Interrupted Time Series with Individual Level Data

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Overview

- What is Interrupted Time Series (ITS) Analysis?
- When is it appropriate?
- Examples
- Strengths/Limitations
- Individual vs aggregated data
- Summary

Interrupted Time Series?

- A time series of a particular outcome of interest used to establish an underlying trend which is interrupted by an **intervention** at a known point in time
- ITS analysis is also known as Segmented Regression

- Assess population level intervention
  - Policy/protocol change
  - Legislative change
- Evaluate impacts of large-scale health policies

When to use ITS analysis

- Intervention occurs at a known point in time
- Well differentiated pre/post periods
- Sufficient data pre/post
- Best with relatively short term outcome
- To evaluate intervention effect
  - Change in level (immediate effect)
  - Change in slope (gradual effect)

When to use ITS

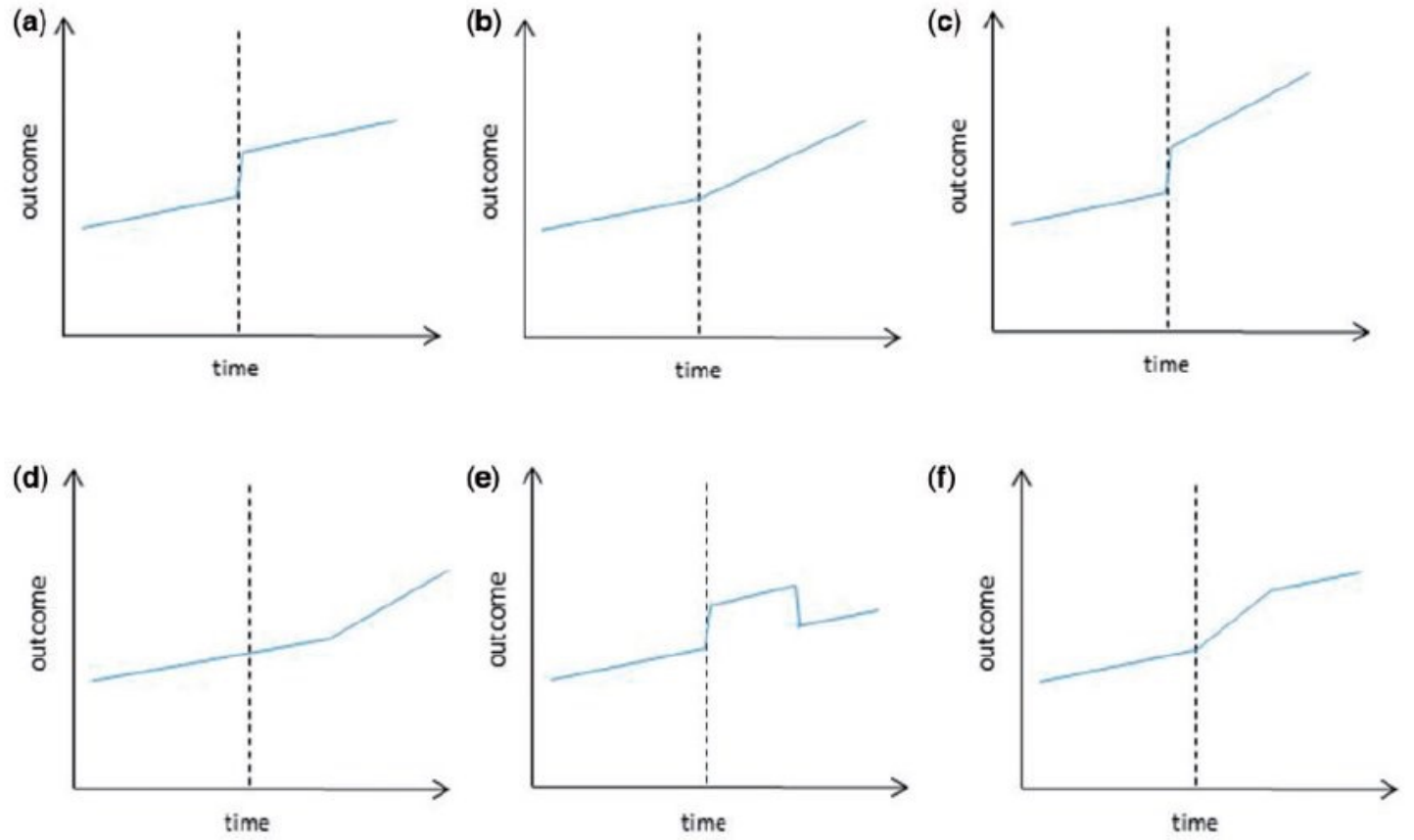


Figure 2 Examples of impact models used in ITS

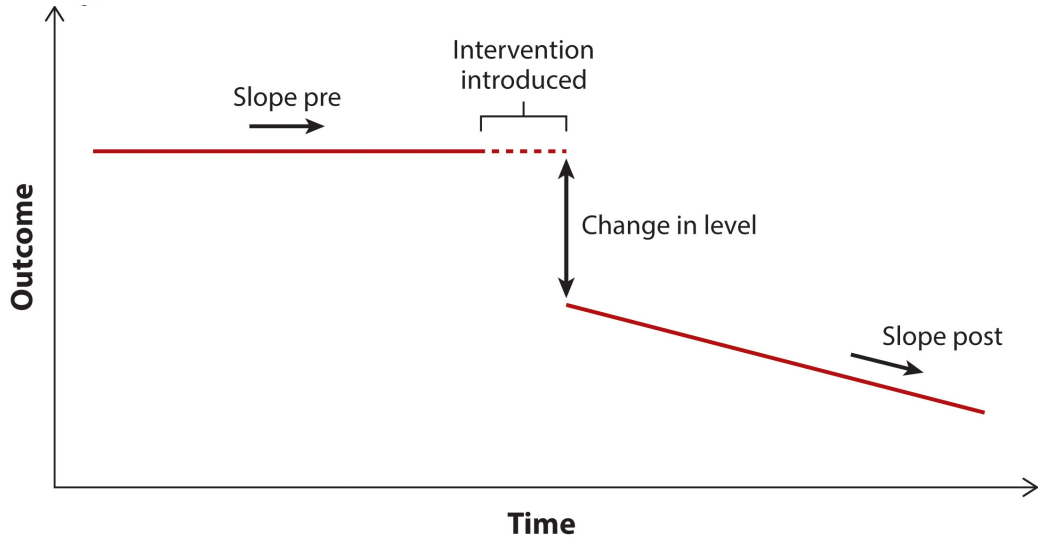
(a) Level change; (b) Slope change; (c) Level and slope change; (d) Slope change following a lag; (e) Temporary level change; (f) Temporary slope change leading to a level change.

Bernal et al, 2017

ITS Basic Model

$$E(Y_t) = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t$$

- T: time elapsed since the start of the study (month, year, quarter)
- X_t: binary variable indicating the post-intervention (X_t=1 post-intervention)
- Y_t: the outcome of interest
- β_0 : baseline level at t=0
- β_1 : slope pre intervention
- β_2 : mean level change
- β_3 : change in slope following intervention

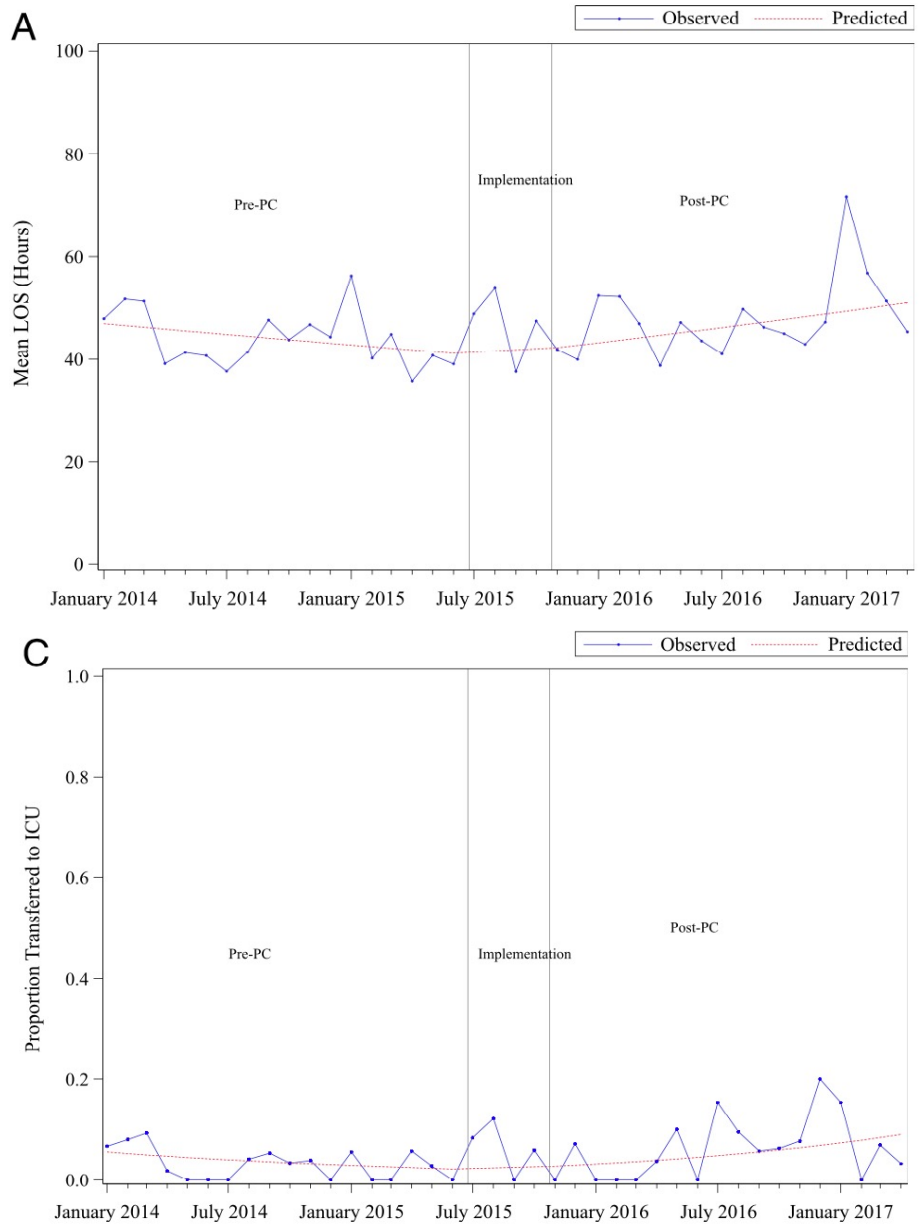


Handley MA, et al. 2018.
Annu. Rev. Public Health. 39:5–25

ITS Examples

1. *Outcomes for Pediatric Asthmatic Inpatients After Implementation of an Emergency Department Dexamethasone Treatment Protocol* (Tyler 2019)

- Compare outcomes before and after protocol change in the ED of adoption of dexamethasone for treatment of acute asthma exacerbation
- Individual level data (with repeated measures)
- Logistic and log gamma models
- Covariates: age, race, financial class, season, admitting service, first asthma score, and need for continuous albuterol.
- Adjusted results:
  - No significant immediate differences
  - The risk of ICU transfers was stable pre-PC and increased by 10% (2%–19%) per month in the post-PC period

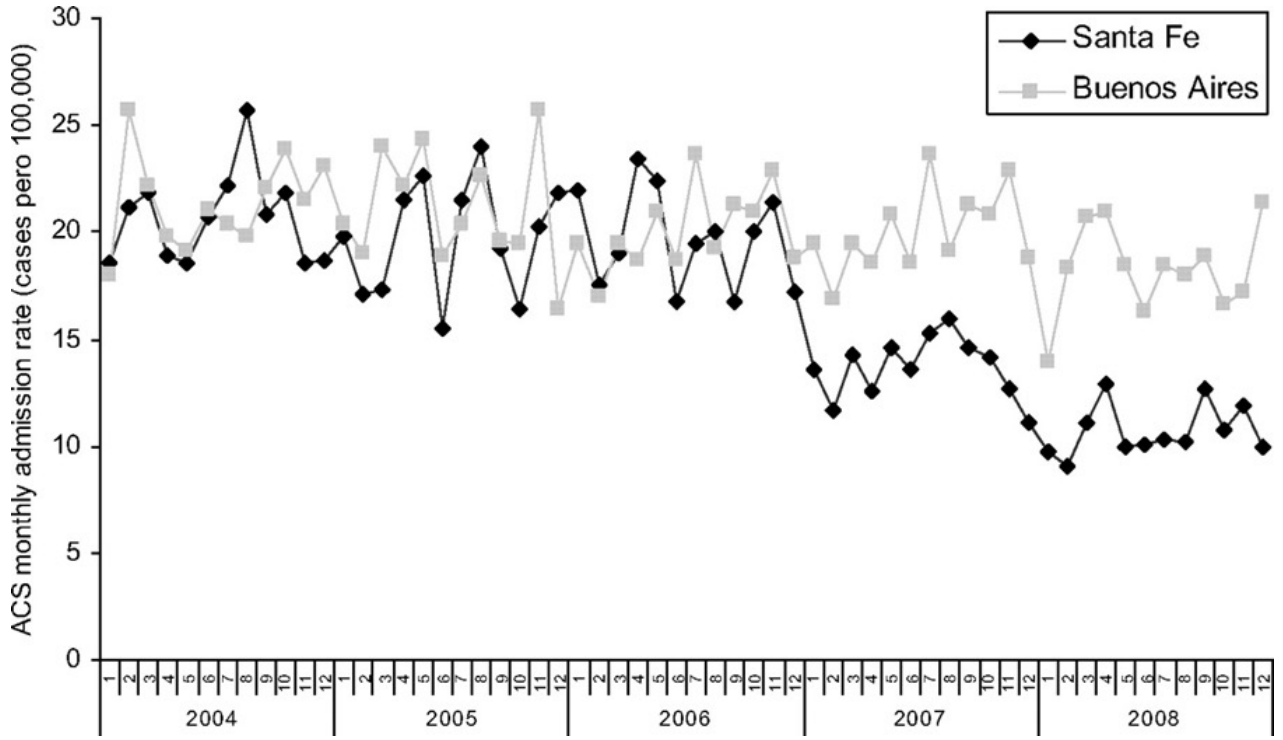


Amy Tyler et al. Hospital Pediatrics 2019;9:92-99

ITS Examples

2. *Reduction in hospital admissions for acute coronary syndrome after the successful implementation of 100% smoke-free legislation in Argentina: a comparison with partial smoking restrictions* (Ferrante, 2012)

- Effect of full and partial smoke free legislation on acute coronary syndrome (ACS) admissions
- Multiple linear regression analysis
- Aggregate data, age standardized ACS
- Covariate seasonal trend
- Results:
  - Santa Fe-**Immediate change** (−2.5 admissions per 100 000, (−4.74, −0.26), and a **persistent change** after the implementation of the law (post-law trend: 0.26 fewer admissions per 100 000 inhabitants per month, (−0.39,-0.13).
  - Buenos Aires city- no immediate effect or a change in the trend.



D Ferrante et al. Tob Control 2012;21:402-406

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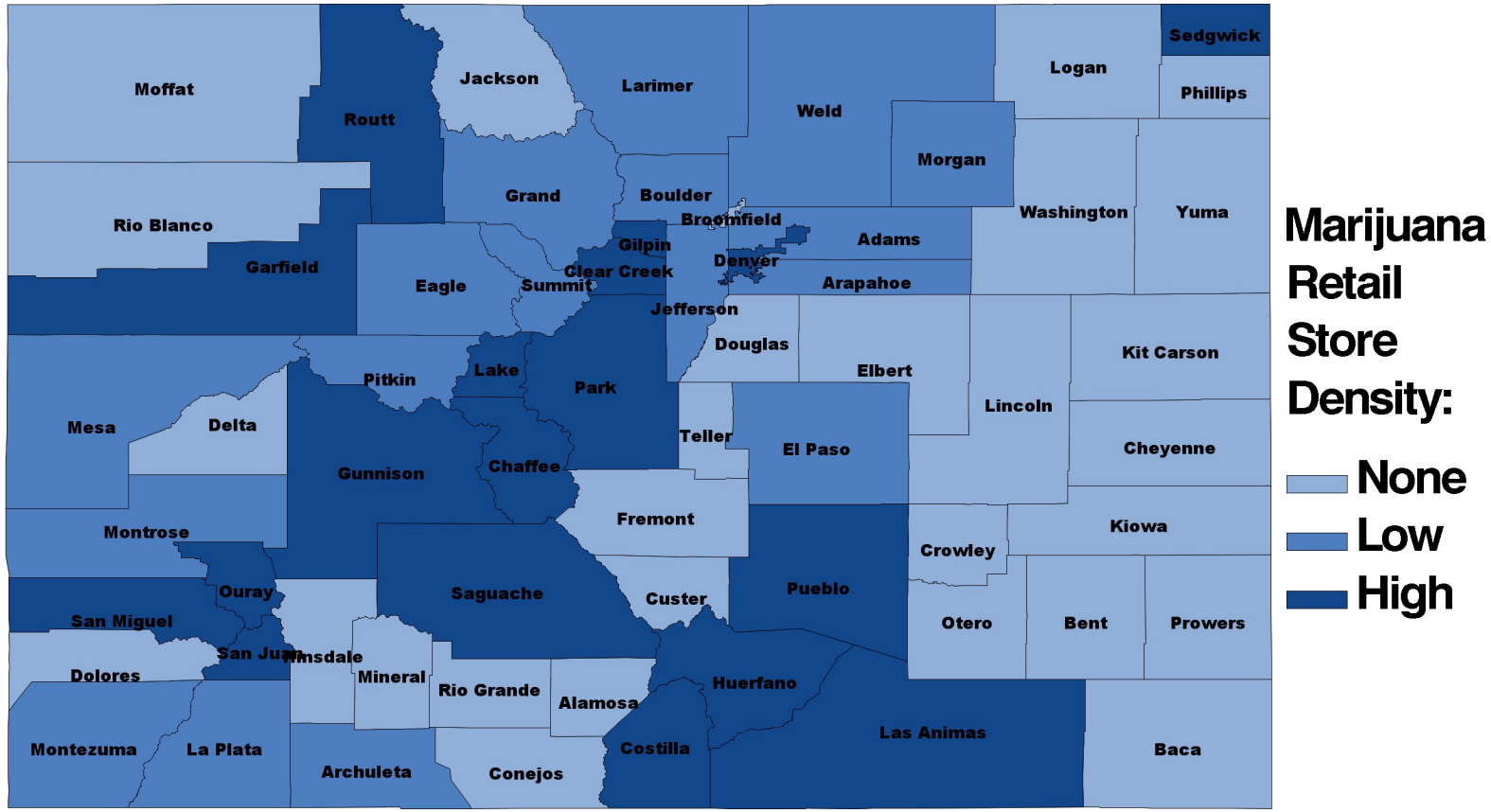
ITS Example-
The association between legalization of recreational marijuana and birth outcomes in Colorado

- Data
  - Colorado Department of Public Health and Environment Vital Statistics Program, Birth Certificate Data for all live Births in Colorado 2012-2016 (n=~270k)
  - Colorado State Demography Office (population projections)
  - Colorado Department of Public Safety (marijuana retail license counts)
- Outcomes
  - Small for gestational age (SGA)=Birth weight < 10th percentile
  - NICU admission for infants born >35 weeks
- Additional Exposure
  - Marijuana outlet density (MOD) in maternal county of residence
    - None (0 per 100,000 population)
    - Low (<17 per 100,000 population)
    - High (>=17 per 100,000 population)
- Covariates
  - Maternal age, Race, Ethnicity, Education, Hypertension, Elevation of residence, Smoking during pregnancy, Drinking during pregnancy, Early prenatal visits

Intervention

Exposure


Moffat
Routt
Jackson
Larimer
Weld
Logan
Sedgwick
Phillips
Morgan
Rio Blanco
Grand
Boulder
Broomfield
Washington
Yuma
Garfield
Eagle
Gilpin
Clear Creek
Summit
Denver
Adams
Arapahoe
Jefferson
Douglas
Elbert
Kit Carson
Pitkin
Lake
Park
Lincoln
Mesa
Delta
Teller
El Paso
Cheyenne
Gunnison
Chaffee
Fremont
Kiowa
Montrose
Crowley
Ouray
Saguache
Custer
Pueblo
San Miguel
Otero
Bent
Prowers
San Juan
Hinsdale
Dolores
Mineral
Rio Grande
Alamosa
Huerfano
Las Animas
Montezuma
La Plata
Archuleta
Conejos
Costilla
Baca
Marijuana Retail Store Density:
None
Low
High

ITS Model/Plan

- ITS Model with Exposure group

$$Y_t=\beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 Z_L + \beta_4 Z_H + \mathbf{BV}$$

$$+\beta_5 T X_t + \beta_6 Z_L X_t + \beta_7 Z_H X_t + \beta_8 Z_L T + \beta_9 Z_H T + \beta_{10} Z_L T X_t + \beta_{11} Z_H T X_t + \varepsilon_t$$

Where:

T= time elapsed since the start of the study (month)

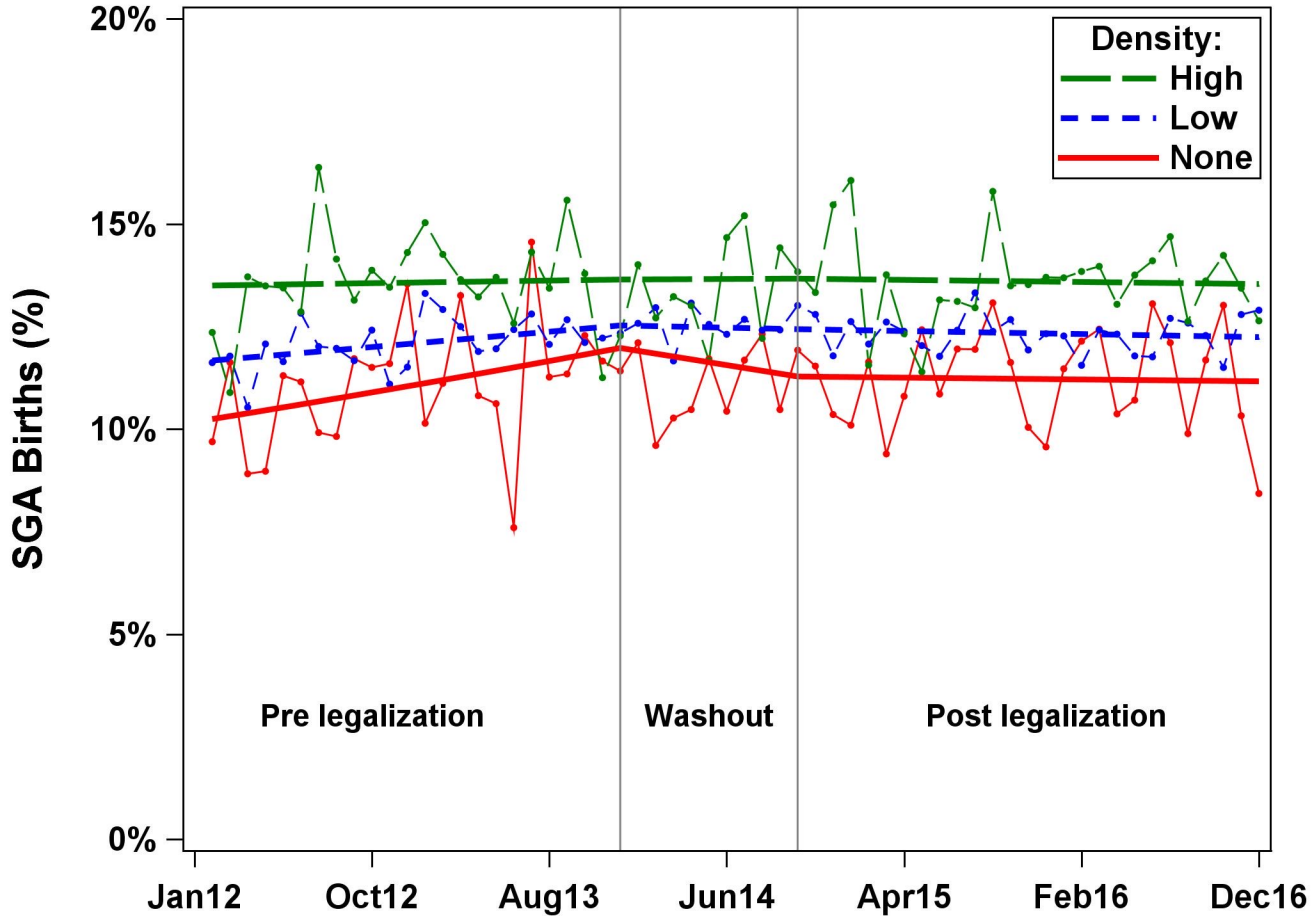
X=binary variable indicating the post-legalization

Z=exposure variable three levels (High, Low, None(ref))

V=covariates

- Analysis Plan
  - Remove washout period Jan 1, 2014-Oct.1, 2014
  - Simple Logistic Regression
  - Aggregate predicted values by month
  - Graph aggregated predicted values with observed values
  - Multivariable Logistic Regression

ITS- Small for Gestational Age



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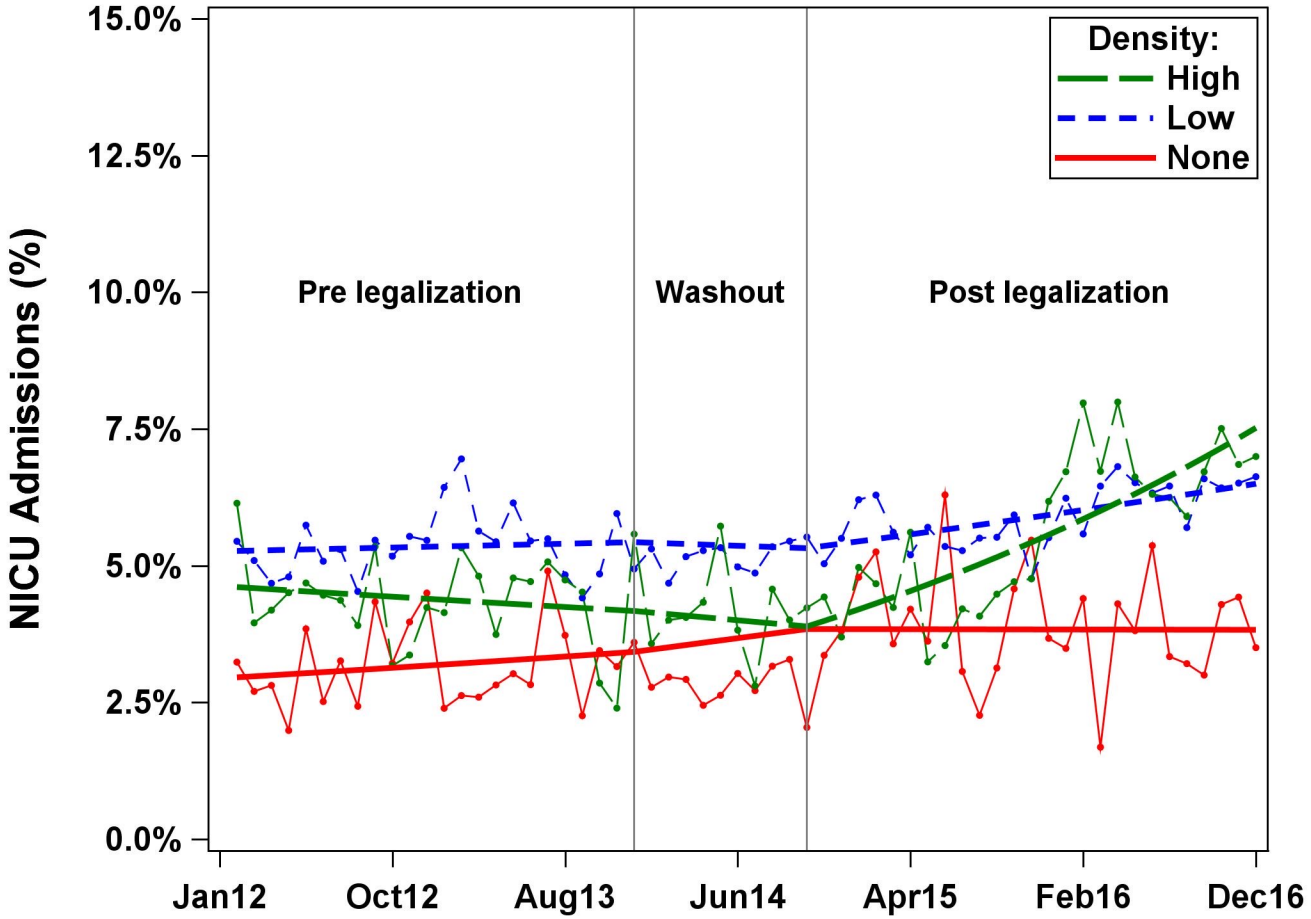
ITS- NICU Admissions



Results - SGA

SGA Outcome

*Adjusted for maternal age, race, ethnicity, education, hypertension, elevation of residence, smoking or drinking during pregnancy, and early prenatal visits

MJ Stores Density	Effect	Adjusted Odds Ratio* (95% CI)	pvalue
None	Trend pre legalization	1.01 (1.00.1.02)	0.0100
	Trend post legalization	1.00 (0.99,1.01)	0.96
	Immediate change post legalization	0.82 (0.66,1.01)	0.07
Low	Trend pre legalization	1.00 (1.00.1.01)	0.0042
	Trend post legalization	1.00 (0.99,1.00)	0.76
	Immediate change post legalization	0.93 (0.86,1.01)	0.10
High	Trend pre legalization	1.00 (0.99.1.01)	0.73
	Trend post legalization	1.00 (0.99,1.00)	0.94
	Immediate change post legalization	0.99 (0.85,1.14)	0.85
High vs Low	Difference in baseline risk	1.16 (1.06,1.27)	0.0020
High vs None	Difference in baseline risk	1.41 (1.22,1.64)	<0.0001
Low vs None	Difference in baseline risk	1.22 (1.07,1.40)	0.0031

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Results - NICU

NICU Outcome

*Adjusted for maternal age, race, ethnicity, education, hypertension, elevation of residence, smoking or drinking during pregnancy, and early prenatal visits

MJ Stores Density	Effect	Adjusted Odds Ratio* (95% CI)	pvalue
None	Trend pre legalization	1.00 (0.99,1.02)	0.58
	Trend post legalization	0.99 (0.98,1.01)	0.44
	Immediate change post legalization	1.18 (0.80,1.72)	0.39
Low	Trend pre legalization	1.00 (0.99,1.01)	0.38
	Trend post legalization	1.01 (1.00,1.01)	<0.0001
	Immediate change post legalization	0.95 (0.85,1.07)	0.46
High	Trend pre legalization	0.99 (0.98,1.00)	0.11
	Trend post legalization	1.03 (1.02,1.03)	<0.0001
	Immediate change post legalization	1.06 (0.83,1.36)	0.64
High vs Low	Difference in baseline risk	0.91 (0.78,1.05)	0.20
High vs None	Difference in baseline risk	1.59 (1.22,2.06)	0.0005
Low vs None	Difference in baseline risk	1.76 (1.39,2.21)	<0.0001

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Strengths of ITS

- Evaluate for intervention effects while accounting for underlying time trends.
- Assess whether intervention effects are short lived or sustained over time
- Can be conducted with population data or individual level data
- Account for time varying confounders
- Stronger design when control series is included
- Intuitive visual displays of results
- Small population, acting as own control
- Alternative designs for more complex interventions (multiple interventions)

Limitations of ITS

- Limits
  - Need stable data and large number of time points
  - Control series may not exist
  - When using population level data ITS cannot be used to make individual level outcome inferences
  - Challenging with rare outcomes
  - No graphical representation of adjusted model
  - Interaction estimates can be difficult to interpret
- Threats to Internal Validity
  - Factors other than the intervention may influence the outcome(competing interventions)
  - Changes in the ability to measure the outcome (missing data)
  - Selection bias (composition of intervention group differs from that of pre group)

ITS using aggregated data

- Outcome:
  - Averages
  - Rates
  - Proportions
- Methodological issues (aspects of modeling)
  - Autocorrelation
  - Seasonality
  - Stationarity
  - Covariates at the aggregate level
  - Overdispersion for count/binary data

Other methodological considerations

- More complex models, e.g. using GLMM, GAMM, models addressing serial correlation (autocorrelation, ARIMA)
- Outliers – sensitivity analyses
- Missing data – differing missing amount and patterns might be reflected in the aggregated data
- When there is a control group observed over time, this is often referred to as Difference in Difference analysis or controlled ITS

Summary

- ITS is a strong quasi-experimental approach for evaluating longitudinal effects of interventions
  - Factors other than intervention might influence the outcome
- ITS is a simple and powerful study design for evaluating the effectiveness of population-level interventions
- ITS allows for considerable design flexibility
  - Multiple interventions
  - Time varying covariates
  - Serial correlation
  - Various modeling techniques

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ITS SAS Code

```
proc genmod data=work.anal2 descending;
class mj_legal(ref='Pre') mjdensity(ref='None')/param=ref;
model SGA = mj_legal time mjdensity  mj_legal*time mj_legal*mjdensity time*mjdensity
mj_legal*time*mjdensity /dist=binomial     link=logit type3  ;

estimate 'slope 0 density pre legalization '        time 1  / exp ;
estimate 'slope LOW density pre legalization'       time 1  time*mjdensity 0 1  / exp ;
estimate 'slope HIGH density pre legalization'      time 1  time*mjdensity 1 0  / exp ;
estimate 'slope 0 density post legalization'        time 1  mj_legal*time 1  / exp ;
estimate 'slope LOW density  post legalization' time 1   mj_legal*time 1  time*mjdensity 0 1
mj_legal*time*mjdensity 0 1  / exp ;
estimate 'slope HIGH density post legalization' time 1   mj_legal*time 1  time*mjdensity 1 0
mj_legal*time*mjdensity 1 0 / exp ;

estimate 'change in level 0 density post to pre legalization' mj_legal 1   mj_legal*time 34 /exp;
*immediate change post in 0 group;
estimate 'change in level Low density post to pre legalization' mj_legal 1  mj_legal*time 34
mj_legal*mjdensity 0 1            mj_legal*time*mjdensity 0 34 /exp;*immediate change post in Low
group;
estimate 'change in levelHigh density post to pre legalization' mj_legal 1   mj_legal*time 34
mj_legal*mjdensity 1 0    mj_legal*time*mjdensity 34 0 /exp; *immediate change post in High group;
estimate 'change in level High vs LOW pre legalization' mjdensity 1 -1 /exp;
estimate 'change in level High vs 0 pre legalization' mjdensity 1 0 /exp;
estimate 'change in level LOW vs 0 pre legalization' mjdensity  0 1 /exp;

output out=sgamodel1 pred=pred;

run;
```

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Individual vs Aggregate

+ Advantages

- Disadvantages

	Individual Data	Aggregate Data
Autocorrelation		
Seasonality/stationarity		
Confounding		
Missing data		
Clustering		
Power Advantage		
GLMM		
GLS		
GAMM		
ARIMA/ARIMAX		