Analysis of temporal trends in opioid prescribing: Assessing the effectiveness of an opioid prescribing policy using segmented regression, difference in difference versus propensity scoring techniques

By

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1.INTRODUCTION:

Pain is one of the most common symptoms of patients presenting to the emergency department (ED); up to 42% of ED visits are related to painful conditions (Pletcher et al.). Pain management has received an increasing emphasis over the past two decades, highlighted by the Joint Commission's focus on patient analgesia in 2000 with the establishment of pain as the "fifth vital sign," and increasing institutional emphasis on patient satisfaction (Phillips). Furthermore, it has been stressed that health care providers have performed poorly in the area of pain management (Institute of Medicine).

One possible unintentional consequence of these efforts to improve pain control is the increasing prevalence of prescription opioid abuse in the United States (DAWN SeriesD-39). Emergency Departments have seen dramatic increase in visits related to non-medical use of prescription opioids and this has coincided with an increase in the number, quantity and potency of opioid prescriptions dispensed by U.S. providers (Mazer-Amirshahi et al.). Opioids are frequently prescribed for acute pain in the ED; Hoppe et al. demonstrated that nearly 20% of patients discharged from the emergency department are prescribed opioid medications.

As opioid analgesic prescribing has increased, a parallel increase in opioid-related addiction and death has occurred as well (Paulozzi, Budnitz and Xi). In 2013 alone, approximately 1.9 million persons abused or were dependent on prescription opioid medications. Furthermore, from 1999-2014 more than 165,000 persons died of overdose related to opioid pain medication in the United States(Centers for Disease and Prevention). This highlights that although relieving pain is a primary emergency physician responsibility, there is also a duty to limit the personal and societal harm that can result from prescription drug misuse and abuse (Cantrill et al.).

Efforts to address the issue of prescription opioid misuse have been implemented across the United States and Canada. These have included the implementation of electronic prescription drug monitoring programs, Emergency Medicine national organization policy statements regarding the treatment of chronic pain, and the development of statewide opioid prescribing guidelines (Cantrill, Utah, Washington ACEP,Baehren). Research suggests that many of these efforts have affected Emergency Department prescribing behaviors (Baehren, Johnson), but data on state and systems-level interventions are still lacking (Haegerich et al.; Beaudoin, Banerjee and Mello). Prescription Drug monitoring programs (PDMP) have demonstrated effects on attitudes, but significant effects on total opioid prescribing or health outcomes have not be clearly concluded (Haegerich et al.). The impact of clinical guidelines on emergency physician behavior is difficult to quantify given the number interventions, such as statewide and national efforts, that occurred alongside these policy statements. Statewide legislation has coincided with a decreased prescription drug overdose deaths (Johnson et al.); however, several other interventions such as PDMP implementation and regional efforts occurred alongside statewide legislation. This makes it hard to attribute effects to the legislation uniquely (Haegerich et al.). Individual emergency physician groups and hospitals have also adopted opioid prescribing guidelines. Kilaru et al. demonstrated that hospital-based opioid guidelines complement and occasionally supersede state and national guidelines (Kilaru et al.). Research has demonstrated that hospital-based guidelines have been shown to decrease possibly inappropriate opioid prescriptions dispensed from the emergency department, but studies have been limited by scope (examination of only dental and/or back pain), sample size, and study duration (Fox, del Portal). Although many studies have characterized opioid abuse populations, few have evaluated the effect of patient and provider characteristics on opioid prescribing (Baehren, Fox, del Portal).

Further, prior studies have not accounted for the effects of factors such as local and national media coverage, educational initiatives through national and state professional organizations, and increasing scientific literature.

2.RESEARCH OBJECTIVES:

Our specific aims were:

1) To determine whether the implementation of an opioid prescribing policy results in decreases in opioid prescribing, specifically:

- Number of opioid prescriptions dispensed at ED discharge (raw total)
- The proportion of opioid prescriptions (out of all analgesics prescribed) by provider
- Amount of opioids given in the ED

2) To determine whether changes in opioid prescribing differ by the prescribing habits of the provider, characterized by their baseline prescribing practices (low, medium or high prescriber of opioids).

3.METHODS:

To achieve our specific aims, we considered three different methods of analyzing policies:

1. Segmented Regression.
2. Difference in Differences.
3. Propensity Score Techniques.

For each method, a brief overview of the of the model is presented along with it's statistical attributes, strengths, and limitations.

3.1 Segmented Regression Analysis

When evaluating effects of intervention at a specific time point, an interrupted time series design is used as powerful quasi-experimental approach (Taljaard et al.). Segmented regression analysis is powerful tool used in estimating the effect of interventions in interrupted time series studies. Comparing the trend in the outcome after the intervention to the existing trend in the pre-intervention period can be used to estimate the intervention effect, which is according to modification to the standard regression analysis (Taljaard et al.). Segmented regression analysis is used to determine the change in intercept and/or slope from pre-intervention to post-intervention.

Segmented regression analysis is used for assessing effects of interventions for a randomized trial as well a natural experiment. Segmented regression requires continuous or counted outcome measures with regular, evenly spaced intervals in the dataset(Wagner et al.). Sequential measures of the outcome for both pre- and post- intervention should be contained in the dataset (Lopez Bernal, Cummins and Gasparrini). Segments of a time series can be defined when the sequence of measures is divided into two or more portions at change points. Change points are specific points in time due to an identifiable real-world event, a policy change, or an experimental intervention, where the values of outcome may change from the previously established pattern (Wagner et al.). There are two parameters—level and trend—defined for each segment of a time series. The level is defined as the value of the series at the beginning of a given time interval (i.e. the y-intercept for the first segment and the value immediately following each change point at which successive segments join). The trend is defined as the slope for each segment, which means the rate of change of a measure (Wagner et al.).

In segmented regression, each segment has different level and trend. Figure 1 illustrates different examples of segmented regression (Wagner et al.), showing the change in level, change in trend or change in both.

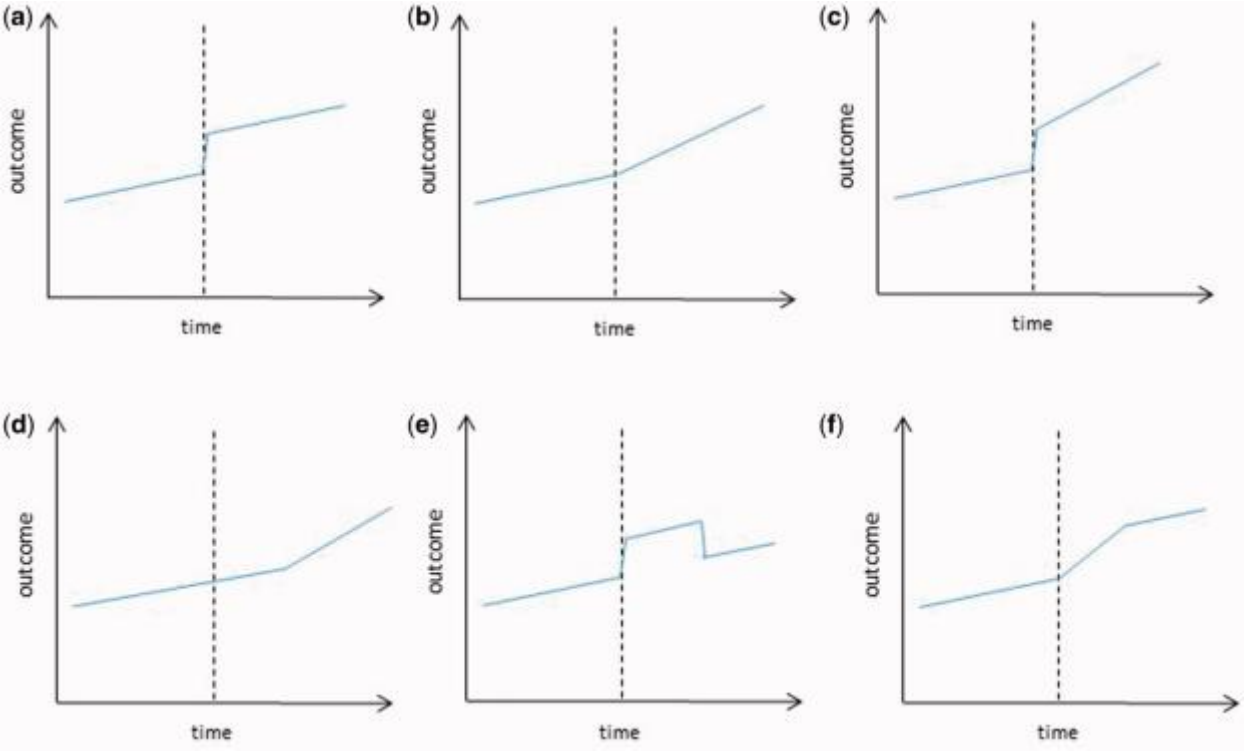

Fig.1 (a) Level change; (b) Trend change; (c) Level and trend change; (d) Slope change following a lag; (e) Temporary level change; (f) Temporary trend change leading to a level change(Wagner et al.).

The Segmented Regression model can be written as:

$$Y = \beta 1 * int1 + \beta 2 * int2 + \beta 3 * date1 + \beta 4 * date2$$

where: (1) Y indicates interest of outcome, (2) **int1** is an indicator variable referring to before policy implementation. **int2** is an indicator variable referring to after policy implementation. **date1** is the date centered around policy implementation date but converted to 0s after policy implementation. **date2** is the date centered around policy implementation date but converted to

0s before policy implementation. $\beta 1$ is the predicted interest of outcome which is just infinitely close to policy implementation date. $\beta 2$ is the predicted interest of outcome which is just right after policy implementation date. $\beta 3$ is the slope for pre-policy. $\beta 4$ is the slope for post-policy.

3.1.1 Strength of Segmented Regression Analysis

The strongest quasi-experimental designs, time series, are used to asses effects of interventions in nonrandomized settings (Shardell et al.). Segmented regression analysis of interrupted time series data allows us to control for prior segment's trend so that we can study the dynamics of change according to an intervention (Wagner et al.). Interrupted time series also visually show whether an effect is immediate or delayed, abrupt or gradual, and persistent or temporary. The size of the effect at different time points, as well as changes of trend over time can be estimated using segmented regression analysis (Wagner et al.). Segmented regression estimate change in mean outcome levels (intercept) and trends (slope), which is better than standard regression (Shardell et al.).

3.1.2 Limitation of Segmented Regression Analysis

Segmented regression analysis fits a least squares regression line and fit linear regression within each segment. Even in non-linear data, the assumption of linearity can hold for a short segment of time. This model also makes the assumption of independence between subjects and time periods (Wagner et al.). In addition, individual-level data is aggregated by time points using segmented regression. Individual-level covariates are not controlled for when using segmented regression analysis. It does not allow for the accounting of individual-level characteristics (Wagner et al.).

3.2 Difference in Difference Analysis

Difference in difference (DiD) analysis is commonly used for estimating causal effects, especially for estimating the effectiveness of a policy intervention. DiD is an attractive choice when using research designs based on controlling for confounding variables or using instrumental variables is deemed unsuitable, and at the same time, pre-treatment information is available (Lechner, Michael). The core of DiD analysis is that if the treated and the control groups have the same time trends, as well as the treatment has had no effect in the pre-treatment period, then using estimate of the effect of the treatment in a period in which it is known to have none can remove the effect of confounding factors to which a comparison of post-treatment outcomes of treated and control may be subject to. To put it another way, the mean changes of the interest of outcome for the control over time can be used and be added to the mean level of the outcome for the treated before treatment to obtain the mean outcome the treated would have experienced if they had not been subjected to the treatment (Lechner, Michael).

DiD analysis requires two groups, a treated group and a control group, as well as two periods of time, pre-intervention and post-intervention. DiD's purpose is to capture the effect of a treatment on an outcome by comparing the average over-time change of the outcome variable in the treatment group to the change in the control group (Tian and Guan).

We then assess the effectiveness of intervention using following linear regression model:

$$Y_{it} = \alpha + \beta * group + \gamma * post + \theta * (group * post) + \epsilon$$

where, Y_{it} represents interest of outcome, respectively, for observation i at period t, **group** is an indicator of treatment, and **post** represents two periods indicating whether the period is under implementation of intervention. The coefficient, θ, for interaction term in linear model is the difference in difference estimator which captures the effectiveness of intervention. It is the expected mean change in outcome from pre- to post-intervention is different in treatment group

and control group. We note that linear regression is often used in DiD analysis, since linear model is much more easily interpreted than logistic model.

3.2.1 Strength of Difference in Difference Analysis

One key strength is that DiD analysis is easy to interpret. We can control for other variables or other confounders to reduce the residual variance or incorrect effects. DiD can use either individual or group level data. Comparison groups can start at different levels of the outcome, since DID emphasize on the change of level instead of absolute values (Columbia University). DiD estimator allows different temporal trend for pre- and post-policy and the pre-policy temporal trends in the control group is exploited to represent the post-policy temporal trends in the treatment group (French and Heagerty).

3.2.2 Limitation of Difference in Difference Analysis

Using ordinary least squares (OLS) in a panel (repeated cross-sections) of data is how DiD estimates and their standard errors are most often derived. This data is of individuals in the treatment and control groups for an allotted time before and after the intervention of interest. Using ordinary least squares (OLS) in a panel (repeated cross-sections) of data is how DiD estimates and their standard errors are most often derived. This data is of individuals in the treatment and control groups for an allotted time before and after the intervention of interest (Bertrand et al.). It therefore requires data of both control group and treatment group.
DiD estimation does have its limitations. DiD analysis has rigorous assumption that may not be met. DiD assumes that unit-level heterogeneity is constant across time and parallel trends in the pre-intervention for treatment and control groups (French and Heagerty). Other time-variant

confounders can be ruled out only when satisfying parallel trends assumptions. If this assumptions does not hold then all of the results may be completely incorrect or biased.

3.3 Propensity Scoring Techniques

Propensity score matching is commonly used to estimate causal effects of an intervention. Propensity score matching could be a popular choice when we want to figure out the difference between the participants' outcome with and without treatment. Apparently, both outcomes for the same individual cannot observed at the same time. Because participants and nonparticipants usually differ even in the absence of treatment, taking the mean outcome of nonparticipants as an approximation is not suitable and advisable. (Caliendo and Sabine). In 1983, Rosenbaum and Rubin proposed a method—propensity score analysis—as an alternative tool, which can adjust for confounding and reduce selection bias in such nonrandomized studies (Rosenbaum and Donald). Propensity score matching approach is one possible solution to mimic a randomized clinical trial. Its basic idea is to find in a large group of nonparticipants those individuals who share similarities to the participants in all relevant baseline characteristics (Caliendo and Sabine). Propensity score matching also could fix the limitation of segmented regression analysis, which doesn't account for individual-level characteristics.

The most straightforward and popular matching estimator is nearest neighbor matching. The individual from the comparison group is chosen as a matching partner for a treated individual that is closest in terms of the propensity score. Several variants of nearest neighbor matching are proposed, e.g. nearest neighbor matching with replacement and without replacement. With replacement means an untreated individual can be used more than once as a match, whereas without replacement means it is considered only once. Nearest neighbor

matching with replacement has a trade-off between bias and variance. With replacement, the average quality of matching will increase as well as the bias will decrease (Caliendo and Sabine). 1:1 matching (nearest neighbor matching without replacement) is an efficient approximation of a type of nearest neighbor matching, where each treated one is matched to the on from comparison group with the closest propensity score, with "closest" commonly defined as the difference in the propensity scores(Rassen et al.). Rosenbaum and Rubin recommend transforming propensity score to the logit scale, determine the standard deviation and use a caliper of 0.25 standard deviations in 1:1 matching (Rosenbaum and Donald).

After 1:1 propensity score matching, standard error between matched groups can be obtained from following table and formula according to Fleiss, Levin and Paik's method. (Fleiss, Levin and Paik)

	Pre-intervention		
post-intervention	Factor Present	Factor Absent	Total
Factor Present	a	b	a+b
Factor Absent	c	d	c+d
Total	a+c	b+d	n

$$\hat{se}\,(p2-p1)=\frac{\sqrt{n(b+c)-(b-c)^2}}{n\sqrt{n}}=\frac{\sqrt{(a+d)(b+c)+4bc}}{n\sqrt{n}}$$

p1 represents the proportion of factor present before intervention. p2 represents the proportion of factor present after intervention. Based on p1, p2 and standard error, confidence interval can be obtained and can show the effectiveness of intervention.

3.2.1 Strength and Limitation of Propensity Scoring Techniques

A big issue about 1:1 matching is that it can discard a large number of observations, which would consequently lead to reduce power (Stuart). However, the reduction in power is usually negligible. First, the precision is largely controlled by the smaller group size in a two-sample comparison of means (Cohen). If the treatment group stays the same size, and only the size of control group decreases, the overall power may not actually be reduced too much (Ho et al.). In addition, the power increases when the groups are more similar size due to the reduced extrapolation and higher precision which is obtained when comparing groups that are similar versus groups that are rather different (Snedecor and Cochran). This yields the increased power in randomized experiments when using matched pairs (Wacholder and Weinberg). Furthermore, even though thousands of observations were discarded in the 1:1 matching , estimates from matching have lower standard deviations comparing to estimates from a linear regression.

4.DATA DESCRIPTIONS:

The data was collected by Newport Hospital (control hospital), The Miriam Hospital (treated hospital) and Rhode Island Hospital (treated hospital) from November of 2012 to November of 2014. Since the opioid prescribing policy was implemented on Oct 31st, 2013, there is one-year of data before and one-year data of after implementation of policy. The dataset is an extraction from the electronic medical records (EMR) at each study site. The data contains patients who went to emergency department (ED) for a pain related complaint—their arrival time and day, gender, race, ethnicity, acuity level, insurance type, ED provider, diagnoses, disposition (e.g. admitted or discharged), medications given in the ED, home medications (medications

taken before the visit), and prescription received at discharge (there were 46259 observations and 243 variables in total).

The following three tables reports descriptive statistics of study population, number of opioids prescriptions dispensed and number of opioids prescriptions dispensed stratified by providers among Rhode Island Hospital, The Miriam Hospital and Newport Hospital.

Table 1. Description of study population at the two study sites and the control hospital

	RIH and TMH			NPT (Control)		
Characteristic	Pre-Policy (n = 18777)	Post-Policy (n = 21845)	Difference (95% CI)	Nov 2012 - Oct 2013 (n = 2522)	Nov 2013 - Oct 2014 (n = 3109)	Difference (95% CI)
Age	43.4	43.5	0.1 (-0.2 , 0.4)	41.3	41.2	-0.1 (-1.1 , 0.9)
Sex						
Male	39.1	37.9	-1.2 **(-2.1 , -0.3)**	38.8	36.6	-2.2 (-4.7 , 0.3)
Race						
Black	17.1	17.0	-0.1 (-0.8 , 0.6)	11.4	12.6	1.2 (-0.5 , 2.9)
White	65.4	64.3	-1.1 **(-2.0 , -0.2)**	86.6	85.2	-1.4 (-3.2 , 0.4)
Other	17.5	18.7	1.2 **(0.5 , 1.9)**	2.0	2.2	0.2 (-0.5 , 1.0)
Ethnicity, (% Hispanic)	20.0	21.5	1.5 **(0.8 , 2.3)**	5.2	5.6	0.4 (-0.8 , 1.5)
Insurance						
Commercial	23.0	24.3	1.3 **(0.5 , 2.1)**	-	-	-
Medicare	19.6	19.5	-0.1 (-0.8 , 0.6)	-	-	-
Medicaid	22.5	31.5	9.0 **(8.2 , 9.8)**	-	-	-
Worker's Compensation/Liability	2.0	1.9	-0.1 **(-0.3 , 0.2)**	-	-	-
Other	32.9	22.8	-10.1 **(-10.9 , -9.3)**	-	-	-
Discharge Diagnosis						
Abdominal Pain	27.9	29.3	1.4 **(0.6 , 2.3)**	48.1	49.2	1.1 (-1.5 , 3.7)
Back Pain	31.5	30.6	-0.9 **(-1.7 , -0.1)**	27.3	27.6	0.2 (-2.1 , 2.6)
Dental Pain	4.6	3.8	-0.8 **(-1.2 , -0.4)**	3.1	3.7	0.5 (-0.4 , 1.5)
Headache/Migraine	17.0	16.7	-0.3 (-1.0 , 0.4)	20.6	19.6	-1.0 (-3.1 , 1.1)
Proportion of Home Opioid	15.2	14.6	-0.6 (-1.2 , 0.1)	21.7	19.6	-2.1 (-4.2 , 0.0)
Length of ED Stay	310.0	310.1	0.1 (-3.0 , 3.2)	233.2	237.0	3.9 (-3.0 , 10.7)
Mean Pain Score	7.6	7.5	-0.1 (-0.1 , 0.0)	7.4	7.3	-0.1 (-0.2 , 0.0)
Disposition						
Admitted	14.2	14.1	-0.1 (-0.7 , 0.5)	7.5	6.6	-0.9 (-2.2 , 0.4)
Discharged	83.9	84.2	0.4 (-0.3 , 1.0)	91.2	92.2	1.0 (-0.4 , 2.4)
Other	2.0	1.7	-0.3 (-0.5 , 0.0)	1.3	1.2	-0.1 (-0.7 , 0.5)
Resident/Midlevel Involved in Care						
PA/NP	23.6	24.2	0.6 (-0.2 , 1.3)	2.7	8.4	5.7 **(4.6 , 6.9)**
PGY1	3.3	1.2	-2.1 **(-2.4 , -1.8)**	-	-	-
PGY2	4.7	5.0	0.4 (0.0 , 0.8)	-	-	-
PGY3	5.3	6.8	1.5 **(1.1 , 1.9)**	-	-	-
PGY4	7.7	10.2	2.5 **(2.0 , 3.0)**	-	-	-
None	55.4	52.5	-2.8 **(-3.8 , -1.9)**	97.3	91.6	-5.7 **(-6.9 , -4.6)**

Continuous data are presented as mean. Categorical data are displayed as proportions (%). * Insurance not available for NPT ; ED = Emergency Department ; PA= Physician Assistant ; NP = Nurse Practitioner

Table 1 shows differences and associated 95% confidence intervals between pre- and post-opioid prescribing policy among the intervention hospitals (the Rhode Island Hospital and Miriam Hospital) and control hospital (Newport Hospital). It is observed that there is significant difference between treated hospital and control hospital, significant difference between pre- and post- policy among treated hospitals and these two groups also differ from the total sample size. The table includes all characteristics of patients in emergency department from two groups including age, sex, race, ethnicity, insurance, discharge diagnosis, proportion of home opioid, length of ED stay, mean pain score, disposition and resident/midlevel involved in care.

Table 2. Number of opioid prescriptions dispensed

	Pre-Implementation		Post-Implementation		Difference (95% CI)
	n	%	n	%	
Visits with Opioids Administered in the ED*					
All Sites	13448	57.7	12054	52.5	-5.2 **(-6.1 , -4.3)**
Hospital 1 - RIH	7311	58.7	6350	52.1	-6.6 **(-7.8 , -5.3)**
Hospital 2 - TMH	4536	56.3	4138	52.2	-4.1 **(-5.6 , -2.6)**
Hospitals 1 and 2	11847	57.8	10488	52.2	-5.6 **(-6.6 , -4.6)**
Control - NPH	1601	57.4	1566	55.1	-2.3 (-4.9 , 3.3)
Discharge Diagnosis*$					
Abdominal Pain	5151	25.1	5329	26.5	1.4 **(0.5 , 2.2)**
Back Pain	6578	32.1	6239	31.0	-1.0 **(-1.9 , -0.1)**
Dental Pain	983	4.8	769	3.8	-1.0 **(-1.4 , -0.6)**
Headache/Migraine	3378	16.5	3269	16.3	-0.2 (-0.9 , 0.5)
Opioids Prescribed at Discharge#					
All Sites	6986	35.7	5859	30.3	-5.4 **(-6.4 , -4.5)**
Hospital 1 - RIH	4032	39.1	3066	30.6	-8.5 **(-9.8 , -7.2)**
Hospital 2 - TMH	1924	28.8	1837	27.4	-1.3 (-2.8 , 0.2)
Hospitals 1 and 2	5956	35.0	4903	29.3	-5.7 **(-6.7 , -4.7)**
Control - NPH	1030	40.5	956	36.5	-4.0 **(-6.6 , -1.3)**
Discharge Diagnosis#$					
Abdominal Pain	3773	22.2	3879	23.2	1.0 **(0.1 , 1.9)**
Back Pain	5926	34.9	5664	33.9	-1.0 (-2.0 , 0.0)
Dental Pain	970	5.7	760	4.5	-1.2 **(-1.6 , -0.7)**
Headache/Migraine	2884	17.0	2849	17.0	0.1 (-0.7 , 0.9)

* = Proportion of total visits; # = Proportion of discharges; $ RIH and TMH only

Table 2 shows the difference and 95% confidence interval of number of opioids prescriptions dispensed between time periods pre- and post-opioid prescribing policy. There is significant difference between pre- and post-policy among both treated hospitals (the Rhode Island Hospital and Miriam Hospital) not only in the ED but also at discharge. For discharge diagnosis, there is slight difference among some pains, such as abdominal pain and dental pain in the ED and at discharge among only treated hospitals.

Table 3. Number of opioid prescriptions dispensed, stratified by provider characteristics for hospital 1 and 2

	Pre-Implementation		Post-Implementation		Difference (95% CI)
	n	%	n	%	
Visits with Opioids Administered in the ED*					
Baseline Prescribing Level[1]					
Low	3888	55.9	3673	51.4	-4.5 **(-6.2 , -2.9)**
Medium	4257	57.6	3797	51.6	-6.0 **(-7.6 , -4.4)**
High	3702	60.0	3018	53.8	-6.1 **(-7.9 , -4.4)**
Level of Training[2]					
PA/NP	3246	59.7	2710	51.0	-8.7 **(-10.6 , -6.9)**
PGY1	409	52.9	143	50.5	-2.4 (-9.2 , 4.4)
PGY2	622	56.9	567	48.8	-8.0 **(-12.1 , -3.9)**
PGY3	726	59.0	805	51.8	-7.2 **(-10.9 , -3.5)**
PGY4	1052	58.6	1332	56.7	-1.8 (-4.9 , 1.2)
None	5792	56.9	4931	52.2	-4.7 **(-6.1 , -3.3)**
Opioids Prescribed at Discharge#					
Baseline Prescribing Level[1]					
Low	1342	23.8	1240	21.0	-2.8 **(-4.4 , -1.3)**
Medium	2254	36.5	1771	28.9	-7.6 **(-9.2 , -5.9)**
High	2360	45.4	1892	40.3	-5.1 **(-7.0 , -3.1)**
Level of Training[2]					
PA/NP	2114	45.2	1548	34.5	-10.7 **(-12.7 , -8.7)**
PGY1	161	24.5	57	23.7	-0.9 (-7.2 , 5.4)
PGY2	261	29.4	266	26.7	-2.7 (-6.8 , 1.3)
PGY3	240	25.9	277	22.8	-3.1 (-6.8 , 0.6)
PGY4	350	29.0	357	21.8	-7.3 **(-10.5 , -4.1)**
None	2830	32.8	2398	30.0	-3.2 **(-4.6 , -1.8)**

* = Proportion of total visits; # = Proportion of discharges; [1] Tertile of prescribing based on pre-policy # of opioids prescribed at discharge; [2] Level of training

Table 3 shows the difference and 95% confidence interval between pre- and post- opioid prescribing policy stratified by provider characteristics only among the Rhode Island Hospital and Miriam Hospital (intervention hospitals). Providers were first stratified by tertile of prescribing based on preference of opioids prescribed at discharger. The table shows there is significance difference between pre- and post- prescribing policy based on providers' baseline

prescribing patterns (low, median and high) not only at emergency department but also at discharge. Next, providers were stratified by level of training. Some of the levels have significant difference between pre- and post- opioids prescribing policy.

5.RESULTS:

5.1 Results from Segmented Regression Analysis

The object of segmented regression is to fit each interval with separate line segment and to learn about the effectiveness of an opioid prescribing policy. The outcome is modified as number of opioids prescriptions per month from October 2012 to October 2014. Here, the official implementation of the opioid prescribing policy was Oct 31st, 2013, is considered as the change point. Level and trend are two parameters which that are shown on the graph for each segment of time series.

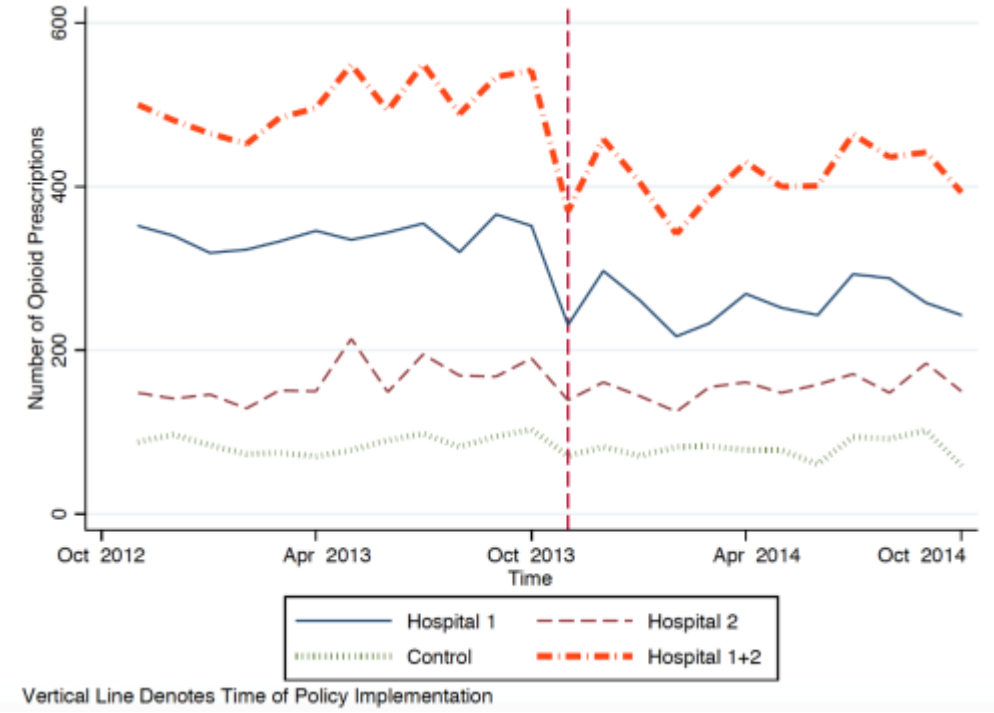

Fig.2 Number of opioids prescriptions per month among hospital 1(Rhode Island Hospital) and hospital 2(Miriam Hospital) as treated hospital and control hospital (Newport Hospital).

Figure 2 shows that the number of opioids prescriptions per month among Rhode Island Hospital (hospital 1) and Miriam Hospital (hospital 2) which represent the treated hospitals and Newton Hospital is the control hospital. An opioid prescribing policy was implemented on Oct 31st, 2013 to limit inappropriate use of opioids. There is a clear drop in opioid prescriptions after the initial policy implementation. However, the month to month variations remain similar pre/post policy. Graphical presentation(Fig.2) of time series data is usually the intuitive way to show the trend of the measure of interest. From figure 2, the pre-policy trend is obviously decreasing when comparing with post-policy trend. With any analysis, we cannot be certain that the changes are purely due to the intervention. To assess the effects of variables on the outcome we will used segmented regression (Wagner et al.).

The results of segmented regression analysis are displayed in table 4.

Table 4. Parameter estimates, standard errors, p-values and 95% confidence interval from segmented regression predicting number of opioids prescriptions per month in hospital 1 and hospital 2 over time.

Parameter	Estimates	Standard Error	P-value	95% CI
Intercept1($\beta 1$)	542.89	16.84	0.000	(507.86, 577.91)
Intercept2 ($\beta 2$)	392.71	16.81	0.000	(357.75, 427.67)
Trend of pre-policy ($\beta 3$)	0.20	0.08	0.019	(0.04, 0.36)
Trend of post-policy ($\beta 4$)	0.11	0.09	0.219	(-0.07, 0.29)

From table 4, the predicted number of opioids prescriptions which is just infinitely close to policy implementation date is 542.89 and the predicted number of opioids prescriptions which is just right after policy implementation date is 392.71. The slope for pre-policy is 0.20, which is significant increase. The slope for post-policy is 0.11, which is insignificant.

Table 5. Parameter estimates, standard errors, p-values and 95% confidence interval for level change and trend change after an opioid prescribing policy.

Parameter	Estimates	Standard Error	P-value	95% CI
Level change	-150.18	23.8	0.000	(-199.66, -100,69)
Trend change	-0.09	0.12	0.440	(-0.33, 0.15)

From table 5, There are 150.2 opioids prescriptions drop abruptly just right after the policy implementation. P-value for the abrupt drop is 0.000, which means statistically significant. P-value for slope change is 0.44, which means there is no significant slope change for pre- and post- policy. There is no significant month-to-month trend for both pre- and post- policy.

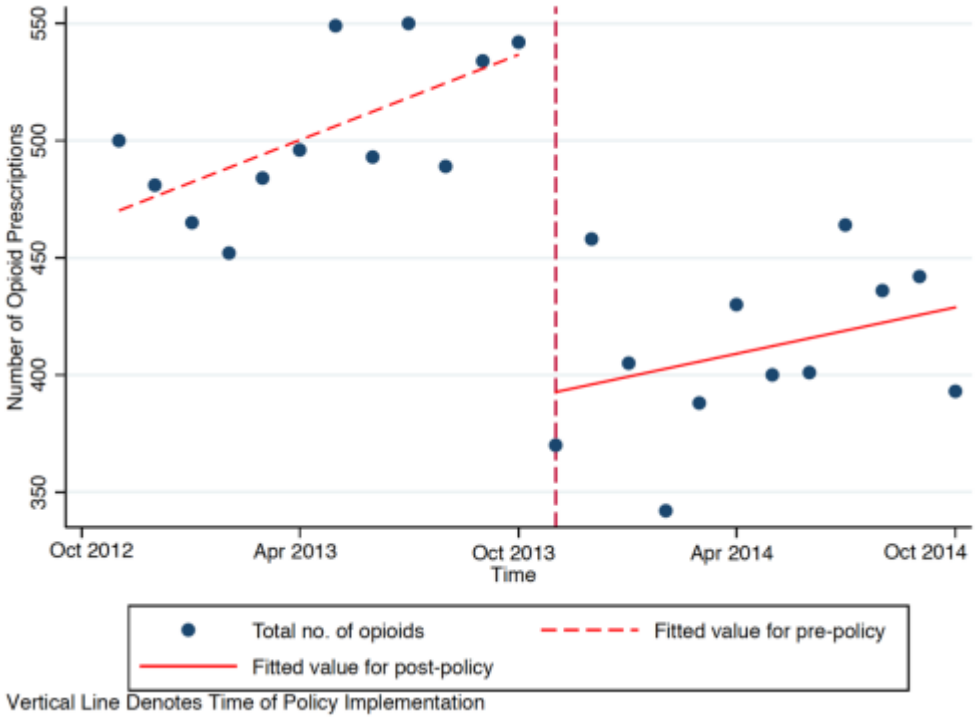

Fig.3 Segmented regression—fitting different linear regression between number of opioid prescriptions and time for each segment over time among hospital 1 and hospital 2.

Figure 3 graphically shows two linear regressions between number of opioids prescription and time for pre- and post- policy. Even though two lines are approximately parallel to each other

(the trend of month-to-month change maintains the approximately same for pre- and post-policy), there is abrupt and significant drop just after implementing the opioid prescribing policy.

5.2 Results from Difference in Difference Analysis

DiD analysis require two groups (treated group and control group) and two periods. The treatment group is both the Rhode Island Hospital and Miriam Hospital and control group is Newport Hospital. Two periods are indicator coded as 0 for pre-policy and 1 for post-policy. Its purpose is to capture the effect of a treatment on an outcome by comparing the average over-time change of the outcome variable in the treatment group to the change in the control group (Tian and Guan).

Table 6. Parameter estimates, standard errors and p-values from Difference in Different in hospital 1, hospital2 and control hospital over time.

Parameter	Estimates	Standard Error	P-value	95% CI
Hospital β	-0.08	0.01	0.000	(-0.09, -0.06)
Post γ	-0.03	0.01	0.006	(-0.06, -0.01)
Interaction θ	-0.02	0.01	0.347	(-0.04, 0.01)
Intercept ε	0.37	0.01	0.000	(0.35, 0.39)

From table 6, the coefficient θ for interaction term -0.015, which means there is decreasing in using opioids after implementing the opioid prescribing policy. Even though p-value for interaction term is 0.237 which is larger than 0.05, the expected mean difference in opioids prescriptions is decreasing from DiD analysis.

The next step is to add information of opioids providers and at same time, it is necessary to add all confounders from table 1 into DiD model. The updated DiD model:

$$OPIOIDS_{it} = \alpha + \beta * Hospital + \gamma * post + \theta * (Hospital * post) + a * age2 + b * gender2 + c * insurance2 + d * pain\_scale + e * los\_min + f * race2 + g * ethnicity2 + h * atid + \epsilon$$

age2 represents age of patients. **gender2** is an indicator of being female. **insurance2** represents different kinds of insurance of patients, coded as 0 for Commercial, 1 for Medicare, 2 for Medicaid, 3 for Worker's Comp/Liability and 4 for Other. **pain_scale** is continuous variable from 0 to 10 representing different levels of pain. **los_min** is denoted as length of emergency room stay. **race2** is an indicator of classifying as black. **ethnicity2** is an indicator of classifying as hispanic. **atid** represents different providers of opioids prescriptions.

Table 7. Parameter estimates, standard errors and p-values from updated Difference in Different in hospital 1, hospital2 and control hospital over time.

Parameter	Estimates	Standard Error	P-value	95% CI
Hospital	-0.02	0.01	0.055	(-0.04, 0.00)
Post	-0.02	0.01	0.053	(-0.05, 0.00)
Interaction	-0.02	0.01	0.128	(-0.04, 0.01)
Age	-0.00	0.00	0.027	(-0.01, 0.00)
Gender	-0.03	0.00	0.000	(-0.04, -0.02)
Insurance	0.02	0.00	0.000	(0.01, 0.02)
Pain_scale	0.03	0.00	0.000	(0.02, 0.03)
Lost_min	-0.00	0.00	0.000	(0.00, 0.00)
Race	-0.01	0.00	0.020	(-0.02, 0.00)
Ethnicity	0.00	0.01	0.494	(-0.02, 0.01)
Atid	0.00	0.00	0.008	(0.00, 0.00)
Intercept	0.26	0.02	0.000	(0.23, 0.29)

From table7, p-value for the interaction term is 0.128, which is smaller than p-value before but still non-significant. The coefficient for interaction term -0.015, this suggests a decrease in using opioids after implementing the opioid prescribing policy, although this is non-significant. In addition, it is interesting to find out that younger people, people with higher level of pain, white

people, are more likely to be affected by opioids prescribing policy while female and Hispanic people are more likely to affected by it.

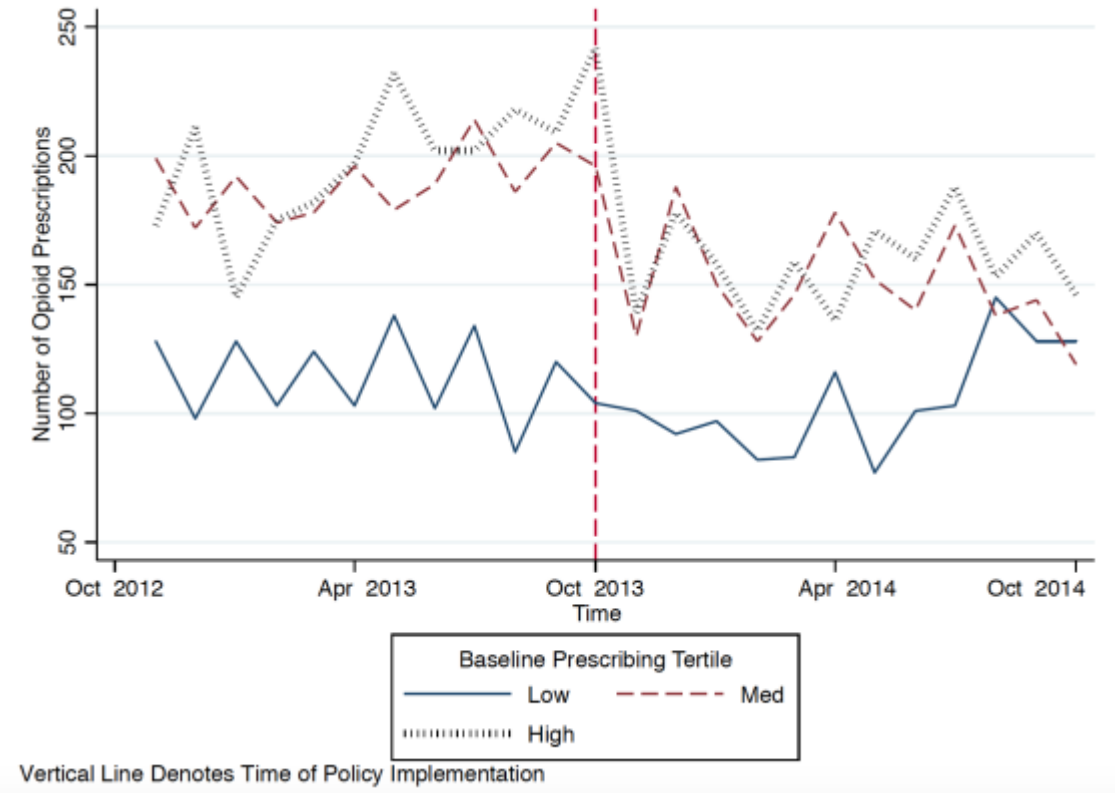

Fig.4 Number of opioids prescriptions per month among Rhode Island Hospital and Miriam Hospital stratified by provider characteristics.

Fig.4 shows number of opioids prescriptions per month among Rhode Island Hospital and Miriam Hospital stratified by tertile of prescribing based on preference of opioids prescribed at discharger. The decreasing trend of high preference and median preference of opioids prescriptions is much more obvious than the trend of low preference.

It is interesting to use DiD analysis stratified by providers' preference on opioids prescriptions. Following are results:

Low level of providers' preference on opioids prescriptions

Table 8. Parameter estimates, standard errors and p-values from Difference in Different in hospital 1, hospital2 and control hospital over time for low level of providers' preference on opioids prescriptions.

Parameter	Estimates	Standard Error	P-value	95% CI
Hospital	0.02	0.02	0.220	(-0.01, 0.05)
Post	-0.01	0.02	0.499	(-0.05, 0.02)
Interaction	-0.01	0.02	0.775	(-0.05, 0.04)
Age	0.00	0.00	0.132	(0.00, 0.00)
Gender	-0.03	0.01	0.000	(-0.04, -0.01)
Insurance	0.01	0.00	0.000	(0.01, 0.02)
Pain_scale	0.02	0.00	0.000	(0.02, 0.02)
Lost_min	0.00	0.00	0.000	(0.00, 0.00)
Race	0.00	0.01	0.587	(-0.01, 0.01)
Ethnicity	-0.02	0.01	0.093	(-0.04, 0.00)
Intercept	0.10	0.02	0.000	(0.06, 0.14)

Median level of providers' preference on opioids prescriptions

Table 9. Parameter estimates, standard errors and p-values from Difference in Different in hospital 1, hospital2 and control hospital over time for median level of providers' preference on opioids prescriptions.

Parameter	Estimates	Standard Error	P-value	95% CI
Hospital	0.07	0.02	0.025	(0.03, 0.11)
Post	0.03	0.03	0.309	(-0.03, 0.08)
Interaction	-0.08	0.03	0.005	(-0.14, -0.03)
Age	0.00	0.00	0.298	(0.00, 0.00)
Gender	-0.03	0.01	0.000	(-0.04, -0.01)
Insurance	0.02	0.00	0.000	(0.02, 0.03)
Pain_scale	0.03	0.00	0.000	(0.02, 0.03)
Lost_min	0.00	0.00	0.000	(0.00, 0.00)
Race	-0.02	0.01	0.000	(-0.03, -0.01)
Ethnicity	0.01	0.01	0.450	(-0.01, 0.03)
Intercept	0.16	0.03	0.000	(0.10, 0.21)

High level of providers' preference on opioids prescriptions

Table 10. Parameter estimates, standard errors and p-values from Difference in Different in hospital 1, hospital2 and control hospital over time for low level of providers' preference on opioids prescriptions.

Parameter	Estimates	Standard Error	P-value	95% CI
Hospital	0.00	0.02	0.764	(-0.03, 0.04)
Post	-0.04	0.02	0.036	(-0.07, 0.00)
Interaction	0.00	0.02	0.891	(-0.04, 0.03)
Age	0.00	0.00	0.073	(0.00, 0.00)
Gender	-0.03	0.01	0.000	(-0.05, -0.02)
Insurance	0.02	0.00	0.000	(0.01, 0.02)
Pain_scale	0.03	0.00	0.000	(0.03, 0.03)
Lost_min	0.00	0.00	0.000	(0.00, 0.00)
Race	-0.01	0.01	0.287	(-0.02, 0.01)
Ethnicity	-0.01	0.01	0.524	(-0.03, 0.02)
Intercept	0.33	0.03	0.000	(0.29, 0.38)

From results based of providers' preference on opioids prescriptions, p-value for interaction term of median preference is smallest (0.001), which is smaller than 0.05. An opioids prescribing policy have largest effect on median preference of opioids prescriptions. For providers who have high preference on opioids prescriptions, they tend to respond sluggishly to an opioid prescribing policy in such small period. For providers who have low preference on opioids prescriptions, the use of opioids prescription will continue to be remaining at a low level.

5.3 Results from Propensity Scoring Techniques

1:1 nearest-neighbor matching was applied to the opioids prescribing policy data to form pairs of pre-policy and post-policy patients matched—the closest probability of being given an opioid in the pre- and post-policy time. According to Rosenbaum and Rubin's recommendation, we transform propensity score to the logit scale, determine the standard deviation and use a caliper of 0.25 standard deviations, which is equal to 0.0029.

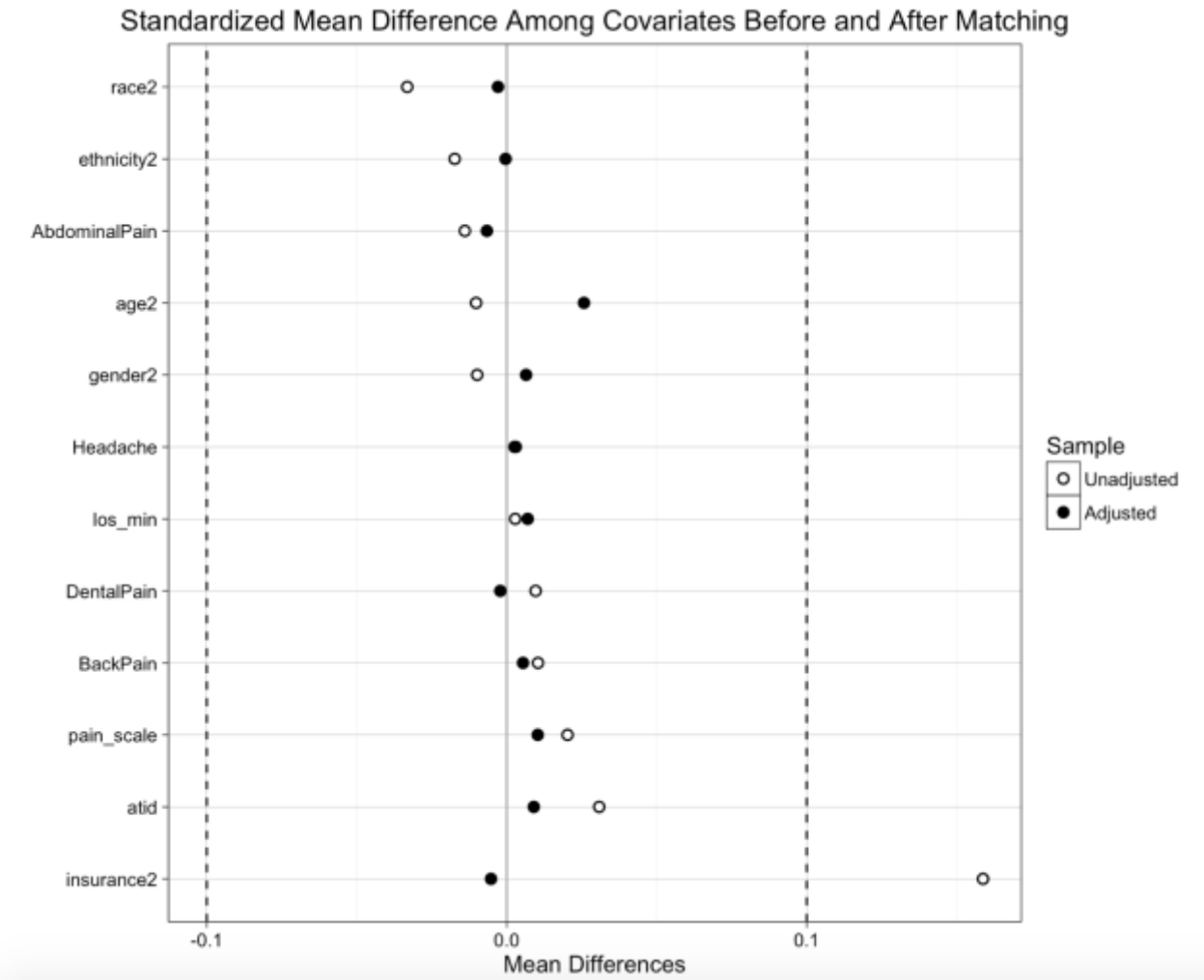

Fig.5 Assess covariates balance conditional on the estimated propensity score.

The final model of propensity score matching is decided by assessing whether covariates are balance according to figure 5. Mean differences of all covariates are within -0.1 to 0.1. The matched sample includes 17690 patients in both pre- and post- opioid prescribing policy group. After 1:1 propensity score matching, standard error between matched groups can be obtained according to Fleiss, Levin and Paik's method. Standard error is equal to 0.0047. 95% confidence interval is equal to (-0.0459, -0.0275), which shows there is significant decrease in opioids prescriptions after implementation of an opioid prescribing policy.

6.DISCUSSION:

We conducted a retrospective before and after cohort study to determine the effects of departmental opioid prescription guidelines on opioid prescribing for patients discharged with diagnoses commonly associated with drug seeking behavior. We found that local, departmental based guidelines are associated with a decrease in the number of prescriptions dispensed from the emergency department. Further, based on our results, this effect is more dramatic for those physicians with median baseline prescribing patterns and patients cared for by advanced practice providers (PA/NP).

To date, only a few studies have examined the effects of departmental based opioid-prescribing guidelines in the ED and these have been limited by qualitative approach, sample size, study duration and study scope. Further, no study has examined a policy's effect based on patient and care team characteristics (Kilaru, Fox, de Portal). Additionally, prior studies have not accounted for ongoing local, statewide, and national initiatives. Our findings are strengthened by the comparison of our hospital's opioid prescribing practices with those of a neighboring hospital unaffected by our institution's opioid guidelines. This controlled for changes in practice patterns as a result of national and statewide efforts directed towards the prescription opioid epidemic; although prescribing decreased at this neighboring hospital, a larger absolute decrease in the number of opioid prescriptions provided was seen at hospitals with opioid guidelines.

Our study has several limitations. This study also is limited by its retrospective nature and reliance on the electronic medical record for patient and provider information. Incomplete records could have led to inaccurate patient characterization. Additionally, this study examined only one institution. Practice patterns and opioid prescribing might vary among providers and institutions and could affect generalizability of the study findings; however, the large size of the

physician group and patient population increases its generalizability.

We present three methods (segmented regression, difference in difference and propensity score techniques) to analysis an opioid prescribing policy. First method is segmented regression using interrupted time series. Interrupted time series design is the strongest, quasi-experimental approach for evaluating longitudinal effects of interventions and segmented regression analysis is a powerful statistical method for estimating intervention effects in interrupted time series studies (Wagner et al.). Second method is difference in difference. The "difference in differences" estimator allows different pre- and post-policy temporal trends and exploits the pre-policy temporal trends in the "control" group to represent the post-policy temporal trends in the "treatment" group (French and Heagerty). Third method is 1:1 nearest neighbor matching with Fleiss, Levin and Paik's method to calculate confidence interval. 1:1 nearest neighbor is used to form matched sample with similar characteristics in pre and post-policy. DiD and segmented regression is commonly used, but have some limitations. "Difference in differences" assumes that unit-level heterogeneity is constant across time and that temporal trends are identical in the "treatment" and "control" groups (Cawley, Schroeder and Simon). "Segmented regression" relies on the rigid assumption of linearity and does not allow adjustment for covariates (Wagner et al.). So for future study, it is good idea to do propensity score matching first to form matched group and then do segmented regression to assess the effectiveness of policy, since propensity score matching can adjust for covariates to fix the limitation of segmented regression analysis.

In summary, we conducted a retrospective study to examine the effects of institution-based opioid prescribing guidelines on opioid prescribing practices. Our findings suggest that local, hospital and physician group based opioid prescribing guidelines limit opi prescribing out of the emergency department.

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