value
Excluding quarter 2 of 2020 to quarter 1 of 2021 (n = 63)		
Prescription rate	4215.1 (3656.3 to 4773.9)	<.001
Claimant rate	157.7 (53.9 to 261.4)	.004
Prescriber rate	20.7 (10.1 to 31.4)	<.001
Hospitalization rate	3.6 (1.7 to 5.5)	<.001
Death rate	2.5 (−0.7 to 5.8)	.12

Table 1. Outcome Changes Associated With the Safer Opioid Supply Policy[a]

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Prescription rate (n = 75)	2619.6 (1322.1 to 3917.0)	<.001
Claimant rate (n = 75)	176.4 (33.5 to 319.4)	.02
Prescriber rate (n = 75)	15.7 (−0.2 to 31.6)	.053
Hospitalization rate (n = 75)	3.2 (0.9 to 5.6)	.01
Death rate (n = 75)	1.6 (−1.3 to 4.5)	.26

Robustness

2) Examined the policy effects separately during the first year (i.e., the policy's launch) and the second year (i.e., the policy's expansion)

A larger policy effect during the policy expansion would indicate a dose-response relationship and suggest that observed outcome changes would be more likely attributed to the policy than the pandemic.

Table 2. Sensitivity Analyses[a]

Outcome	Difference-in-differences estimates, per 100 000 population (95% CI)
Addressing confounding effects of COVID-19 pandemic	
Policy introduction and expansion (n = 75)	
Prescription rate	
Introduction	2624.6 (1193.6 to 4055.6)
Expansion	3418.5 (1848.1 to 4988.9)
Claimant rate	
Introduction	176.7 (27.6 to 325.7)
Expansion	211.4 (21.1 to 401.8)
Prescriber rate	
Introduction	15.7 (−0.9 to 32.3)
Expansion	19.8 (1.8 to 37.9)
Hospitalization rate	
Introduction	3.2 (1.0 to 5.4)
Expansion	4.3 (1.3 to 7.3)
Death rate	
Introduction	1.6 (−1.2 to 4.4)
Expansion	3.0 (−1.6 to 7.5)

Sensitivity analysis

- We examined the sensitivity of our results to
  - Expanded set of comparison provinces
    - 4 comparison provinces (+ Alberta, Nova Scotia)
    - 6 comparison provinces (+ Alberta, Nova Scotia, Ontario, New Brunswick)
  - Alternative regression specification
    - exclusion of province-specific linear time trend
    - exclusion of demographic controls
    - exclusion of the COVID-19 stringency index

Expanded set of comparison provinces

Table 1. Outcome Changes Associated With the Safer Opioid Supply Policy[a]

Outcome (province-quarter data points)	Difference-in-differences estimates, per 100 000 population (95% CI)	*P* value
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Prescriber rate (n = 75)	15.7 (−0.2 to 31.6)	.053
Hospitalization rate (n = 75)	3.2 (0.9 to 5.6)	.01
Death rate (n = 75)	1.6 (−1.3 to 4.5)	.26

Table 2. Sensitivity Analyses[a]

Outcome	Difference-in-differences estimates, per 100 000 population (95% CI)	*P* value
Expanded sets of comparison provinces		
Difference-in-differences with 4 comparison provinces (n = 125)[b]		
Hospitalization rate	2.4 (0.5 to 4.3)	.01
Death rate	1.2 (−0.7 to 3.2)	.21
Synthetic difference-in-differences with 6 comparison provinces[c]		
Hospitalization rate	2.0 (0.6 to 3.4)	.007
Death rate	0.4 (−4.8 to 5.5)	.89

We also obtained evidence of an increase in hospitalizations in the regression analyses. The increases in deaths remained statistically insignificant.

Alternative regression specification

Table 2. Sensitivity Analyses[a]

Outcome	Difference-in-differences estimates, per 100 000 population (95% CI)	*P* valu
Alternative regression specifications		
Excluding linear time trend (n = 75)		
Prescription rate	4211.7 (3111.1 to 5312.3)	<.001
Claimant rate	156.8 (82.1 to 231.5)	<.001
Prescriber rate	15.3 (6.4 to 24.2)	.001
Hospitalization rate	3.2 (1.9 to 4.5)	<.001
Death rate	1.4 (−0.5 to 3.3)	.15
Excluding demographic covariates (n = 75)		
Prescription rate	3022.7 (1999.5 to 4045.8)	<.001
Claimant rate	186.2 (57.1 to 315.3)	.006
Prescriber rate	19.2 (6.4 to 32.1)	.004
Hospitalization rate	2.9 (1.0 to 4.8)	.003
Death rate	1.5 (−1.1 to 4.1)	.25
Excluding COVID-19 stringency index (n = 75)		
Prescription rate	2621.2 (1324.1 to 3918.3)	<.001
Claimant rate	175.7 (29.7 to 321.7)	.02
Prescriber rate	15.7 (−0.008 to 31.3)	.050
Hospitalization rate	3.2 (1.0 to 5.4)	.006
Death rate	1.6 (−1.1 to 4.3)	.24

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The results were also robust to the exclusion of control variables for demographic factors, province-specific linear time trend, and the COVID-19 stringency index.

Conclusion

- Two years after its launch, the SOS Policy in British Columbia was associated with higher rates of prescribing of opioids but also with a significant increase in opioid related hospitalizations.
- These findings may help inform ongoing debates about this policy not only in British Columbia but also in other jurisdictions that are contemplating it.

Limitations

- Used only Manitoba and Saskatchewan as comparison provinces
  - Sensitivity analyses including other provinces indicated that our results were robust.
- Since the drugs could be used for other conditions, the increase in prescriptions cannot be solely attributed to the policy.
- Prepolicy fluctuations in hospitalizations and deaths
  - Although the prepolicy trends were broadly similar between British Columbia and the comparison provinces, future work that uses longer term data to identify meaningful trends would be helpful.
- Unable to examine heterogeneity in the policy effects due to inconsistent aggregate-level data across demographic groups

Take home messages

- DID is a quasi-experimental design for estimating causal effects of interventions
- DID is often used to study interventions adopted on a larger scale and under less controlled conditions.
  - In contrast, RCTs are usually small scale, use strict inclusion criteria, and randomly assign participants to treatment, which can weaken external validity.
- The validity of the DID conclusion depends on the credibility of the assumptions.
  - Parallel (Common) trends assumption
  - No anticipation assumption

Take home messages

- Limitations of the DID Design
  - The common trend and no anticipation assumptions are not controlled by the researcher. These assumptions can be probed using data from multiple periods, but such checks are sometimes inconclusive.
  - The DID design may have low statistical power because of clustering and serial correlation
  - Implementing a DID requires data on outcomes overtime, which are not always available.

Thank you