Interrupted Time Series:

Overview of Design and Analysis

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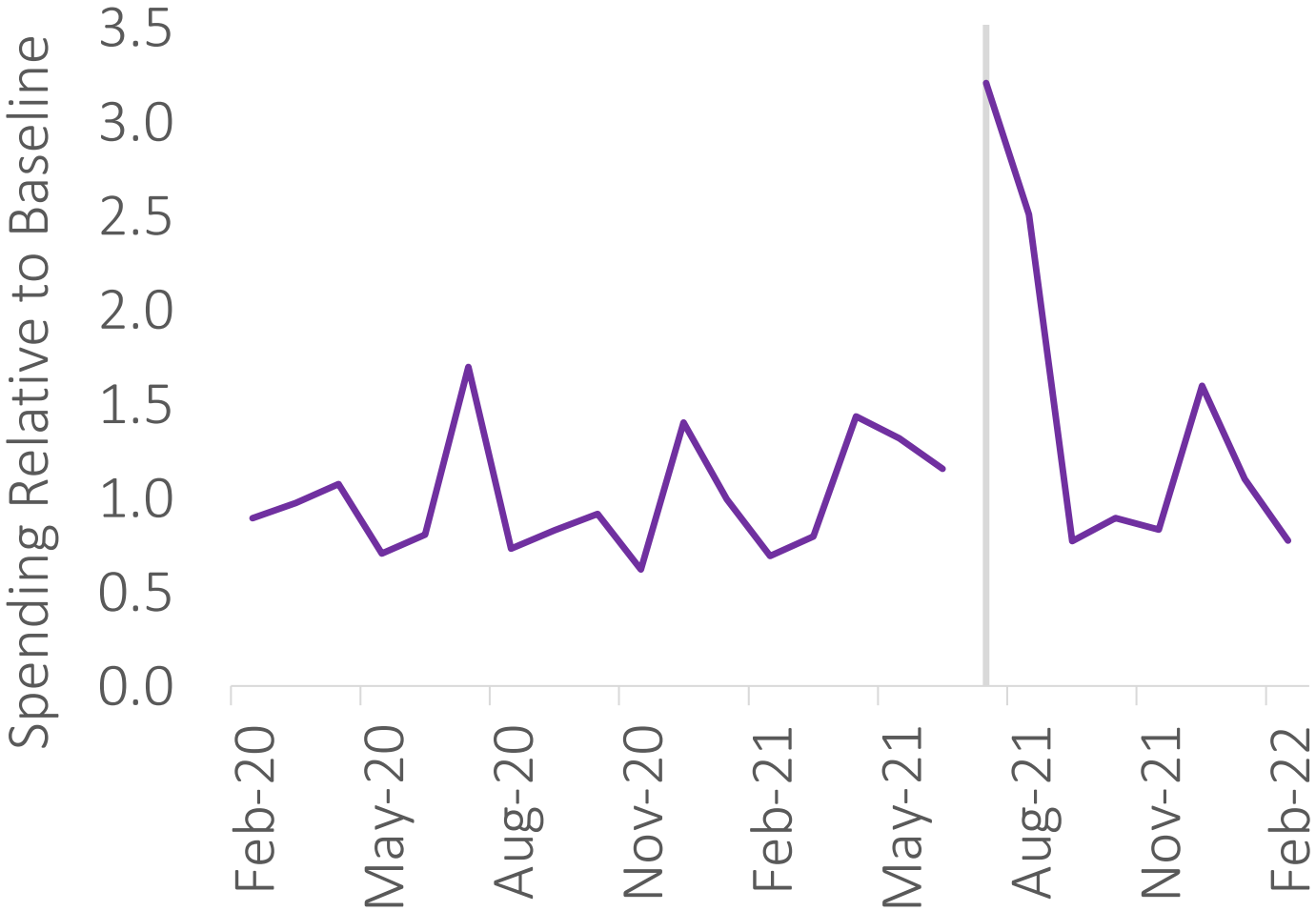
Outline

1. Brief review of observational research designs
2. What is interrupted time series (ITS) design?
3. Benefits & limitations of ITS designs
4. ITS *without* control group
   - Practical considerations and examples
5. ITS *with* control group
   - Practical considerations and examples
6. Overview of segmented regression analysis

This talk applies to …

- Observational studies using longitudinal data
- Mostly to data sources with a denominator
  - E.g., health insurance claims data
- But many ideas extrapolate to other data sources
  - Electronic health record data
  - Serial cross-sectional survey data

A picture


Spending Relative to Baseline
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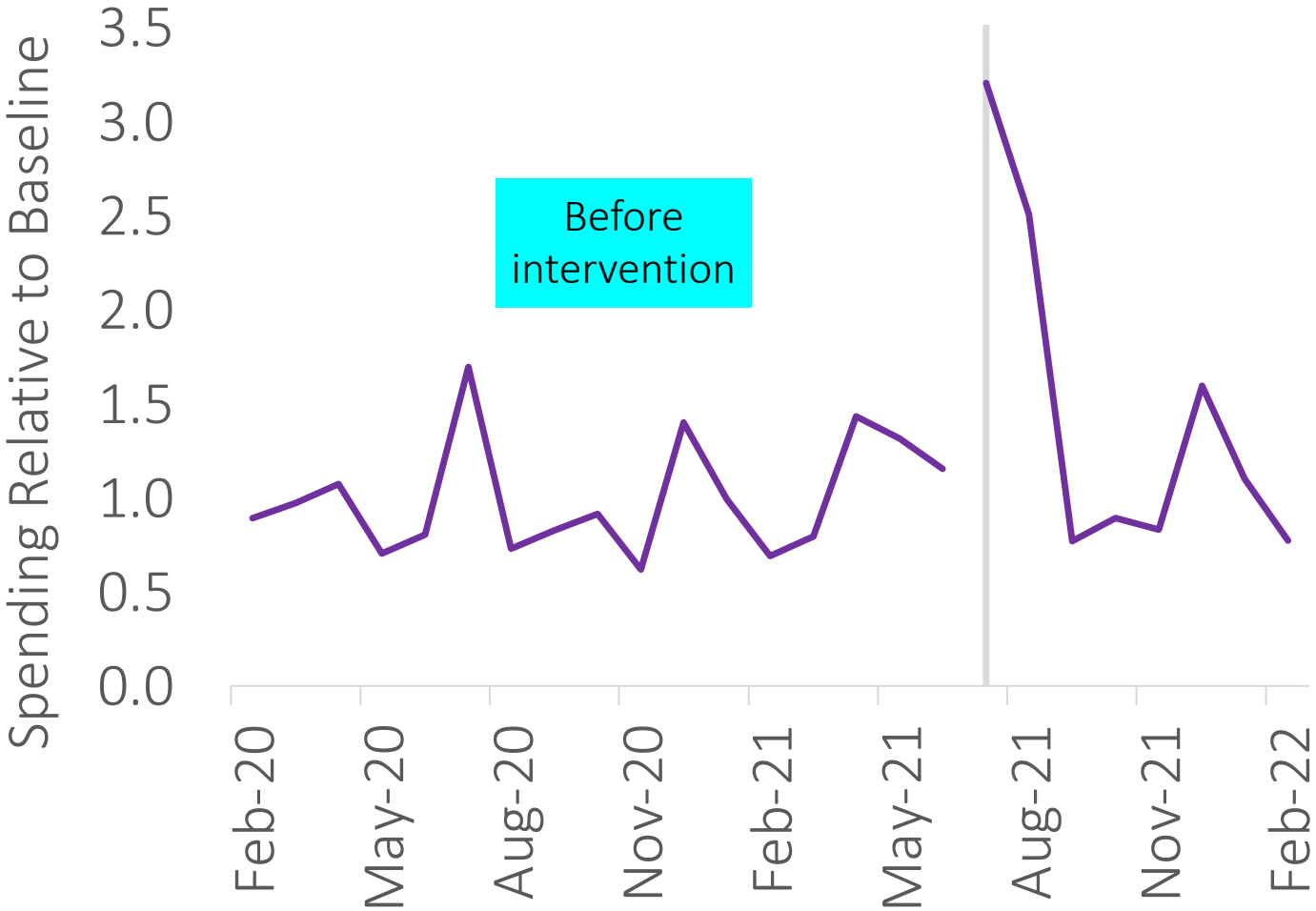
A picture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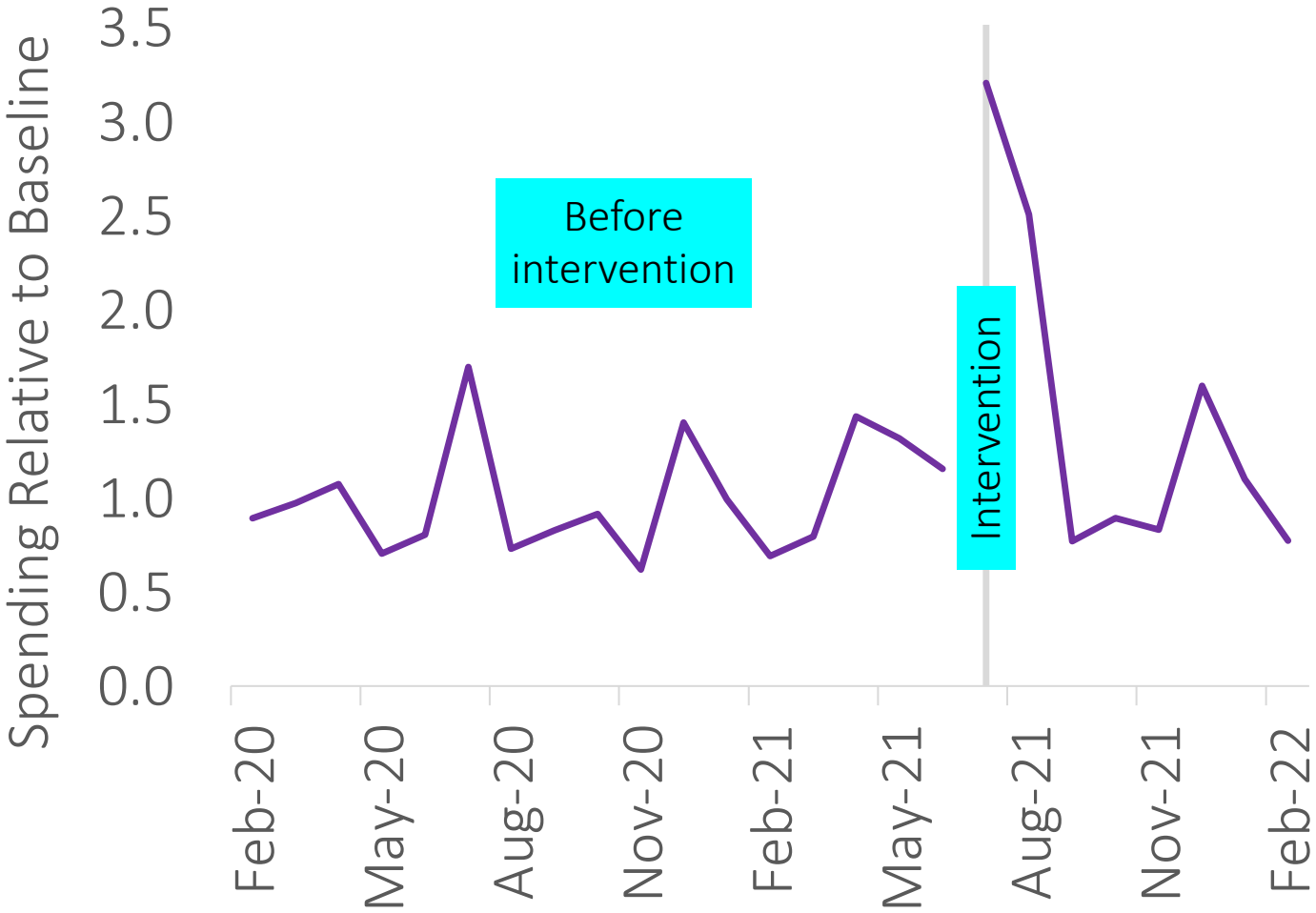
A picture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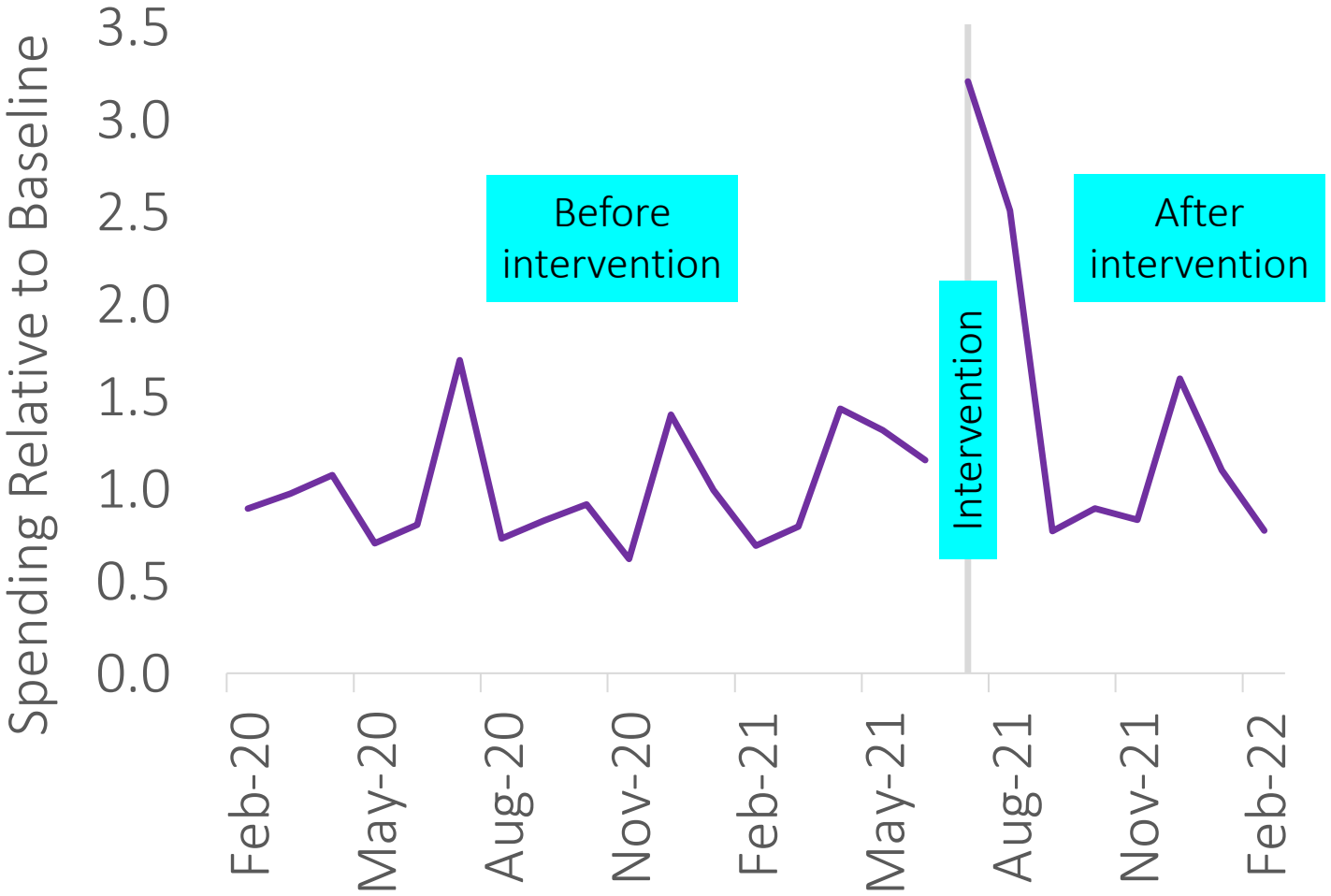
A picture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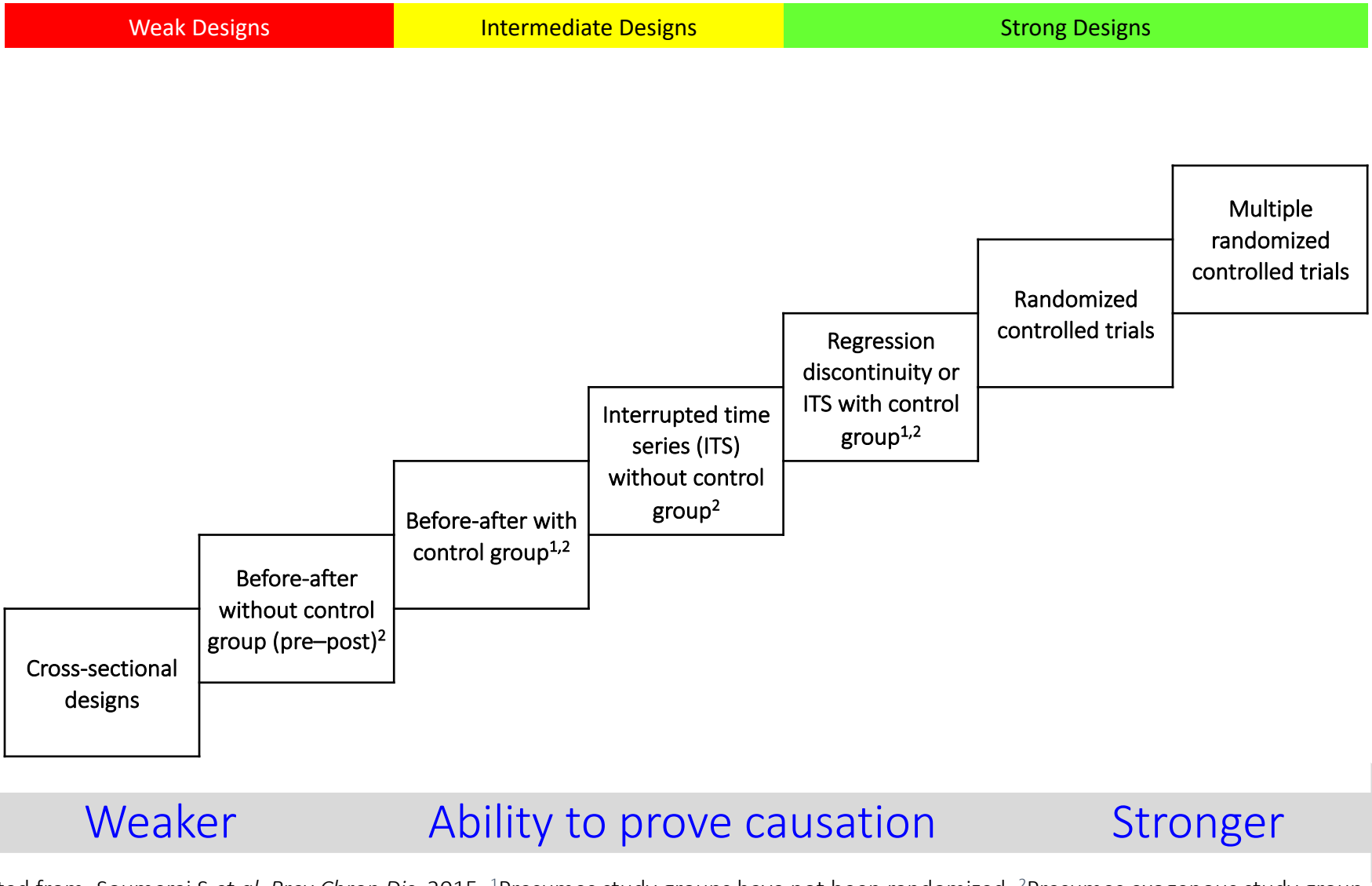
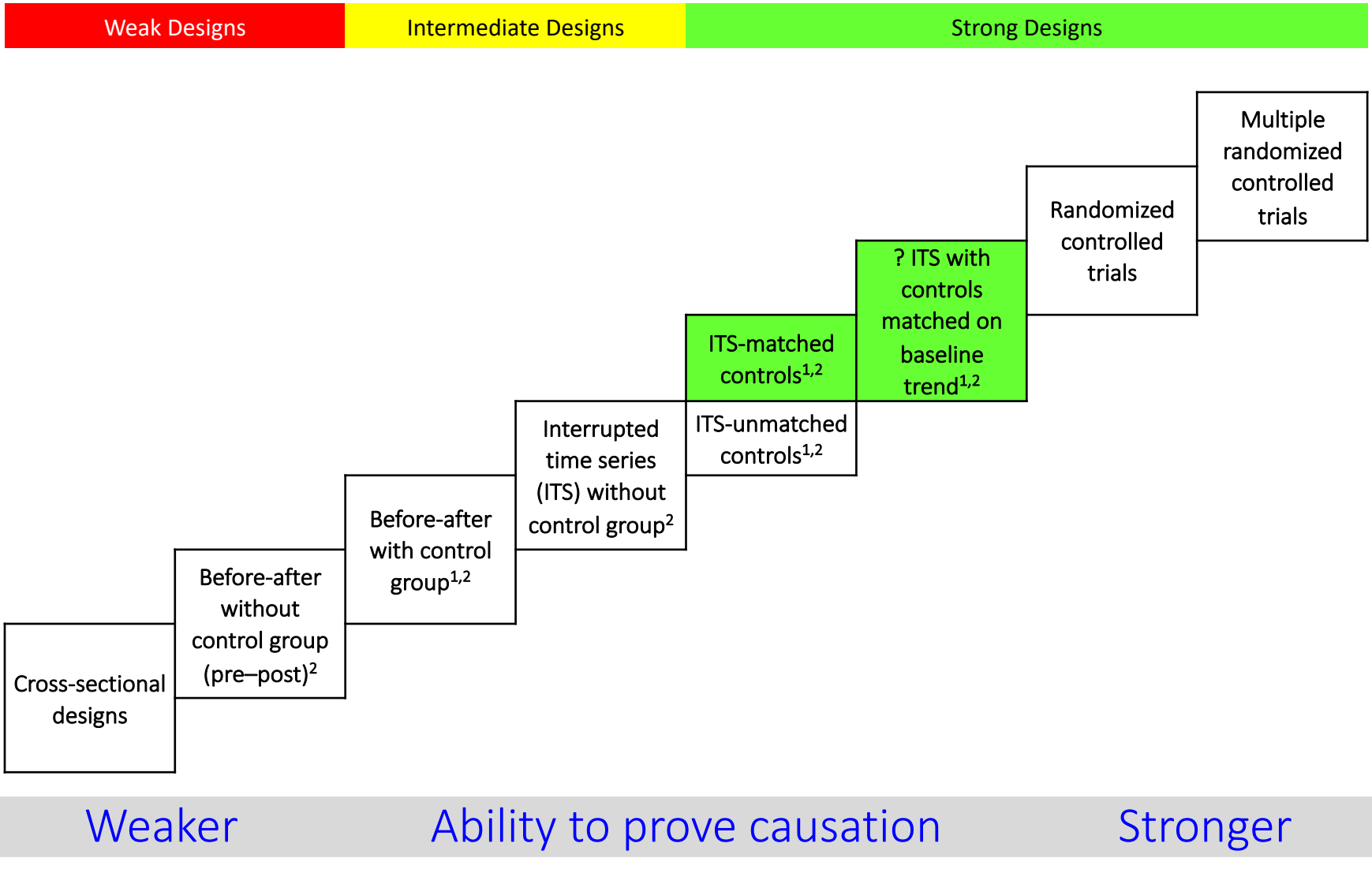
Hierarchy of research design



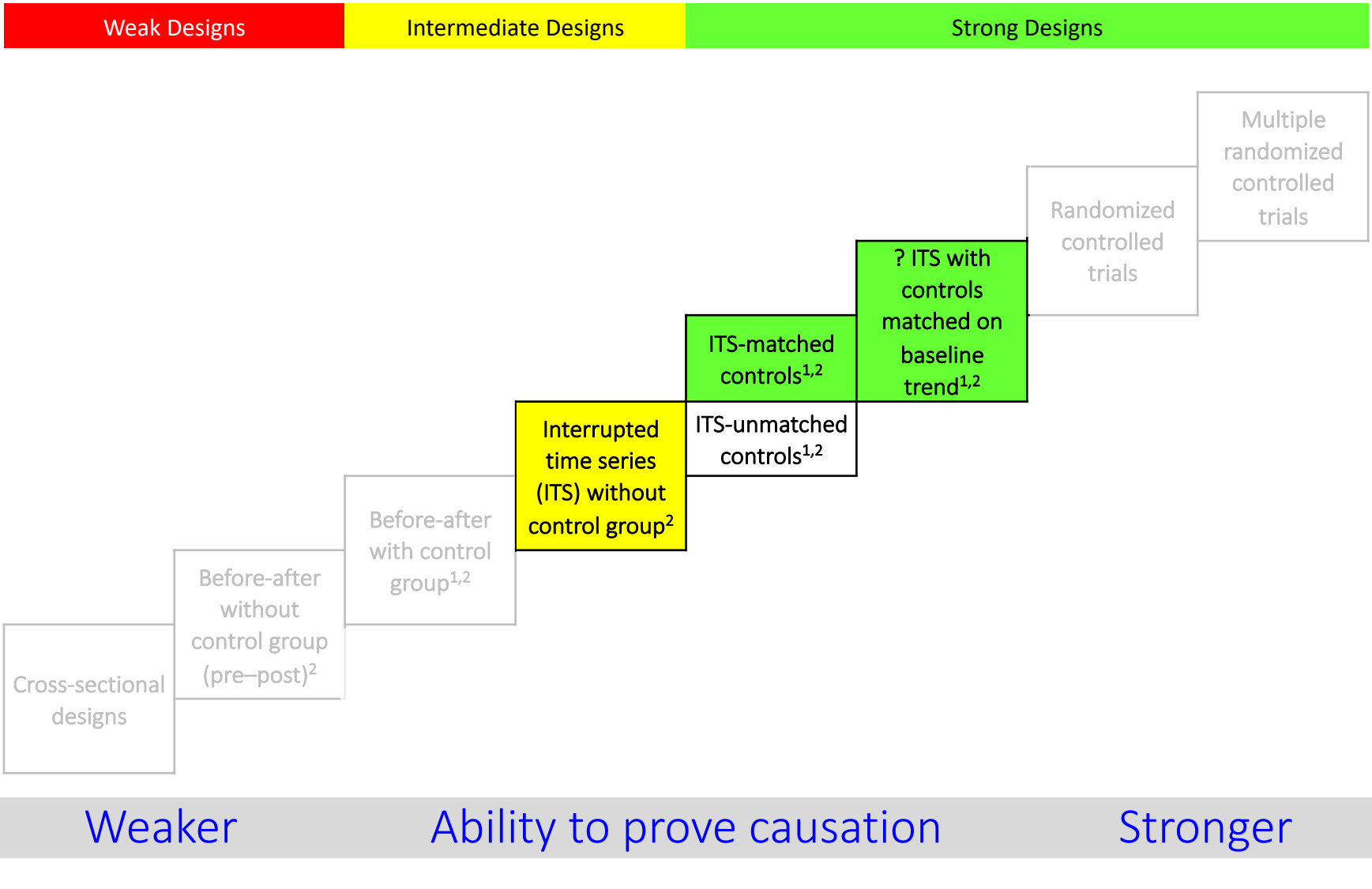
Adapted from: Soumerai S *et al. Prev Chron Dis.* 2015. [1]Presumes study groups have not been randomized; [2]Presumes exogenous study group assignment

Cutting edge



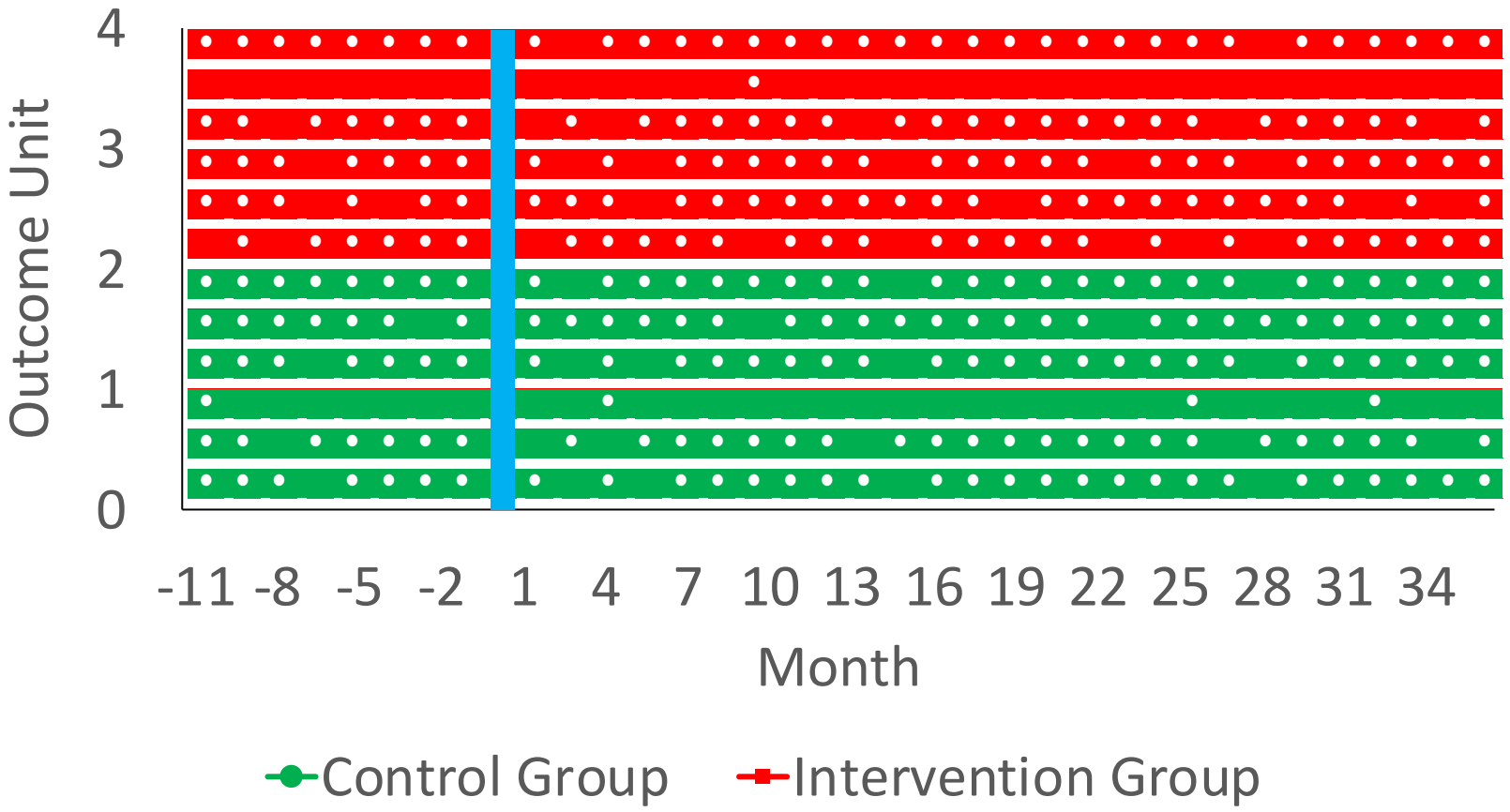
Hallberg, K., Cook, T. D., Steiner, P. M., Clark, M. H. *Prev Sci*. 2018. [1]Presumes study groups have not been randomized; [2]Presumes exogenous study group assignment

This talk will focus on:

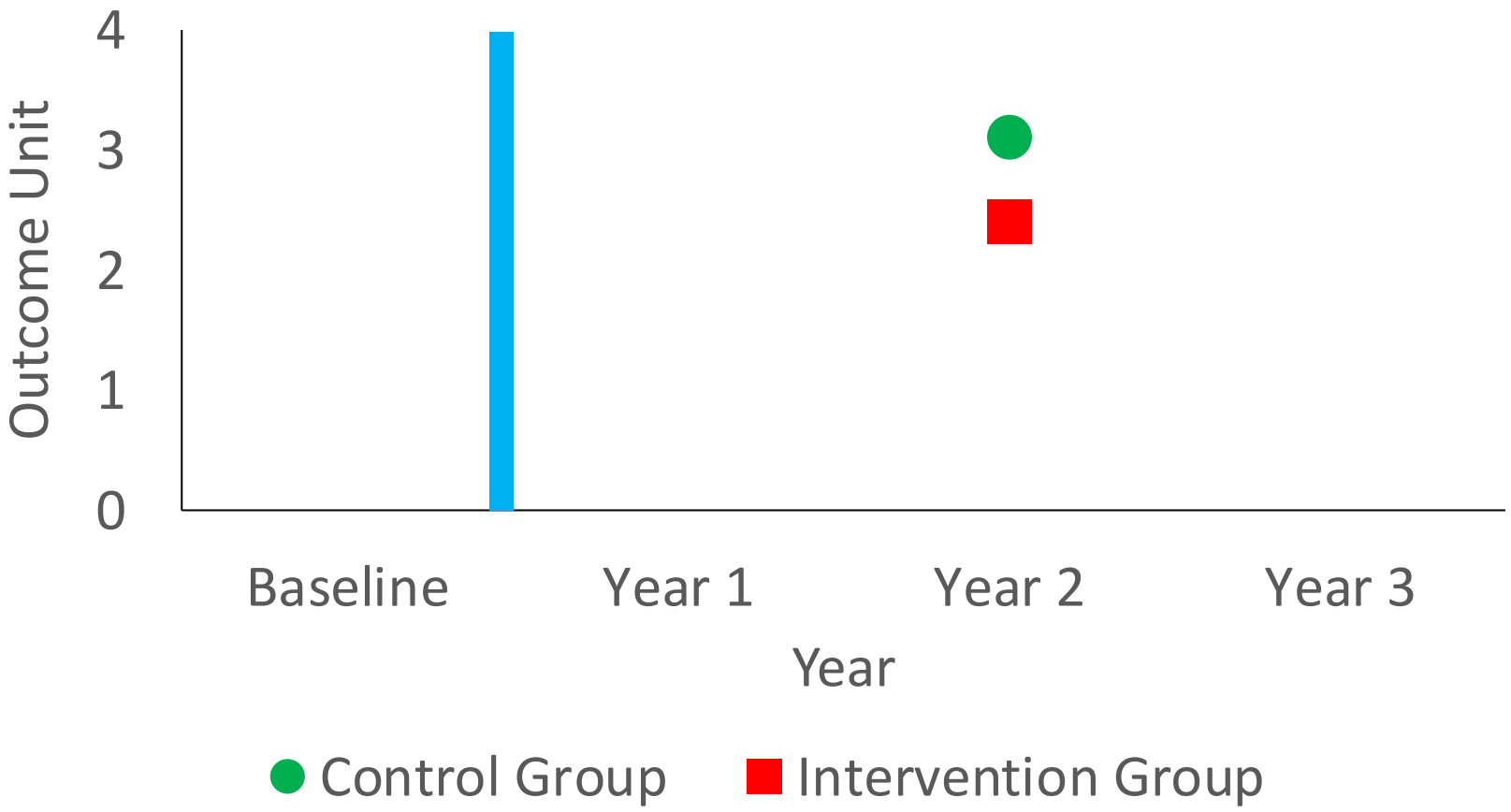


[1]Presumes study groups have not been randomized; [2]Presumes exogenous study group assignment

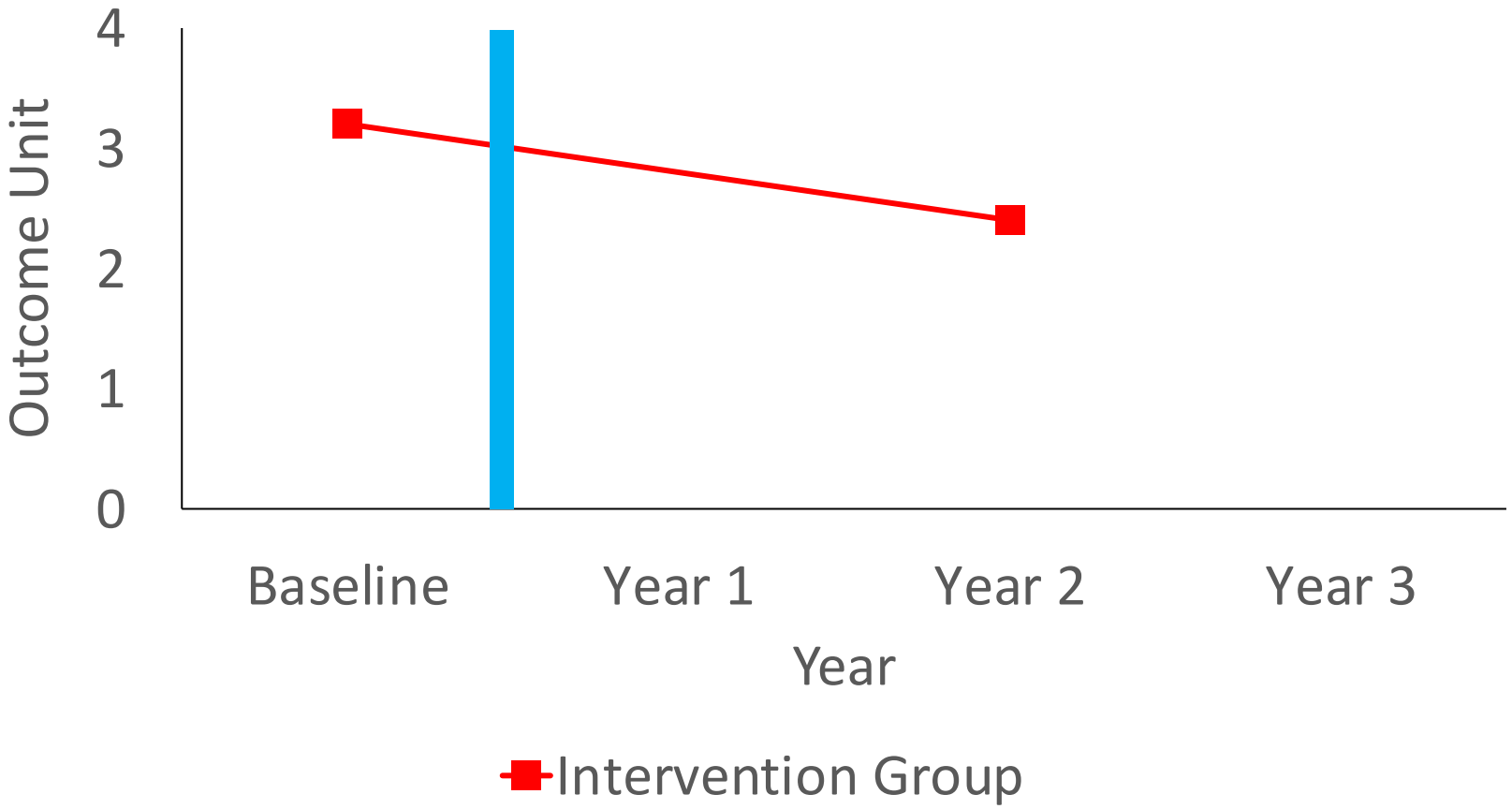
Example data



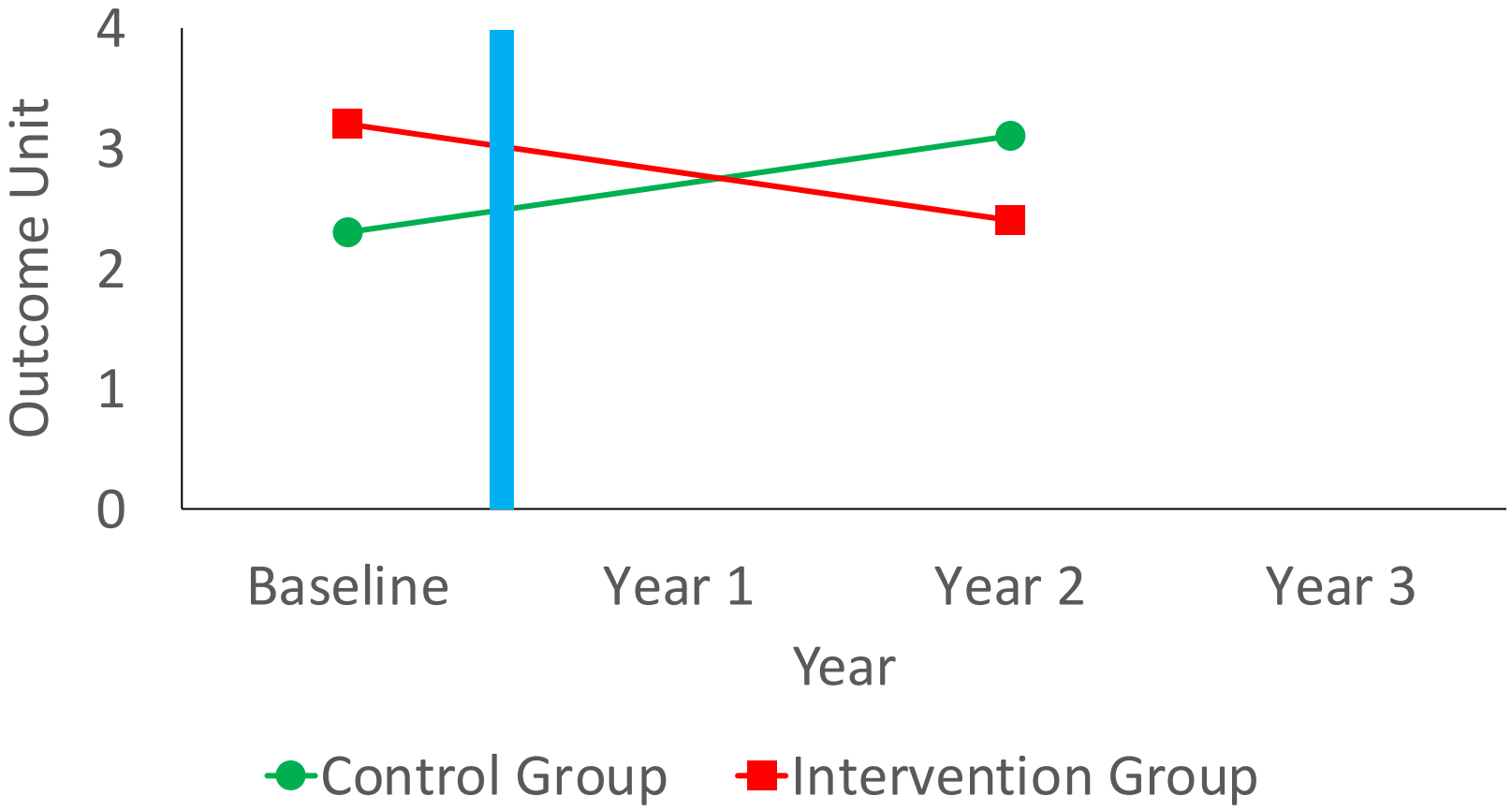
Cross-sectional



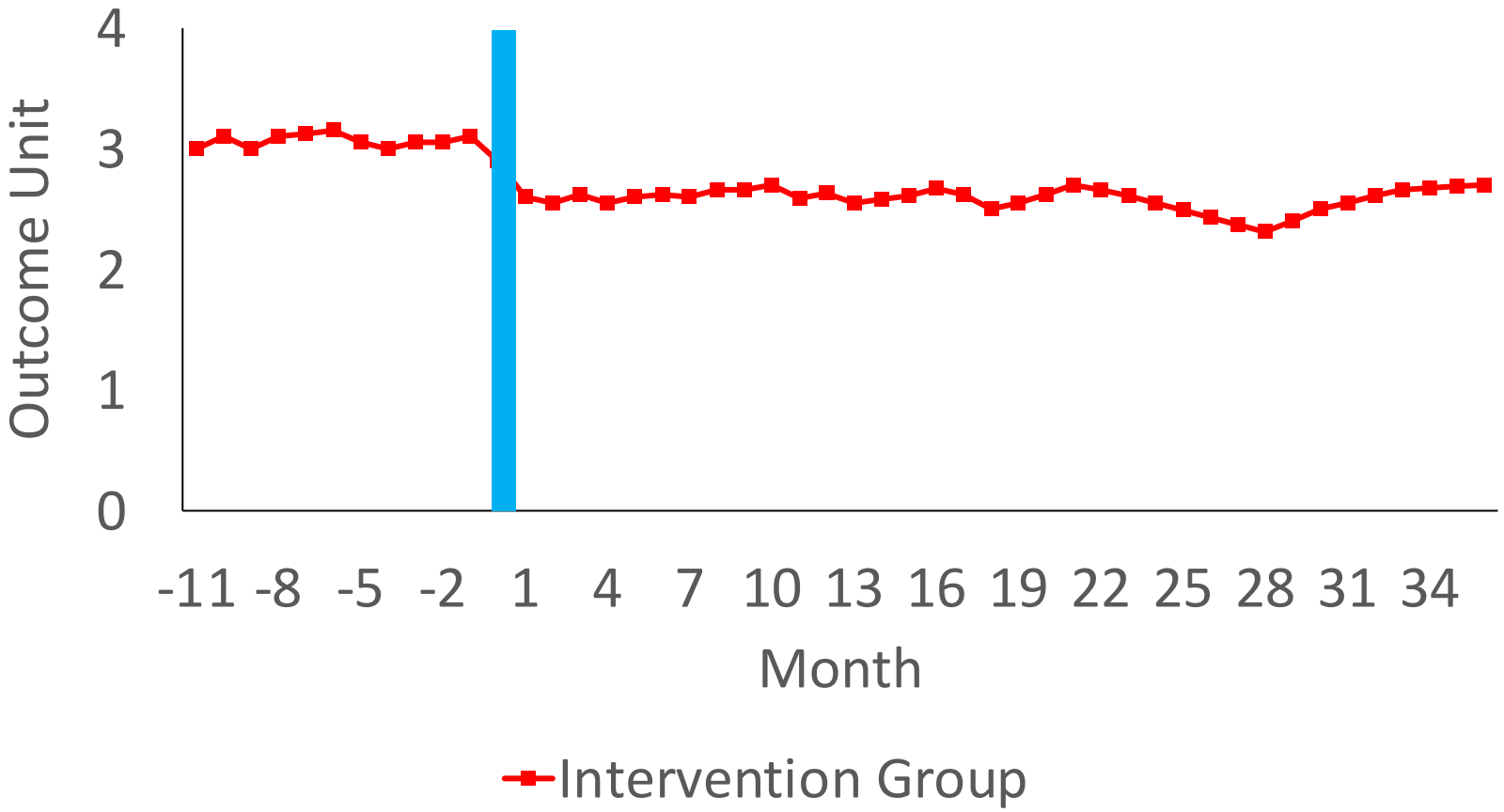
Before-after without control group



Before-after with control group



ITS without control group



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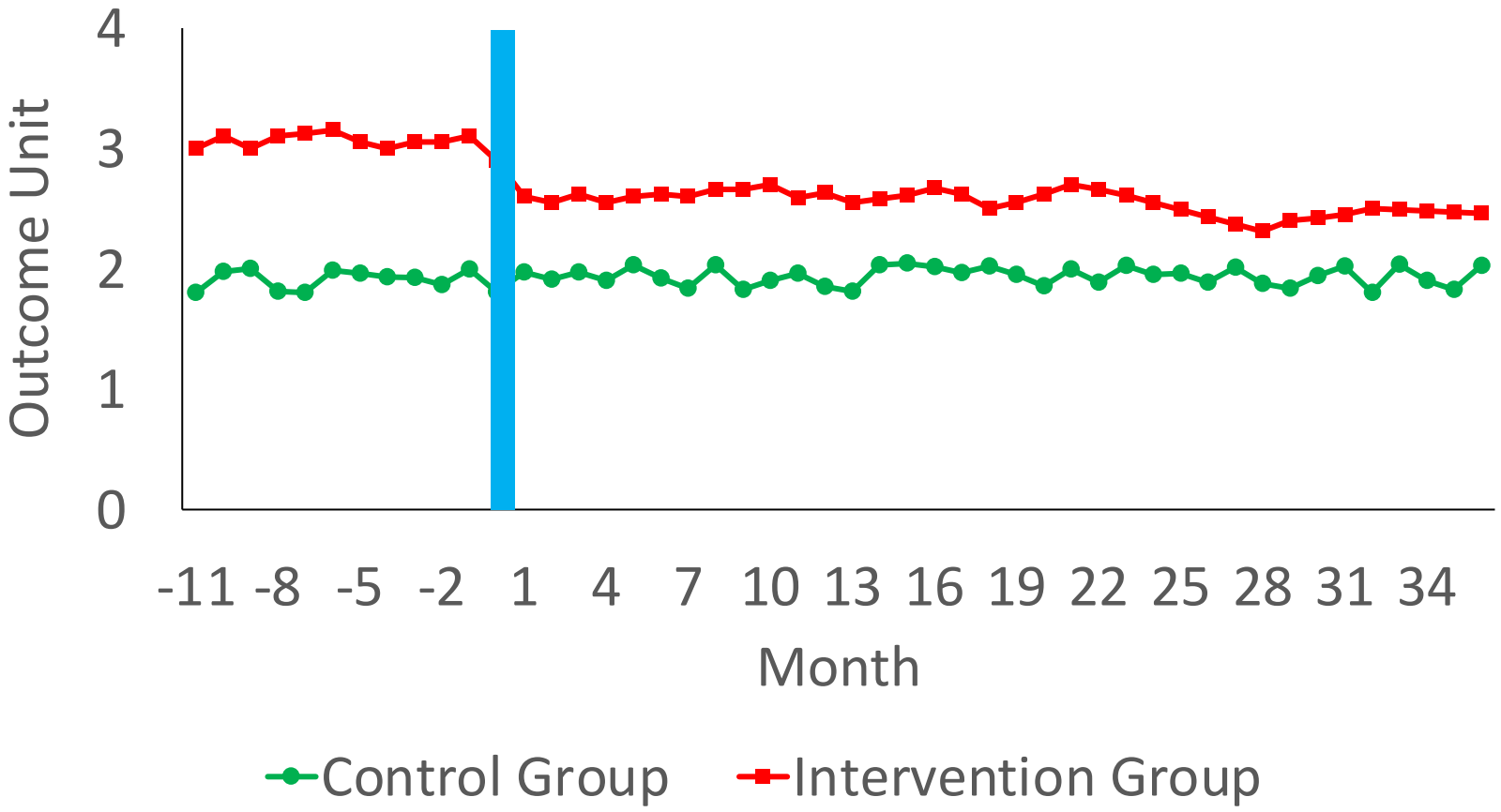
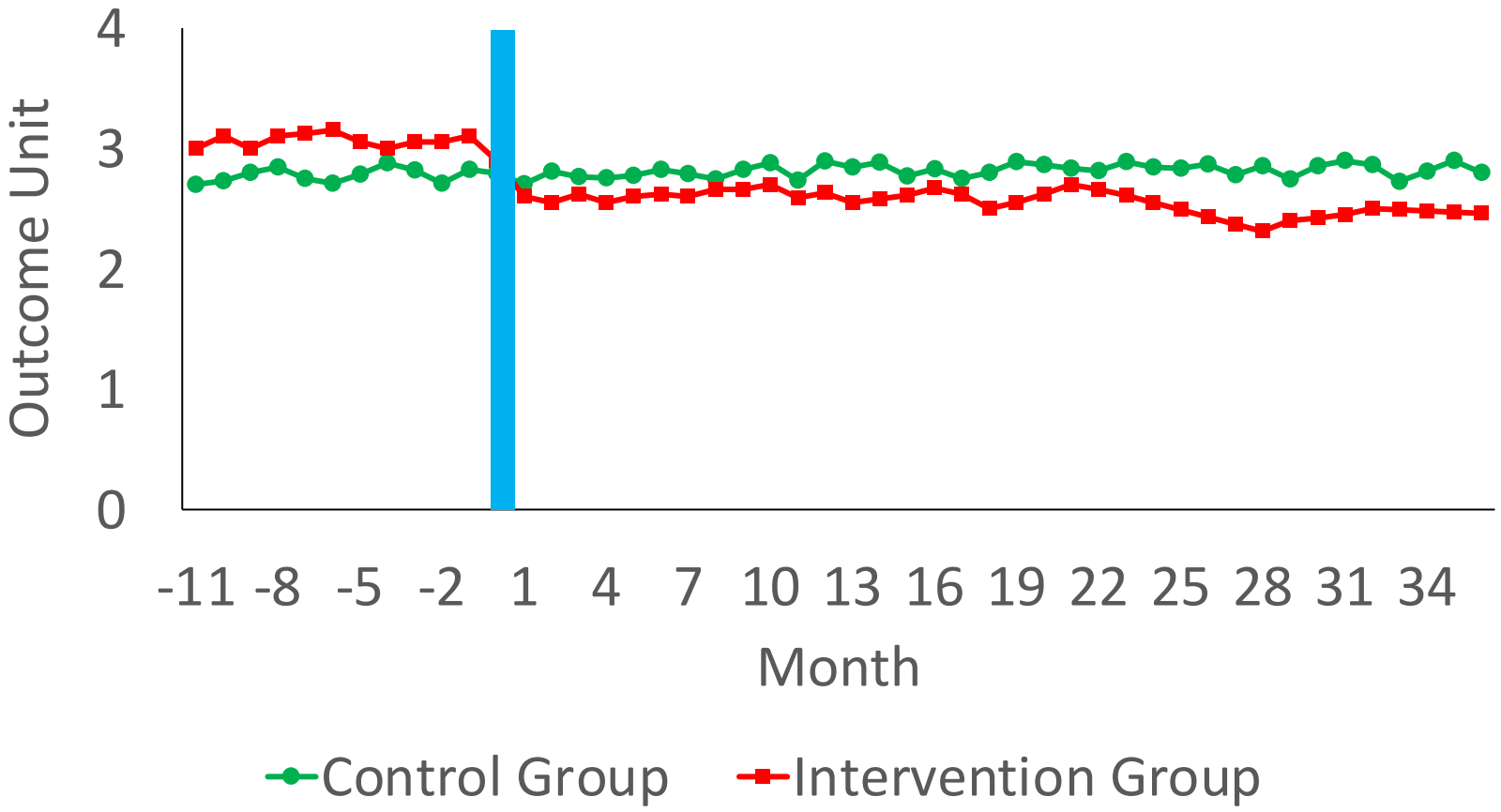
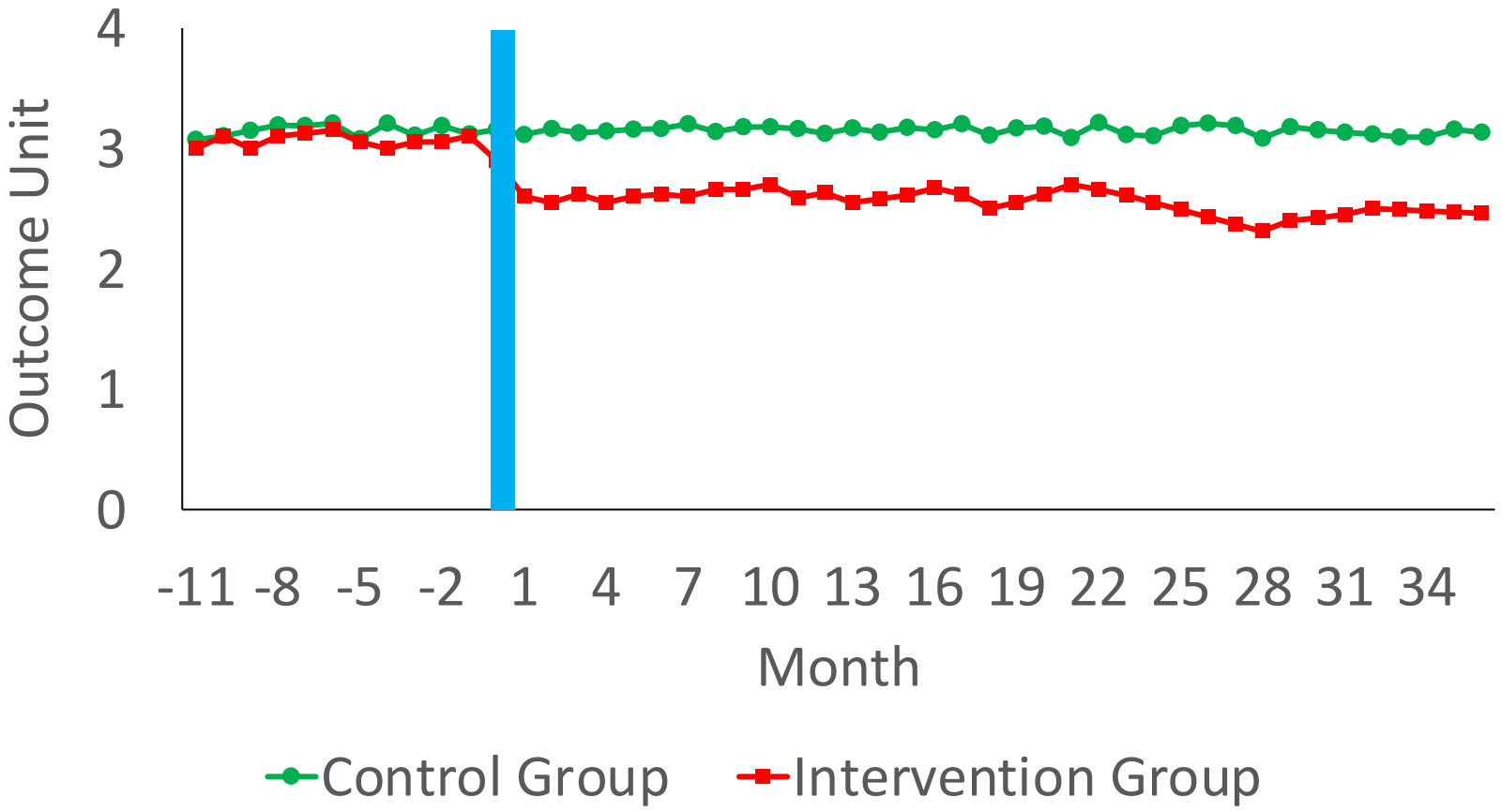


ITS with matched control group



ITS with control group matched on the baseline trend



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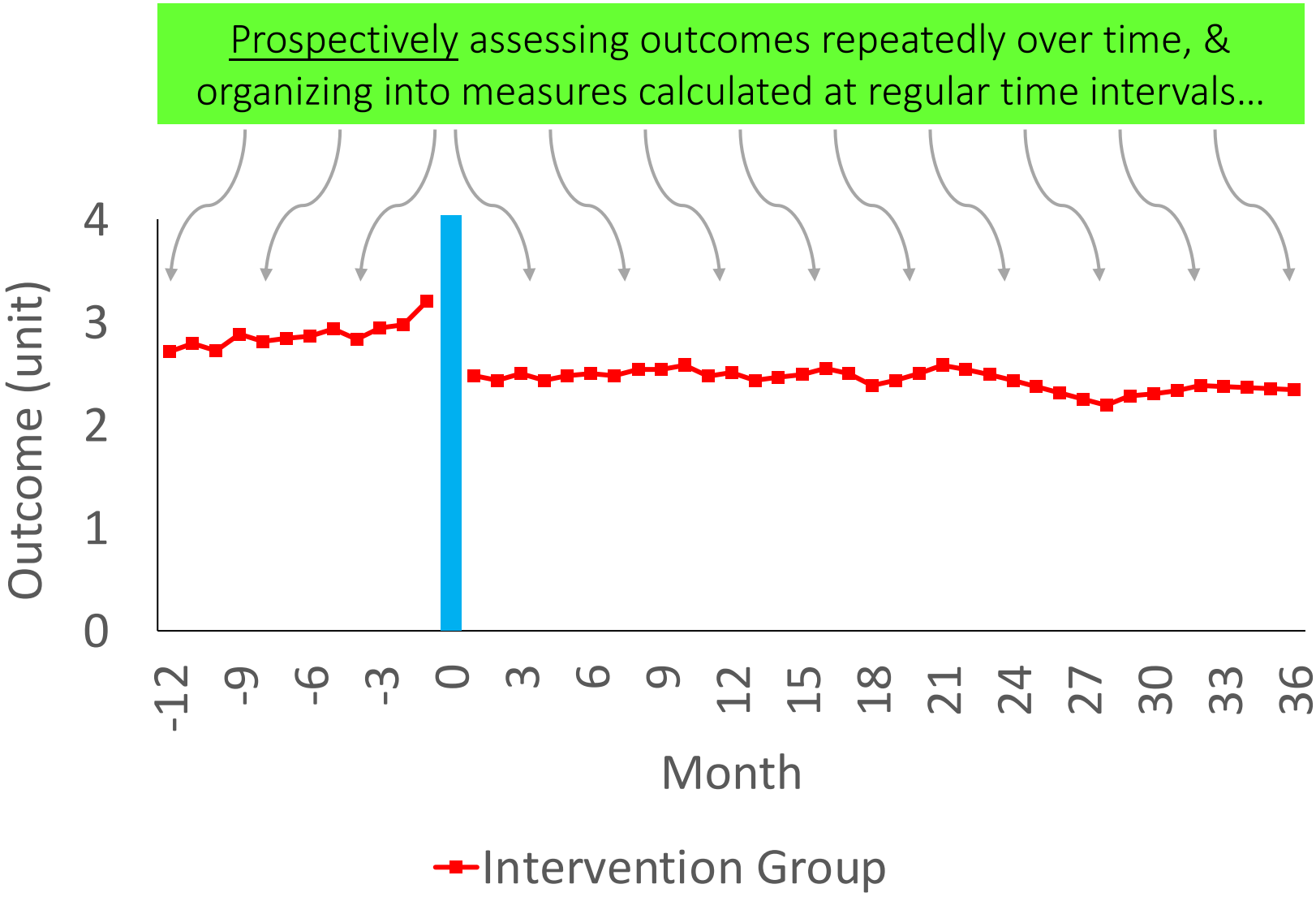
What is ITS study design?



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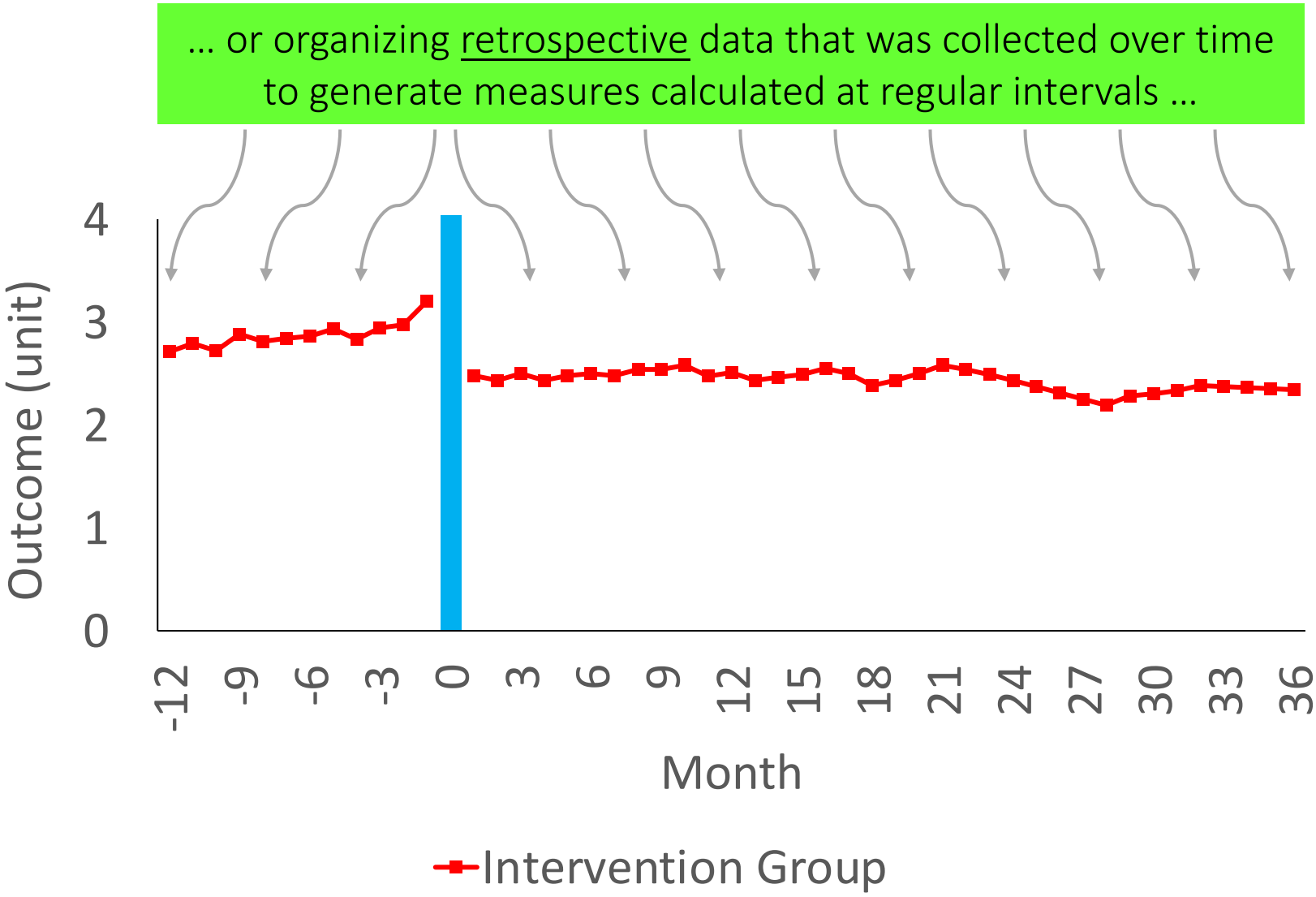
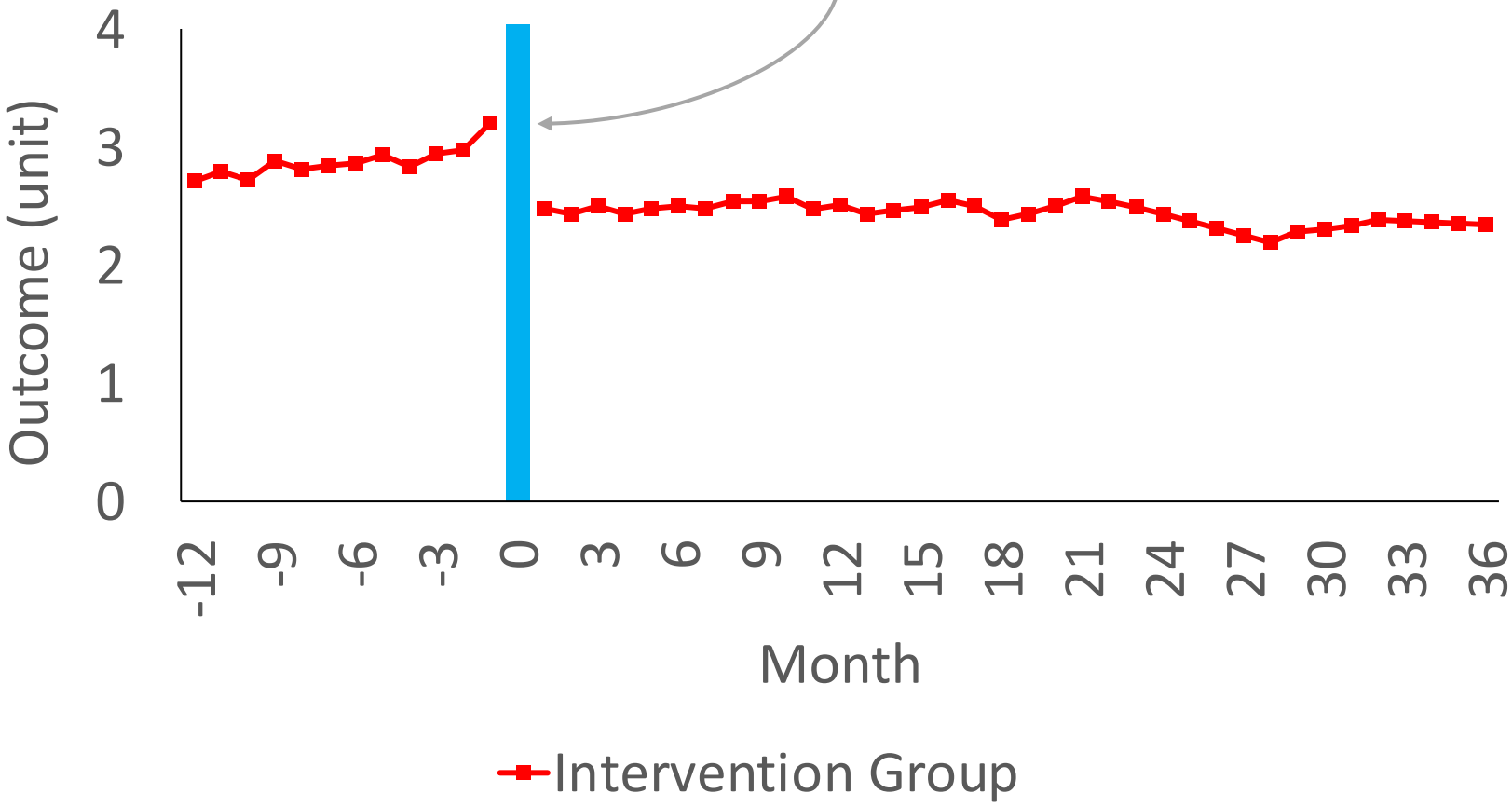


What is ITS study design?

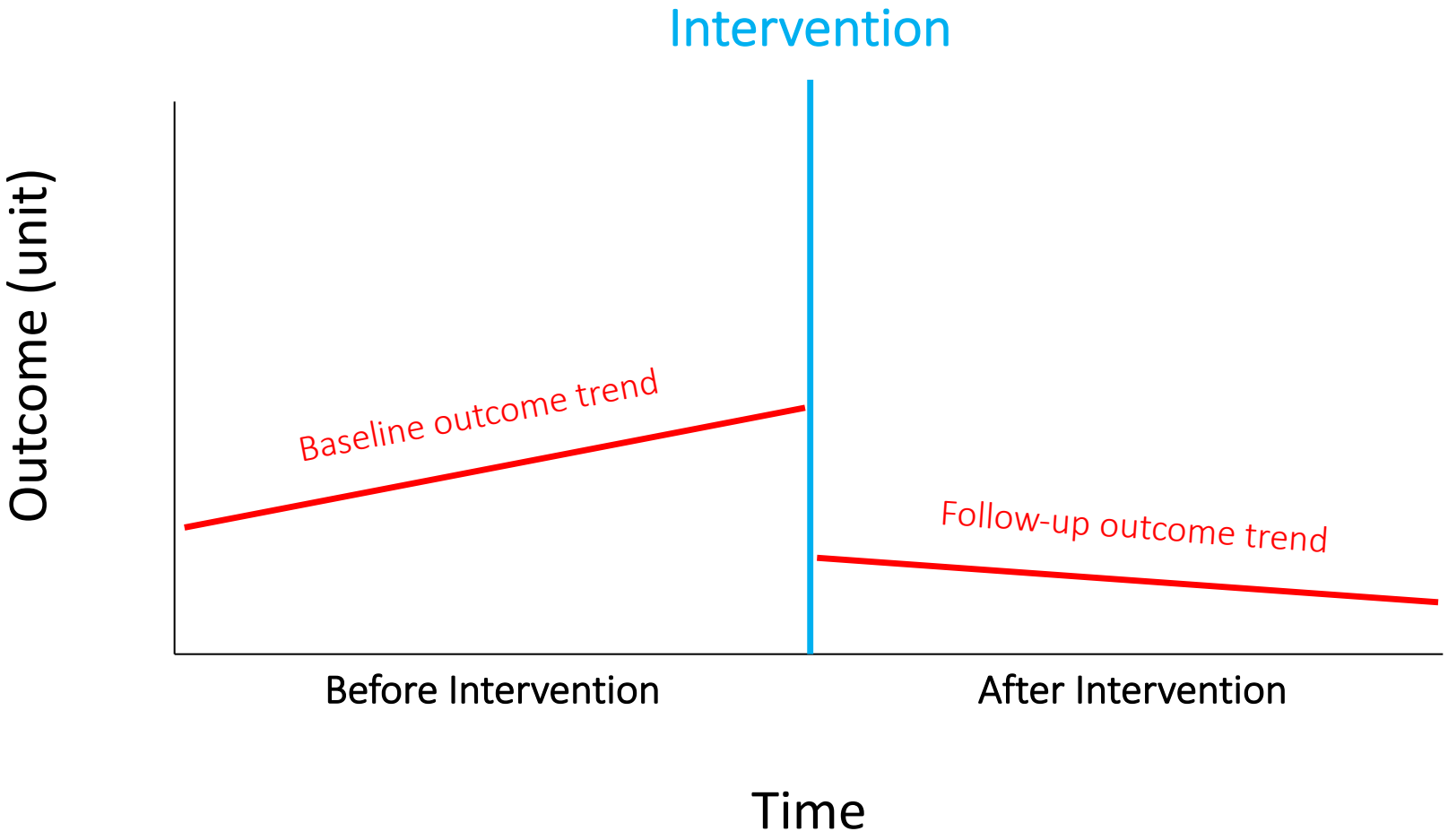
… before & after an “interruption” (intervention, new policy, event, or natural experiment) that is hypothesized to affect the outcome measure.



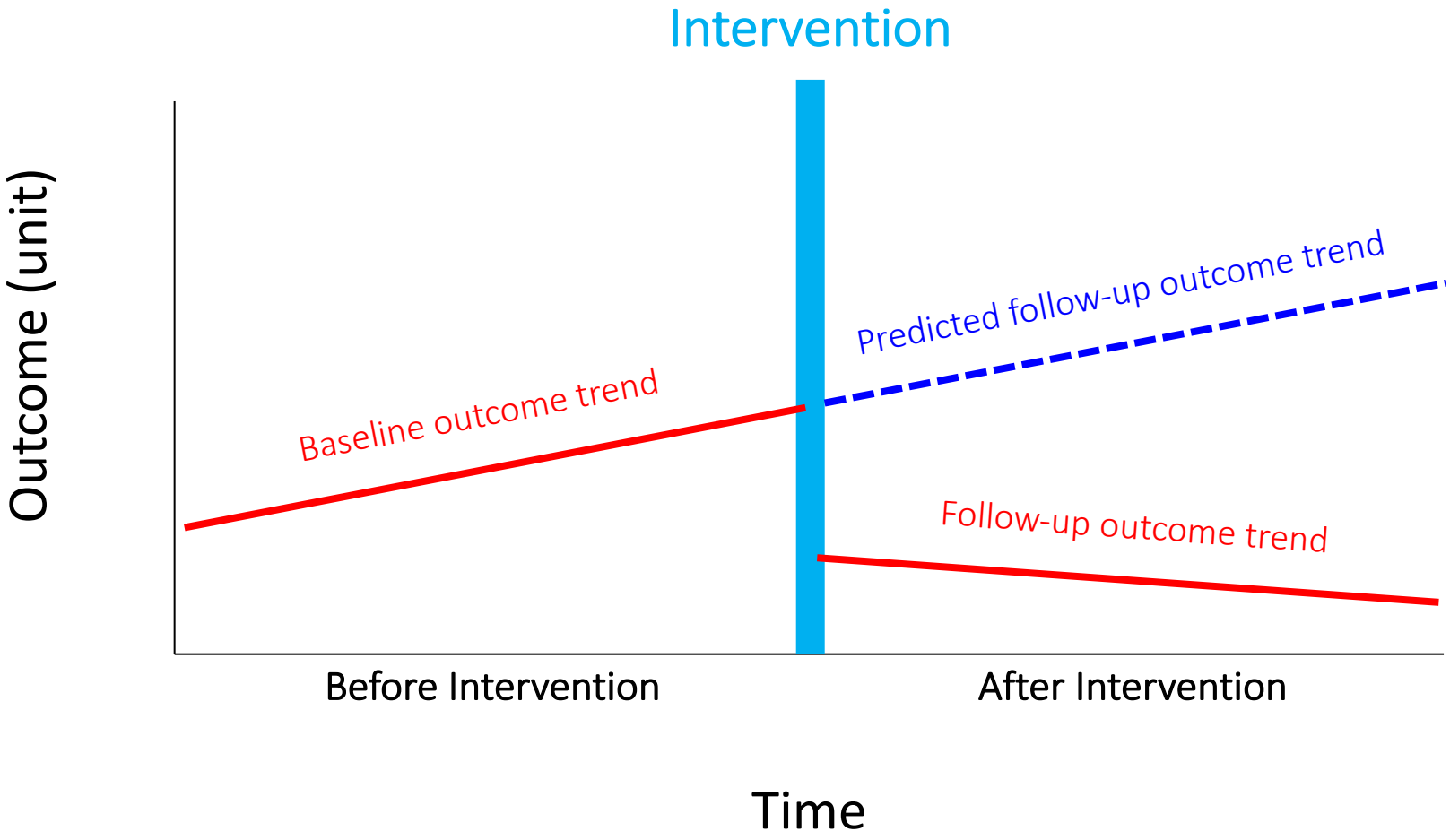
Clarifications: what ITS is not

- Not an analytic method, though it implies use of certain analytic approaches
  - Such as aggregate-level segmented autoregressive models or person-level segmented regression models
  - However, possible to display ITS plots, yet use controlled pre-post difference-in-differences *analyses*
- Not a method of allocating intervention & control groups
  - E.g., study groups used in ITS designs can be generated by:
    - Prospective randomization in a randomized controlled trial
    - An **"exogenous"** / mandated policy applied to a cohort that is retrospectively analyzed
    - Self-selection by patients/clinicians into a given intervention or treatment

Basic structure of ITS plots

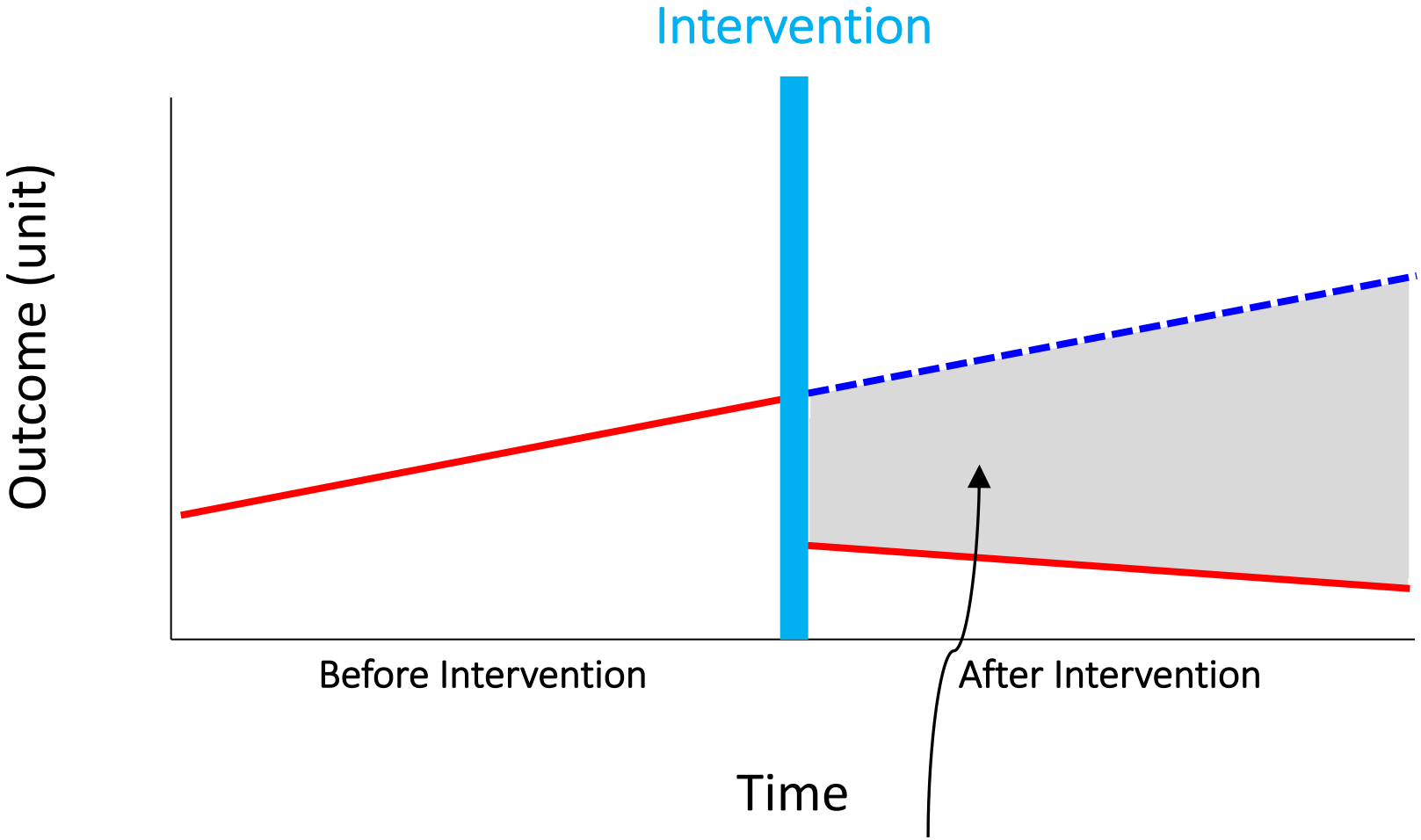


Basic assumption of ITS plots



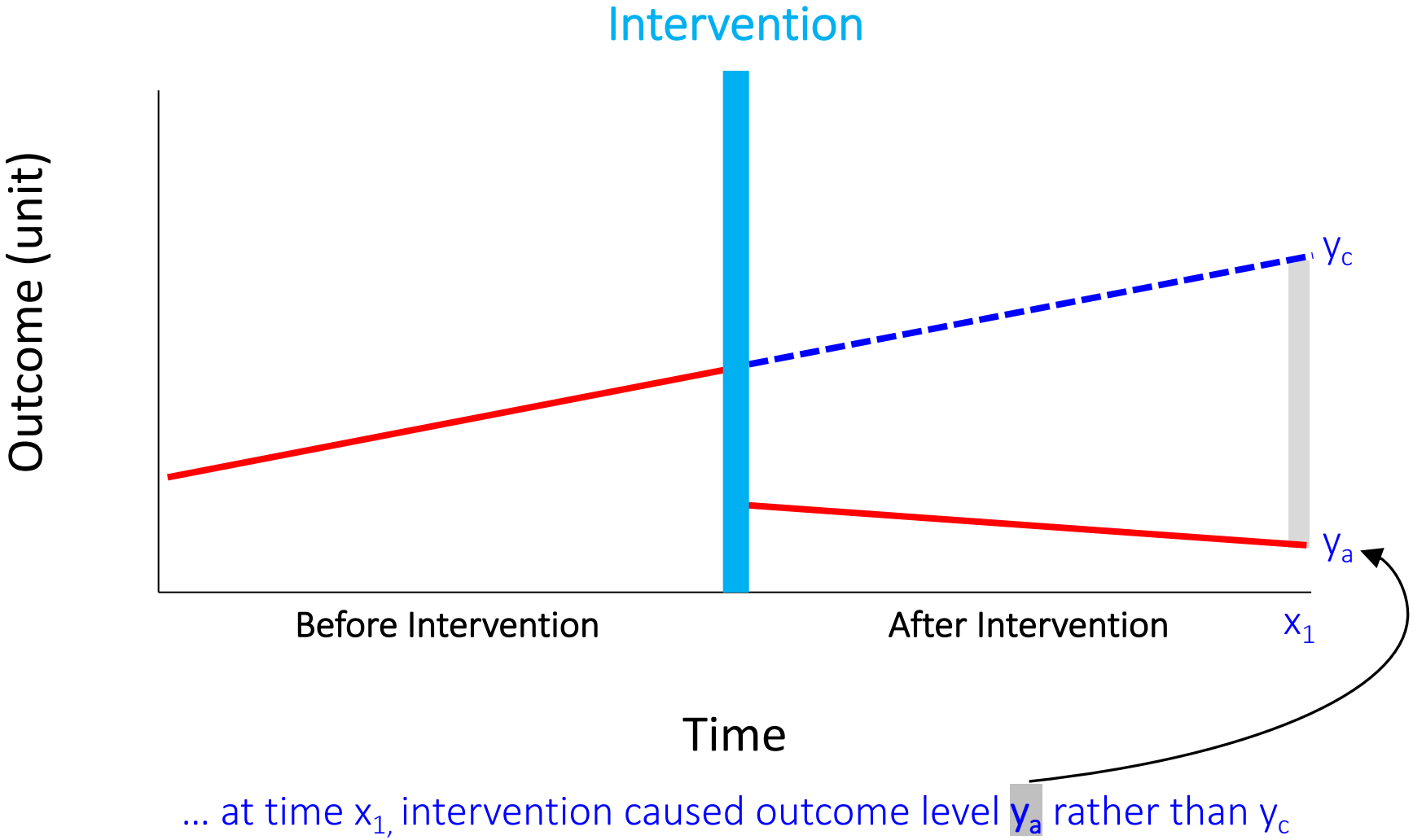
Primary assumption: The extension of the baseline trend correctly reflects what would have happened without intervention

Basic interpretation of ITS plots



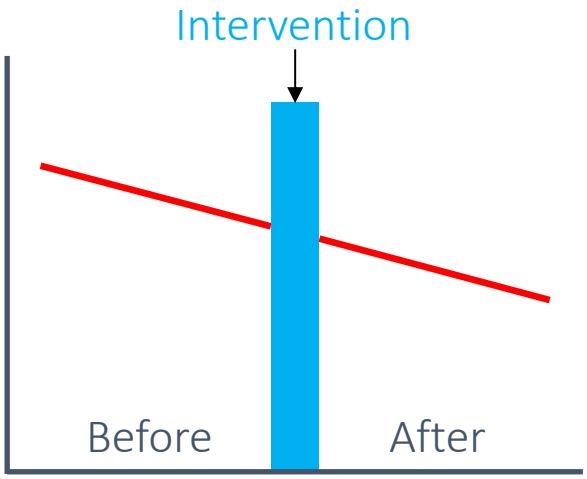
Interpretations: Intervention caused **this volume** of reduced outcome over the measured intervention period, or…

Basic interpretation of ITS plots

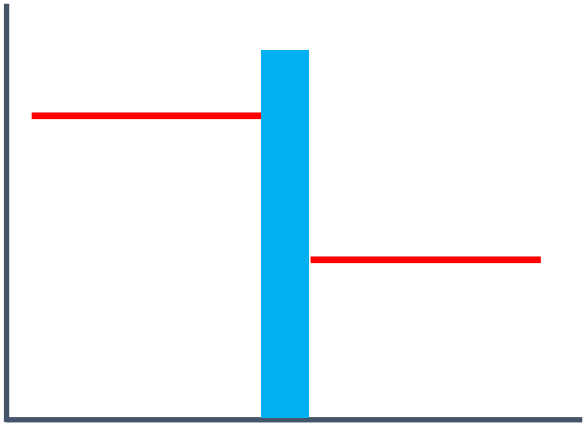


… at time x_1, intervention caused outcome level y_a rather than y_c

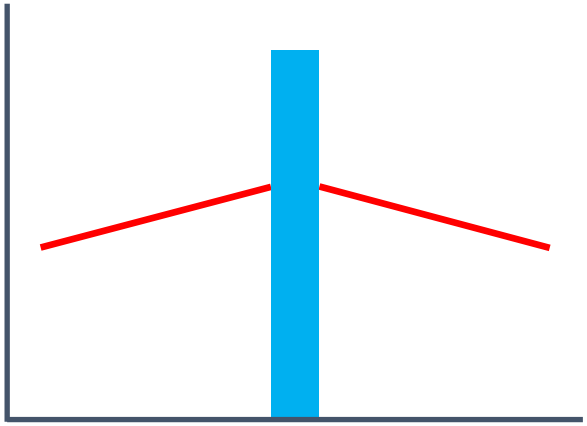
Possible intervention effects



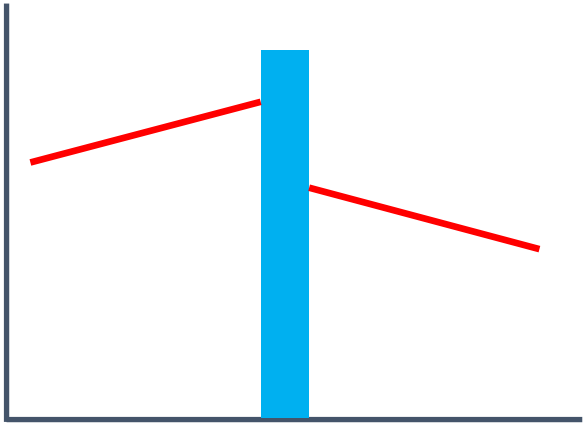
No change



Change in level only



Change in trend only



Change in level & trend

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Benefits of ITS: why use vs. other designs?

- Rigor: controlled ITS highest on study design hierarchy (among feasible retrospective approaches)
  - Controlled ITS can be "quasi-experimental;" i.e. a viable approach for *causal inference*
  - Well-constructed controlled ITS designs yield similar effect estimates to randomized controlled trials
- Communication: ITS plots can quickly and clearly communicate study results
  - Can often be understood by both experts and non-experts
- Cost: less expensive & potentially more generalizable than RCTs

(1) http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/Study_design_guide2013.pdf (2) St. Clair T *et al*. *Am J Eval*. 2014. (3) Schneeweiss *et al*. *BMJ*. 2004. (4) Fretheim *et al.* *J Clin Epi*. 2015. (5) Somers M *et al. MDRC.* 2013. (6) Ferraro PJ, & Miranda JJ. *Resource Energy Econ*. 2013.

Benefits of ITS: why use vs. other designs?

- "Transparency:" simply *displaying* data in ITS plots can be highly revealing regarding:
  - Data issues/errors
    - Unexpected loss / gain of denominator population
    - Outlier measurements: their influence & temporal occurrence
    - Changes in how / whether an outcome was measured
  - Secular trends & seasonality
  - Selection effects, especially if differing between intervention & control groups
  - Regression to the mean
  - Co-occurring interventions
- Relatively simple analytic approaches

Limitations of ITS

- Rigor: compared to randomized experiments, retrospective ITS has suboptimal ability to prove causation
  - ITS not guarantee of rigor
  - Rigor depends heavily study group assignment: (self- < exogenous- < randomized-selection)
- Complexity:
  - Important details can hide "under the hood"
  - Can be complex to implement and check
  - Effect estimates can be unintuitive
- Threats to validity & reliability (below): especially for ITS without controls

(1) http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/Study_design_guide2013.pdf (2) St. Clair T *et al*. *Am J Eval*. 2014. (3) Schneeweiss *et al*. *BMJ*. 2004. (4) Fretheim *et al.* *J Clin Epi*. 2015. (5) Somers M *et al. MDRC.* 2013. (6) Ferraro PJ, & Miranda JJ. *Resource Energy Econ*. 2013.

Threats to validity of ITS designs

1. *Selection: pre-intervention factors affect study group assignment (e.g., baby due in 7 months)
2. History / co-intervention: another event occurred around time of intervention that affects outcomes
3. Pre-to-post regression to the mean: study group assignment associated with pre-intervention outcome values above/below population mean
4. Maturation, secular trends, non-linear trends:
   - Natural/pre-existing development of subjects explains effect
   - Floor/ceiling effects, or near boundary (e.g., 0% or 100%)
5. Instrumentation: change in measurement "device"

Shadish WR, Cook TD, Campbell DT. Experimental & quasi-experimental designs for generalized causal inference. 2001.

Important notes

- ITS with control group design:
  - If selection bias avoided, other threats to validity should generally only bias effect estimates if they are *differential* between the intervention & control group
- ITS without control group
  - Greater concern that above threats to validity might be misinterpreted as causal effects

Threats to reliability of ITS estimates

1. "Confines" of study setting / environment
   - Too few time points before/after intervention
   - Unstable data / low frequency events (high point-to-point variability)
   - Changing denominators or differential dropout (without adjustment for characteristics influencing trends)
2. Data quality or characteristics
   - Extreme outlier data points
   - Missing data, data entry errors, incorrectly labelled variables, poor accuracy/precision measures, incorrectly merged data etc
3. Chance effects at beginning/end of segment
   - Estimates sensitive to points near beginning/end of segment

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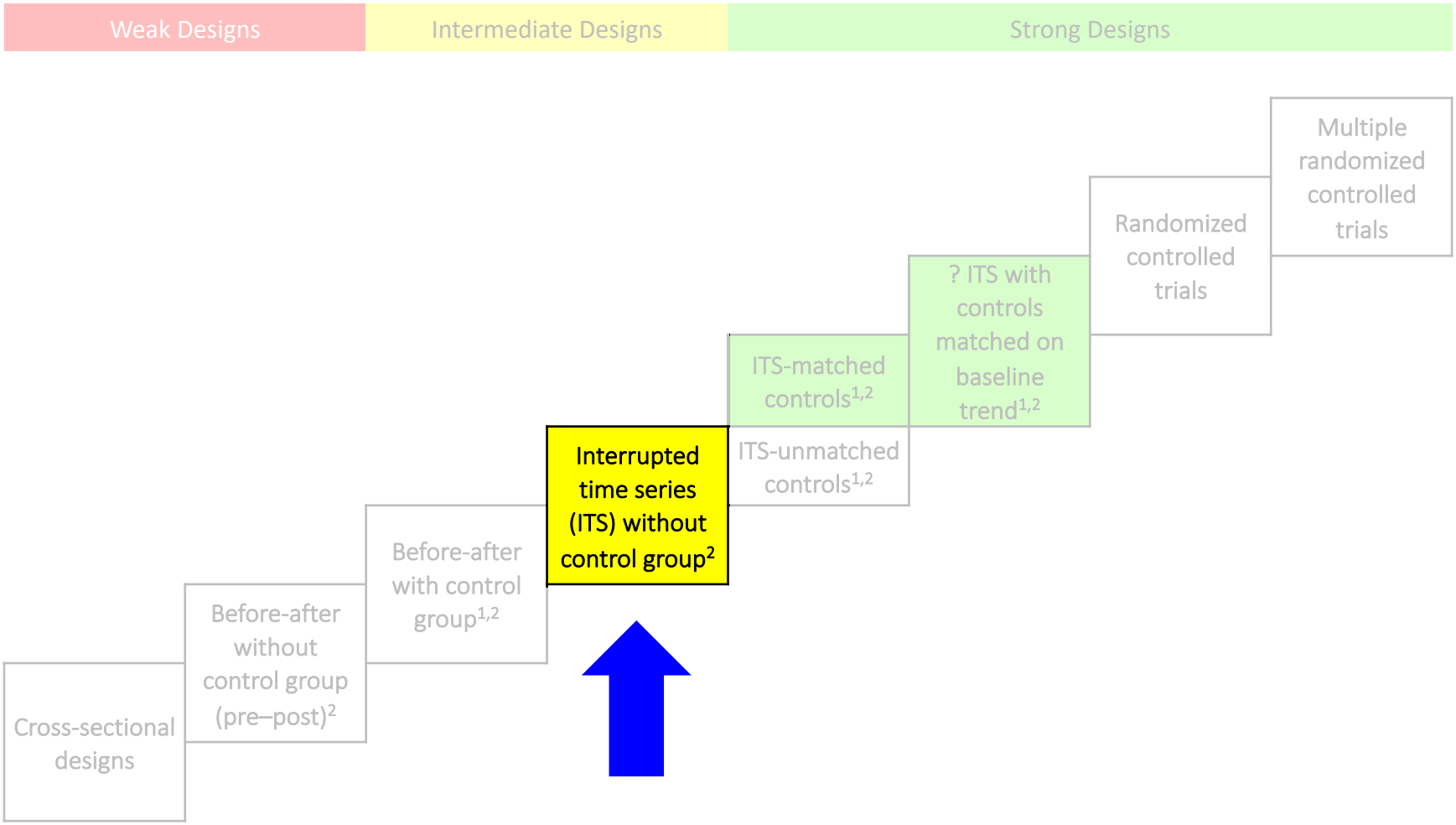
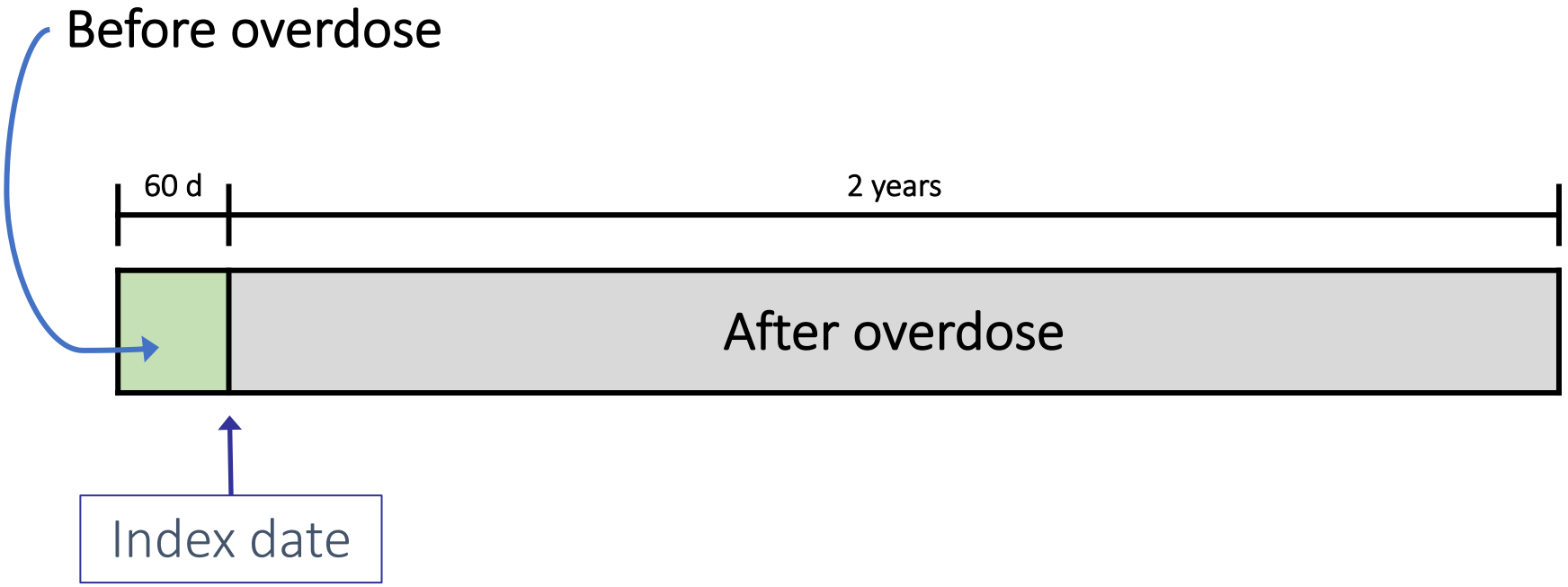
ITS without control group



ITS without control group: why use instead of ITS with control group?

- No control group needed
- No viable control group
  - National policy that affects everyone
  - Data not available
  - (But sometimes can be clever and find a control group…)

ITS without control group: overdose / opioids example



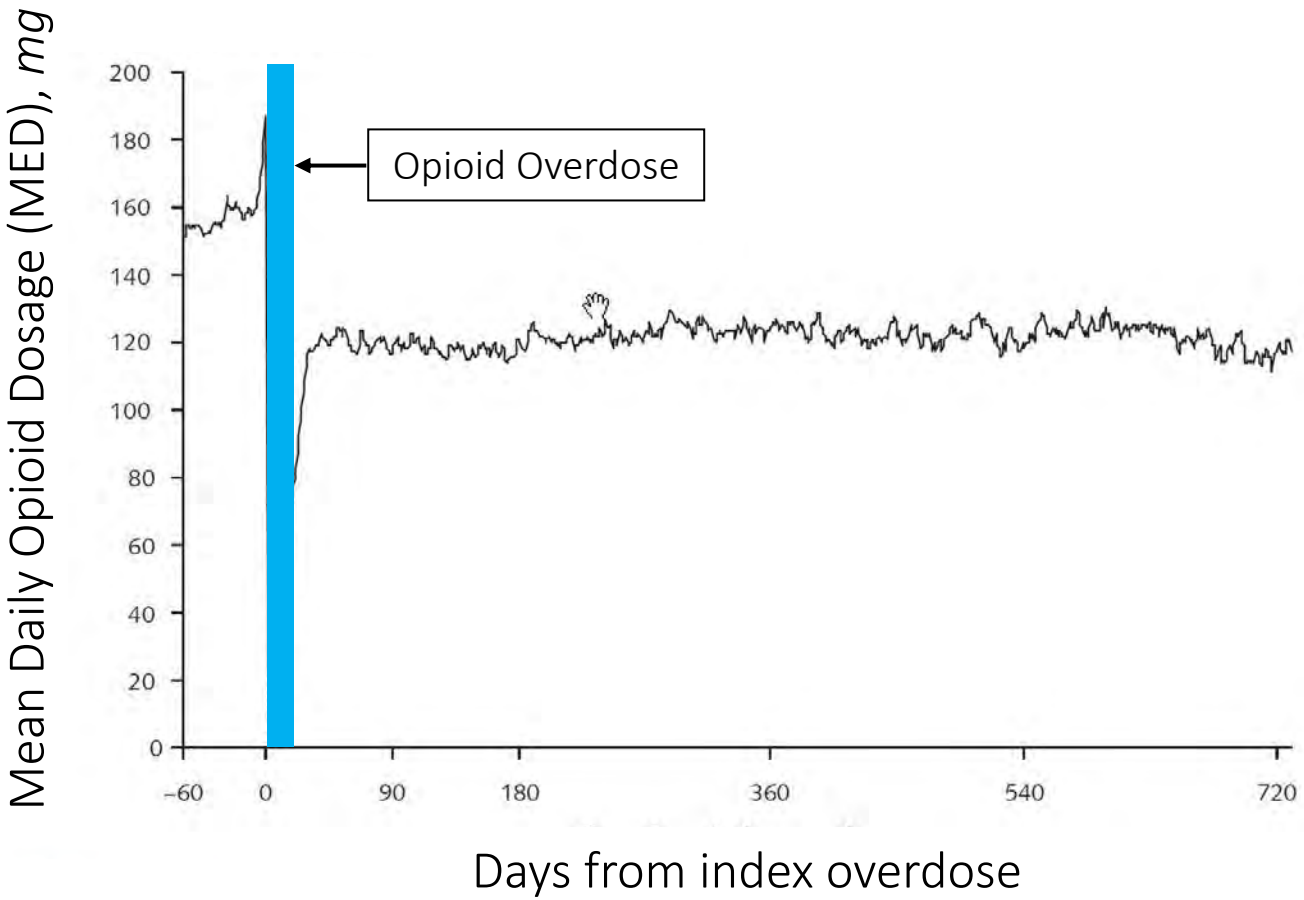
Larochelle M *et al. Annals Int Med*. 2015

Opioid overdose and dispensing: study design considerations

- Drug that nearly kills a patient should most likely be discontinued
- Hypothesis
  - Opioids are so addictive that prescriptions will continue even after an overdose
- If high rate of dispensing after overdose, less need for control group
  - Also, challenging to determine appropriate control group

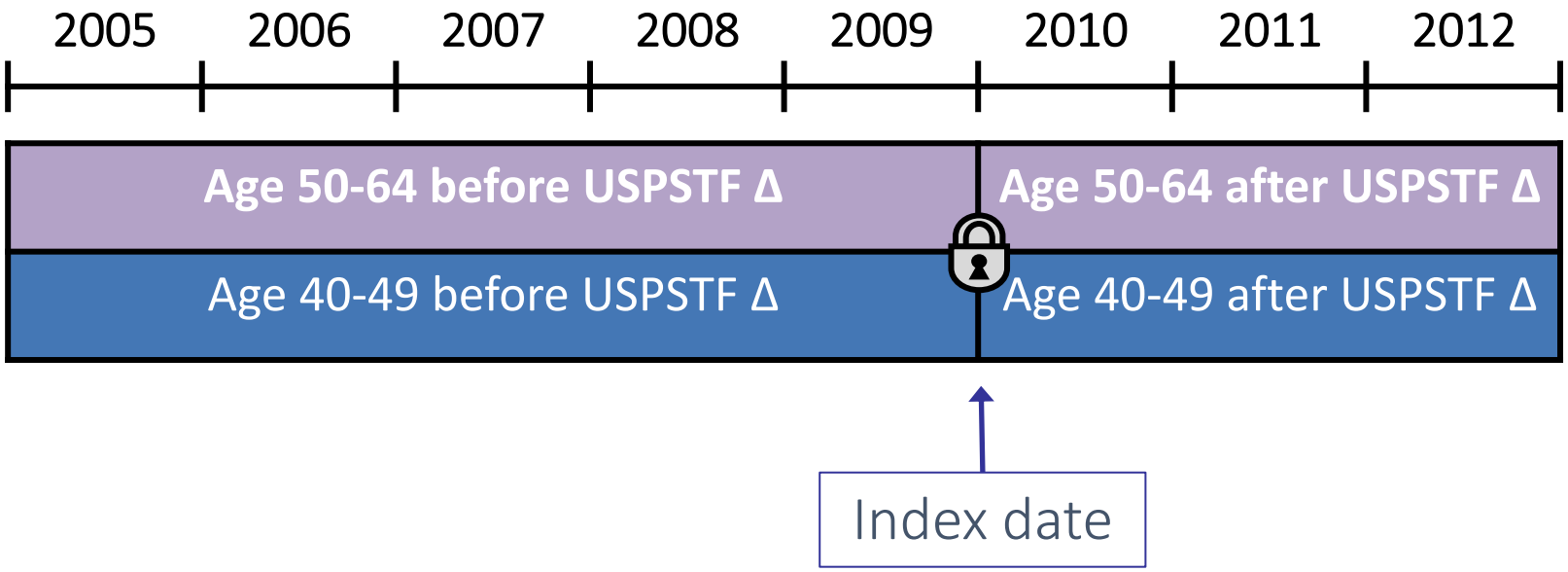
Larochelle M *et al. Annals Int Med*. 2015

Daily opioid dosage before-after index opioid overdose



Larochelle M *et al. Annals Int Med*. 2015

ITS without control group: USPSTF / breast cancer example



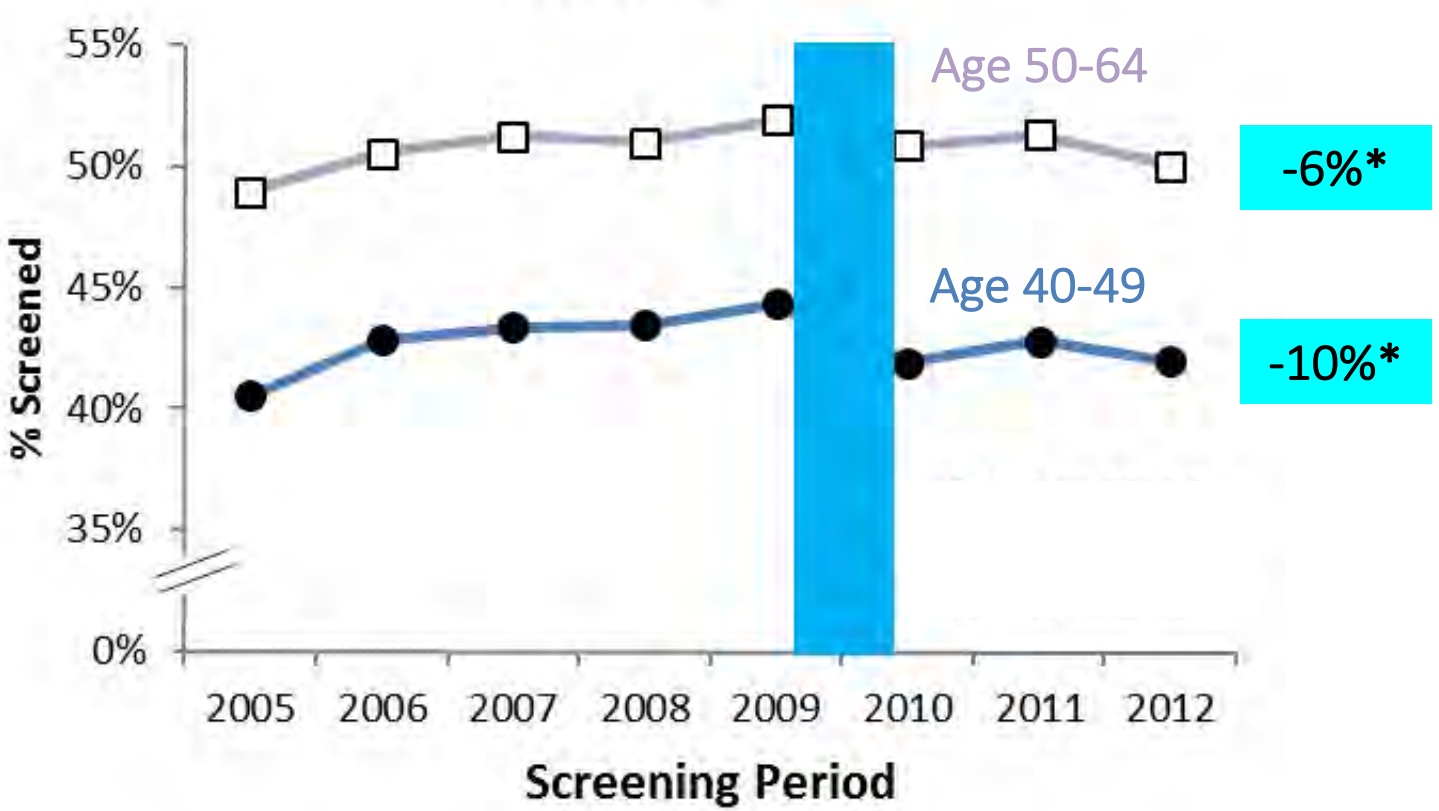
Wharam JF *et al. J Clin Oncol*. 2015. *p<0.05

USPSTF and mammography: study design considerations

- 2009 guidelines change:
  - Women 50-74: every 2 years
  - Women 40-49: “personalized” decision
- Applied to all of U.S.
  - No viable control group
  - ~ “Non-equivalent controls:” women 50-64 expected to be affected less than women 40-49
- Annual or biennial rate most intuitive
  - Having sufficient baseline and follow-up points challenging

Wharam JF *et al. J Clin Oncol*. 2015. *p<0.05

Mammography before-after 2009 USPSTF change



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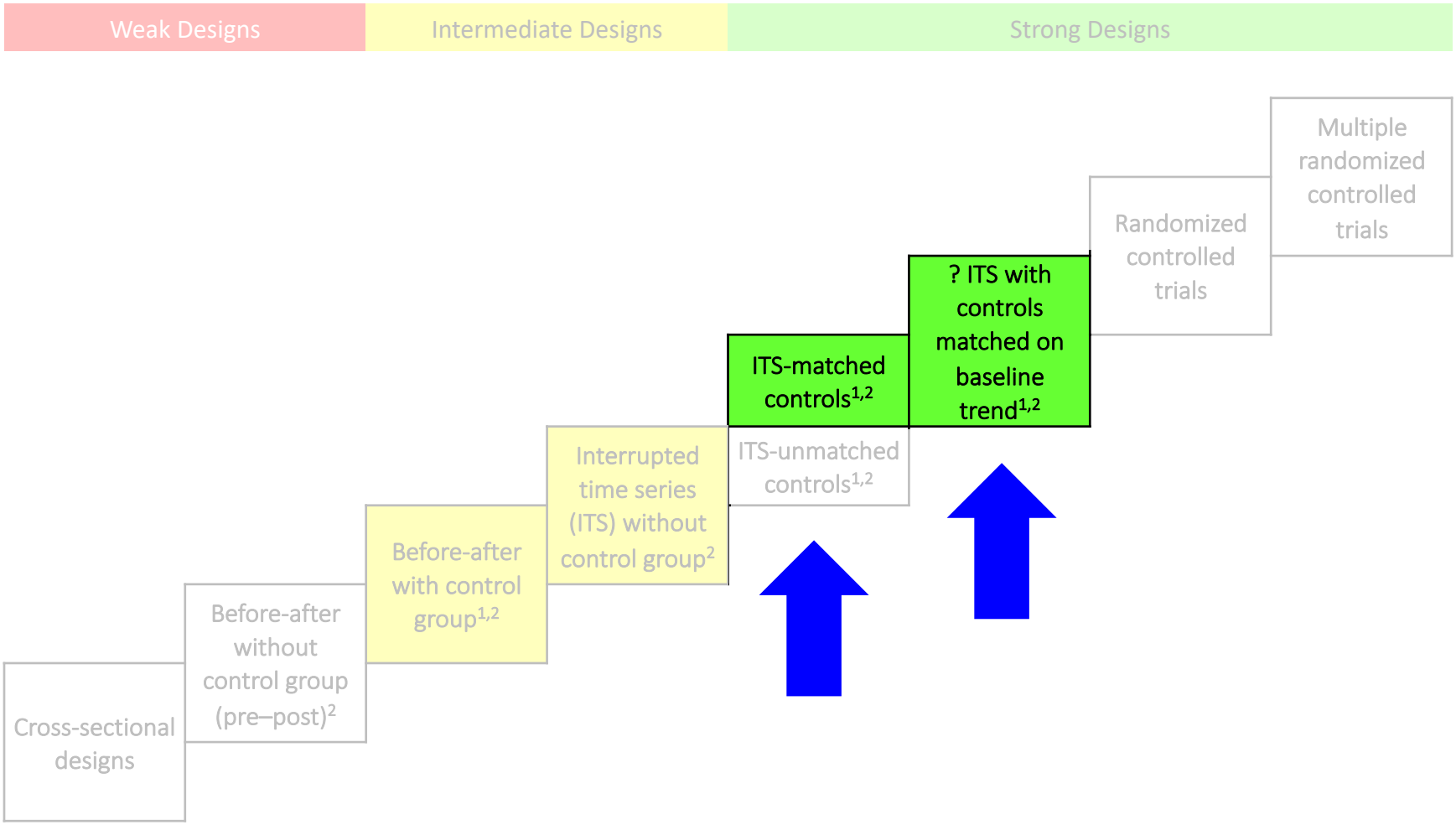
ITS with matched control group

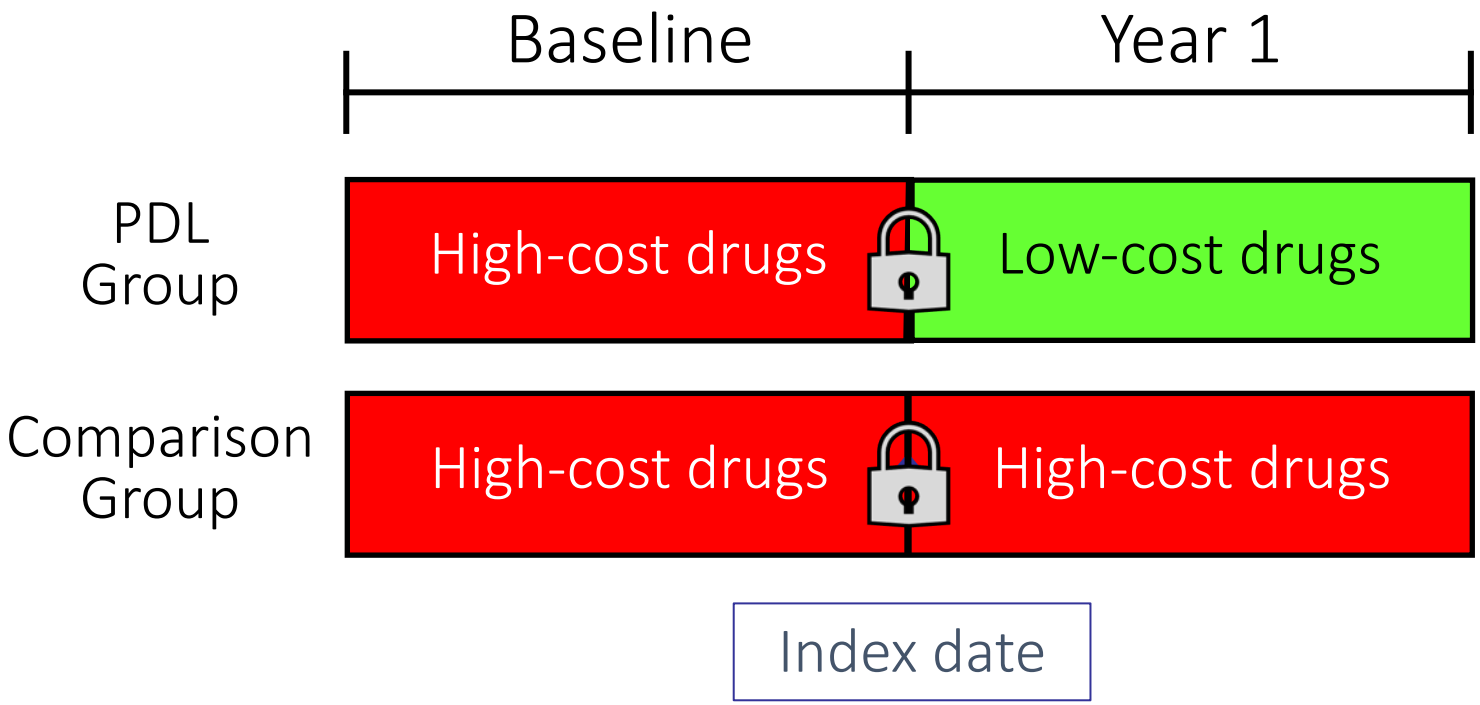


ITS with matched control group: basics

- Find similar, contemporaneous group not experiencing intervention of interest
- Propensity score and coarsened exact matching: common approaches
  - Both balance matched baseline characteristics of the intervention and control groups
  - We use Stata *kmatch* that combines benefits of both approaches
- Hope: increased similarity of observed characteristics will increase similarity of unobserved
  - Controversial, but in ITS setting might be true

(1) Rosenbaum P.R., Rubin D.B. *Biometrika*. 1983. (2) Iacus SM, King G, Porro, G. *Journal of the American Statistical Association*. 2011

ITS with matched control group: Low-cost drugs / diabetes example

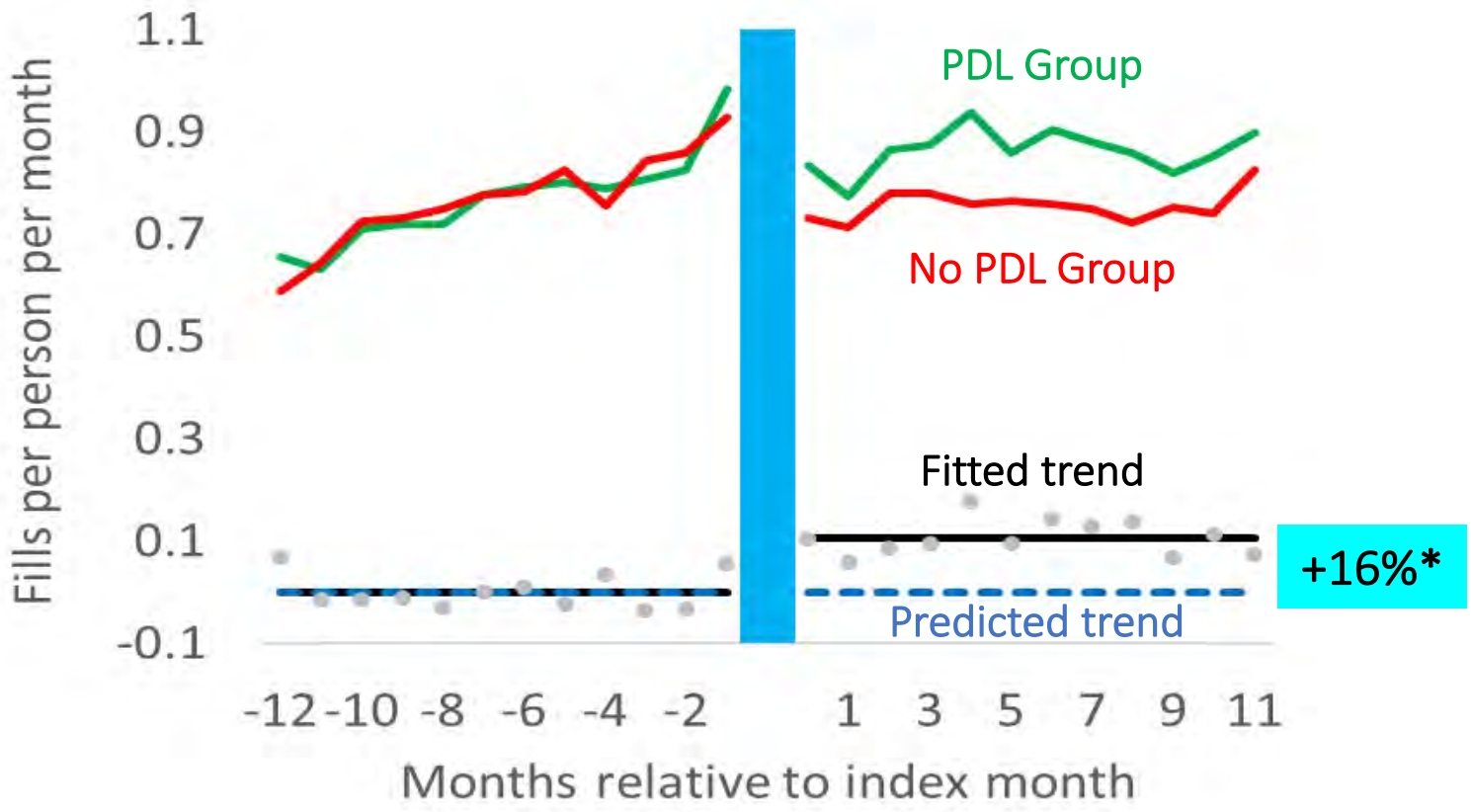


Low-cost drugs and diabetes: study design considerations

- Some employers purchase an insurance benefit that makes preventive meds have low out-of-pocket costs for enrollees (preventive drug lists, PDLs)
- Initial study found increased med use; but crucial to assess effect on health outcomes
- Wide range of baseline high deductible levels and exact baseline deductible unknown
- Employer selection
- Acute, preventable diabetes complication outcome rare but maybe common enough to study with ITS

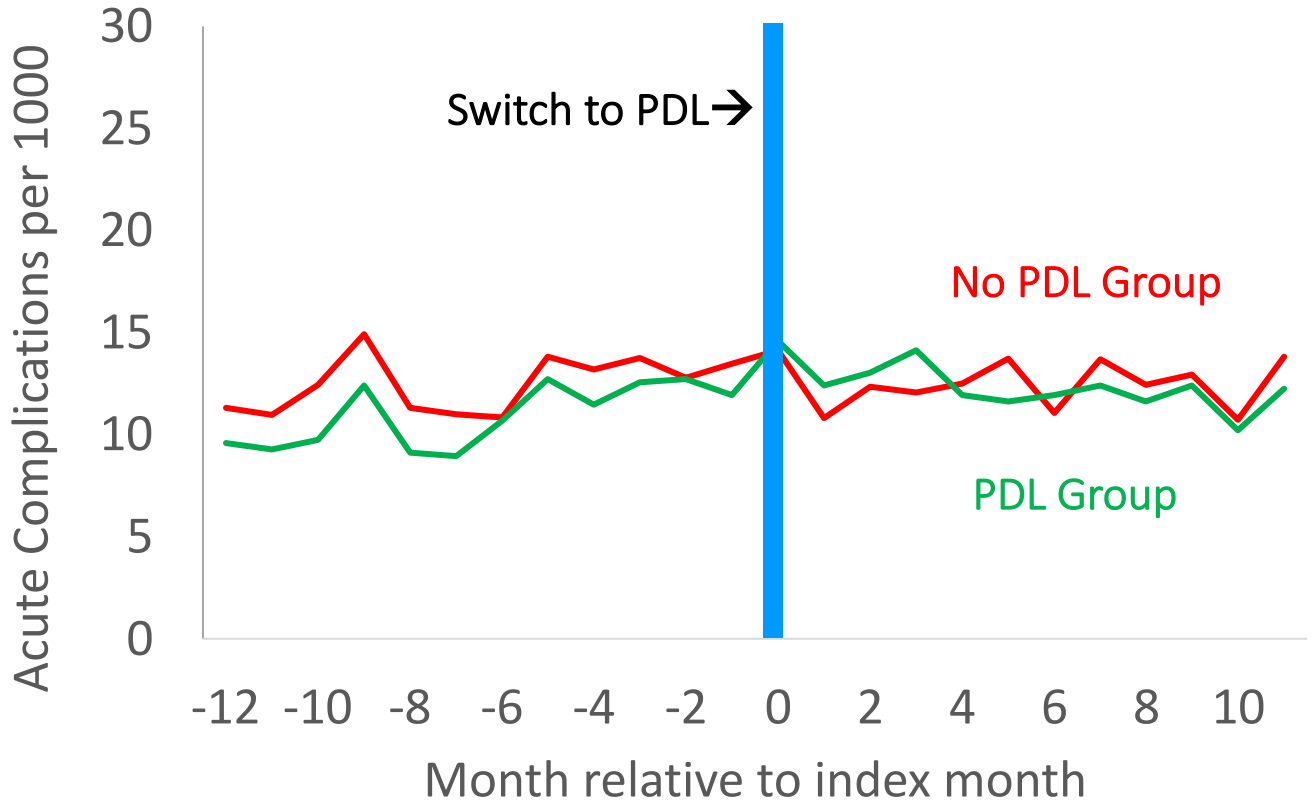
(1) Ross-Degnan D. *et al. Medical Care*. In press. (2) Hallberg, K., Cook, T. D., Steiner, P. M., Clark, M. H. *Prev Sci*. 2018.

Oral antidiabetic fills after PDL switch



Ross-Degnan D. *et al. Medical Care*. In press; *p<0.05

Acute diabetes complication outpatient visits before-after PDL switch



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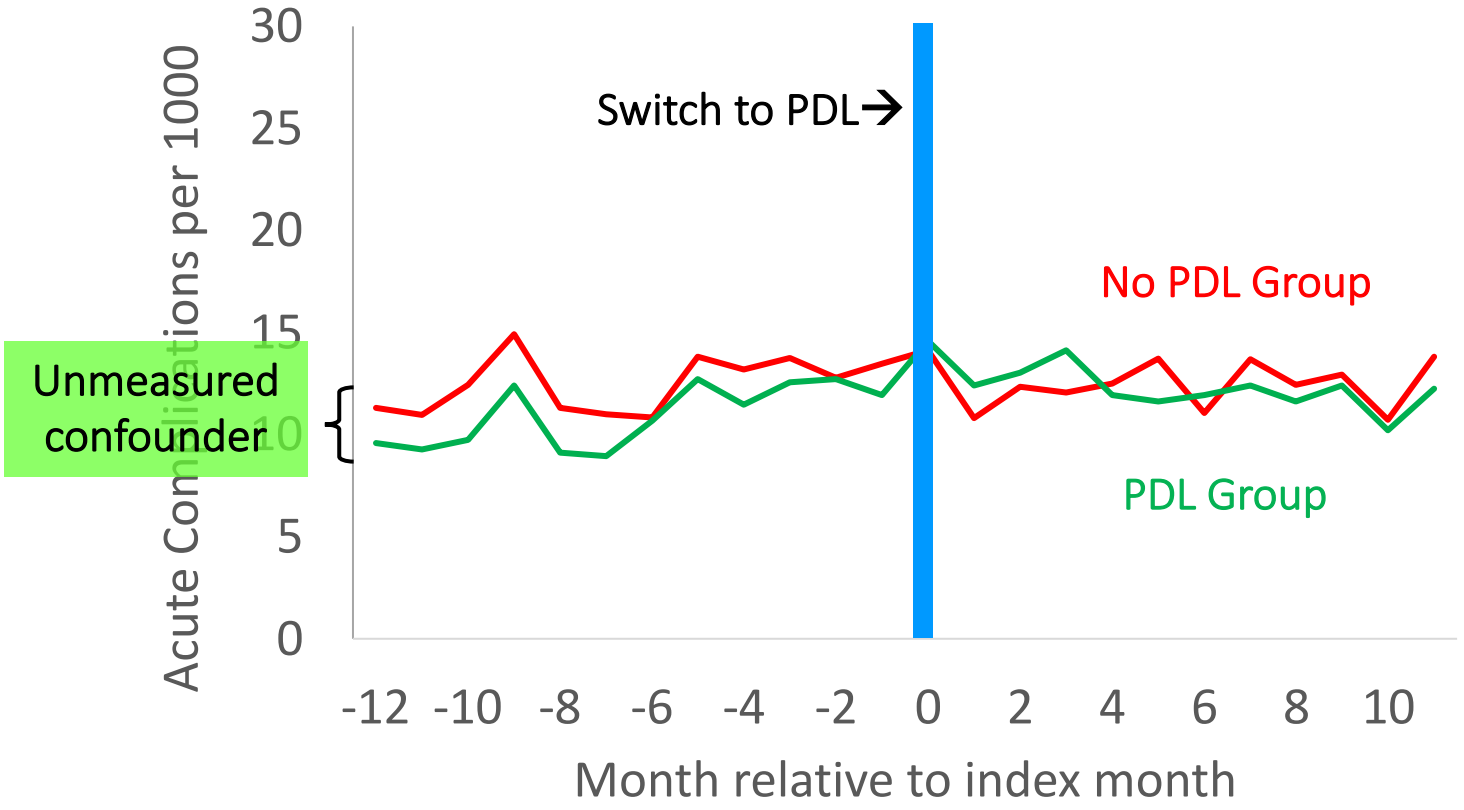
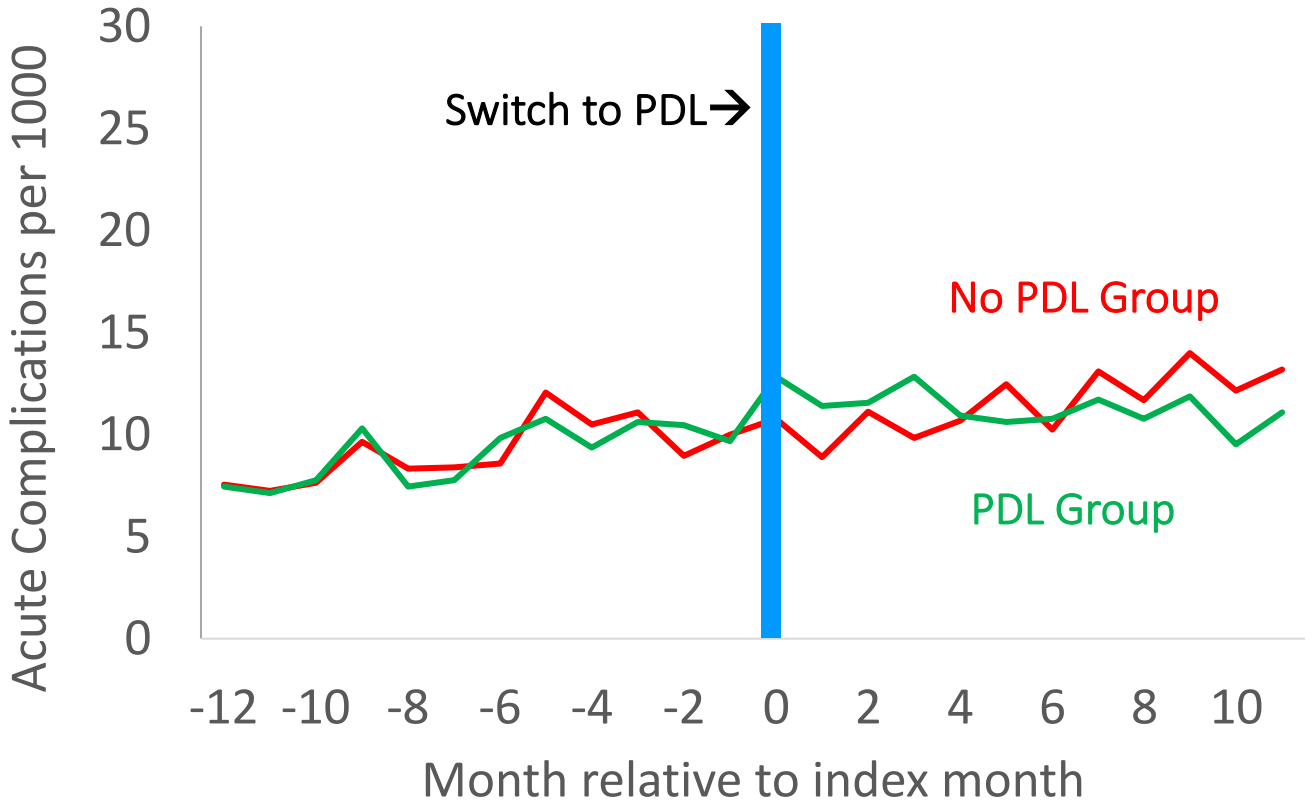


HDHPs and diabetes: additional design considerations

- Possible that employers are selecting into HDHPs based on expenses of these chronically ill members
  - Thus, regression to the mean could occur
- Exact baseline deductible amount uncertain
- "Functional form" of baseline trends unclear
  - Therefore, match on baseline trend per St. Clair, Cook *et al*. (as well as multiple other covariates)
- Reasons for special role of baseline outcomes in matching:
  - High correlation with follow-up outcomes
  - Likely correlation with selection

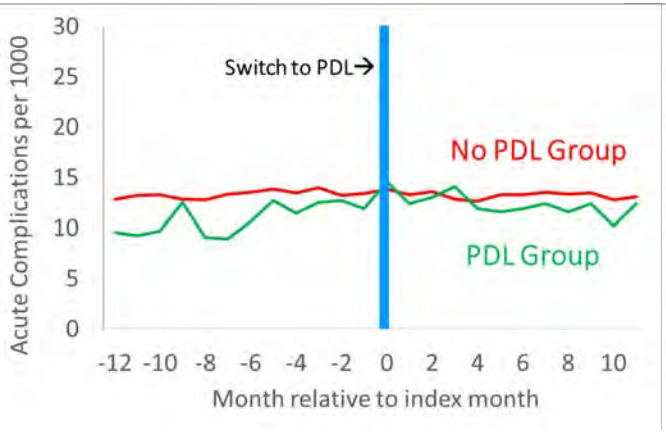
(1) Hallberg K. Cook TD. http://teams.mspnet.org/media/data/TEAMSMayWebinar.pdf?media_000000008372.pdf (2) Hallberg, K., Cook, T. D., Steiner, P. M., Clark, M. H. Prev Sci. 2018.

ITS with controls matched on covariates + baseline trend



Comparison: ITS with unmatched controls & matched on covariates +/- trend

Unmatched



Matched on covariates except baseline trend

Matched on covariates plus baseline trend

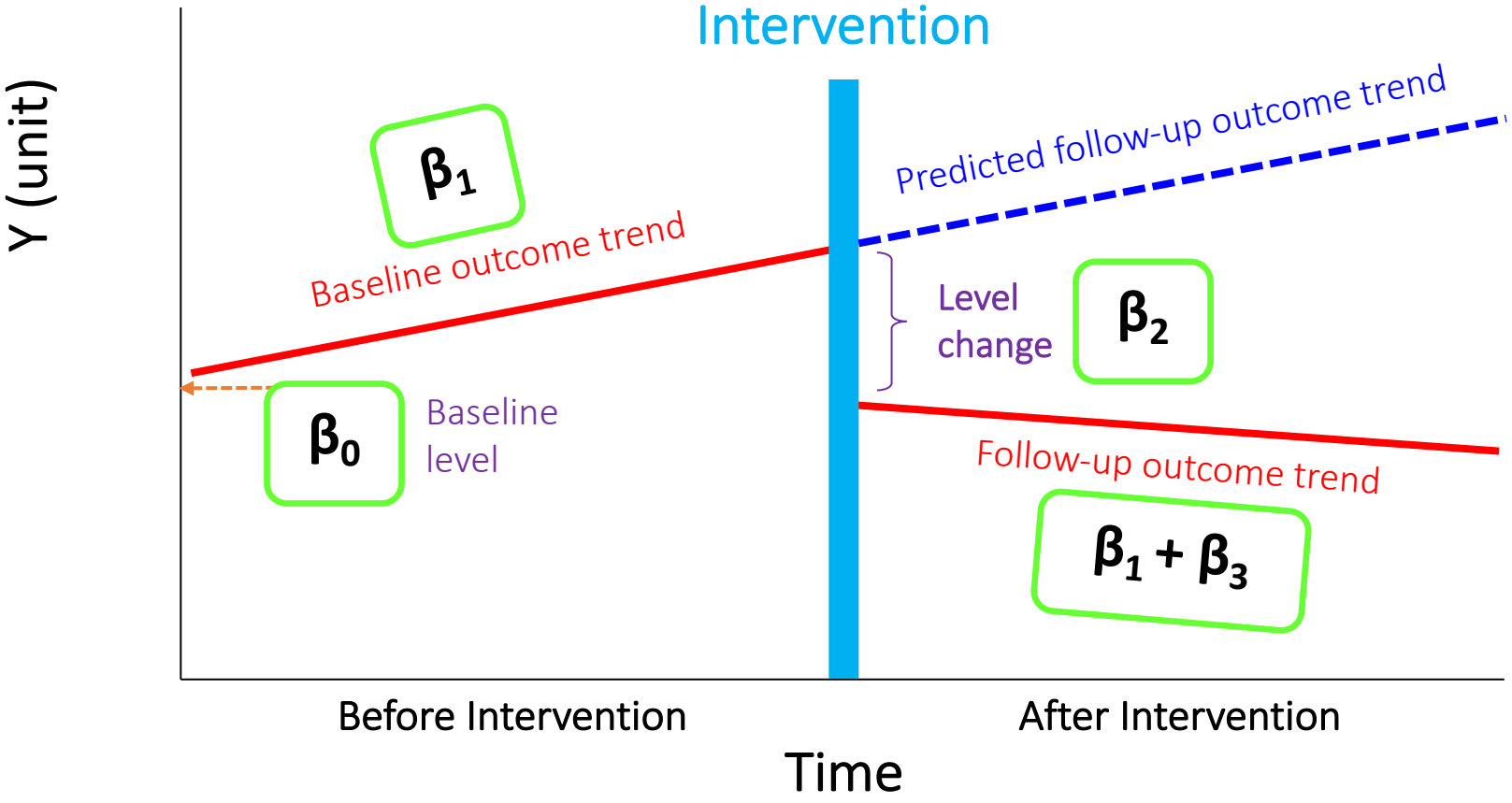
Outline

1. Brief review of observational research designs
2. What is interrupted time series (ITS) design?
3. Benefits & limitations of ITS designs
4. ITS *without* control group
   - Practical considerations and examples
5. ITS *with* control group
   - Practical considerations and examples
6. Overview of segmented regression analysis

How to organize data for ITS plotting & analysis

- Person-level analysis
  - Typically have event dataset with rows containing date of measured event (e.g. day, month, & year) & ID for person experiencing event
  - Ideally also have subject enrollment dataset displaying time period when a subject's events could potentially have occurred
- Population-level (aggregate-level) analysis
  - Typically have dataset with outcome summarized over a population during regular time intervals

Parameters to calculate effect estimates of interest



$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{intervention}_t + \beta_3 * \text{time after intervention}_t + e_{t2}$$

Overview of analysis of ITS data

- Segmented ("piecewise") regression models
  - Intervention effect estimated by "segmented" model with independent variable (time) broken into ≥2 segments with different intercept & slope coefficients
  - Avoids the major potential bias of ignoring secular trends
- Adjustment needed for serial autocorrelation
  - (because repeated observations usually correlated)
- Can be run on individual-level data or aggregate-level data

```
proc autoreg data=sampleITS;
    model mean_MED_KY = baseline_trend level_change trend_change/
        method=ml nlag=5 backstep dwprob;
        output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

Summary

- In health services research, typically aim for interrupted time series with control group or stronger designs
  - But other designs can sometimes be sufficient, necessary, or almost as rigorous
- Key benefits of ITS include rigor and communicating intervention effects to audience
- Important to remember that study group "assignment" is crucial in affecting rigor of ITS designs
  - Aim for "exogenous" intervention (not self-selected group)
- Early evidence suggests that matching on baseline characteristics including outcomes trend might reduce bias

Thank you!

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Additional slides

Additional & advanced ITS topics

- Modelling short follow-up periods
- Modelling multiple interventions
- Person-level segmented regression
- Generating intuitive relative effect estimates from controlled ITS
  - Controlled cumulative ITS
- Adjusting for person-level characteristics but maintaining simplicity of aggregate segmented regression
- Insights from within-study comparison studies about ideal ITS matching approaches

Key references

Journal of Clinical Pharmacy and Therapeutics (2002) **27**, 299–309

RESEARCH NOTE

Segmented regression analysis of interrupted time series studies in medication use research

A. K. Wagner*† PharmD, MPH, S. B. Soumerai* ScD, F. Zhang* MS and D. Ross-Degnan* ScD

Additional references

1. Lagarde M. How to do (or not to do) …Assessing the impact of a policy change with routine longitudinal data. Health Policy & Planning 2012;27:76-83.
2. Schneeweiss S, Maclure M, Walker AM, Grootendorst P, Soumerai SB. On the evaluation of drug benefits policy changes with longitudinal claims data: the policy maker's versus the clinician's perspective. Health Policy 2001;55:97-109.
3. Larochelle M, Zhang F, Ross-Degnan D, Wharam JF. Opioid dispensing & overdose after introduction of abuse-deterrent OxyContin & withdrawal of propoxyphene JAMA Internal Medicine. 2015 Jun 1;175(6):978-87.
4. Lewis KH, Zhang F, Arterburn DE, Ross-Degnan D, Gillman MW, Wharam JF. Comparing Medical Costs & Use After Laparoscopic Adjustable Gastric Banding & Roux-en-Y Gastric Bypass. JAMA Surg. 2015 Aug 1;150(8):787-94.
5. Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid Prescribing After Nonfatal Overdose & Association With Repeated Overdose: A Cohort Study. Annals of Internal Medicine. 2016 Jan 5;164(1):1-9.
6. Wharam JF, Zhang F, Eggleston EM, Lu CY, Soumerai S, Ross-Degnan D. Diabetes Outpatient Care & Acute Complications Before & After High-Deductible Insurance Enrollment: A Natural Experiment for Translation in Diabetes (NEXT-D) Study. JAMA Intern Med. 2017.

Additional references

7. Serumag`a B, Ross-Degnan D, Avery A, Elliott RA, Majumdar SR, Zhang F, Soumerai SB. Effect of pay for performance on the management & outcomes of hypertension in the United KingdomL interrupted time series study. BMJ 2011.
8. Ross-Degnan D. Benzodiazepine use & hip fractures in the elderly: Who is at greatest risk? Archives of Internal Medicine 2004;164:1567-1572.
9. Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol 2009;62:143-148.
10. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. J Clin Epidemiol. 2011; 64: 1252-61.
11. Linden A, Adams JL. Applying a propensity score-based weighting model to interrupted time series data: improving causal inference in programme evaluation. J Evaluation in Clinical Practice 2010;1-8.
12. Fretheim A, Zhang F, Ross-Degnan D, et al. A reanalysis of cluster randomized trials showed interrupted time-series studies were valuable in health system evaluation. Journal of clinical epidemiology. 2015;68(3):324-333Hallberg K, Cook TD, Steiner PM, Clark MH. Pretest Measures of the Study Outcome & the Elimination of Selection Bias: Evidence from Three Within Study Comparisons. Prev Sci 2016.
13. St.Clair T, Cook TD, Hallberg K. Examining the Internal Validity & Statistical Precision of the Comparative Interrupted Time Series Design by Comparison With a Randomized Experiment. American Journal of Evaluation 2014;35:311-27.

Internet resources

- Study design
  - http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/Study_design_guide2013.pdf
- General programming language resource (STATA, SAS, R, SPSS)
  - http://www.ats.ucla.edu/stat/
- SAS proc autoreg
  - https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf
- Stata resources
  - https://stats.idre.ucla.edu/stata/faq/how-can-i-run-a-piecewise-regression-in-stata/
  - http://www.stata.com/manuals13/tscorrgram.pdf

Coarsened Exact Matching

The basic idea of CEM is to coarsen each variable by recoding so that substantively indistinguishable values are grouped and assigned the same numerical value (groups may be the same size or different sizes depending on the substance of the problem). Then, the "exact matching" algorithm is applied to the coarsened data to determine the matches and to prune unmatched units. Finally, the coarsened data are discarded and the original (uncoarsened) values of the matched data are retained.

Put differently, after coarsening, the CEM algorithm creates a set of strata, say $s \in \mathrm{S}$, each with same coarsened values of $\mathbf{X}$. Units in strata that contain at least one treated and one control unit are retained; units in the remaining strata are removed from this sample. We denote by $\mathcal{T}^s$ the treated units in stratum s and by $m_T^s = \#\mathcal{T}^s$ the number of treated units in the stratum, similarly for the control units, that is, $\mathcal{C}^s$and $m_C^s = \#\mathcal{C}^s$. The number of matched units are, respectively, for treated and controls, $m_T = \cup_{s\in S}\, m_T^s$ and $m_C = \cup_{s\in S}\, m_C^s$. To each matched unit i in stratum s, CEM assigns the following weights:

$$w_i = \begin{cases} 1, & i \in T^s \\ \frac{m_C}{m_T}\frac{m_T^s}{m_C^s}, & i \in C^s \end{cases}. \tag{6}$$

Unmatched units receive weight $w_i = 0$.

CEM therefore assigns to matching the task of eliminating all imbalances (i.e., differences between the treated and control groups) beyond some chosen level defined by the coarsening. Imbalances eliminated by CEM include all multivariate nonlinearities, interactions, moments, quantiles, comoments, and other distributional differences beyond the chosen level of coarsening. The remaining differences are thus all within small coarsened strata and so are highly amenable to being spanned by a statistical model without risk of much model dependence.

Like exact matching, CEM produces variable-sized strata. If this is not convenient and enough data are available, users can produce a one-to-one match by randomly selecting the desired number of treated and control units from those within each stratum or apply an existing method within strata (see Section 5.2).

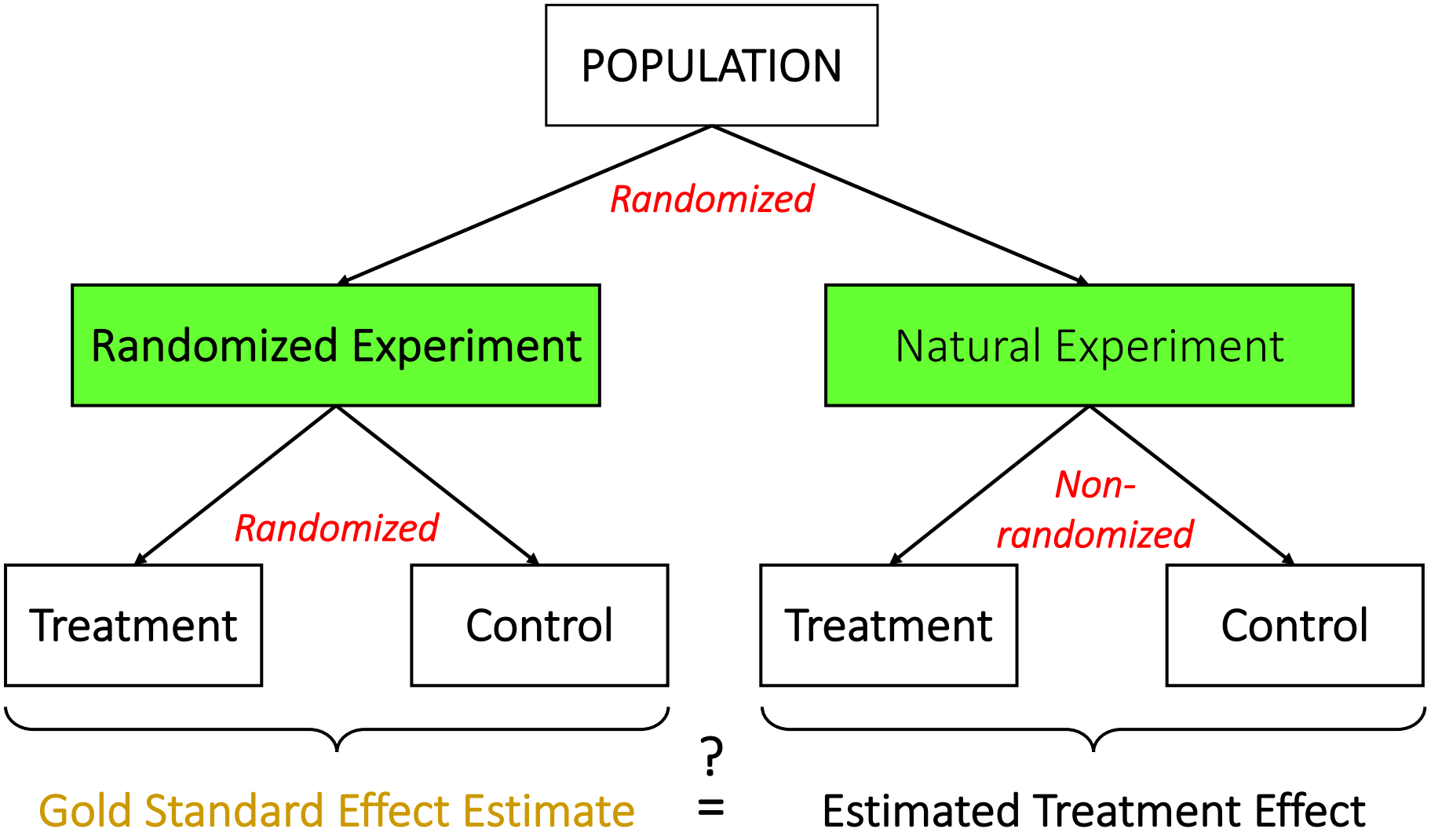
https://gking.harvard.edu/files/political_analysis-2011-iacus-pan_mpr013.pdf.

Stata regression and margins example

- use yrlyop_hsa1_t1
- xtset patid yr
- quietly xtgee oopmxrxyr c.emptot i.yr i.hdhp i.hdhp#i.yr i.female i.age1 i.age2 i.black i.mixed i.hispan i.asian i.povc2 i.povc3 i.povc4 i.educ2 i.educ3 ///
- i.educ4 i.regc2 i.regc3 i.regc4 c.patacg c.indexmon c.dm_dx_month, i(patid) fam(nb) link(log) vce(robust) offset(logtime2)
- margins hdhp#yr, post
- mgin

- program define mgin
- nlcom (absolute_yr3:(_b[3.yr#1.hdhp]-_b[1.yr#1.hdhp]*_b[3.yr#0.hdhp]/_b[1.yr#0.hdhp]))
- nlcom (relative_yr3:(_b[3.yr#1.hdhp] -_b[1.yr#1.hdhp] *_b[3.yr#0.hdhp]/_b[1.yr#0.hdhp])/(_b[1.yr#1.hdhp]*_b[3.yr#0.hdhp]/_b[1.yr#0.hdhp]))
- end
- clear

Within-study comparison design



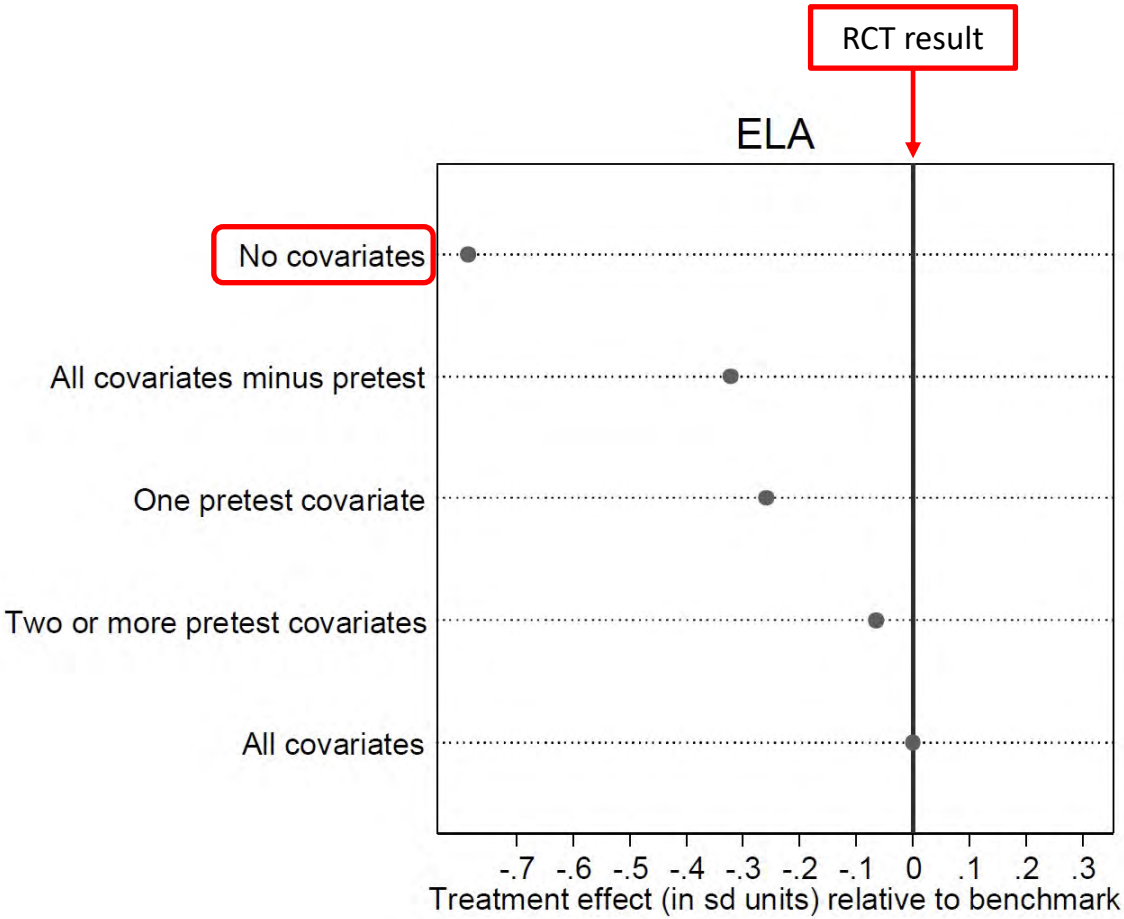
Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Within-study comparison studies

- Previous within-study comparison studies have shown that ITS with control group can replicate RCT results
- More recently, St. Clair, Cook, and Hallberg have conducted the most rigorous studies to date
  - 4 arm randomized approach as on previous slide
  - In addition to determining if ITS with control group designs yield results similar to RCTs, investigators are determining optimal ITS matching approaches
  - (Education setting; not medical setting)

(1) Ferraro PJ, and Miranda JJ. *Resource Energy Econ*. 2013. (2) Schneeweiss *et al*. *BMJ*. 2004. (3) Fretheim *et al.* *J Clin Epi*. 2013. (4) Somers M *et al. MDRC.* 2013 (5) Hallberg, K., Cook, T. D., Steiner, P. M., Clark, M. H. *Prev Sci*. 2018

Bias reduction: controls not matched



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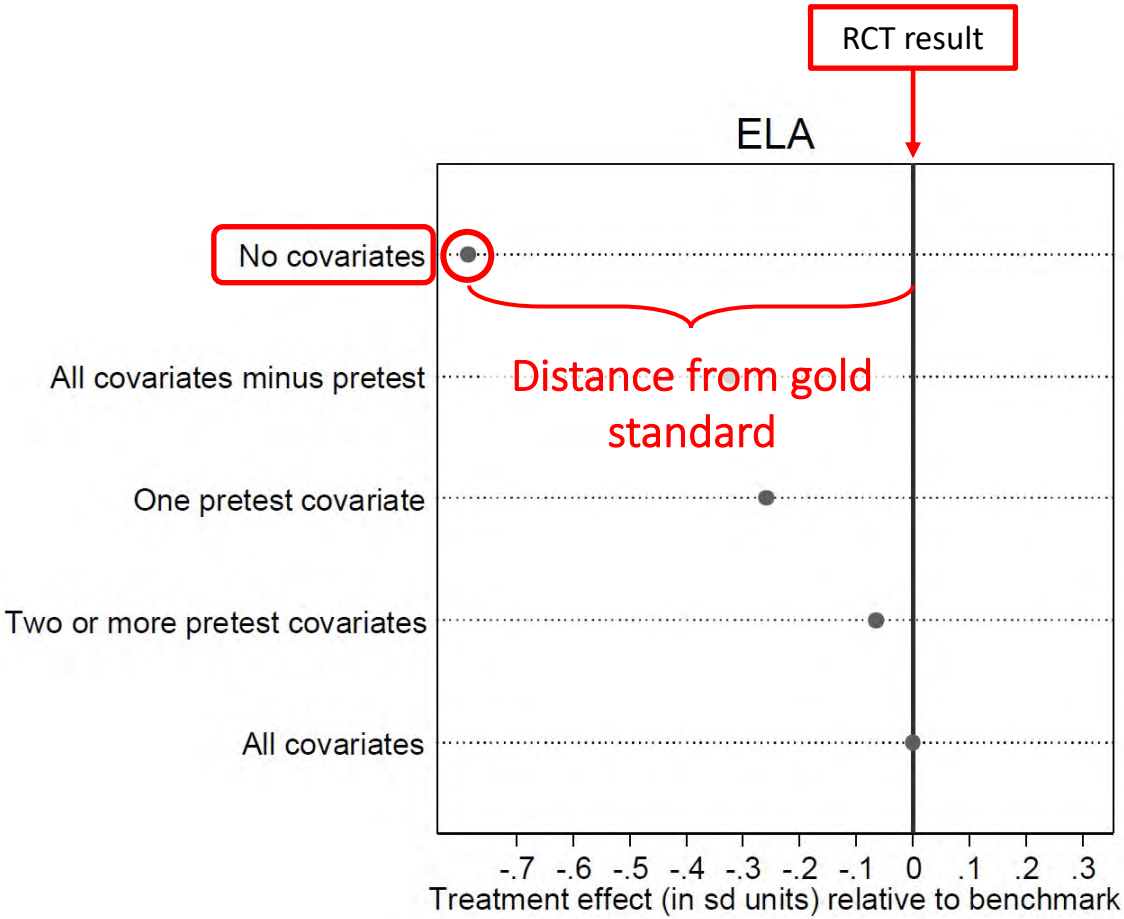
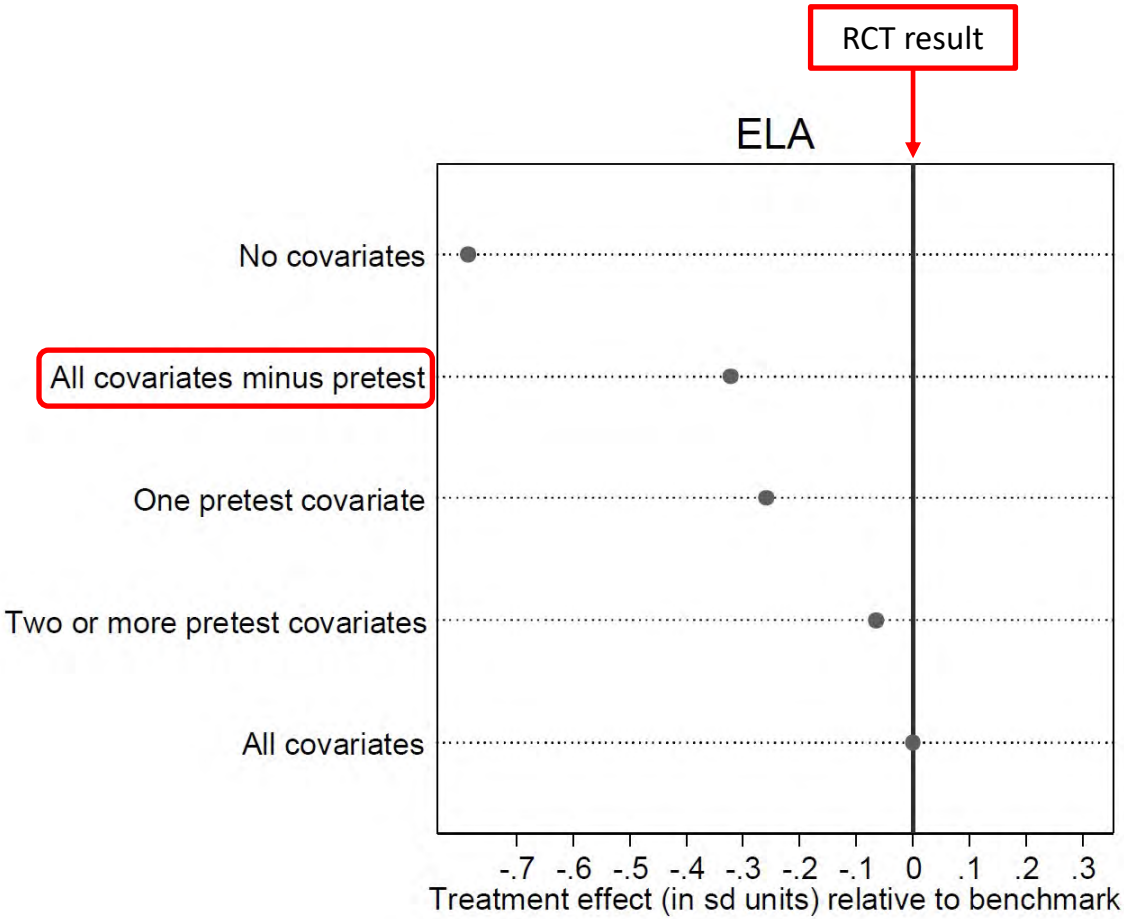
Bias reduction: controls not matched



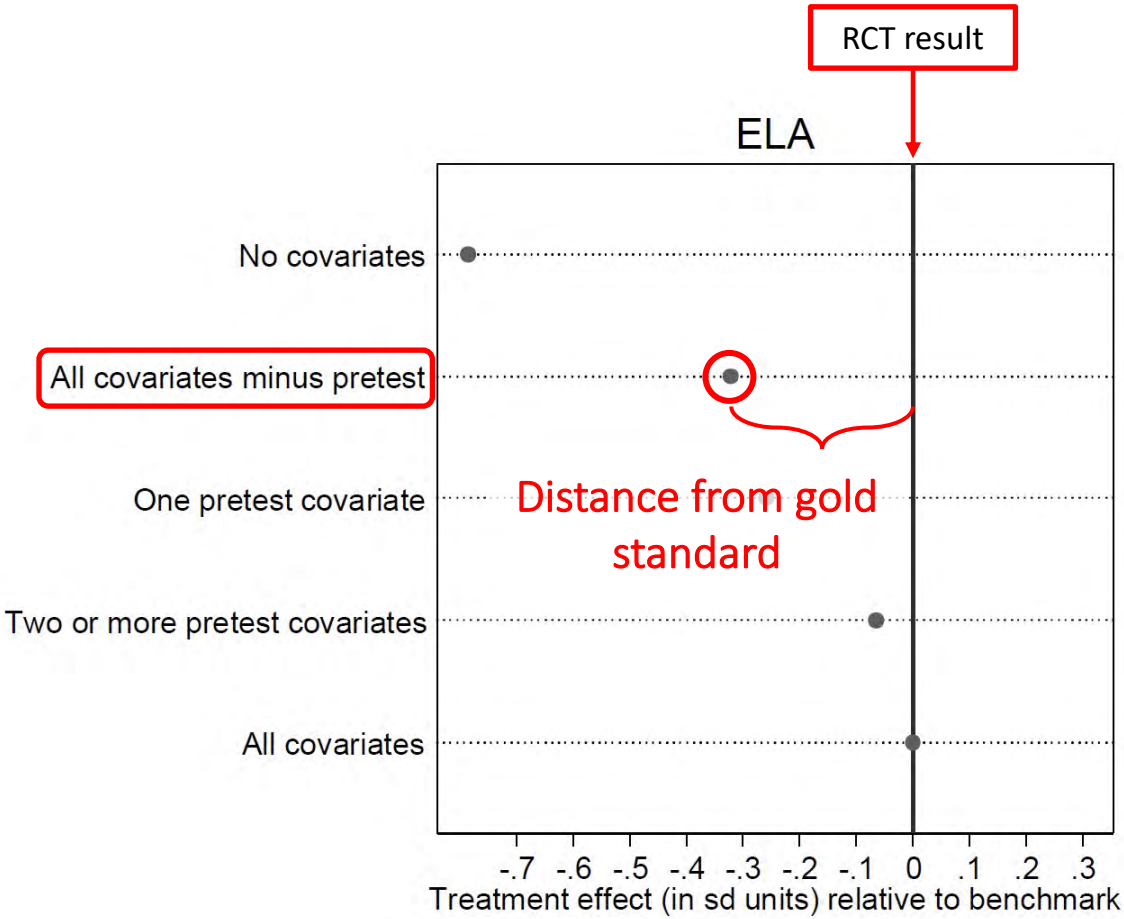
Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Bias reduction: controls matched on covariates but not baseline trend



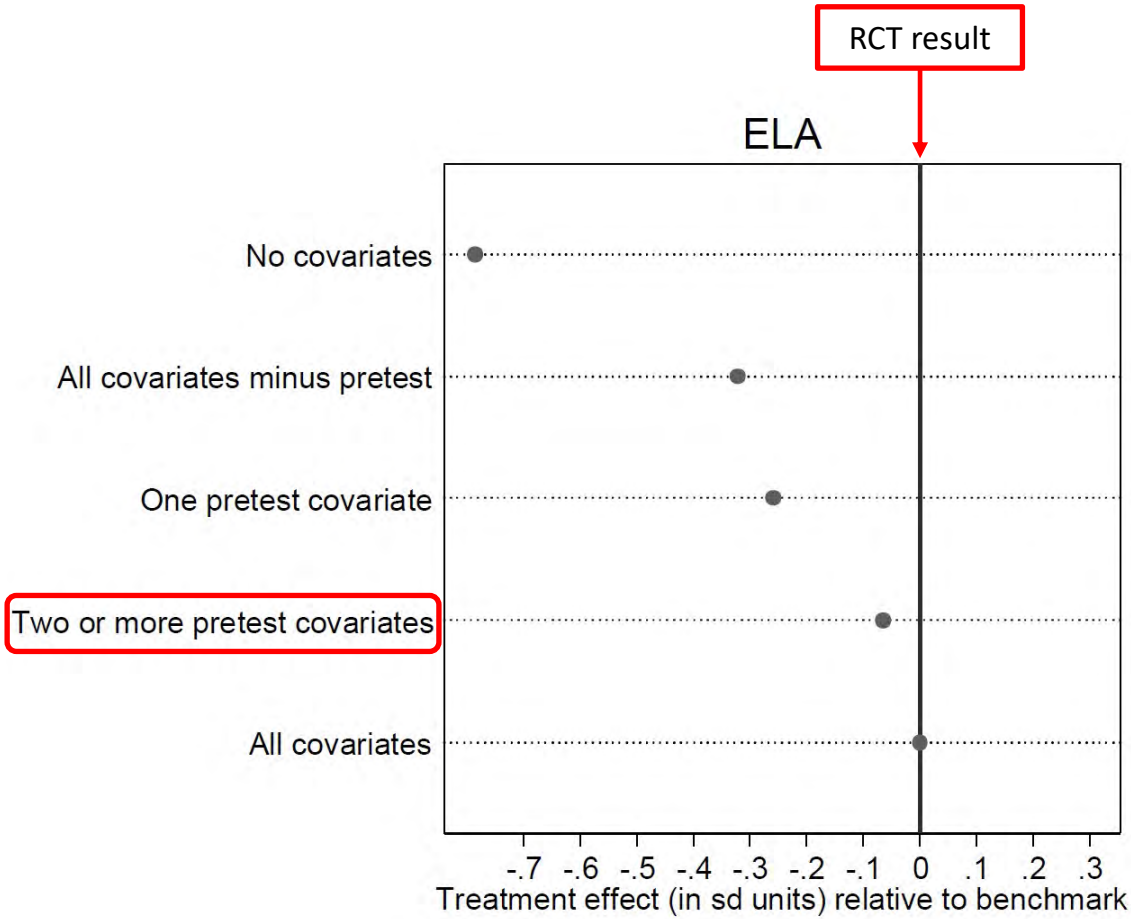
Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Bias reduction: controls matched on covariates but not baseline trend



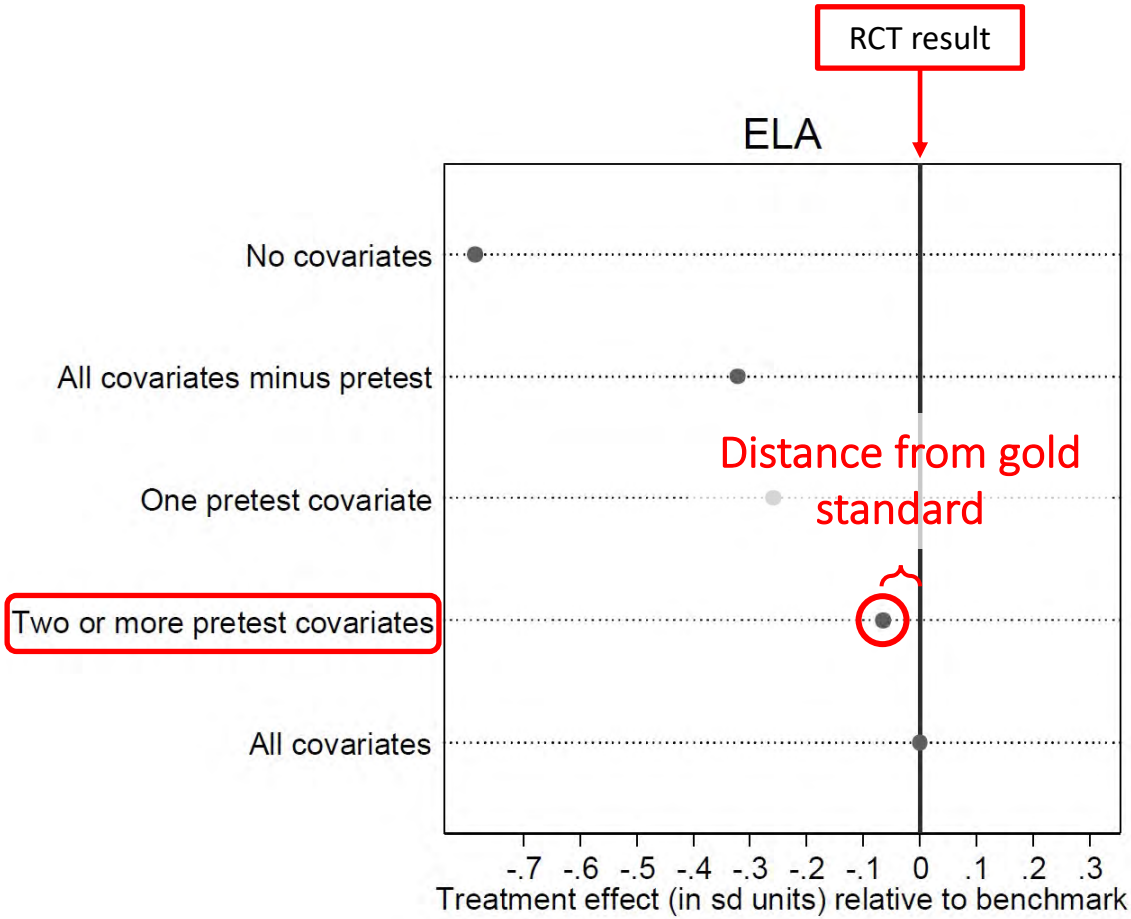
Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Bias reduction: matching on baseline trend only



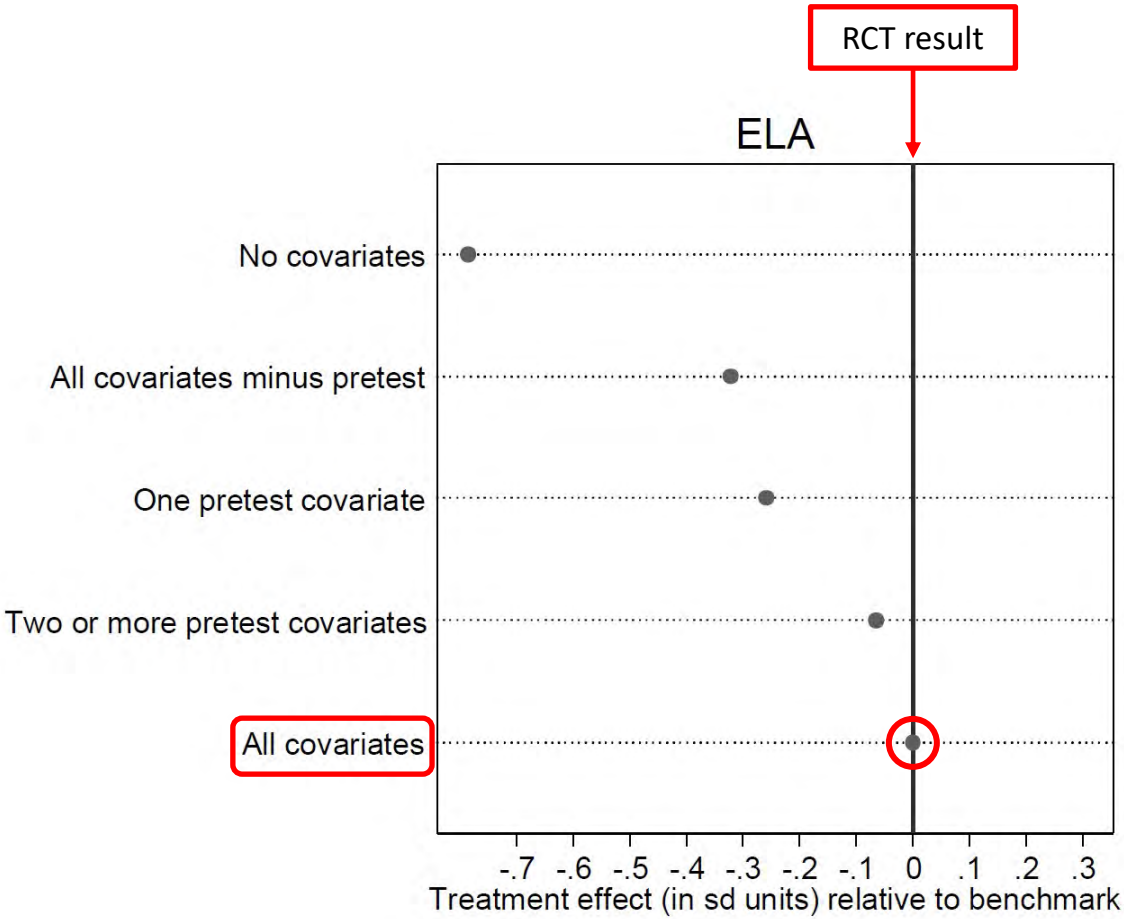
Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Bias reduction: matching on baseline trend only



Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Bias reduction: matching on baseline trend and other covariates



Hallberg K. and Cook TD. https://arc.uchicago.edu/sites/default/files/Cook_NSF%20ARC%20Presentation_10.28.13-1.pdf

Data structure for segmented regression analysis

Population-level data, no control group

Quarter relative to intervention quarter	Calendar date start of quarter	Study period quarter number (time)	Intervention period? (intervention)	Intervention period quarter number (time after intervention)	Mean morphine equivalent dosage - Kentucky (Y_t)	Mean morphine equivalent dosage - Missouri	Mean morphine equivalent dosage - Difference
-11	January-10	1	0	0	165.3	137.4	27.9
-10	April-10	2	0	0	170.4	142.9	27.5
-9	July-10	3	0	0	176.5	148.2	28.3
-8	October-10	4	0	0	179.2	146.5	32.7
-7	January-11	5	0	0	166.1	128.8	37.3
-6	April-11	6	0	0	177.8	134.4	43.4
-5	July-11	7	0	0	190.2	142.1	48.1
-4	October-11	8	0	0	201	151.6	49.4
-3	January-12	9	0	0	187	143.6	43.4
-2	April-12	10	0	0	192.2	148.6	43.6
-1	July-12	11	0	0	187.5	154.8	32.7
1	October-12	12	1	1	183.4	165	18.4
2	January-13	13	1	2	162.8	151.7	11.1
3	April-13	14	1	3	162.9	155	7.9
4	July-13	15	1	4	166.9	156.1	10.8
5	October-13	16	1	5	173.8	162.1	11.7
6	January-14	17	1	6	154.1	154.1	0.0
7	April-14	18	1	7	155.1	155.9	-0.8
8	July-14	19	1	8	157.9	158.1	-0.2
9	October-14	20	1	9	162.5	169.2	-6.7

Data structure for segmented regression analysis

Population-level data, no control group

Quarter relative to intervention quarter	Calendar date start of quarter	Study period quarter number	Intervention period?	Intervention period quarter number	Mean morphine equivalent dosage - Kentucky	Mean morphine equivalent dosage - Missouri	Mean morphine equivalent dosage - Difference
		(baseline_trend)	(level_change)	(trend_change)	(mean_MED_KY)		
-11	January-10	1	0	0	165.3	137.4	27.9
-10	April-10	2	0	0	170.4	142.9	27.5
-9	July-10	3	0	0	176.5	148.2	28.3
-8	October-10	4	0	0	179.2	146.5	32.7
-7	January-11	5	0	0	166.1	128.8	37.3
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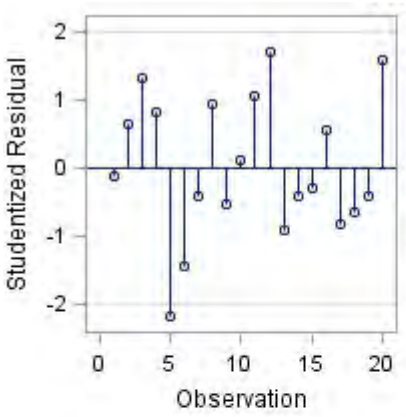
-3	January-12	9	0	0	187	143.6	43.4
-2	April-12	10	0	0	192.2	148.6	43.6
-1	July-12	11	0	0	187.5	154.8	32.7
1	October-12	12	1	1	183.4	165	18.4
2	January-13	13	1	2	162.8	151.7	11.1
3	April-13	14	1	3	162.9	155	7.9
4	July-13	15	1	4	166.9	156.1	10.8
5	October-13	16	1	5	173.8	162.1	11.7
6	January-14	17	1	6	154.1	154.1	0.0
7	April-14	18	1	7	155.1	155.9	-0.8
8	July-14	19	1	8	157.9	158.1	-0.2
9	October-14	20	1	9	162.5	169.2	-6.7

Check segmented regression assumptions

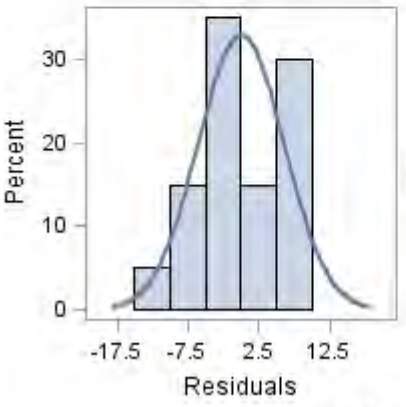
Check linearity & normality of errors:

- Run regression of outcome & time; plot residuals vs fitted lines
- Residuals should be symmetrically & normally distributed around fitted line



Check for autocorrelation:

- Visually inspect a plot of residuals against time – positive autocorrelation = consecutive residuals on same side of regression line
- Run Durbin Watson test to statistically assess autocorrelation & seasonality



https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

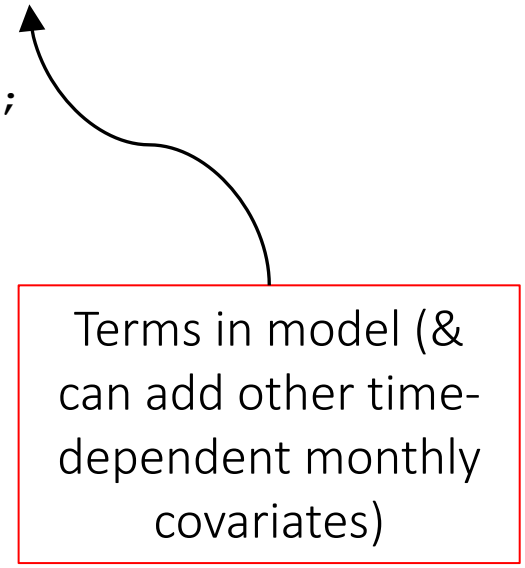
SAS code: simple aggregate-level segmented regression model

```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: simple aggregate-level segmented regression model

```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```



https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: simple aggregate-level segmented regression model

```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

Estimation method (maximum likelihood)

https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: simple aggregate-level segmented regression model

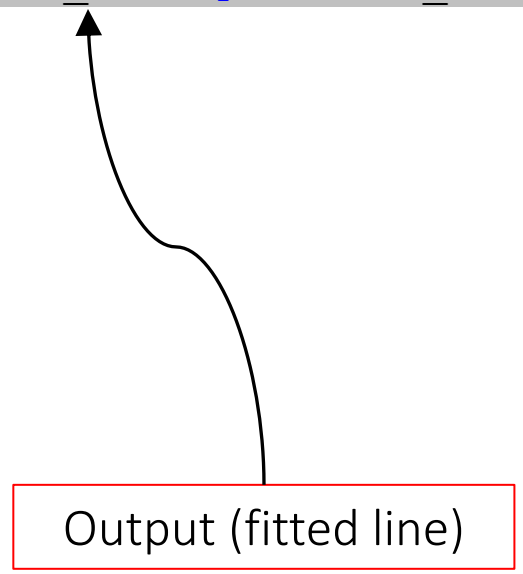
```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

Autoregressive error model order selection (stepwise autoregression)

https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: simple aggregate-level segmented regression model

```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```



https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: If terms are not significant

```
proc autoreg data=sampleITS;
   model mean_MED_KY = baseline_trend level_change trend_change /
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
   model mean_MED_KY = baseline_trend level_change /
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out2 p=fitted_MED_KY;
   model mean_MED_KY = baseline_trend trend_change /
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out3 p=fitted_MED_KY;
run;
```

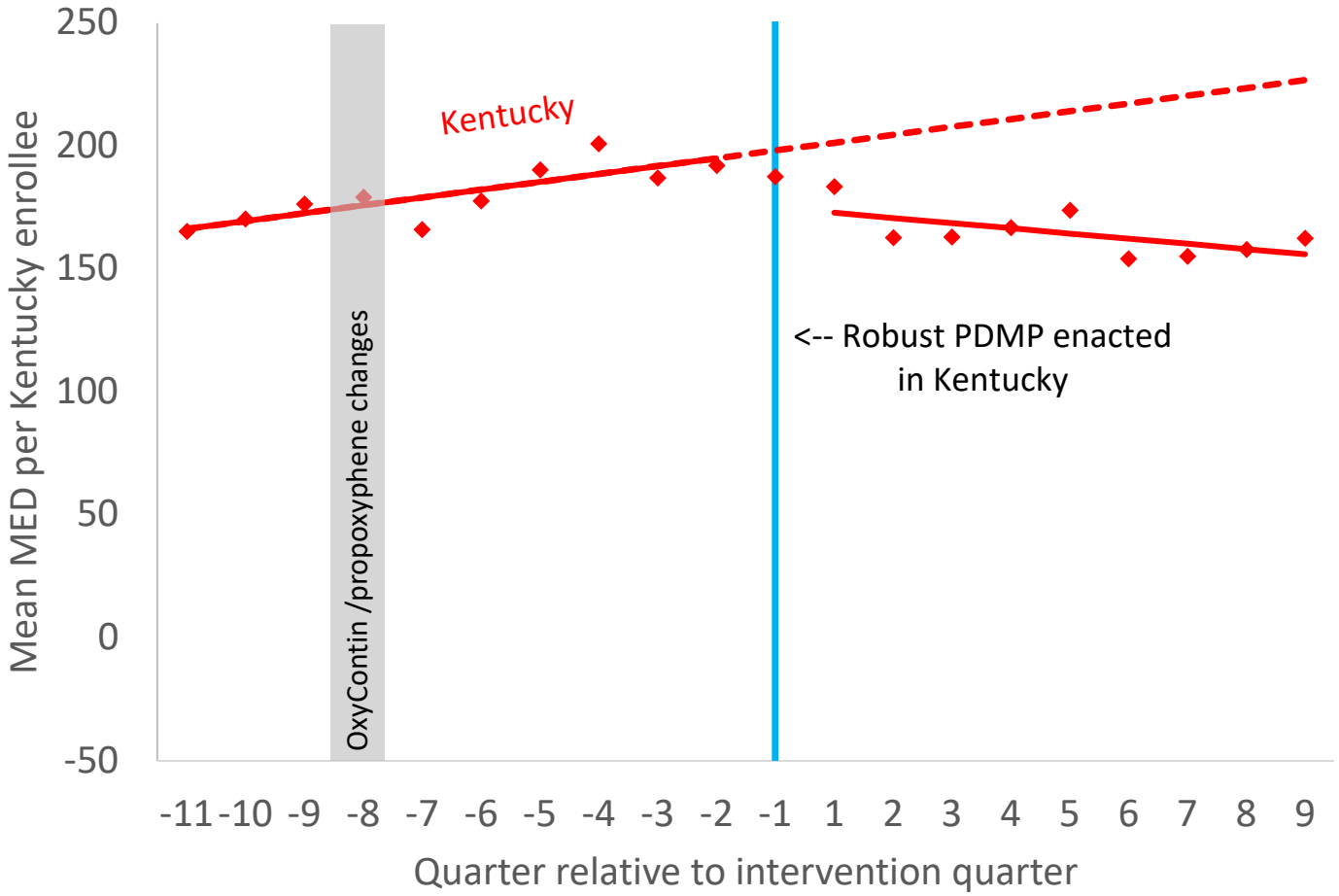
https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS proc autoreg output

		Parameter Estimates				
		Variable	DF	Estimate	Standard Error	t Value	Approx Pr > |t|
	β_0	Intercept	1	164.9782	4.9295	33.47	<.0001
(time)	β_1	Baseline_trend	1	2.7036	0.7268	3.72	0.0019
(intervention)	β_2	Level_change	1	-19.7821	7.0112	-2.82	0.0123
(time after intervention)	β_3	Trend_change	1	-4.8153	1.2234	-3.94	0.0012

Prescription drug monitoring programs:

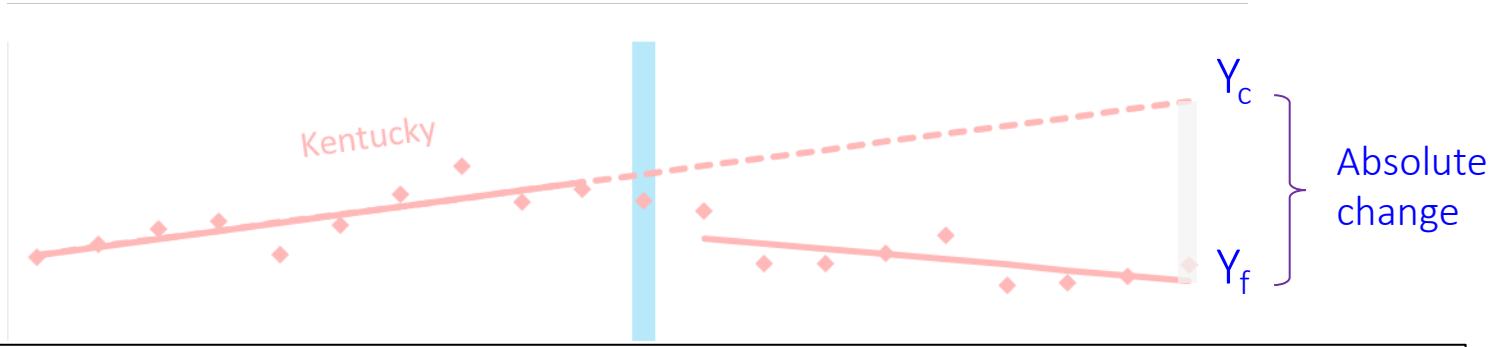
Plot: intervention group with fitted lines



Interpreting & communicating effect estimates

- Can simply describe level change & trend changes:
  - “Members in Kentucky experienced a mean reduction of 19.8 mg MED per person in the quarter immediately after robust PDPM adoption, then a downward trend of -4.8 mg MED per quarter.”
- Calculate absolute & relative change at a given follow-up time point (below)
  - E.g., “Members in Kentucky experienced 31% relative reduction in mean mg MED nine quarters after robust PDMP adoption.”

Interpretation: absolute change at given time point



$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{intervention}_t + \beta_3 * \text{time after intervention}_t + e_t$$

Absolute = Fitted value at quarter 20 minus counterfactual value at quarter 20

$= Y_{f@q20} - Y_{c@q20}$

$Y_{f@q20} = \beta_0 + (\beta_1 * 20) + \beta_2 + (\beta_3 * 9)$

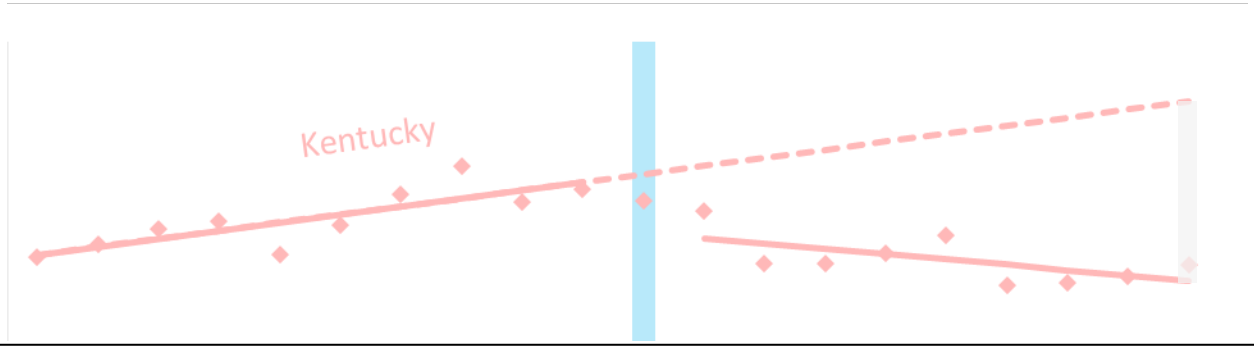
$Y_{c@q20} = \beta_0 + (\beta_1 * 20)$

$= [\beta_0 + (\beta_1 * 20) + \beta_2 + (\beta_3 * 9)] - [\beta_0 + (\beta_1 * 20)]$

$= \beta_2 + (\beta_3 * 9)$

95% CI $= \beta_2 + (\beta_3 * 9) \pm 1.96 * \sqrt{\text{VAR}(\beta_2 + [\beta_3 * 9])}$

Interpretation: relative change at given time point



$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{intervention}_t + \beta_3 * \text{time after intervention}_t + e_t$$

Relative = Absolute change at quarter 20 divided by counterfactual value at quarter 20

$= \beta_2 + (\beta_3 * 9) / (\beta_0 + (\beta_1 * 20))$

95% CI = Need to use multivariate delta method or bootstrapping (Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol 2009;62:143-148)

How to organize data for ITS plotting & analysis

- In aggregate-level analyses, control group outcomes are simply “another column” in dataset
- Calculate “differenced” trend of intervention group relative to control group:
  - = $Y_{t,Intervention} - Y_{t,Control}$

How to organize data for ITS plotting & analysis

Population-level data, with control group

Quarter relative to intervention quarter	Calendar date start of quarter	Study period quarter number	Intervention period?	Intervention period quarter number	Mean morphine equivalent dosage - Kentucky	Mean morphine equivalent dosage - Missouri	Mean morphine equivalent dosage - Difference
-11	January-10	1	0	0	165.3	137.4	27.9
-10	April-10	2	0	0	170.4	142.9	27.5
-9	July-10	3	0	0	176.5	148.2	28.3
-8	October-10	4	0	0	179.2	146.5	32.7
-7	January-11	5	0	0	166.1	128.8	37.3
-6	April-11	6	0	0	177.8	134.4	43.4
-5	July-11	7	0	0	190.2	142.1	48.1
-4	October-11	8	0	0	201	151.6	49.4
-3	January-12	9	0	0	187	143.6	43.4
-2	April-12	10	0	0	192.2	148.6	43.6
-1	July-12	11	0	0	187.5	154.8	32.7
1	October-12	13	1	1	183.4	165	18.4
2	January-13	14	1	2	162.8	151.7	11.1
3	April-13	15	1	3	162.9	155	7.9
4	July-13	16	1	4	166.9	156.1	10.8
5	October-13	17	1	5	173.8	162.1	11.7
6	January-14	18	1	6	154.1	154.1	0.0
7	April-14	19	1	7	155.1	155.9	-0.8
8	July-14	20	1	8	157.9	158.1	-0.2
9	October-14	21	1	9	162.5	169.2	-6.7

How to organize data for ITS plotting & analysis

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How to organize data for ITS plotting & analysis

Population-level data, with control group

Quarter relative to intervention quarter	Calendar date start of quarter	Study period quarter number (baseline_trend)	Intervention period? (level_change)	Intervention period quarter number (trend_change)	Mean morphine equivalent dosage – Kentucky	Mean morphine equivalent dosage - Missouri	Mean morphine equivalent dosage - Difference (mean_MED_diff
-11	January-10	1	0	0	165.3	137.4	27.9
-10	April-10	2	0	0	170.4	142.9	27.5
-9	July-10	3	0	0	176.5	148.2	28.3
-8	October-10	4	0	0	179.2	146.5	32.7
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SAS code: simple aggregate-level segmented regression model

```
proc autoreg data=sampleITS;
   model mean_MED_Diff = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS code: simple aggregate-level segmented regression model

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proc autoreg data=sampleITS;
   model mean_MED_Diff = baseline_trend level_change trend_change/
      method=ml nlag=5 backstep dwprob;
      output out=sampleITS_out1 p=fitted_MED_KY;
run;
```

Same exact model structure; just change the dependent variable to the differenced outcome!

https://support.sas.com/documentation/onlinedoc/ets/132/autoreg.pdf

SAS proc autoreg output: Kentucky relative to Missouri (differenced)

		Parameter Estimates				
		Variable	DF	Estimate	Standard Error	t Value	Approx Pr > |t|
	β_0	Intercept	1	27.9600	3.5276	7.93	<.0001
(time)	β_1	Baseline_trend	1	1.6173	0.5201	3.11	0.0067
(intervention)	β_2	Level_change	1	-26.4083	5.0174	-5.26	<.0001
(time after intervention)	β_3	Trend_change	1	-4.3256	0.8755	-4.94	0.0001