Interrupted Time Series with Aggregated Data - A review of Methods

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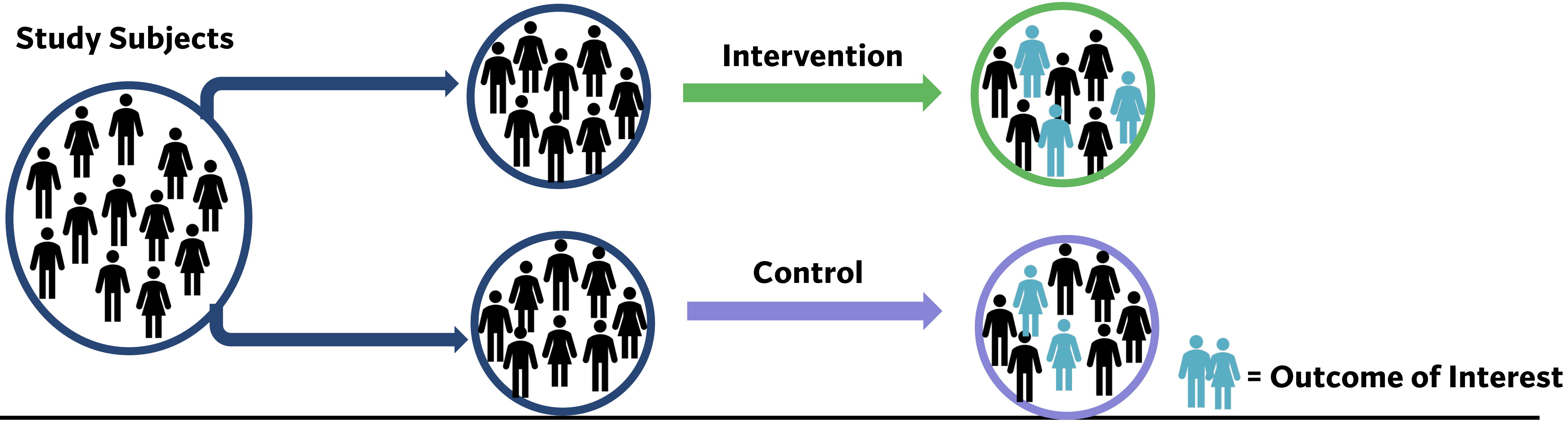
CHL5250 – Special Topics in Biostatistics

Background

Randomized control Trials (RCTs)

- used to evaluate the causal effects of health interventions in a population.
- subjects are randomly allocated to either an intervention or control group
- predefined outcomes are compared between the control and intervention groups.



Limitations of Randomized Control Trials

Cannot account for variations in health and overall health care complexity

(Cruz, 2017).

Costly

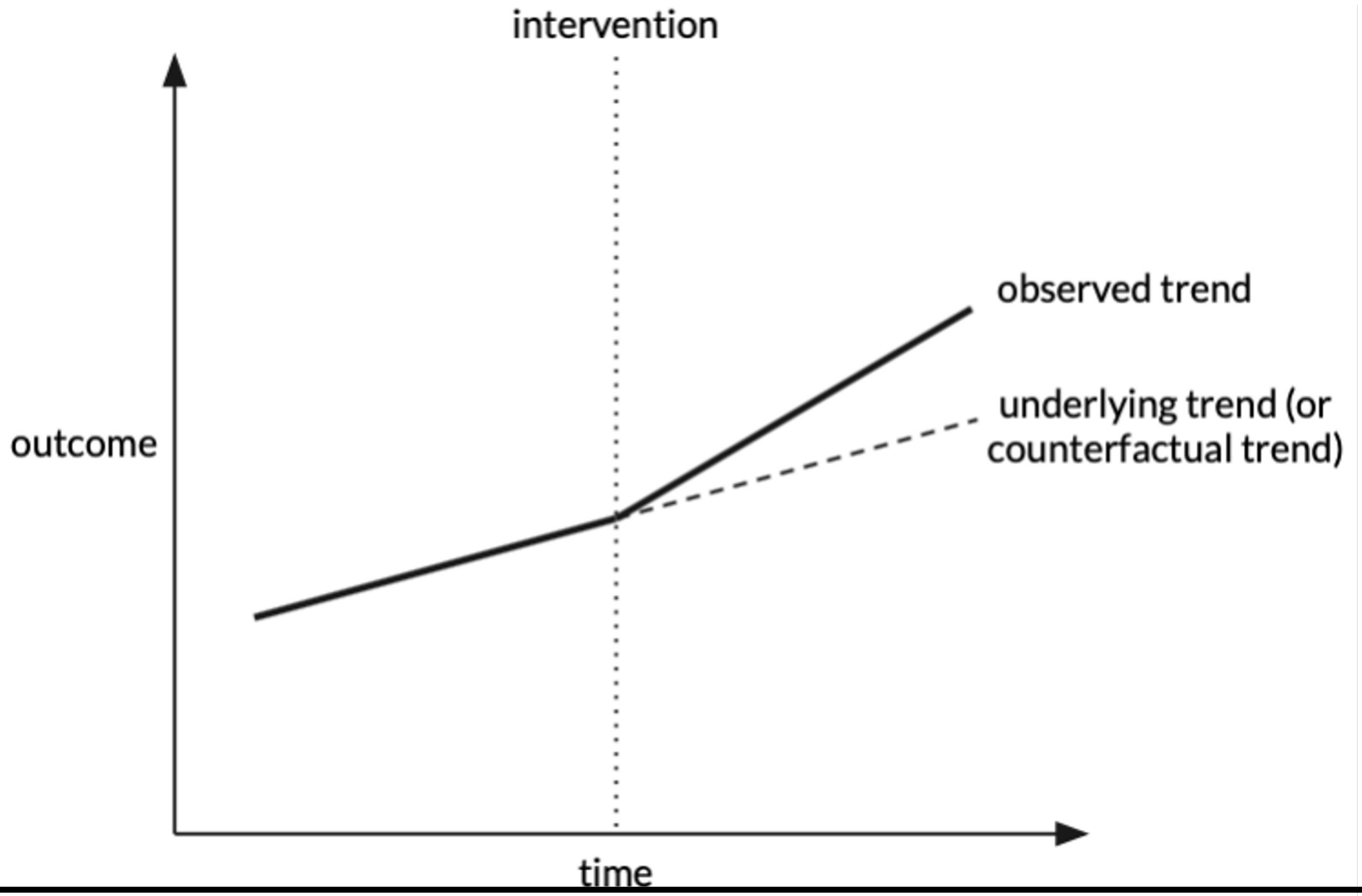
Unethical

Not possible for health policies targeted at the population level (Bonell et al., 2011).

Interrupted Time Series

- Alternative study design for RCTs
- Allows for the inference of causality while still accounting for contextual and temporal factors (Cruz, 2017)
- Especially suitable for population-level interventions over defined and equally spaced time points (Bernal, 2017).
- Use repeated observations of an outcome over time

Interrupted Time Series Design



Motivation

Many studies fail to account for heterogeneity across patients or sites.

Not accounting for this heterogeneity is associated with increased bias and decreased precision when used on aggregated data (Sen, 1997).

Current methods do not account for imprecision due to variability of patient outcomes or variability across sites at a certain time point, leading to spurious results.

Methods

Segmented Regression

- Special case of multiple linear regression

$$Y_t = \beta_0 + \beta_1 t + \beta_2 X + \beta_3 Xt$$

t: time elapsed since start of study
X: indicator variable for time period (0 = pre-intervention, 1 = post-intervention)
Y: outcome of interest at time t

β_0: baseline level at t = 0
β_1: change in outcome associated with unit increase in time
β_2: change in outcome level following intervention
β_3: interaction between time and intervention

Weighted Segmented Regression
(Ewusie et al., 2019)

- addresses limitation of OLS approach using weighted least squares
- data are weighted to account for differences in variance.
- estimators through minimizing weighted sum of squares.

$$\sum w_i \epsilon_i^2 = (Y - X\beta)'(Y - X\beta)$$

$$= Y'WY - Y'WX\beta - \beta X'WY + \beta' X' W X \beta$$

Model estimators: $\widehat{\beta_w} = (X\ WX)\ X'WY$

Where W represents a diagonal matrix with the vector w= $(w_1, w_2, \ldots, w_k)$.

Segmented generalized mixed effect model
(French & Heagerty, 2008)

- generalized mixed models may be used in combination with segmented regression
- random effects reflect heterogeneity across repeated measures or groupings.
- allows for less rigid assumptions to produce consistent estimates.

$$Y = (\beta_0 + \nu_{i0}) + (\beta + \nu_{i1})t + \beta_2 X + \beta_3 Xt$$

$\beta' s$: fixed effects
ν_{i0}: random intercept
ν_{i1} : random slope

Literature Review – Current Findings

Weighted Segmented Regression (WSR) (Ewusie et al., 2021)

- Performed extensive simulations, considering 550 scenarios with various parameter values, variabilities, and sample sizes.
- Data at each time point generated independently from normal distribution
- Data were then aggregated as a mean to represent aggregated nature of ITS data
- Segmented regression and proposed weighted segmented regression method applied
- Empirical bias, empirical square error (MSE, type I error rate and power based on 5000 simulations calculated

Summary of Simulation Results

- Both SR and WSR produce estimates with minimal to no bias when within patient variance was small
- WSR overall produced estimates with relatively less bias
- WSR produced estimates with uniformly lower mean squared error (MSE) compared
- WSR had higher power to detect a 0.1 change in trend compared to SR method across all sample sizes

Literature Review – Current Findings

Segmented Generalized Model with Mixed Effects (SGLMM) (French & Heagerty, 2008)

- Data provided from large prospective cohort of HIV–HCV co-infected individuals with repeated health-related quality of life measures before and after treatment
- Participants self-reported current health from 0 to 100 (worst to best health) using visual analog scale (VAS).
- Between 2014 and 2016, 231 individuals initiated DAA (*exposure at time zero)*.
- A total of 1765 observations
- by having repeated measures on the same individual before and after an exposure, by design both known and unknown time-invariant confounders are controlled.
- time-varying confounders and the possibility of lead time effects may bias results.
- Study did not compare SGLMM with SR

Illustrative Example: Fertility rates in Oklahoma after the Oklahoma City Bombing

- We compare segmented regression to weighted segmented regression (WSR) and generalized mixed effect models with segmented regression (SGLMM).
- Methods are then applied to data investigating birth rate after intervention.

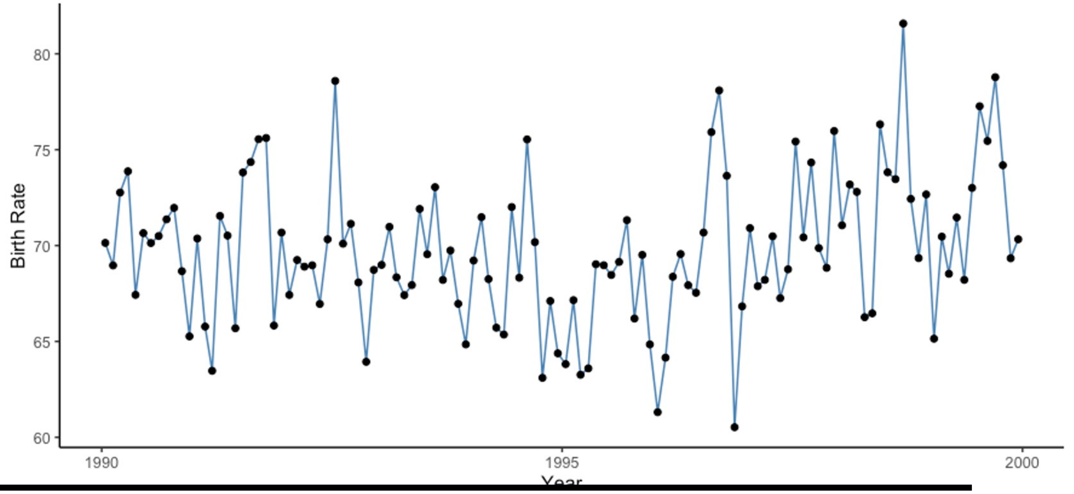
Hypothesis:

WSR and SGLMM will produce more precise results compared to the conventional SR approach

Data:

- 1440 observations aggregated across 12 Oklahoma counties, with 756 observations pre- intervention and 684 post intervention
- Intervention: domestic terrorist attack occurring in Oklahoma City on April 19, 1995

Figure 1: Birth rates for 12 Oklahoma Counties from 1990 - 2000.



Results

Table 1: Estimates for Intervention Effects and 95% Confidence Intervals for 3 Methods

Variable	Segmented Regression Estimate (95% CI)	Weighted Segmented Regression (95% CI)	Generalized linear mixed effects segmented regression (95% CI)
β_0 **(Baseline level)**	58.37 (56.94, 59.80)	52.762 (48.42, 57.104)	63.90 (52.53, 73.95)
β_1 **(time)**	-1.023 *** (-2.30, 0.26)	-1.46 ** (-2.76, -0.16)	-0.0029 (-0.015, 0.011)
β_2**(Difference in level following intervention)**	0.0043 (0.003, 0.006)	0.077 * (0.02, 0.134)	-4.45 ** (-7.7, -1.8)
β_3 **= interaction between time and intervention**	-0.077 (-0.13, -0.024)	-0.078 (-0.14, -0.021)	-0.0011 (-0.0043, -0.0038)

Note. P-value < 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Conclusion

we aimed to extend on the existing literature of interrupted time series by exploring alternative methods to the traditional segmented regression approach to consider heterogeneity across groups.

Ewusie et al., (2020) found that among SR, pooled analysis, and WSR, WSR had the narrowest confidence interval. SR had the widest confidence interval.

Similar to their study, the parameter estimates of our models were comparable for the two segmented regression methods.

Contrary to Ewusie et al., (2020), we did not find that WSR performed considerably better than SR. In some cases, such as the estimate for level differences following intervention, SR appears to a narrower confidence interval.

Although our study does not show that these the models accounting for aggregation performed better, we have low generalizability by comparing the methods on a single data set. However, the difference in variance among the methods emphasize the need to further explore ways to account for differences in participant populations and settings

Limitations and Next Steps

More extensive simulations are needed to test the different methods under different scenarios.

Methods should be compared under different scenarios that consider ITS data from different data distributions.

Data set analyzed was only aggregated at one level. We did not consider a scenario where there is aggregation at two levels: site (location, hospital, etc.) and patient level.

References

Bernal, J. L., Cummins, S., & Gasparrini, A. (2017). Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International Journal of Epidemiology*, *46*(1), 348-355. https://doi.org/10.1093/ije/dyw098

Bonell CP, Hargreaves J, Cousens S, Ross D, Hayes R, Petticrew M, Kirkwood BR. Alternatives to randomisation in the evaluation of public health interventions: design challenges and solutions. J Epidemiol Community Health. 2011 Jul;65(7):582-7. doi: 10.1136/jech.2008.082602. Epub 2009 Feb 12. PMID: 19213758.

Cook TD, Campbell DT. A. Quasi-experimentation: Design & analysis issues for field settings. Boston: Houghton Mifflin; 1979.

Cruz M, Bender M, Ombao H. A robust interrupted time series model for analyzing complex health care intervention data. Stat Med. 2017 Dec 20;36(29):4660-4676. doi: 10.1002/sim.7443. Epub 2017 Aug 29. PMID: 28850683.

Ewusie J. E., Soobiah C, Blondal E, Beyene J, Thabane L, Hamid JS. Methods, Applications and Challenges in the Analysis of Interrupted Time Series Data: A Scoping Review. J *Multidiscip Healthc*. 2020;13:411-423 https://doi.org/10.2147/JMDH.S241085

Ewusie, J. E., Thabane, L., Beyene, J., Straus, S. E., & Hamid, J. S. (2019). MultiCenter Interrupted Time Series Analysis: Incorporating Within and Between-Center Heterogeneity. *Clinical Epidemiology*, *12*, 625-636. https://doi.org/10.2147/CLEP.S231843

French B, Heagerty PJ (2008) Analysis of longitudinal data to evaluate a policy change. Stat Med 27:5005–5025. https://doi.org/10.1002/sim.3340

James Lopez Bernal, Steven Cummins, Antonio Gasparrini, Interrupted time series regression for the evaluation of public health interventions: a tutorial, *International Journal of Epidemiology*, Volume 46, Issue 1, February 2017, Pages 348–355, https://doi.org/10.1093/ije/dyw098

Kong M, Cambon A, Smith MJ. Extended logistic regression model for studies with interrupted events, seasonal trend, and serial correlation. *Commun Stat Theory Meth*. 2012;**41**(19):3528–3543. doi: 10.1080/03610926.2011.563020)

Muggeo, Vito. (2008). Segmented: An R Package to Fit Regression Models With Broken-Line Relationships. R News. 8. 20-25.

Pape, U. J., Millett, C., Lee, J. T., Car, J., & Majeed, A. (2013). Disentangling secular trends and policy impacts in health studies: use of interrupted time series analysis. *Journal of the Royal Society of Medicine*, *106*(4), 124-129. https://doi.org/10.1258/jrsm.2012.110319\

Rodgers JL, St John CA, Coleman R. Did fertility go up after the Oklahoma City bombing? An analysis of births in metropolitan counties in Oklahoma, 1990-1999. Demography. 2005 Nov;42(4):675-92. doi: 10.1353/dem.2005.0034. PMID: 16463916.

Saeed S, Moodie EEM, Strumpf EC, Klein MB. Segmented generalized mixed effect models to evaluate health outcomes. Int J Public Health. 2018 May;63(4):547-551. doi: 10.1007/s00038-018-1091-9. Epub 2018 Mar 16. PMID: 29549396.

Sen, A., & Srivastava, M. (1997). Regression analysis: theory, methods, and applications. Springer Science & Business Media.

Strumpf EC, Harper S, Kaufman JS (2017) Fixed effects and difference-in-differences. In: Methods in social epidemiology, 2nd edn. Jossey-Bass, San Francisco, pp 341–368

Wagner, A.K., Soumerai, S.B., Zhang, F. and Ross-Degnan, D. (2002), Segmented regression analysis of interrupted time series studies I n medication use research. Journal of Clinical Pharmacy and Therapeutics, 27: 299-309. https://doi.org/10.1046/j.1365-2710.2002.00430.x

Wang JJ, et al. A comparison of statistical methods in interrupted time series analysis to estimate an intervention effect. Australasian Road Safety Research, Policing and Education Conference 2013

Yelland, J., Riggs, E., Szwarc, J. et al. Bridging the Gap: using an interrupted time series design to evaluate systems reform addressing refugee maternal and child health inequalities. *Implementation Sci* 10, 62 (2015). https://doi.org/10.1186/s13012-015-0251-z