# Estimate the Impact of Opioid Control Policies (For Nick)

Beibei Du, Wafiakmal Miftah, Suzanna Thompson, Alisa Tian

December 12, 2022

## Motivation

A nationwide opioid epidemic has reached unprecedented levels in the United States. Opioids, which include both prescription painkillers and illegal drugs, have become a major threat to public health and global health. These highly addictive substances can lead to overdose and death, and the number of overdose deaths from opioids is something we want to find out in this project. The problem is particularly severe in certain parts of the country.

One potential solution is to implement policies that reduce the availability of these drugs. In order to evaluate the effectiveness of such policies, we plan to select three states and compare them to controlled states. By analyzing the data, we aim to determine whether the implementation of policies has had a positive effect on reducing the opioid crisis. Addressing the opioid crisis is crucial for protecting the health and well-being of citizens in the United States and can serve as an example for other countries. Once again, opioids are highly addictive and potentially fatal if intake overdoses. It will make people lose control of the nervous system and their involuntary breath control will be affected as well. Therefore, a policy control protects public health to minimize the death risk from an overdose of opioids.

To solve this problem, an effective policy will be the first choice. To evaluate whether the policy intervention is effective, we will implement research designs to answer some motivating questions. We are considering the problem within the United States. We hope that our project result can be extended to a broader application. But our main focus is on the United States and the research design can be replicated towards other regions once the data is ready. We also want to take opioids as an example of drugs and it can be applied into analyses for other drugs as well. The goal is to study the death rate before and after the policy intervention to see if the policies are effective. Specifically, we want to see after the policy intervention, the mortality rate and the opioid prescription rate drops.

For this project, we are trying to address the problem of rising opioid usage and its connection with death by drugs in the United States. We have two specific questions: What effect did the opioid policies in Texas, Washington, and Florida have on the number of opioid deaths and overall drug deaths in those states? In other words, how do opioid deaths and overall drug deaths differ in Texas, Washington, and Florida from our chosen control states?

# Motivation for Research Design

The research design methods that we are using are pre-post comparison and difference-in-difference regression. Since this problem can't be randomly assigned and policies are different from each state, we want to compare the Opioids per Capita before and after the policy to see if there's any decreasing trend after the policy change (our initial assumption) and other potential variables. However, this research design can't wipe out the possibility of other confounding variables. Thus, difference-in-difference regression will play an imperative role in encountering the issues. Instead, we compare the chosen states with other states that don't have the policy change. We will observe the trend after the policy intervention and see if it will decrease the death rate/opioids per capita.

#### Pre-Post Analysis

Our first methodology is a **pre-post analysis**. We compare the change of mortality rate and prescription rate before and after the policy implementation.

We are interested in the effect of opioid policy change for the state directly with the comparison (before and after the policy intervention). This is a very simple way to see if there's a difference before and after the policy intervention. However, there are many other potential confounding variables causing the change in the trend of death rate or Opioids per Capita. For example, the death rate drops could be due to other reasons such as the development of the medical system across time. Thus, this is a baseline analysis we will take a look at in the first step.

#### Difference in Difference analysis

Simply using the pre-post analysis is not enough to make our results more reliable and persuasive. For example, we are interested in analyzing the effect of policy change on mortality rate in Washington (around 2012), and compared the mortality rate in Washington before and after 2012 (the policy implementation). Suppose, one type of hallucinogens is banned nationwide in the same year, which will possibly lead to a decrease in overdose death. However, we do not know whether this is caused by the policy change or this hallucinogen ban. Thus, we need our second approach – difference-in-difference analysis. The difference is that we are comparing the state with another state that does not have the policy intervention, but with a similar trend before the policy intervention. Thus our

focus will shift to the trend after the policy intervention. We expect to see the overdose mortality rate and prescription rate drops after the policy change.

#### Details of the Data

1. Opioids Prescription/shipment data (Washington Post):

In this dataset, it holds most of the information of the opioids prescription across the years in all states in the United States. This dataset is about 100GB and we select the 3 states and their controlled states to preprocess. The unit of observation for this dataset is at the county-level. We sum the all data of all counties in a state and take that into our analyses.

2. Mortality Rate data (CDC Wonder):

In this dataset, we have state, county, year, opioid-related cause of death, and the number of deaths per county and state. The unit of observation for this data is at the county-level.

For both the Prescription and Shipment Data and the Mortality Rate Data, we found inconsistencies at the county level. In that, there were missing counties in excess of a thousand, country-wide. This is because deaths are not reported per county if they do not exceed 10. To combat this, we imputed the quantity of death per county with 5, which we understand to be an adequate average.

To select our comparison states, we use an additional four datasets and we reuse the death rate dataset. We use an income dataset, which has average income per state per year. We also use an educational ranking dataset. The educational ranking dataset has each state's ranking for education. For our purposes, the pure ranking is enough for evaluation and our understanding of 'closenses.' We use a population dataset that has population per year, per state. Because we're selecting states on the whole for comparison and the policy implementations are state-wide, our unit of observation for the state selection is on the state level.

#### Selecting States

For our analysis, we are comparing the opioid prescription rates and the opioid death rate for each policy state, Texas, Washington, and Florida, to suitable comparison states respectively. Our methodology for selecting states for comparison is a conditional closeness calculation. Closeness is computed by taking an average of four similarity scores. We're choosing to define similarity as a function of 4 socioeconomic and demographic factors, which are education, income, population, and rate of drug-related deaths. The similarity score is calculated by dividing each candidate state by the current policy-state. As an example, we compute this as an income similarity score for Arkansas and Florida:

 $Similarity_{Income, AR \ vs \ FL} = Income_{Arkansas} \div Income_{Florida}$ 

So, for this example, an output close to 100% is interpreted to mean that the average income in Arkansas is sufficiently similar to the average income in Florida. Our bounds for being sufficiently similar are:

 $80\% \le \text{Similarity Score } \le 120\%$ 

Once the similarity score is calculated for income, population, education, and rate of drug-related deaths, the four scores are averaged to create a combined similarity metric. The bounds for being sufficiently similar in the combined similarity metric are:

 $80\% \le \text{Combined Similarity Score } \le 120\%$ 

After we've compiled the list of states that fall within the bounds, we then compare each state's quantity of implemented opioid-crisis related policies. For this comparison, we use How States Are Tackling the Opioid Crisis by Shalini Wickramatilake, et. al. In their paper, they use questionnaire data from state alcohol and drug agency directors and designated senior agency managers to understand what policies are implemented in each state. In their Table 1, they diagram what states have implemented what policies. The polices they're investigating are Education on Risks of Opioids, Education on Prescribing of Opioids, Good Samaritan Law, Funding for MAT, Access to Naloxone, PDMP Reporting Required, Pain Clinic Regulation, and Prescriber Guidelines. Each education category is also separated by subcategories. For our purposes, we are only using the 'General Population' subcategory within the Education on Risks of Opioids Category, and all three subcategories, 'Physicians and Other Prescribers,' 'Patients and Families,' 'Pharmacists,' within the Education on Prescribing of Opioids category.

For context, the Good Samaritan Law legally protects individuals who attempt to help a person in crisis. In our case, if a person is experiencing an opioid overdose and a bystander attempts to help, but instead hurts the situation, then the bystander has legal protection from being sued by the person who was overdosing. Funding for MAT (medically assisted treatment) "Aims to decrease opioid misuse and opioid-related overdose deaths by offering financial and technical assistance to state, local, and tribal government entities." Access to Naloxone gives funding to local agencies to keep Naloxone on hand, which is a nasal spray used to treat narcotic overdoses. PDMP (prescription drug monitoring programs) are databases used to track the distribution of prescription drugs.

We use the information from their paper to create a final, conditional metric for evaluating candidate states. We count the quantity of policies that are missing from each state. The questionnaire is from 2015 and all of the policy implementations of our three policy states were before 2015. So, we decide to count the number of missing policies to ensure a stable timeline for the other policies that candidate states may or may not have implemented. In that, we can safely assume that policies that were missing in 2015, were also missing in 2007 (Texas), 2010 (Florida), and 2012 (Washington).

So, from our list of candidate states for each policy state, we limit to states that only have more missing policies than the respective comparison states. In turn, we're comparing each Florida, Texas, and Washington to states that have similar demographic and socio-economic statuses while having a lesser response to the opioid crisis. Below is a table showing each treatment state and a list of their respective control states.

Treatment State	Control States
Texas Washington Florida	Arkansas, California, Georgia, Missouri, New York, Wyoming Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Da California, Nevada, New York

Table 1. Summary of Treatment and Control States

It is worth noting that for Texas, we are not using population in its combined similarity metric calculation because its population is much larger than other states and creates a weighting-effect on the metric towards population.

#### **Summary Statistics**

This table shows the summary statistics for the mortality rate. For Florida, the mean mortality rate per capita dropped from 61.60 to 57.33 after the policy implementation. For control states, however, we observe an increase in the mortality rate from 145.48 to 156.15. For the other states: Washington, the mean of mortality rate also decreased after the policy change. On the contrary, for Texas, the mortality rate increased from 194.77 to 231.08 after 2007.

Descriptive Statistics for Mortality Rate							
	Before	mean	min	25%	50%	75%	max
	or						
	after						
	policy						
	$_{\rm change}$						
Florida (2010)	Before	62.70	0.21	6.20	20.35	59.04	2057.4
	After	50.91	0.18	4.79	11.85	48.04	928.74
Control States	Before	135.26	0.10	4.43	13.89	49.58	21097
	After	70.97	0.04	0.04	10.11	10.11	10.11
Washington (2012)	Before	111.07	0.26	7.23	24.74	95.14	2375.7
	After	101.53	0.21	6.78	25.41	97.08	97.08
Control States	Before	81.36	0.44	15.36	40.11	88.05	5487.4
	After	78.93	0.39	14.32	40.54	91.81	1611.9
Texas $(2007)$	Before	194.77	0.13	15.88	48.53	133.33	7709.0
•	After	231.08	0.10	11.92	43.31	147.81	8916.4
Control States	Before	56.47	0.10	7.70	21.89	50.43	3332.6

Descriptive Statistics for Mortality Rate							
	After	53.98	0.04	5.77	19.73	49.33	4774.7

Table 2. Summary of Treatment and Control States for Mortality Rate

This table shows the summary statistics for the prescription data. We only include the Florida table because Texas started the policy change in 2007 and Washington in 2012. Due to the limitations of the data, we can only do the summary statistics for Florida. We have a lot of 0s in our data.

Descriptive Statistics for Prescription I	Data					
	Before	mean	min	25%	50%	75%
	or after policy change					
Florida (2010)	Before	10113.31	0	0	0	0
	After	$8.920751\mathrm{e}{+03}$	0	0	0	0
Control States	Before	$4.412498\mathrm{e}{+03}$	0	0	0	0
	After	$5.794056\mathrm{e}{+03}$	0	0	0	0

Table 3. Summary of Treatment and Control States for Prescription & Shipment data

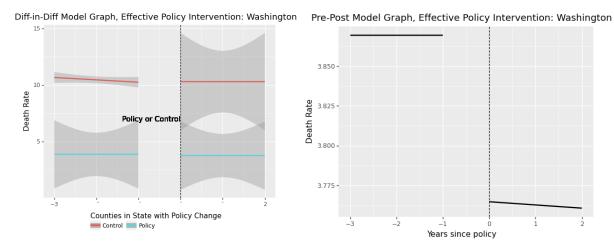
#### Analysis

With our selected states, we analyze them against their respective policy states. To do this, we first take an average of all of the selected states within their groups. So, for Florida, we average the death rate and prescription and shipment rate in county level. We take the average to account for any inconsistencies between states and to have just one metric for comparison.

After averaging the rates, we create the pre-post plots and the difference-indifference plots. The pre-post plots show us a fitted line of our averages only looking at each policy state. This gives us a method to analyze what effect the policy had locally in the state. The difference-in-difference plots show us our comparison state average, which operates as a control, and our policy state before and after the policy implementation.

### Interpretation

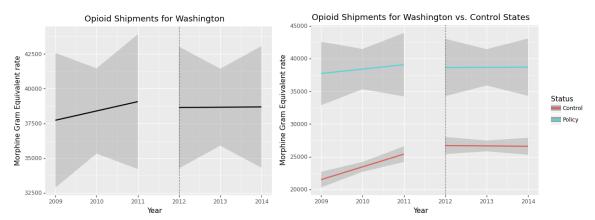
#### Washington: Mortality Rate



 $\label{eq:continuous_problem} \begin{tabular}{ll} Figure~1.~Diff-in-Diff~Model~and~Pre-Post~Model~for~Mortality~Rate~in~Washington \\ \end{tabular}$ 

This figure shows the pre-post graph for the death rate related to drug use per 100,000 people in Washington and the difference-in-difference graph for control states (Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Dakota, Oregon, South Dakota, Virginia, Wyoming). Washington showed a stagnant trend in the death rate before 2012, when the opioid policy was implemented. The pre-post graph showed that after implementing the policy, the death rate decreased and showed a downward trend, but not as steep as before. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states was stagnant after policy implementation in 2012. This slightly decreasing graph for Washington hints that the opioid policy had a positive impact in decreasing drug-related death in Washington.

#### Washington: Prescription & Shipment Rate



 $\label{eq:continuous_problem} \begin{tabular}{ll} Figure~2. & \textit{Diff-in-Diff}~\textit{Model}~\textit{and}~\textit{Pre-Post}~\textit{Model}~\textit{for}~\textit{Prescription}~\textit{Rate}~\textit{in}\\ \textit{Washington} \end{tabular}$ 

This figure shows the pre-post graph for opioid shipment in Morphine Gram Equivalent in Washington and the difference-in-difference graph for control states (Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Dakota, Oregon, South Dakota, Virginia, Wyoming). Washington showed an upward trend of opioid shipment per 100,000 people before 2012, when the opioid policy was implemented. The pre-post graph also showed the shipment rate in a stagnant trend after implementing the policy. Meanwhile, the difference-in-difference analysis showed that the opioid shipment in the control states stagnated after policy implementation in 2012. This decreasing graph for Washington hints that the opioid policy had a slightly positive impact on decreasing opioid shipments in Washington.

#### Texas: Mortality Rate

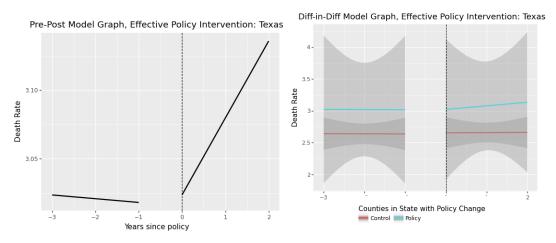


Figure 3. Diff-in-Diff Model and Pre-Post Model for Mortality Rate in Taxes

This figure shows the pre-post graph for the death rate related to drug use per 100,000 people in Texas and the difference-in-difference graph for control states (Arkansas, California, Georgia, Missouri, New York, and Wyoming). Texas showed a downward trend in the death rate before 2007, when the opioid policy was implemented. The pre-post graph showed that after implementing the policy, the death rate remained upward and even steeper from before. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states stagnated after policy implementation in 2007. This increasing graph for Texas hints that the opioid policy had a negative impact in decreasing drug-related death in Texas.

#### Florida: Mortality Rate

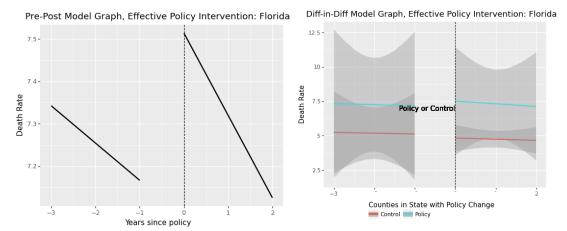


Figure 4. Diff-in-Diff Model and Pre-Post Model for Mortality Rate in Florida

This figure shows the pre-post graph for the death rate related to drug use per 100,000 people in Florida and the difference-in-difference graph for control states (California, Nevada, New York, and Texas). Florida showed a downward trend in the death rate before 2010, when the opioid policy was implemented. The pre-post graph showed that the death rate dropped even more significantly after implementing the policy. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states decreased slightly. This decreasing graph for Florida hints that the opioid policy had a positive impact on decreasing drug-related death in Florida.

#### Florida: Prescription & Shipment Rate

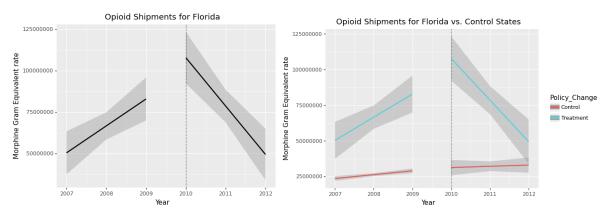


Figure 5. Diff-in-Diff Model and Pre-Post Model for Prescription Rate for Florida

When we looked at the opioid prescription rate, it is obvious that this figure shows an upward trend before 2010, when the policy was implemented. After its implementation in the year 2010, however, the prescription per capita dropped significantly. We also compare it with the control states: Arkansas, California, Georgia, Missouri, New York, and Wyoming, and observe that the prescription rate continues to increase after 2010, which is the same as our assumption. This difference-in-difference analysis suggests that the opioid policy in Florida is successful.

# References

Centers for Disease Control and Prevention. (2022, September 6). FASTSTATS - deaths and mortality. Deaths and Mortality. Retrieved November 10, 2022, from https://www.cdc.gov/nchs/fastats/deaths.htm

Home Page. LHSFNA. (2022, October 3). Retrieved November 29, 2022, from https://www.lhsfna.org/

# Estimate the Impact of Opioid Control Policies (for policymakers)

Beibei Du, Wafiakmal Miftah, Suzanna Thompson, Alisa Tian

December 12, 2022

## Motivation

For this project, we are trying to address the problem of rising opioid usage and its connection with death by drugs in the United States. We have two specific questions: What effect did the opioid policies in Texas, Washington, and Florida have on the number of opioid deaths and overall drug deaths in those states? In other words, how do opioid deaths and overall drug deaths differ in Texas, Washington, and Florida from our chosen control states? We will mention how we decide the control states in the OverView of the Data part.

To change if the policy intervention is effective is vital for the policymakers to improve on the past enactment of the policies on opioid usage. There are many papers concerning the drug overdose problem since opioid is prescribed as a medication for chronic pain. By the neurological property of opioids, the neurotransmitters acetylcholine and dopamine are released, which controls people's Central Nervous System (CNS) and Peripheral Nervous System (PNS) and makes people feel happy accordingly (Janice C. Froehlich). On the other hand, an overdose can lead to a lot of severe problems, including death. Thus, to minimize the possibility of overdose, we try to answer the two questions mentioned above.

#### Overview of the Data

Upon choosing the control states, we aim to select the states with similar social-demographic characteristics. The following factors are considered: state population, education ranking, average income, and drug-related death rate, as well as the state's policy response to the opioid crisis. We choose the individual treatment state as the baseline. For example, when calculating the state's average income based on that of Florida, we divide the individual state's population by Florida's population. A percentage close to 100% means the state's population is similar to Florida's.

After calculating the similarity for these five indicators (state population, education ranking, average income, rate of drug-related death, and state's policy response to opioid crisis), the States are chosen by a combined weighted metric. Percentages are summed and divided by 4. The population is over-impacting the combined metric for Texas, so it is excluded. Our control states are decided based on if they are in the interval (80%, 120%). Also, due to the county designations confusion in Alaska in 2010, we have excluded Alaska from our control states.

The list of our treatment states and accompanying control states:

Treatment State	Control States
Texas Washington	Arkansas, California, Georgia, Missouri, New York, Wyoming
Washington Florida	Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Dako California, Nevada, New York

The source of our data are:

1. Opioids Prescription/Shipment data (Washington Post):

In this dataset, it holds all the information of the opioids prescription across the years in all states in the United States. This dataset is about 100Gb and we select the three states and their controlled states to preprocess. The unit of observation for this dataset is at the county level. We sum all the data of all counties in a state and take that into our analyses.

2. Mortality Rate data (CDC Wonder):

In this dataset, we have state, county, year, opioid-related cause of death and the number of deaths per county and state. The unit of observation for this data is at the county level.

3. Population data (CDC Wonder):

CDC is a reliable system for holding public health data and information across the United States.

For the shipment & prescription question, we are excluding Texas as we do not have an adequate sample of data.

# Analysis

Our methodology for this project is pre-post and difference-in-difference analysis.

#### Hypothesis:

We hypothesize that there is a causal effect between policy change in opioid use and the case of overdose deaths in Florida, Washington, and Texas State. We also hypothesize that while opioid prescriptions decrease, drug-related deaths as a whole increase or remain stable. We suggest this result as there is evidence to suggest that removing a drug from an addict does not necessarily imply that the addict will recover. In some cases, the addict will switch to a new drug of choice. In other cases, the opioid addict will be in recovery and later overdose once they're able to find an opioid. This is a well known phenomena as addicts may forget that their tolerance for the opioid decreases during times of recovery and then try to use the same opioid dose as they were using active addiction. In turn, the addict will accidentally overdose. We also suppose that opioid prescriptions decrease in Texas, Washington, and Florida.

# Interpretation of the Analysis (Strengths and Limitations) Florida

Effects of Regulations on Opioid Shipments

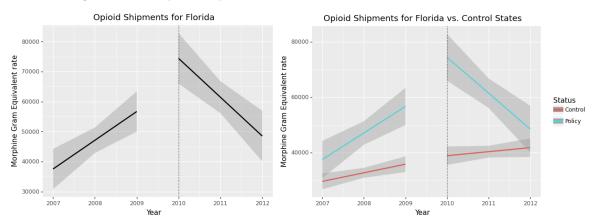


Figure 1. Pre-Post and Diff-in-Diff Model for Opioid Shipments in Florida and All Control States

When we looked at the opioid prescription rate, it is obvious that Figure 1 shows an upward trend before 2010, when the policy was implemented. After its implementation in the year 2010, however, the prescription per capita dropped significantly. We also compare it with the control states: California, Nevada, and New York. We observe that the prescription rate continues to increase after 2010, which is the same as our assumption. This difference-in-difference analysis suggests that the opioid policy in Florida is successful.

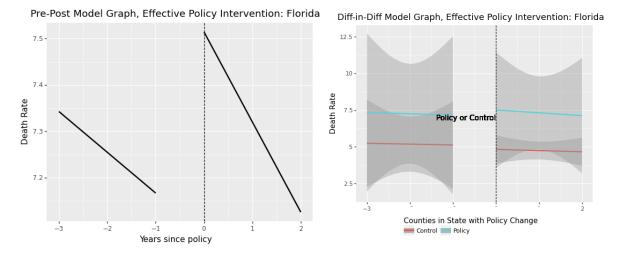


Figure 2. Pre-Post and Diff-in-Diff Model for Mortality Rate in Florida and All Control States

Figure 2 shows the pre-post death rate related to drug use per 100,000 people in Florida and the difference-in-difference graph for control states (California, Nevada, and New York). Florida showed a downward trend in the death rate before 2010, when the opioid policy was implemented. The pre-post graph showed that the death rate tren line dropped even steeper after implementing the policy. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states decreased slightly. This decreasing graph for Florida hints that the opioid policy had a positive impact on decreasing drug-related death in Florida.

#### Texas

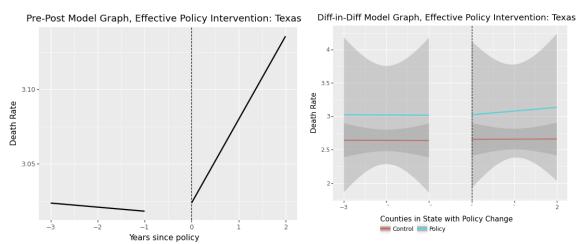


Figure 3. Pre-Post and Diff-in-Diff Model for Mortality Rate in Texas and All Control States

Figure 3 shows the pre-post graph for the death rate related to drug use per 100,000 people in Texas and the difference-in-difference graph for control states (Arkansas, California, Georgia, Missouri, New York, and Wyoming). Texas showed a downward trend in the death rate before 2007, when the opioid policy was implemented. The pre-post graph showed that after implementing the policy, the death rate remained upward and even steeper from before. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states stagnated after policy implementation in 2007. This increasing graph for Texas hints that the opioid policy had a negative impact in decreasing drug-related death in Texas.

#### Washington

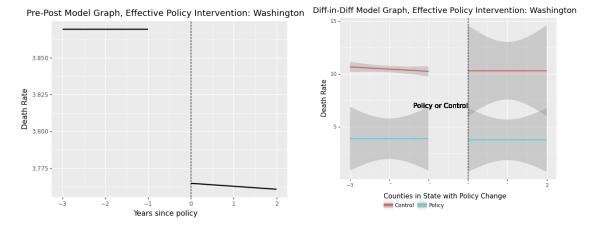


Figure 4. Pre-Post and Diff-in-Diff Model for Mortality Rate in Washington and All Control States

Figure 4 shows the pre-post graph for the death rate related to drug use per 100,000 people in Washington and the difference-in-difference graph for control states (Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Dakota, Oregon, South Dakota, Virginia, Wyoming). Washington showed a stagnant trend in the death rate before 2012, when the opioid policy was implemented. The pre-post graph showed that after implementing the policy, the death rate decreased and showed a downward trend, but not as steep as before. Meanwhile, the difference-in-difference analysis showed that the death rate in the control states was stagnant after policy implementation in 2012. This slightly decreasing graph for Washington hints that the opioid policy had a positive impact in decreasing drug-related death in Washington.

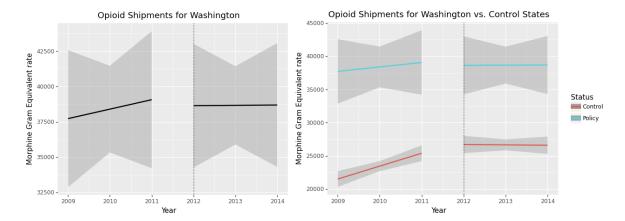


Figure 5. Pre-Post and Diff-in-Diff Model for Opioid Shipments in Washington and All Control States

Figure 5 shows the pre-post graph for opioid shipment in Morphine Gram Equivalent in Washington and the difference-in-difference graph for control states (Hawaii, Iowa, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, North Dakota, Oregon, South Dakota, Virginia, Wyoming). Washington showed an upward trend of opioid shipment per 100,000 people before 2012, when the opioid policy was implemented. The pre-post graph also showed the shipment rate in a stagnant trend after implementing the policy. Meanwhile, the difference-in-difference analysis showed that the opioid shipment in the control states also stagnated after policy implementation in 2012. This stagnated graph for Washington hints that the opioid policy had a slightly positive impact on decreasing opioid shipments in Washington.

# Conclusion

It is with great importance that you, the policymaker, should take appropriate action when handling the opioid crisis. The greatest positive impact from our analysis comes from Florida. Florida's death rate and prescription & shipment rate had the biggest change. The rate of shipments & prescriptions decreased as well as the rate of death. In conclusion, if you, the policymaker, is seeking a state to model your policy after, Florida is the best state to consider when serving your constituents.

#### References

Centers for Disease Control and Prevention. (2022, September 6). FASTSTATS - deaths and mortality. Deaths and Mortality. Retrieved November 10, 2022, from https://www.cdc.gov/nchs/fastats/deaths.htm

Home. Funding for Medication-Assisted Treatment (MAT) - Rural Community Toolbox. (n.d.). Retrieved November 29, 2022, from https://www.ruralcommunitytoolbox.org/funding/topic/medication-assisted-treatment

Home Page. LHSFNA. (2022, October 3). Retrieved November 29, 2022, from https://www.lhsfna.org/

Mital, S., Wisdom, A. C., & Wolff, J. G. (2022). Improving partner-ships between public health and public safety to reduce overdose deaths: An inventory from the CDC overdose data to action funding initiative. *Journal of Public Health Management and Practice*, 28 (Supplement 6). https://doi.org/10.1097/phh.000000000001637

Opioid peptides - National Institutes of Health. (n.d.). Retrieved November 29, 2022, from https://pubs.niaaa.nih.gov/publications/arh21-2/132.pdf

Wickramatilake, S., Zur, J., Mulvaney-Day, N., Klimo, M. C. von, Selmi, E., & Harwood, H. (2017). How states are tackling the opioid crisis. Public health reports (Washington, D.C.: 1974). Retrieved November 29, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5349480