MONASH University

Introduction to analysis and meta-analysis of interrupted time series studies with continuous outcomes

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Monash University, Australia

Webinar outline

- What is an ITS study and how to conduct an ITS analysis
    - What to do when we need to reanalyse the ITS studies
    - Effect measures commonly used and how to interpret them
    - Complexities of time series data
- Meta-analysing ITS studies
    - How to conduct a meta-analysis of ITS studies
    - Difficulties that may arise

Interrupted Time series (ITS) outline

- Description of an ITS study
- Measuring the impact of an interruption
- Example of an ITS model
- Obtaining estimates of the effect measures of interest
- Considering complex features of time series data
- Why you may need to re-analyse data as a systematic reviewer

Interrupted Time series (ITS)

- Not all public health interventions can be evaluated with an RCT

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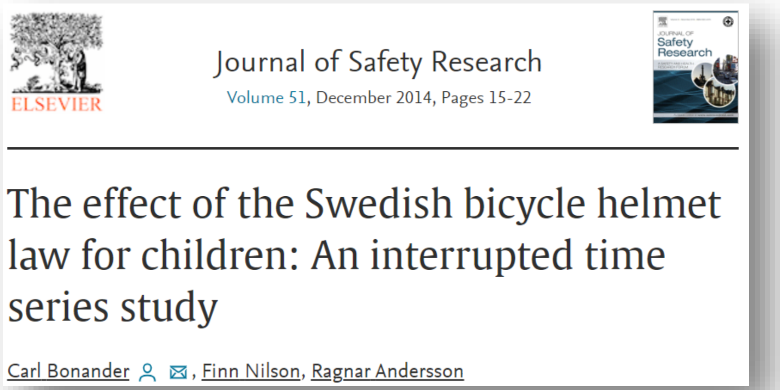
  - A country-wide implementation of a bicycle helmet law



Journal of Safety Research
Volume 51, December 2014, Pages 15-22

The effect of the Swedish bicycle helmet law for children: An interrupted time series study

Carl Bonander, Finn Nilson, Ragnar Andersson

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Impact of antibiotic restriction on resistance levels of *Escherichia coli*: a controlled interrupted time series study of a hospital-wide antibiotic stewardship programme

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- An ITS study can be used to estimate the impact of public health and policy interventions. Here are some examples:
  - A country-wide implementation of a bicycle helmet law
  - A single hospital implementing an anti-biotic stewardship program
- An ITS study can also be used to estimate the impact of natural disasters or other "exposures"
  - This example looks at the impact of the economic recession

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IEA

International Journal of Epidemiology, 2015, 969–977
doi: 10.1093/ije/dyv058
Advance Access Publication Date: 16 June 2015
Original article

Recession and Suicide

Impact of the economic recession and subsequent austerity on suicide and self-harm in Ireland: An interrupted time series analysis

Paul Corcoran,[1,2*] Eve Griffin,[1] Ella Arensman,[1,2] Anthony P Fitzgerald,[2] and Ivan J Perry[2]

Example

BMJ

BMJ 2013;346:f403 doi: 10.1136/bmj.f403 (Published 7 February 2013) Page 1 of 9

Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses

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- **P**opulation: England and Wales
- **I**ntervention: In September 1998 UK legislation restricted pack sizes of paracetamol
- **C**omparison: Before and after the intervention (September 1998)
- **O**utcome: Mortality (ages 10 years and over) involving single drug ingestion of paracetamol

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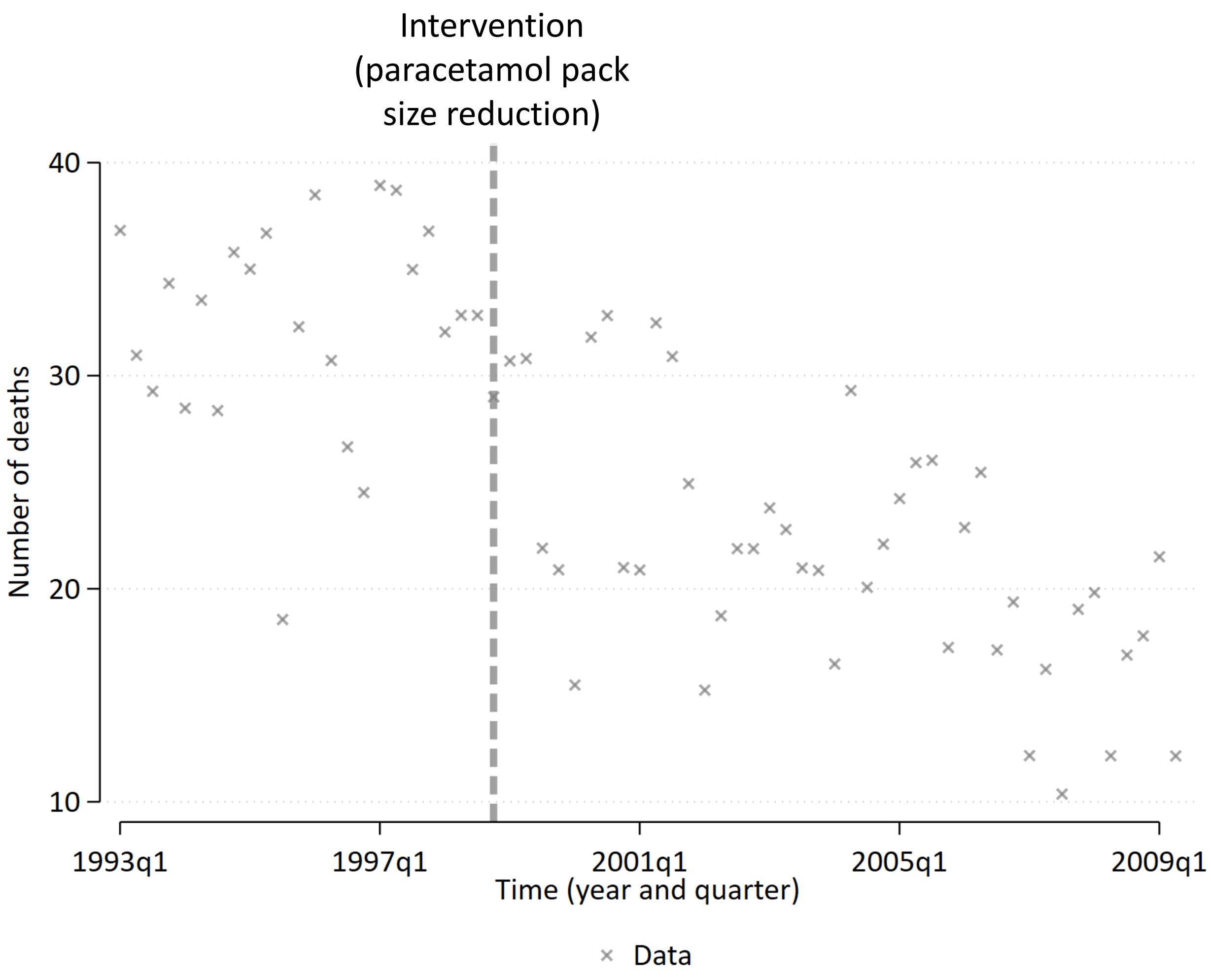
Interrupted Time Series



- Data is collected from a group of individuals (here from England and Wales)

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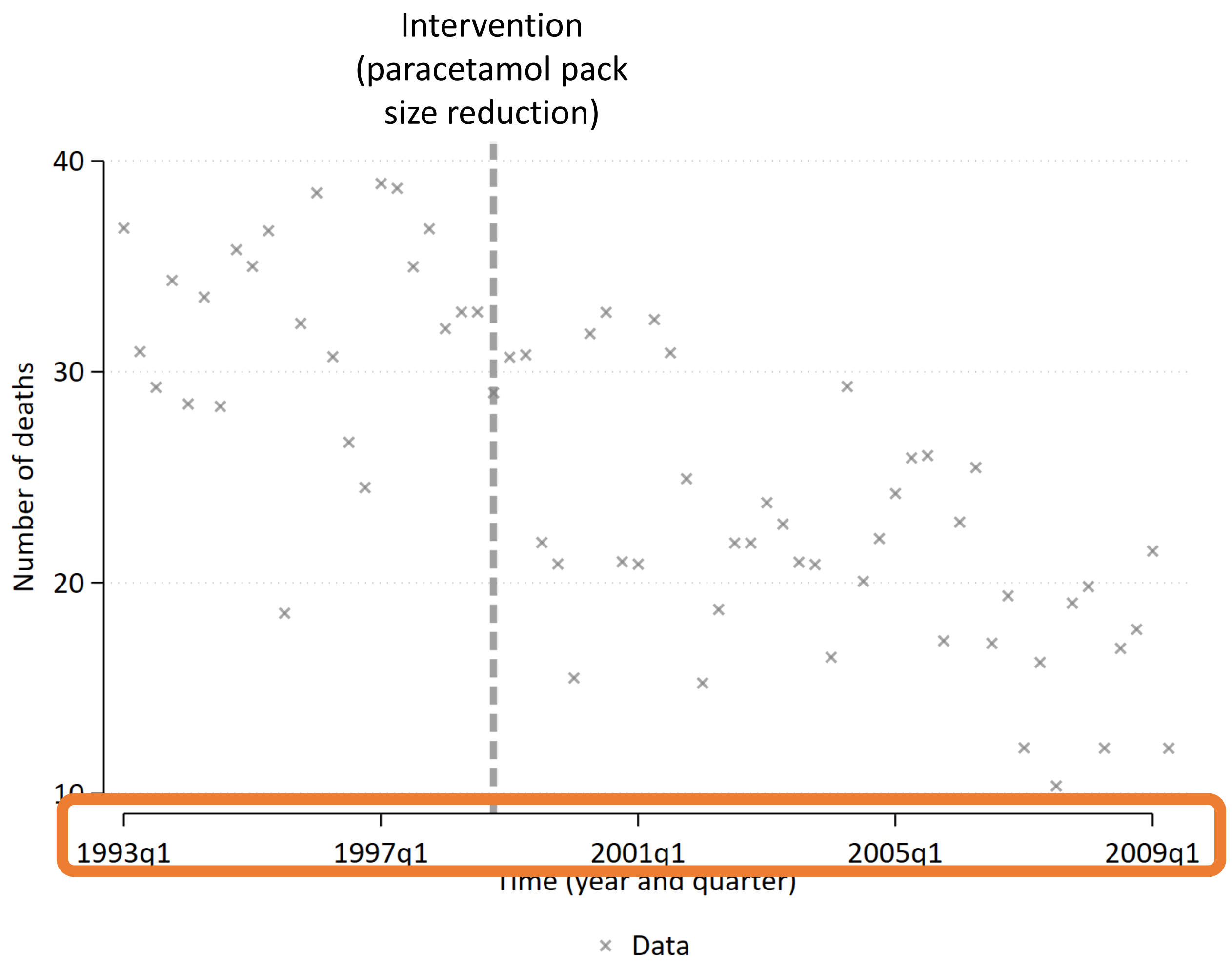
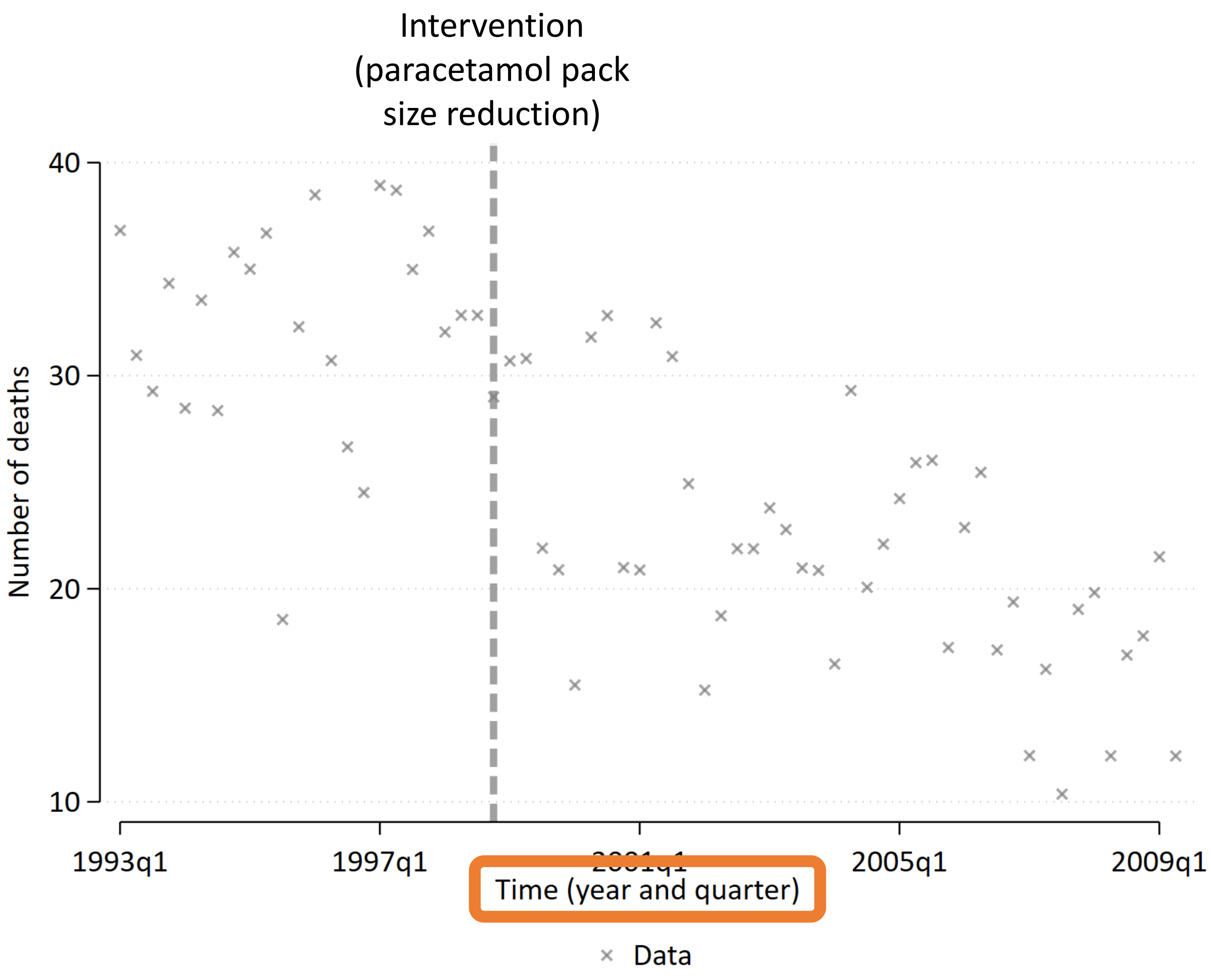


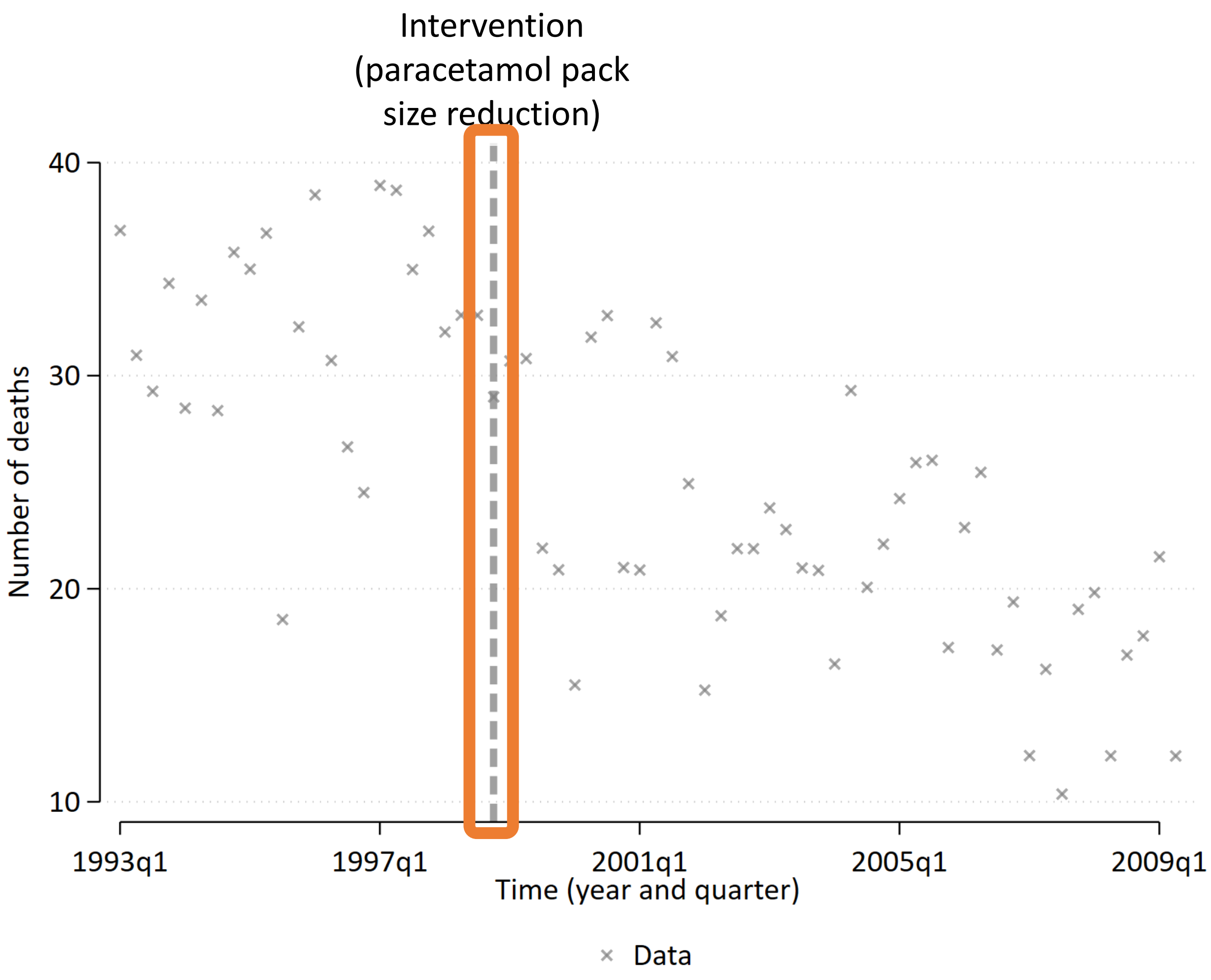
- Data is collected from a group of individuals (here from England and Wales)
- over a period of time
(here from 1993 to 2009)

Interrupted Time Series



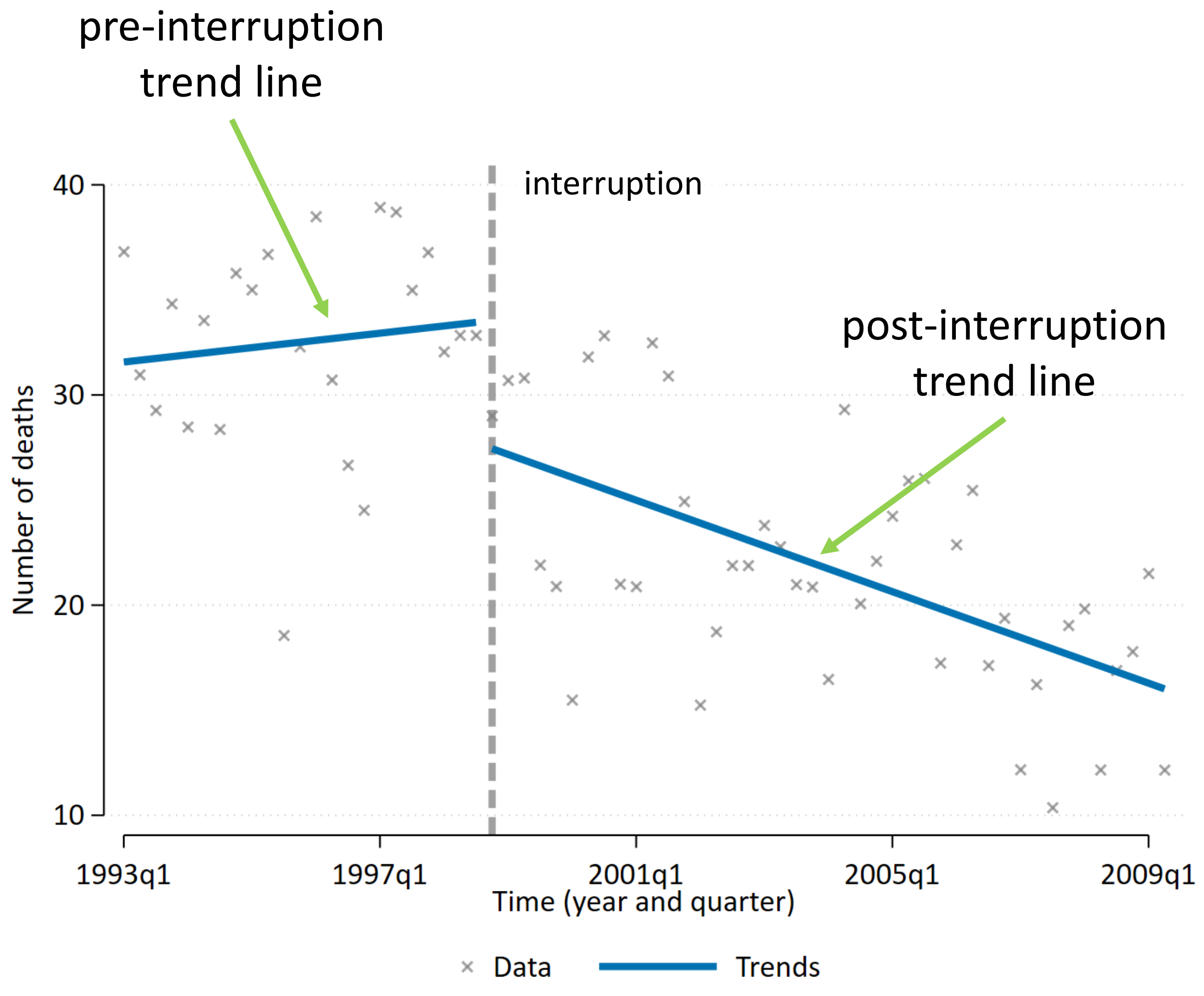
- Data is collected from a group of individuals (here from England and Wales)
- over a period of time (here from 1993 to 2009)
- and aggregated at time points (here quarterly)

Interrupted Time Series



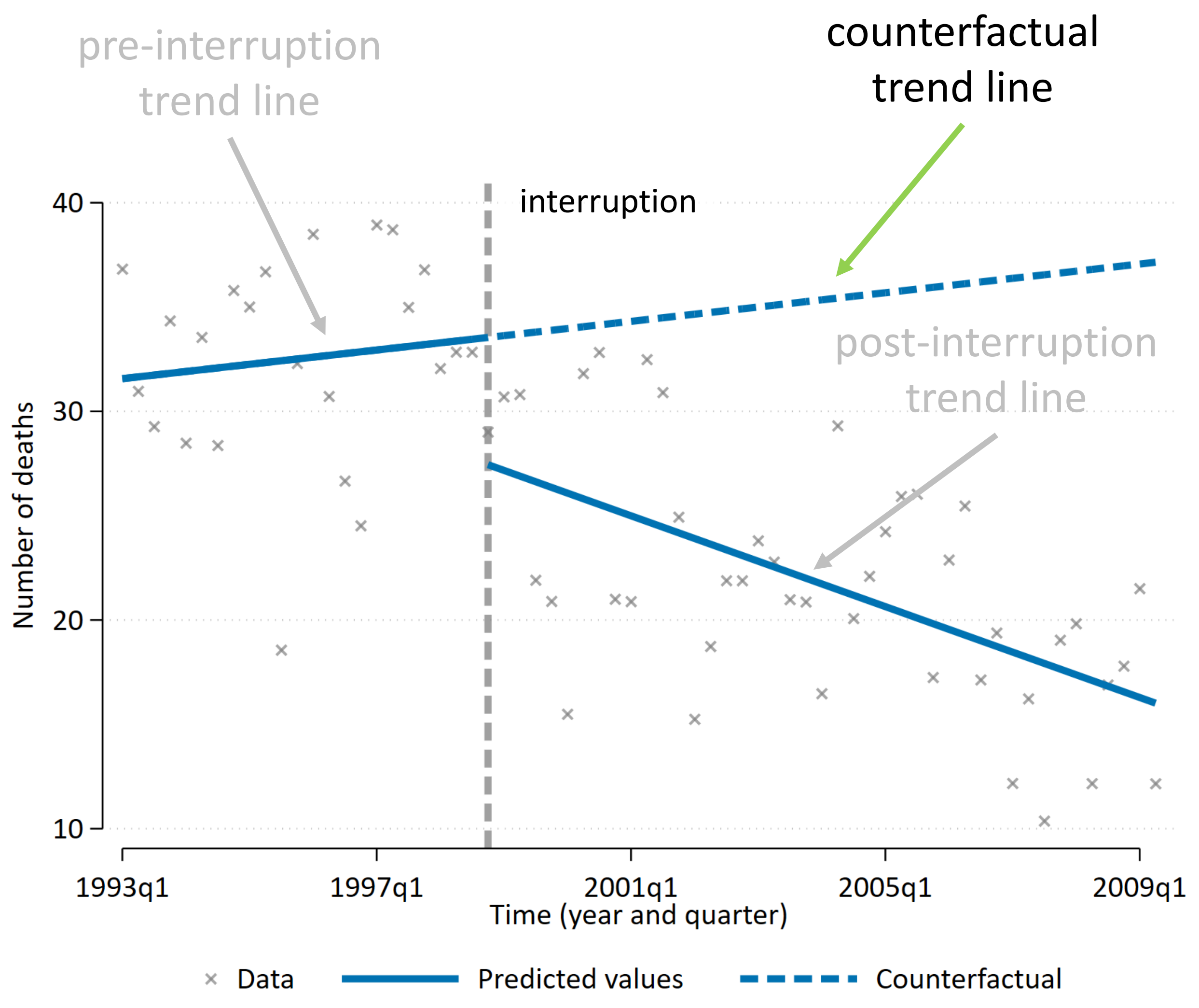
- Data is collected from a group of individuals (here from England and Wales)
- over a period of time (here from 1993 to 2009)
- and aggregated at time points (here quarterly)
- with a clear intervention time (first impact in 1998, quarter 4)

Interrupted Time Series



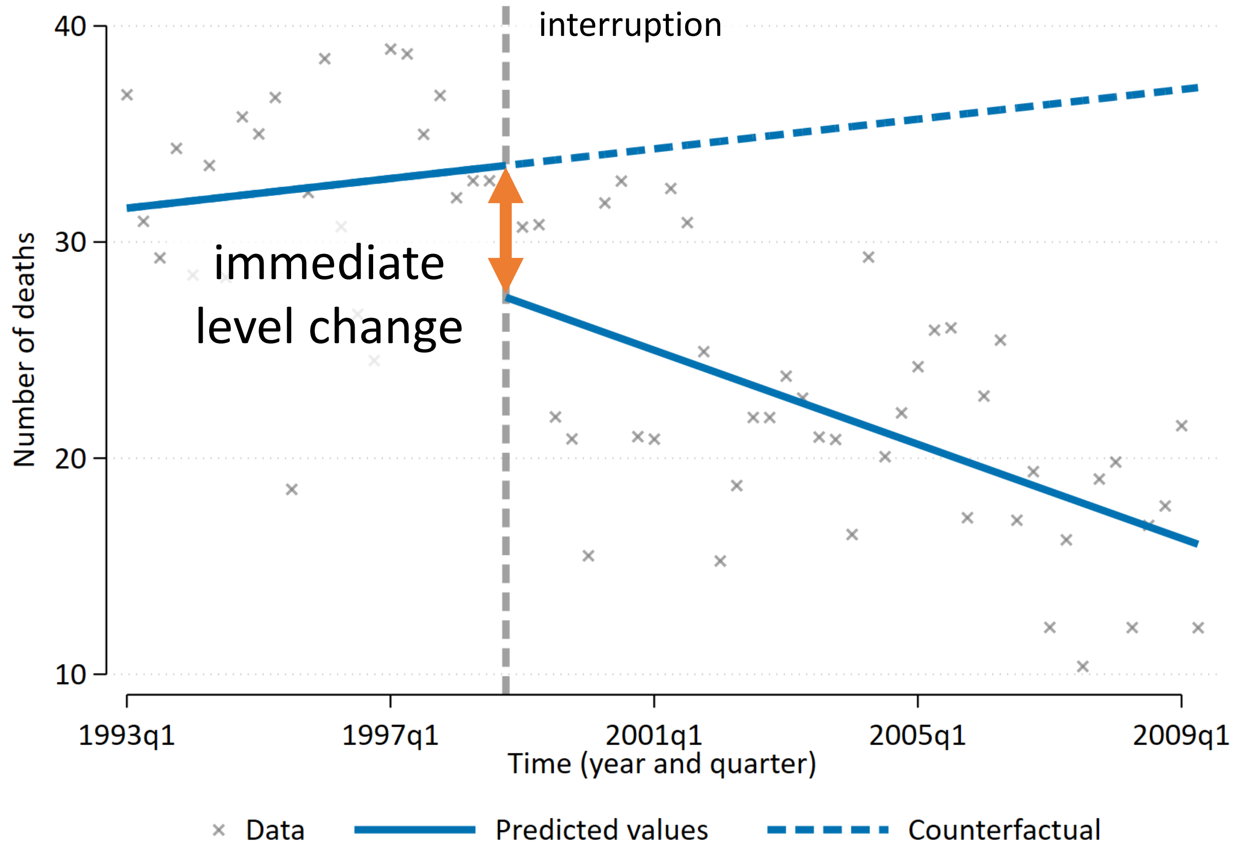
- Data from ITS are particularly amenable to visual display
- “Simple” before/after investigations ignore any underlying trends

Interrupted Time Series



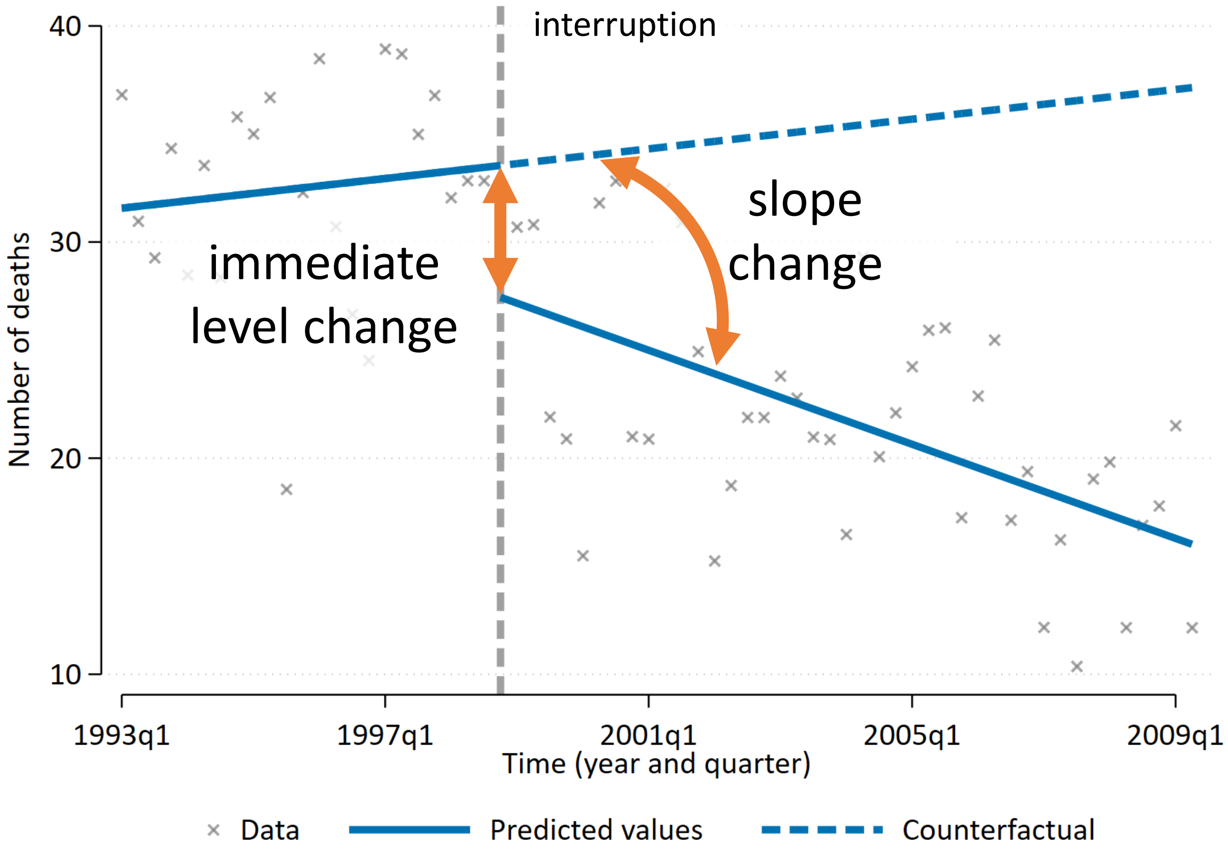
- Data from ITS are particularly amenable to visual display
- "Simple" before/after investigations ignore any underlying trends
- A counterfactual can be created by modelling the pre-interruption trend and using this to predict what would have happened in the absence of the interruption

Interrupted Time Series – estimating impact



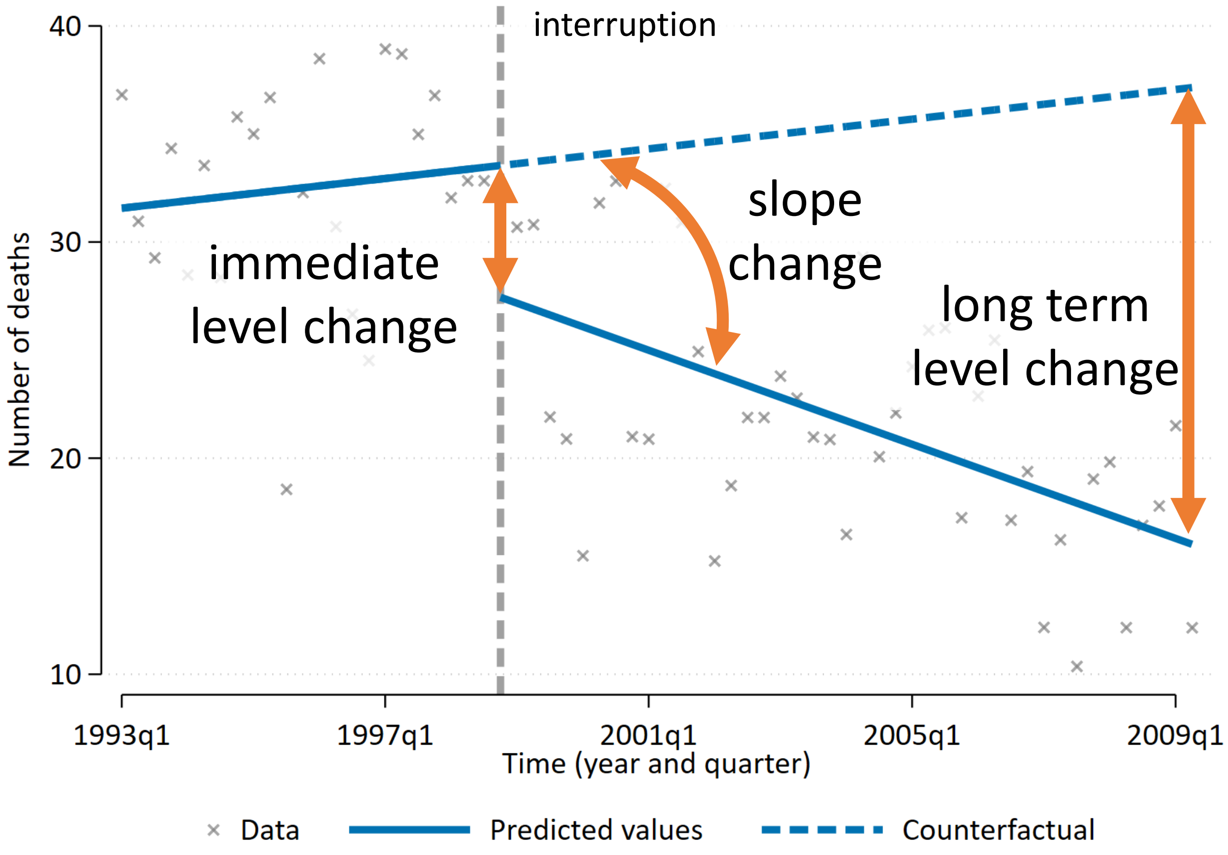
- The impact of the interruption can be measured in numerous ways
- e.g. differences between the counterfactual and post-interruption trend
  - immediate level change

Interrupted Time Series – estimating impact



- The impact of the interruption can be measured in numerous ways
- e.g. differences between the counterfactual and post-interruption trend
  - immediate level change
  - slope change

Interrupted Time Series – estimating impact

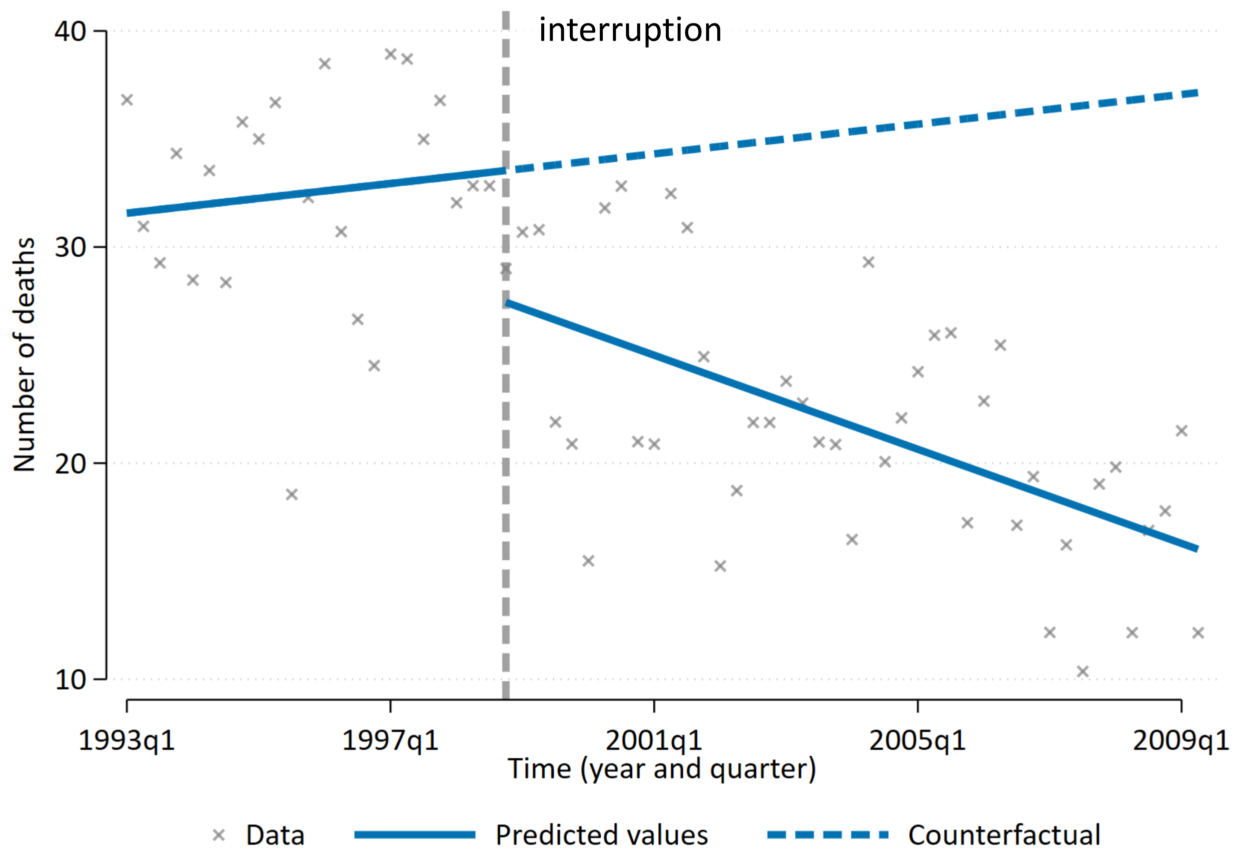


- The impact of the interruption can be measured in numerous ways
- e.g. differences between the counterfactual and post-interruption trend
  - immediate level change
  - slope change
  - long term level change

Interrupted Time Series - Model

Segmented linear regression

$$Y_t = \beta_0 + \beta_1 t + \beta_2 I_t + \beta_3 [t - T_I] I_t + \varepsilon_t$$



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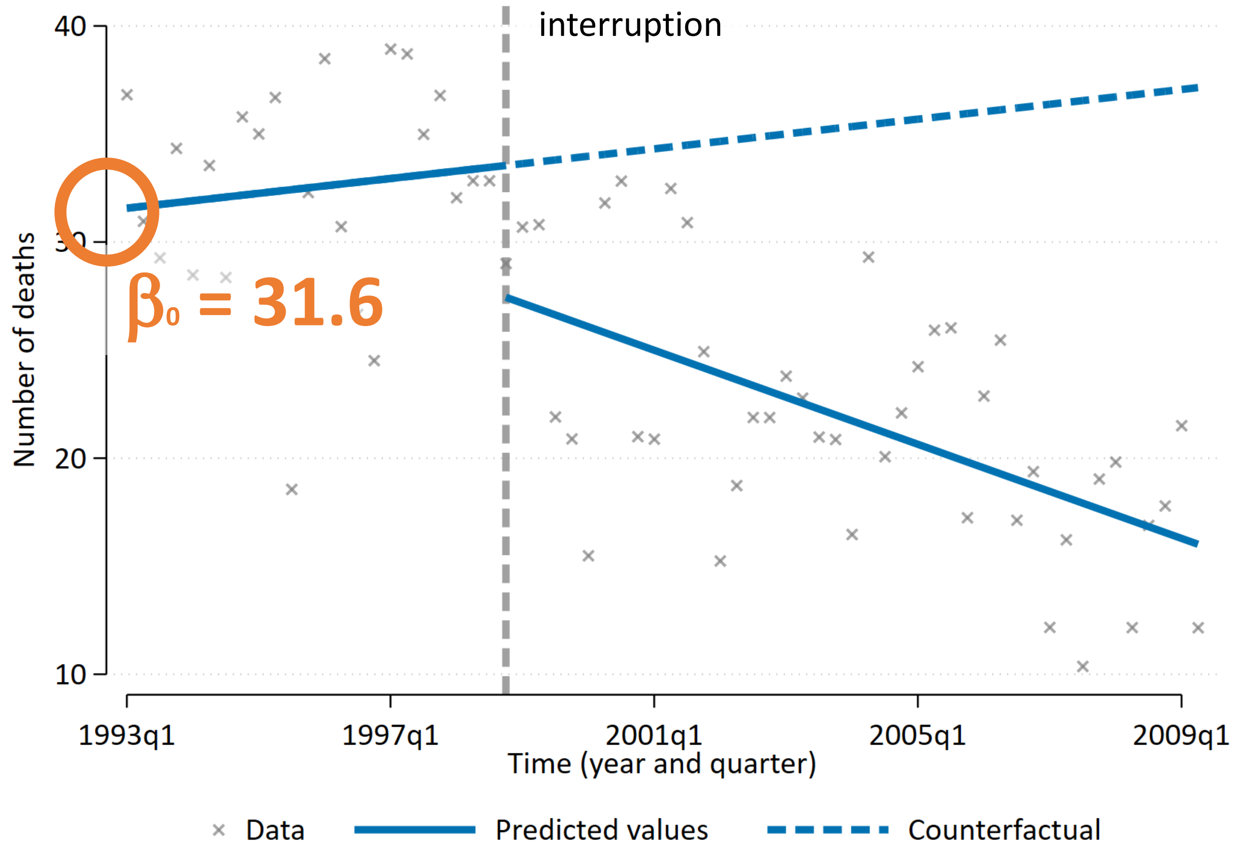
β_0 y-intercept



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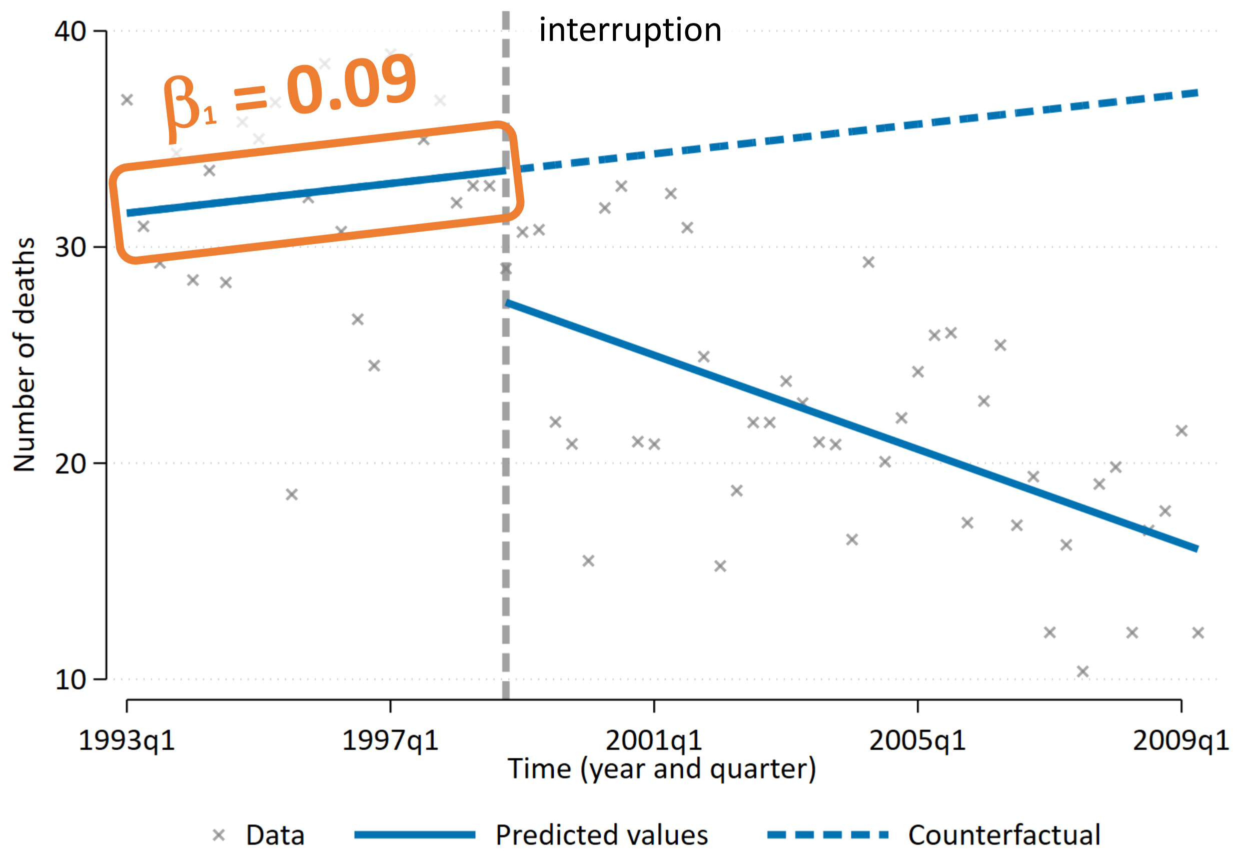

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β_1 pre-interruption slope (*t*=time)

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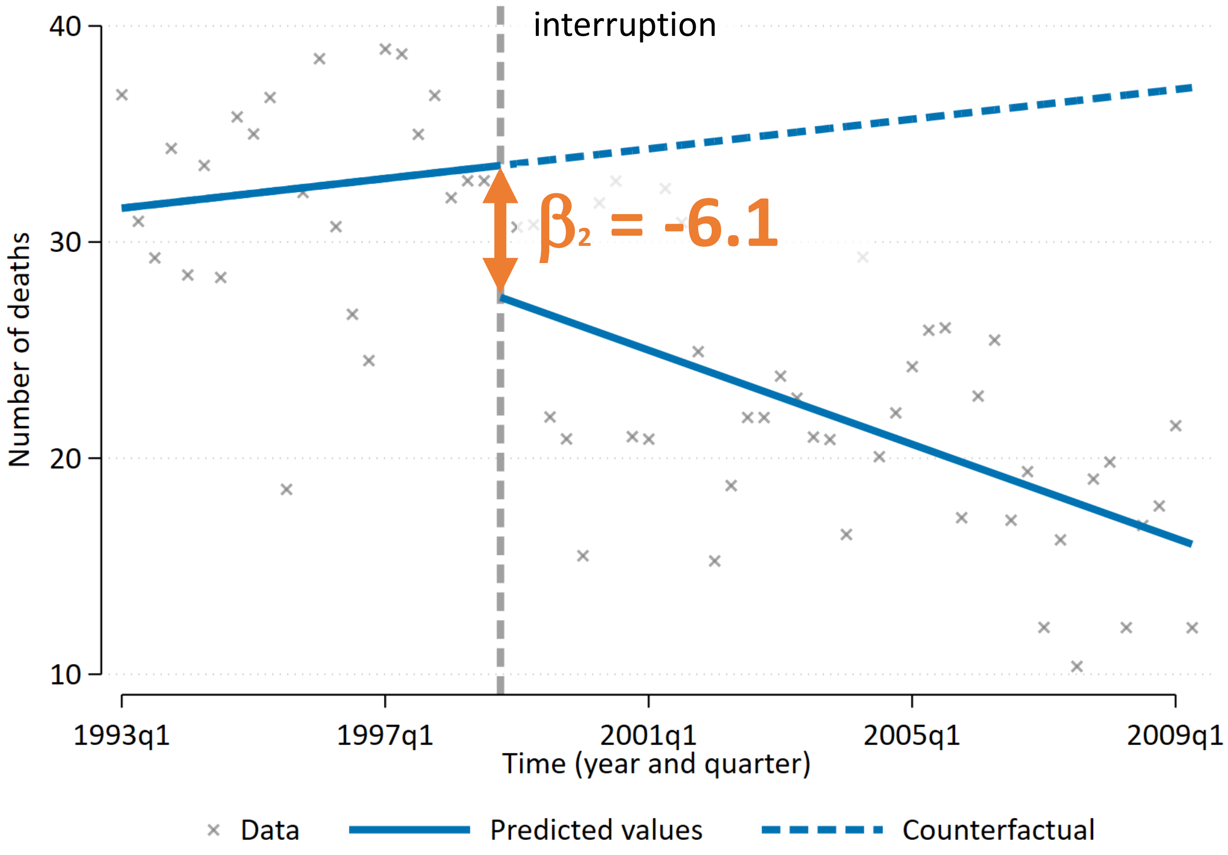

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I_t is an indicator variable which is

0 before the interruption and

1 after the interruption

β_2 level change

Interrupted Time Series - Model

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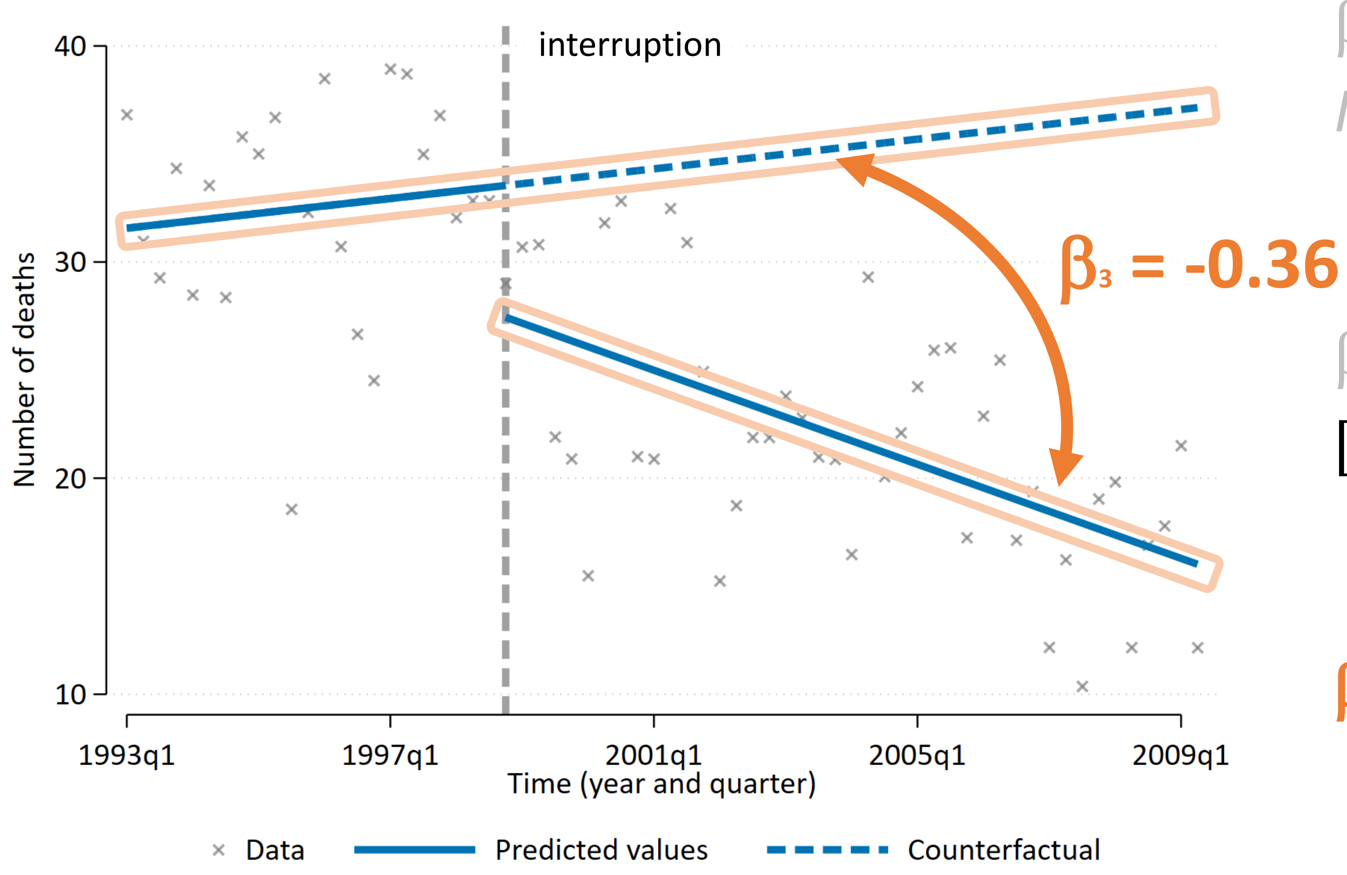

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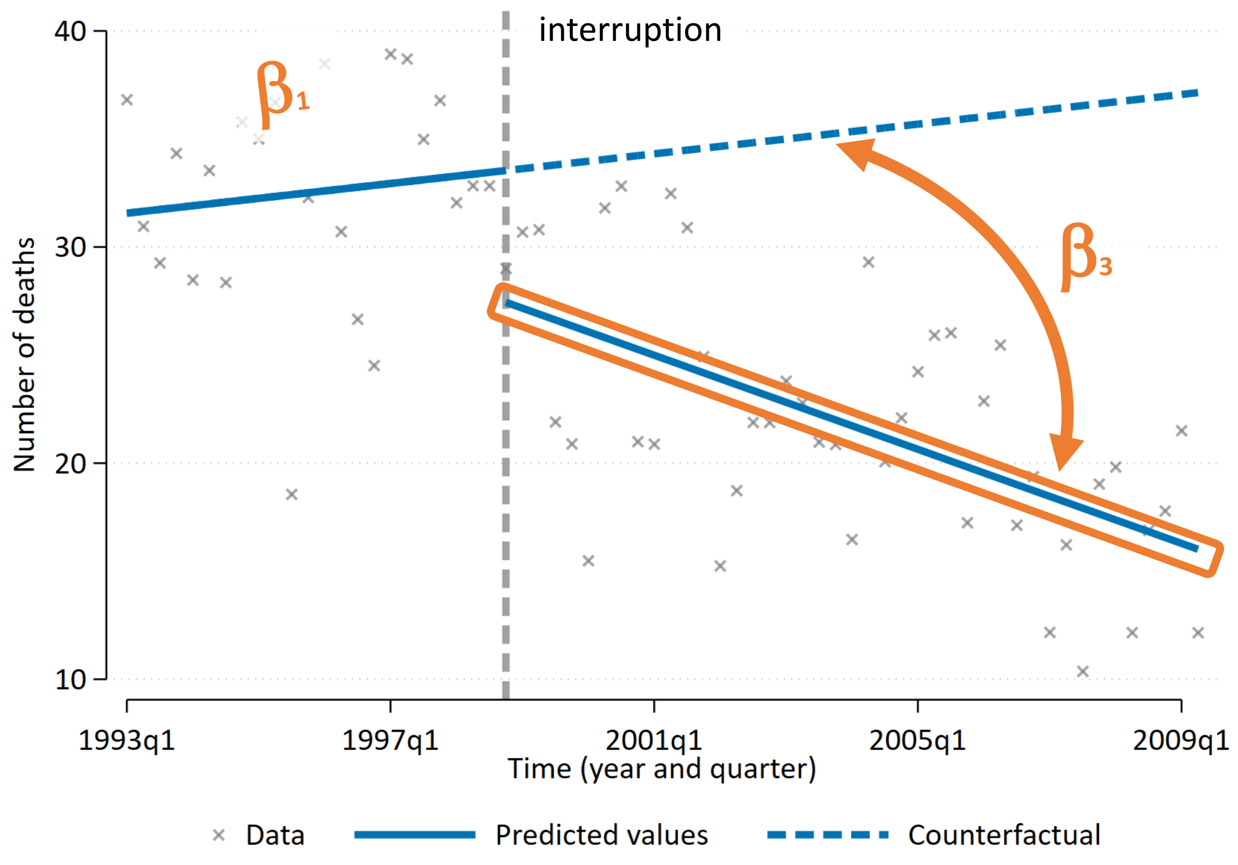
$[t - T_I] I_t$ gives us how many time units have passed since the interruption time (T_I=24)
0 before and 0,1,… after the interruption

β_3 slope change

Interrupted Time Series - Model

Segmented linear regression



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slope post-interruption = $\beta_1 + \beta_3$ = **-0.27**

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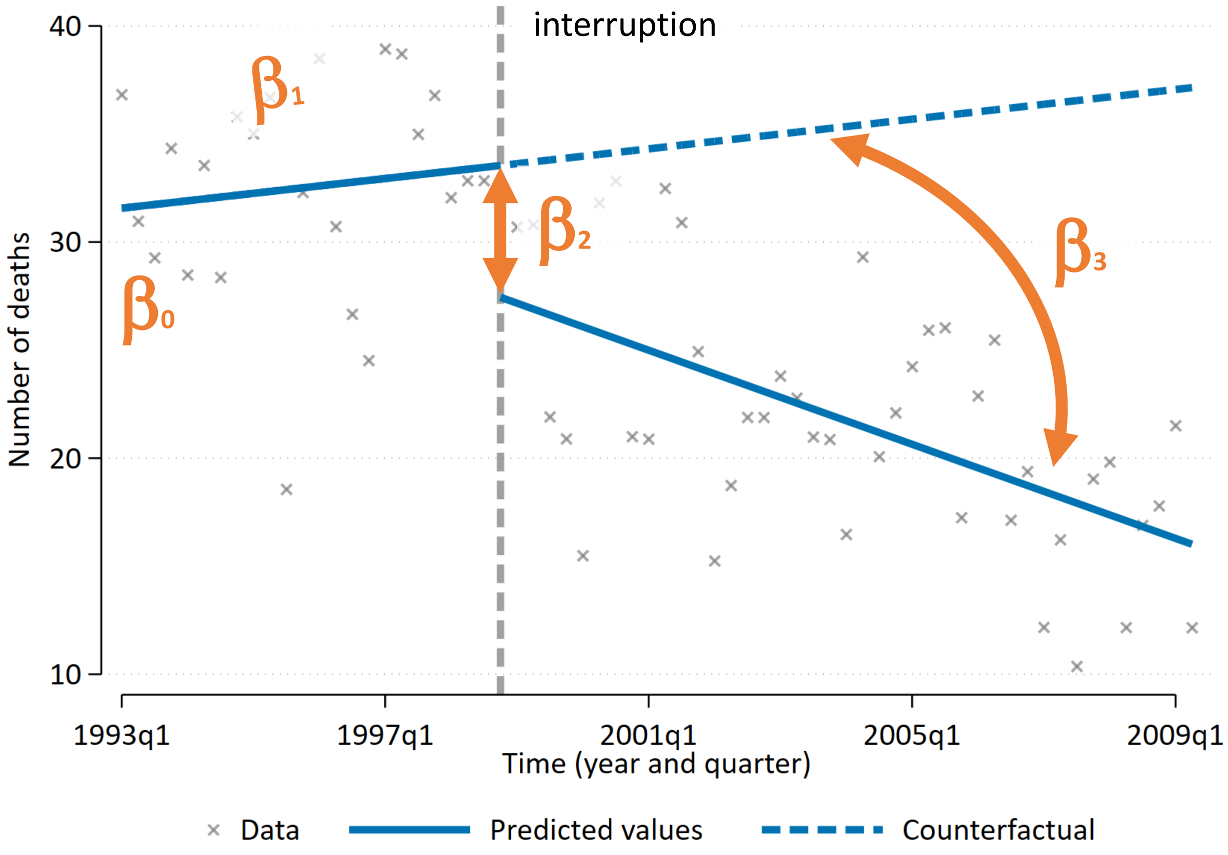

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β_3 slope change

slope post-interruption = $\beta_1 + \beta_3$

ε_t= error terms (deviations from the model)

Common ITS impact effect estimates

$$Y_t = \beta_0 + \beta_1 t + \beta_2 I_t + \beta_3 [t - T_I] I_t + \varepsilon_t$$

Immediate level-change	The absolute increase (or decrease) in the number of paracetamol related deaths when the interruption first occurs compared to if it had not occurred	$\beta_2 = -6.1$
Slope-change	The additional increase (or decrease) in the number of deaths that occur per quarter compared with the pre-interruption trend	β_3
Long-term level-change	The absolute increase (or decrease) in the number of deaths at the timepoint of interest (denoted by p) compared to if the interruption had not occurred. For example, if the time of interest was the 4th quarter of 2005 timepoint, $T_I = 24$ and $p = 52$. $(p - T_I)$ = (52-24) = 28, ie. 7 years after interruption.	$\beta_2 + \beta_3 (p - T_I)$

James Lopez Bernal et al, 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

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

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ITS Complexities

(why you might need to consult a statistician)

- Time series data are not always independent

$$Y_t = \beta_0 + \beta_1 t + \beta_2 I_t + \beta_3 [t - T_I] I_t + \varepsilon_t$$

ITS Complexities

(why you might need to consult a statistician)

- Time series data are not always independent
  - Autocorrelation

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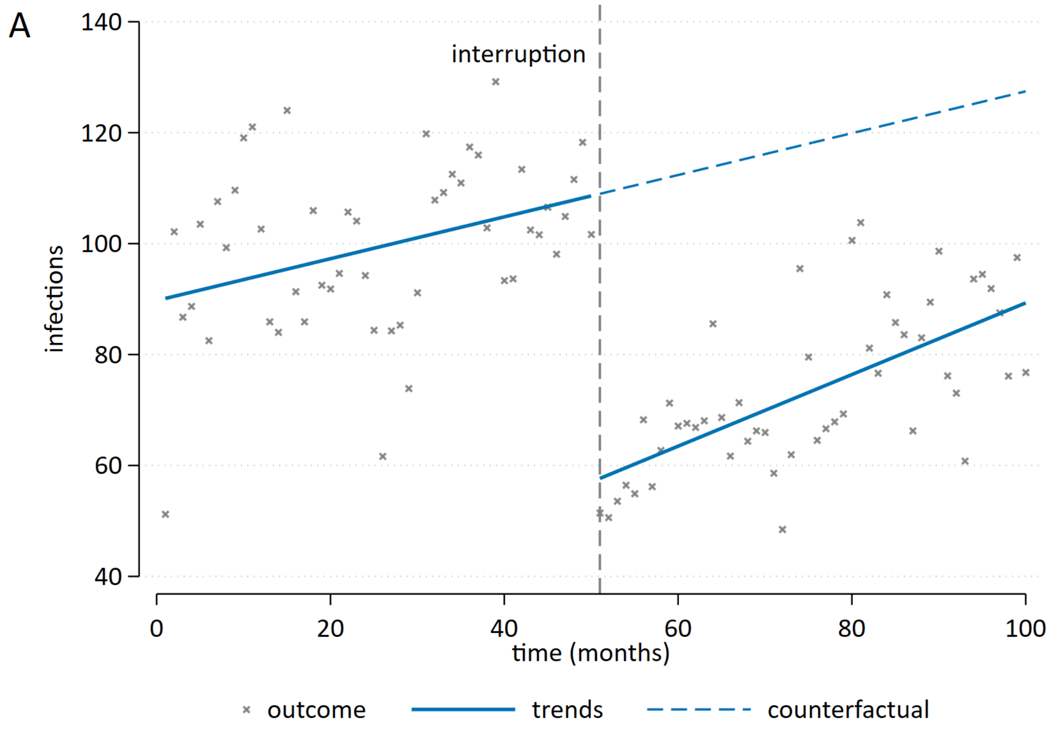
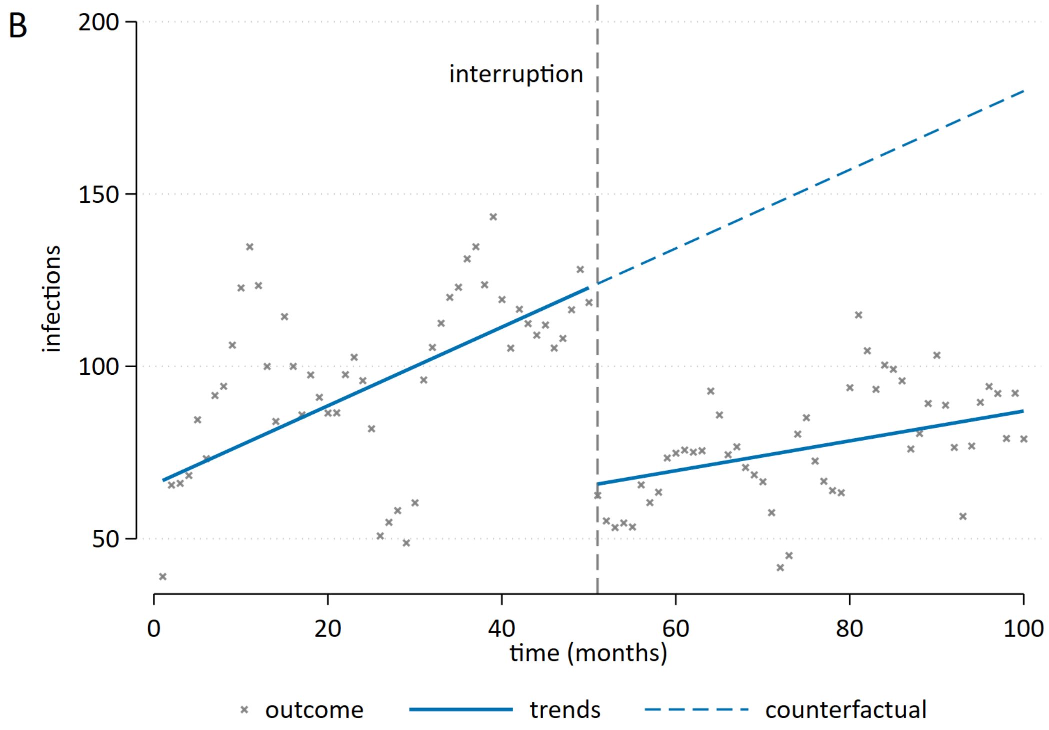
A: No autocorrelation – random error terms



B: Autocorrelation – error terms influenced by previous data



ITS Complexities

(why you might need to consult a statistician)

- Time series data are not always independent
  - Autocorrelation
  - Seasonality

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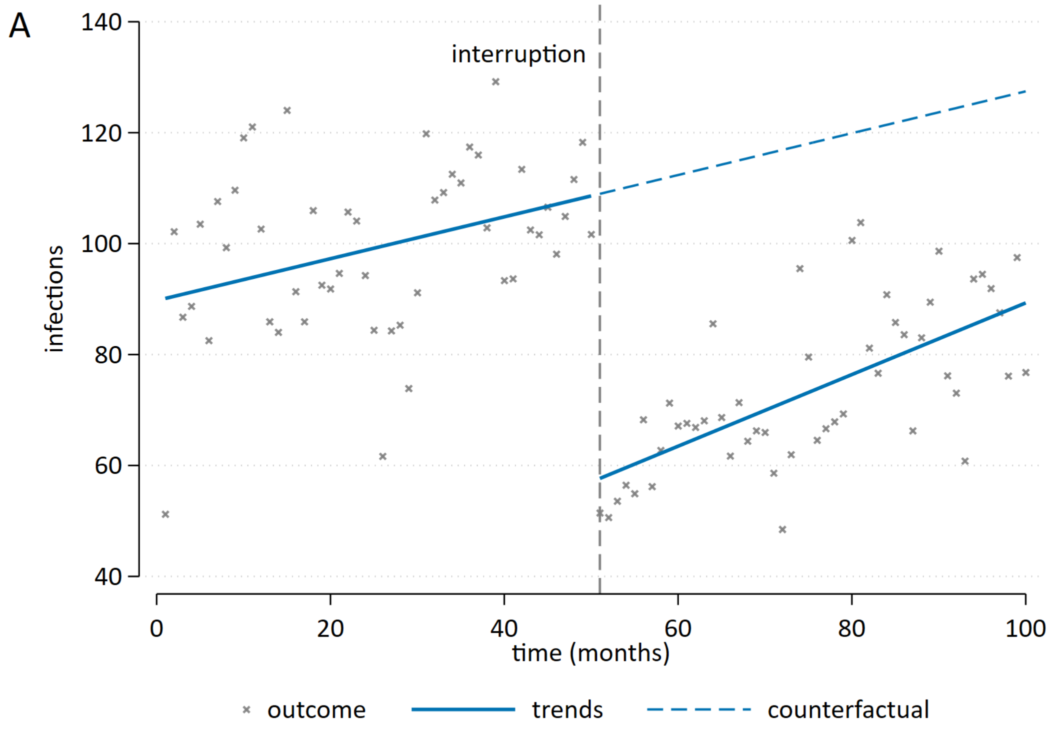
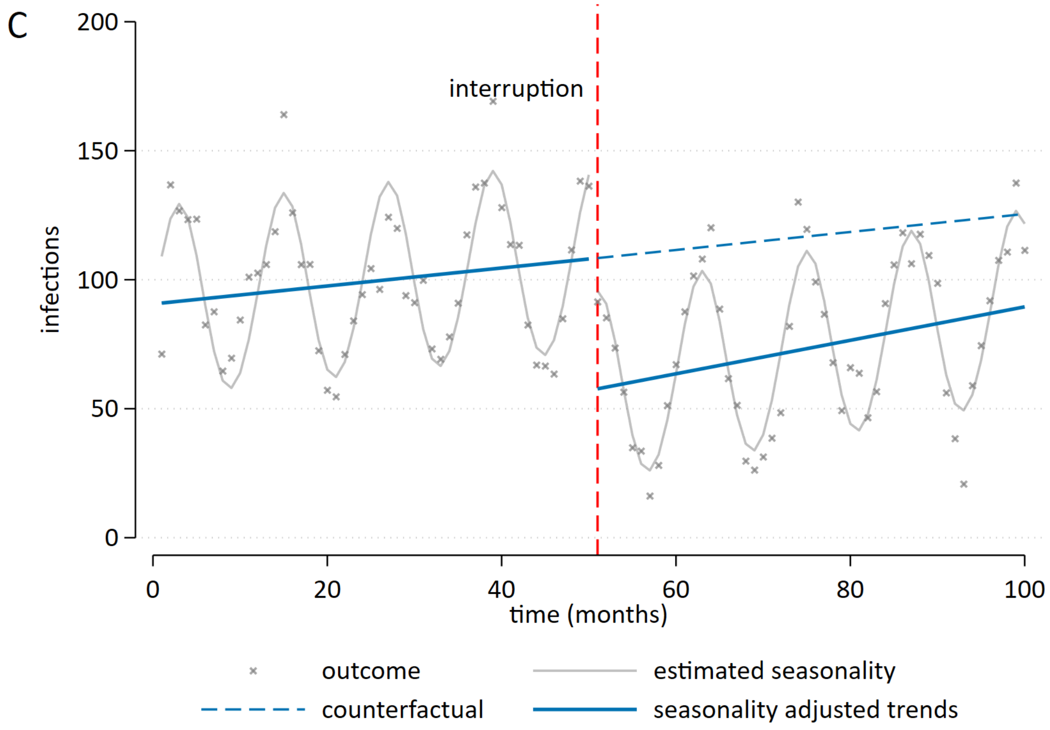
A: No autocorrelation – random error terms



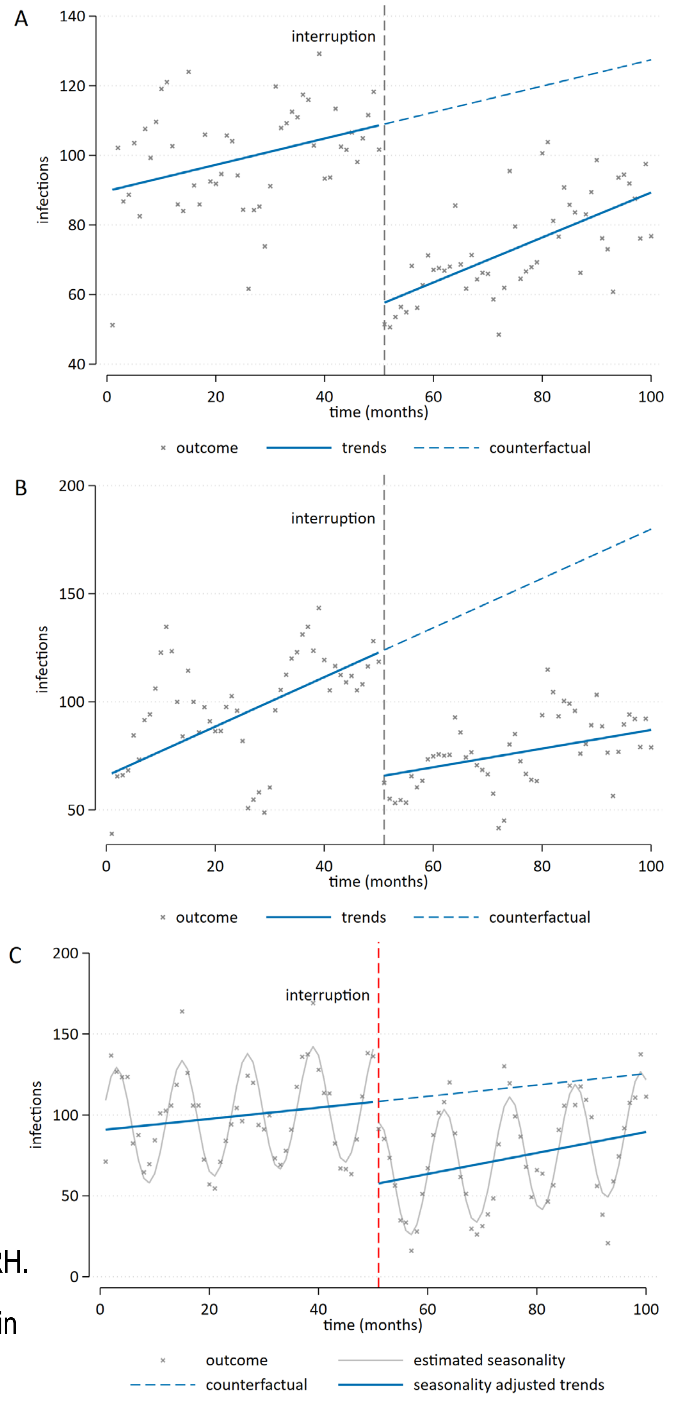
C: Seasonality – periodic patterns in the data (here 12 monthly)



ITS Complexities

(why you might need to consult a statistician)

- Time series data not always independent
  - Autocorrelation
  - Seasonality
- Statistical method performance depends on:
  - Number of datapoints
    - Need a reasonable number of points (12-24) to estimate and adjust for autocorrelation
    - With few datapoints, ordinary least squares regression may be the preferred method
    - Need several “cycles” to be able to adjust for seasonality well



Turner, S.L., Forbes, A.B., Karahalios, A. et al. Evaluation of statistical methods used in the analysis of interrupted time series studies: a simulation study. BMC Med Res Methodol 21, 181 (2021). https://doi.org/10.1186/s12874-021-01364-0

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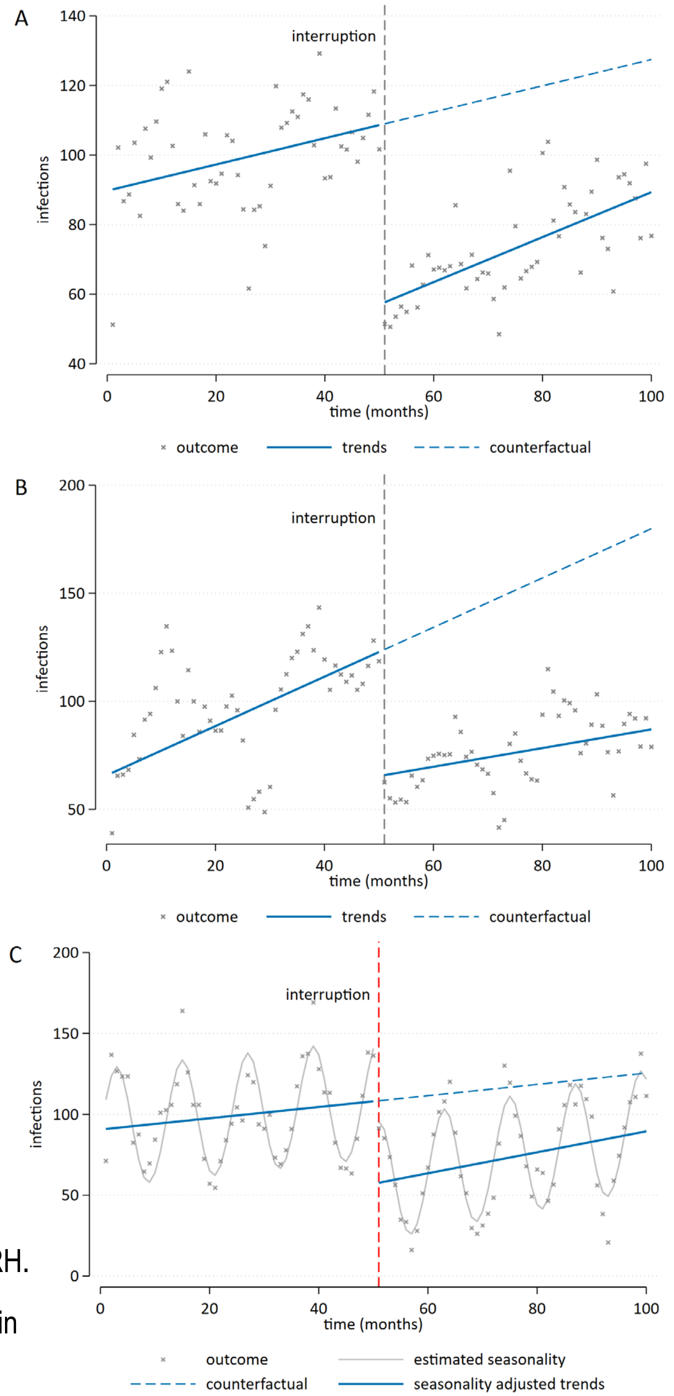
Bottomley C, Ooko M, Gasparrini A, Keogh RH. In praise of Prais-Winsten: An evaluation of methods used to account for autocorrelation in interrupted time series. Stat Med. 2023 Apr 15;42(8):1277-1288. doi: 10.1002/sim.9669.

ITS Complexities

(why you might need to consult a statistician)

- Time series data not always independent
  - Autocorrelation
  - Seasonality
- Statistical method performance depends on:
  - Number of datapoints
    - Need a reasonable number of points (12-24) to estimate and adjust for autocorrelation
    - With few datapoints, ordinary least squares regression may be the preferred method
    - Need several “cycles” to be able to adjust for seasonality well
- Type of data (continuous, count, …)



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ITS Complexities
(why you might need to consult a statistician)

- A variety of impact models
  - Changes in level/slope (immediate/delayed, sustained/temporary)
  - Transition periods
  - Multiple interruptions

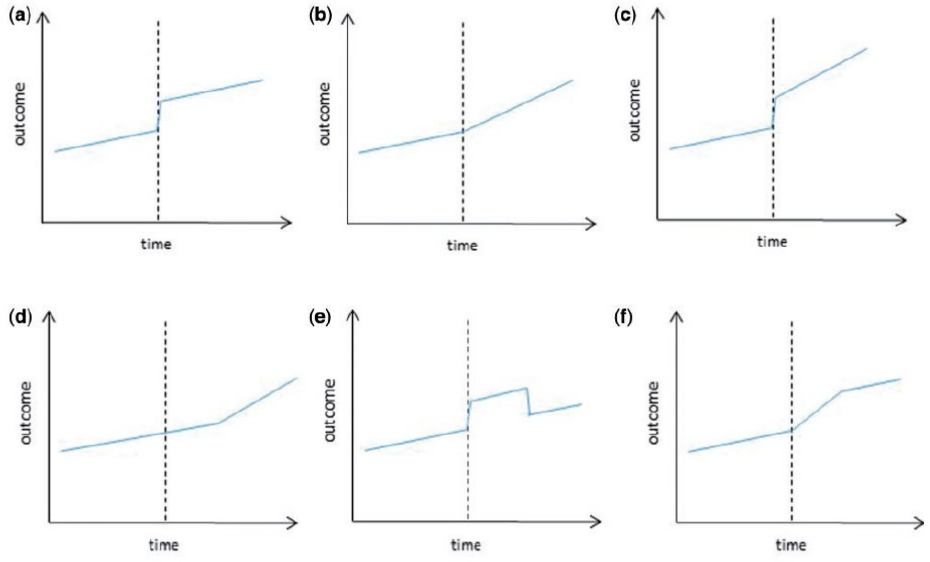


Figure 2 from Lopez Bernal et al. Interrupted time series regression for the evaluation of public health interventions: a tutorial, International Journal of Epidemiology, Volume 46, Issue 1, February 2017, Pages 348–355, https://doi.org/10.1093/ije/dyw098

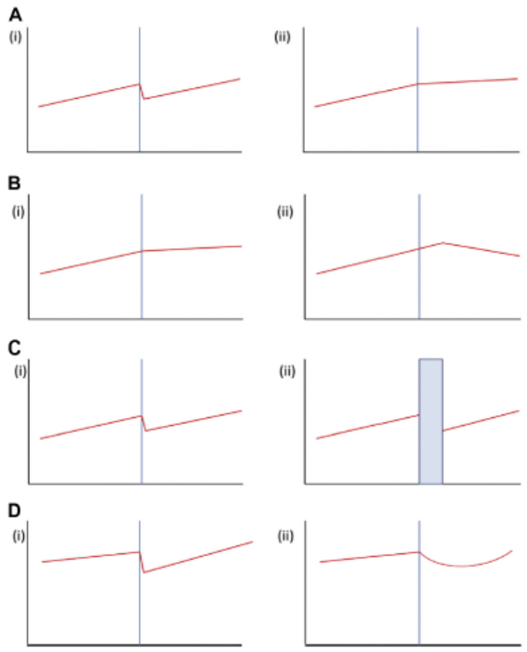
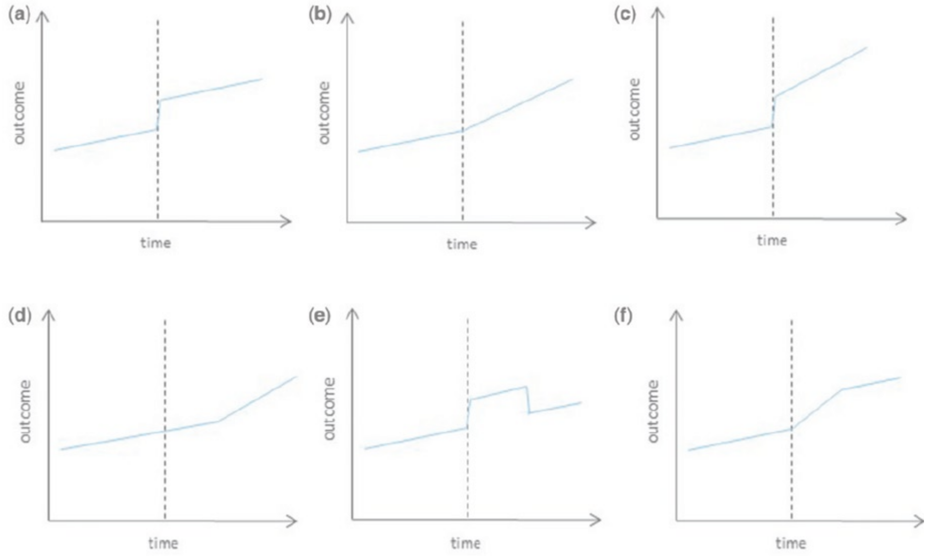


Figure 3 from Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. J Clin Epidemiol. 2018 Nov;103:82-91. doi: 10.1016/j.jclinepi.2018.05.026. Epub 2018 Jun 6. PMID: 29885427.

ITS Complexities
(why you might need to consult a statistician)

- A variety of impact models
  - Changes in level/slope (immediate/delayed, sustained/temporary)
  - Transition periods
  - Multiple interruptions
- Control series



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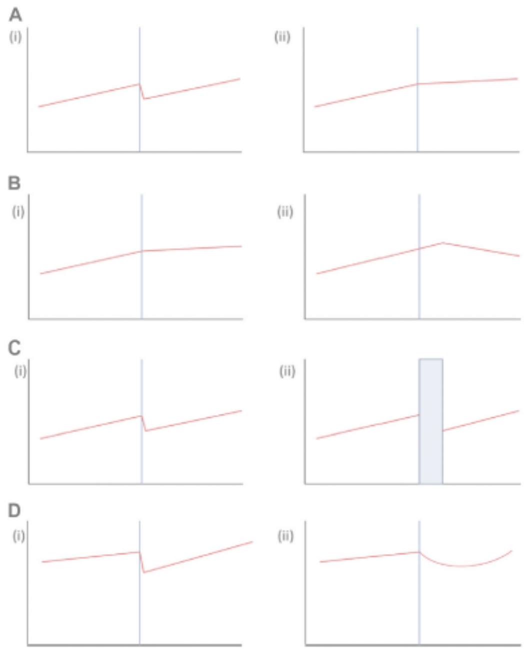

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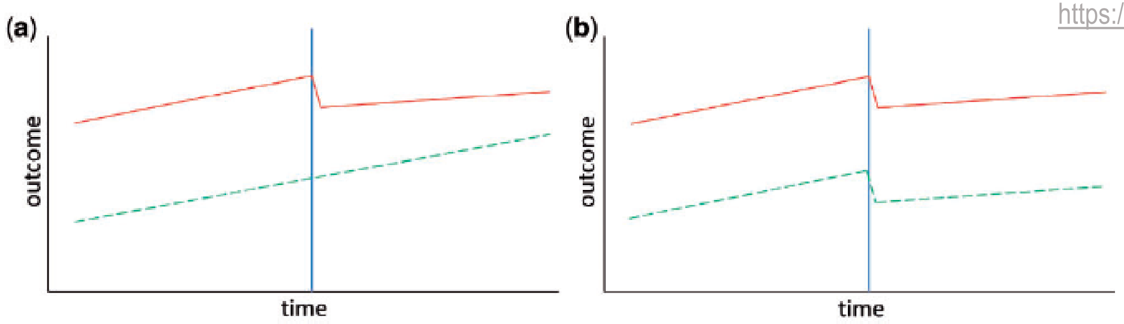

Figure 1 from Lopez Bernal et al. The use of controls in interrupted time series studies of public health interventions, International Journal of Epidemiology, Volume 47, Issue 6, December 2018, Pages 2082–2093, https://doi.org/10.1093/ije/dyy135

Why might a systematic reviewer need to reanalyse?

- Methods and results are often incompletely reported

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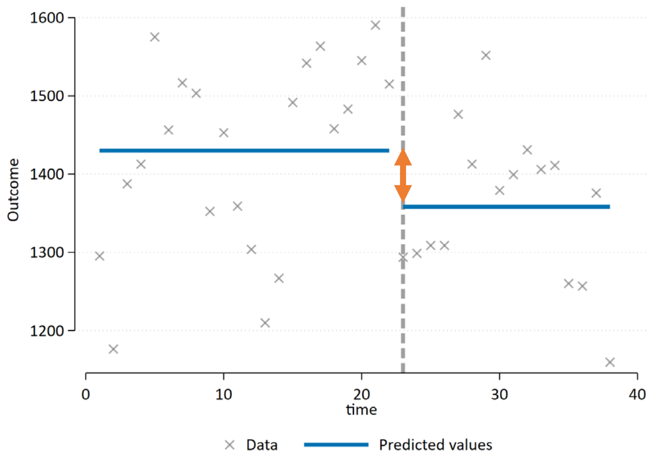
- Impact measures may be inconsistently reported across studies
    - Before/after (note – this is equivalent to comparing the means of the pre and post periods)



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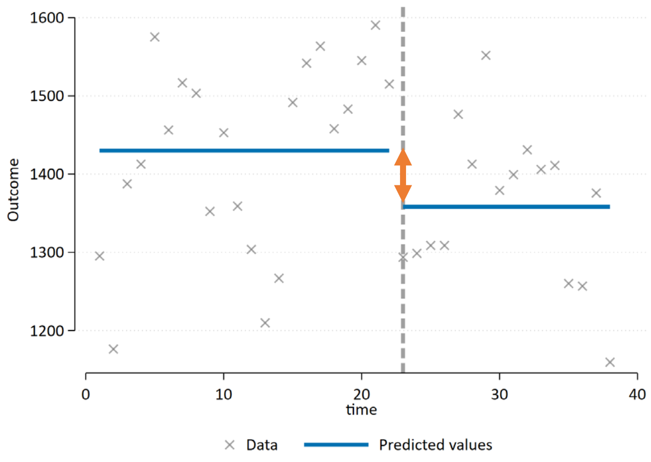

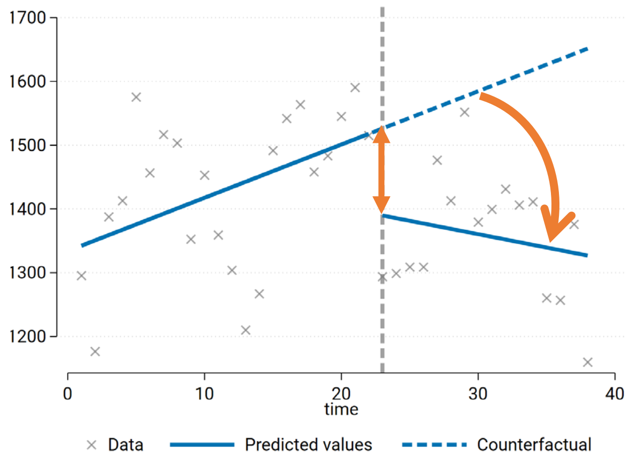

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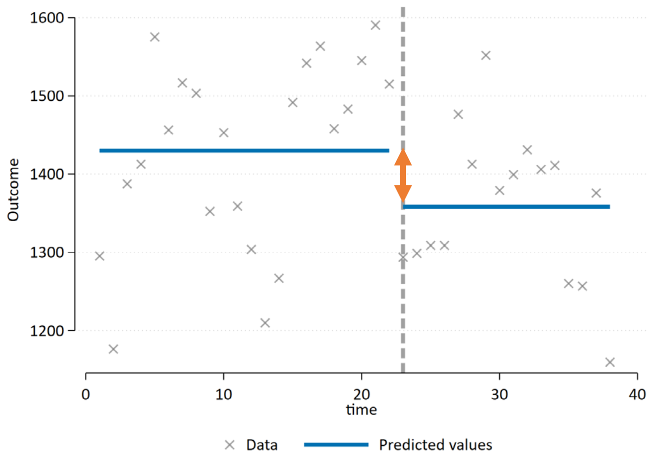
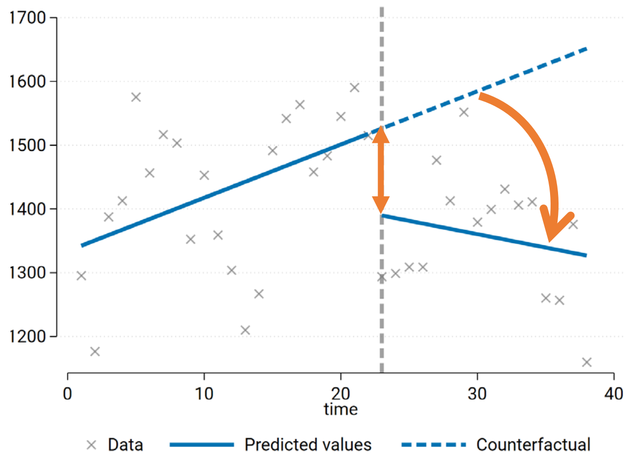
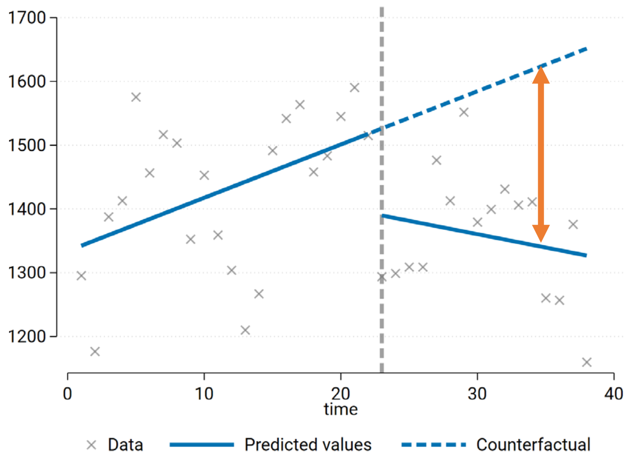
  - Level change at later time







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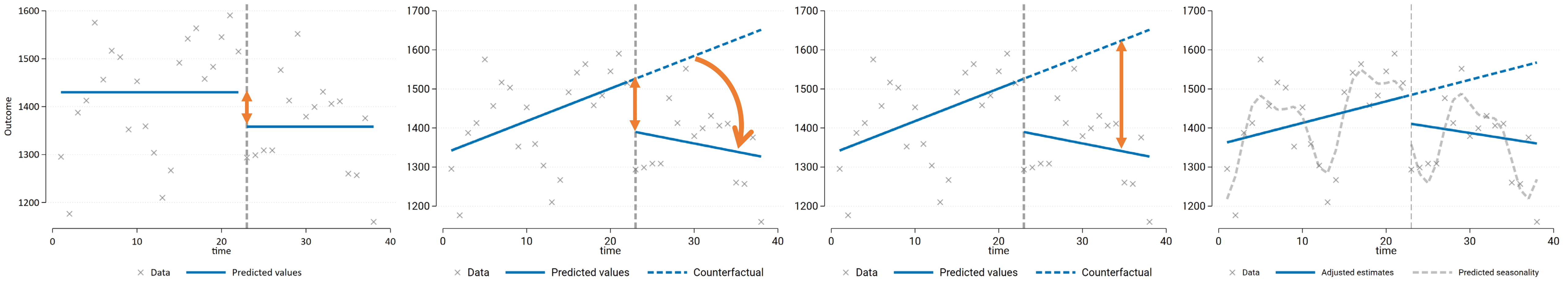

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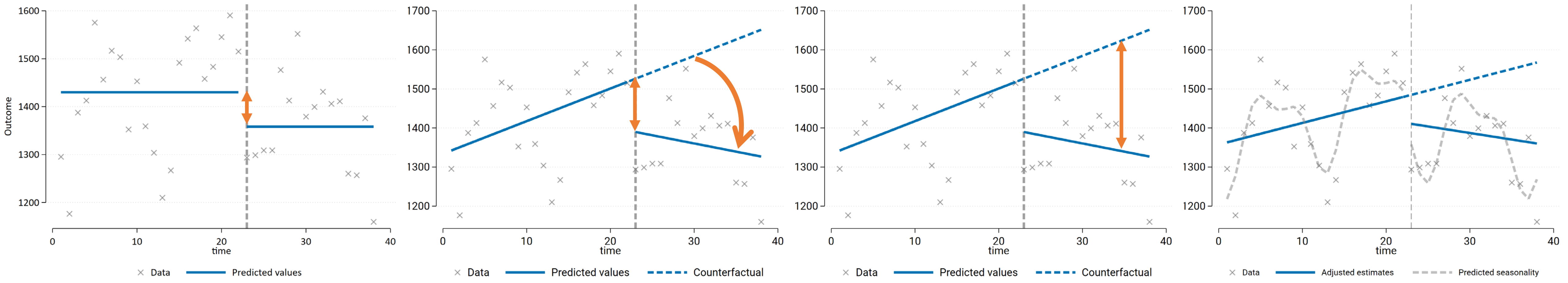
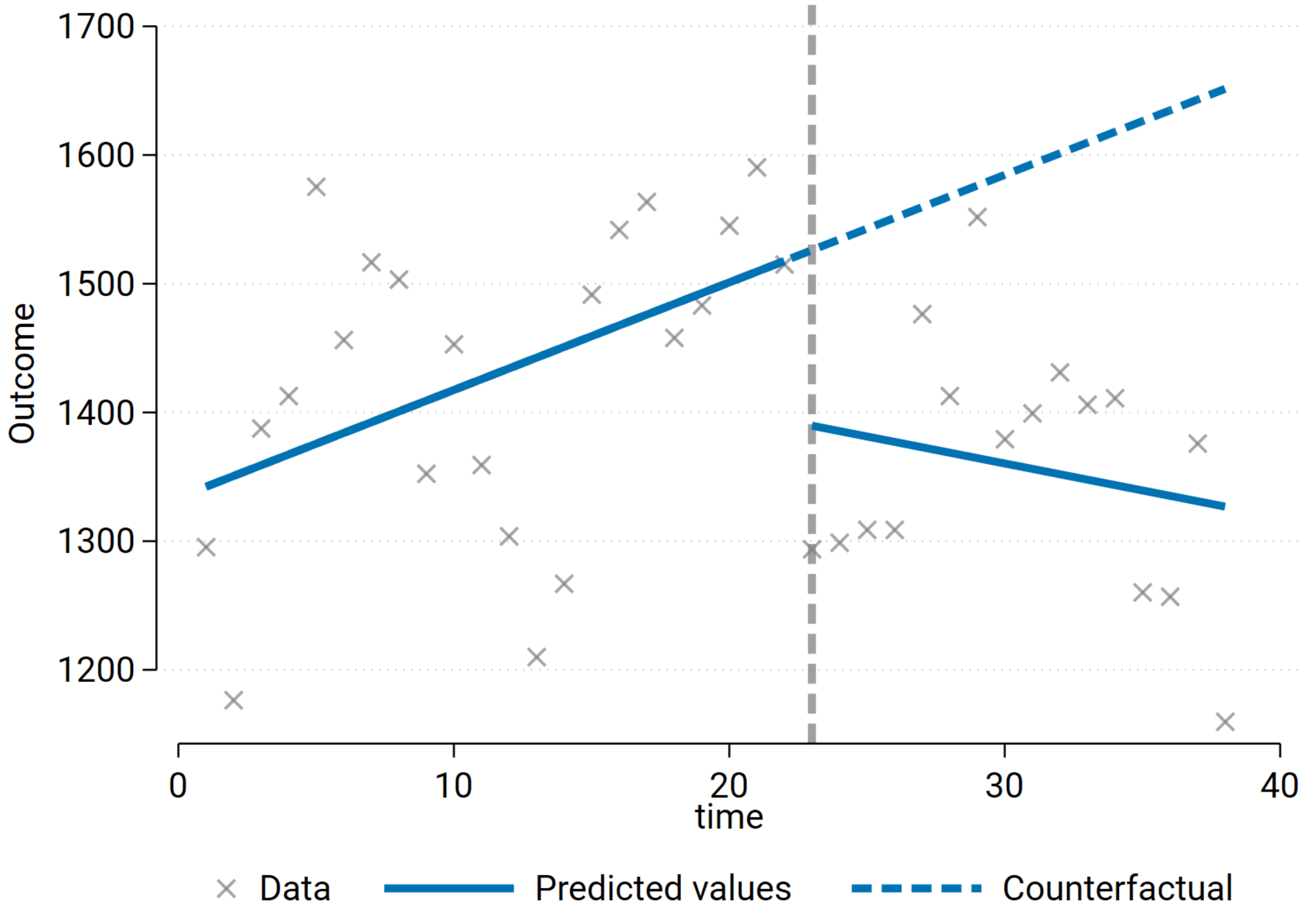


* 68% of ITS reviews reanalysed study data "Methodological systematic review recommends improvements to conduct and reporting when meta-analyzing interrupted time series studies", Korevaar et al., 2022, DOI: 10.1016/j.jclinepi.2022.01.010

Obtaining data

- Unlike other study designs, ITS analyses do not require individual participant data
- Most ITS studies include a graph of time series data (>90%*)
- Digital data extraction can be used to obtain data**



* "Design characteristics and statistical methods used in interrupted time series studies evaluating public health interventions: a review", Turner et al., 2020 https://doi.org/10.1016/j.jclinepi.2020.02.006

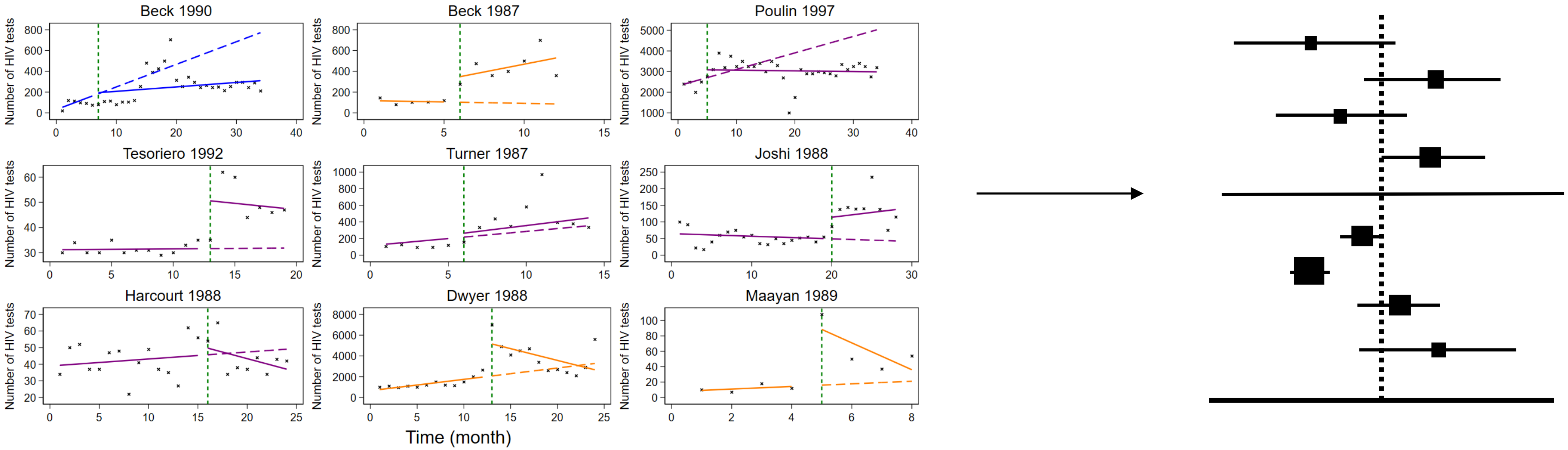
** "Effect estimates can be accurately calculated with data digitally extracted from interrupted time series graphs", Turner et al., 2023 https://doi.org/10.1002/jrsm.1646

Questions on ITS analysis?

- Description of an ITS study
- Measuring the impact of an interruption
- Example of an ITS model
- Obtaining estimates of the effect measures of interest
- Considering complex features of time series data
- Why you may need to re-analyse data as a systematic reviewer

Meta-analysis outline

- Obtaining estimates of the effect measures of interest
- Standardisation
- Selecting the meta-analysis methods
- Retrieving and interpreting the meta-analytic results



Meta-analysis outline

- **Obtaining estimates of the effect measures of interest**
- Standardisation
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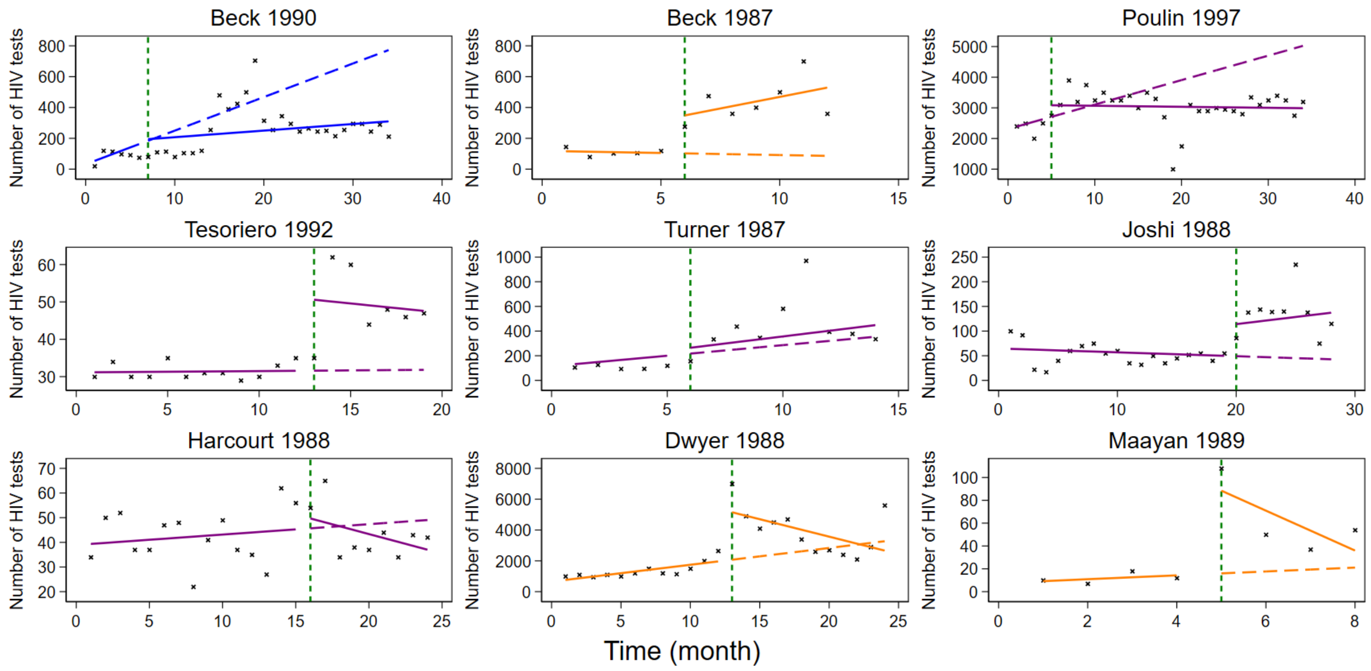
- Retrieving and interpreting the meta-analytic results

Obtaining estimates of the effect measures of interest

- Can we extract the effects of interest from the primary ITS studies?
  - Did they calculate our desired effect measures?
  - Report the desired effect measures (with both effect estimate and standard error)?
  - Use the appropriate/desired ITS analysis method?
- Do we need to reanalyse?
- What effect measures are possible for a given ITS study?



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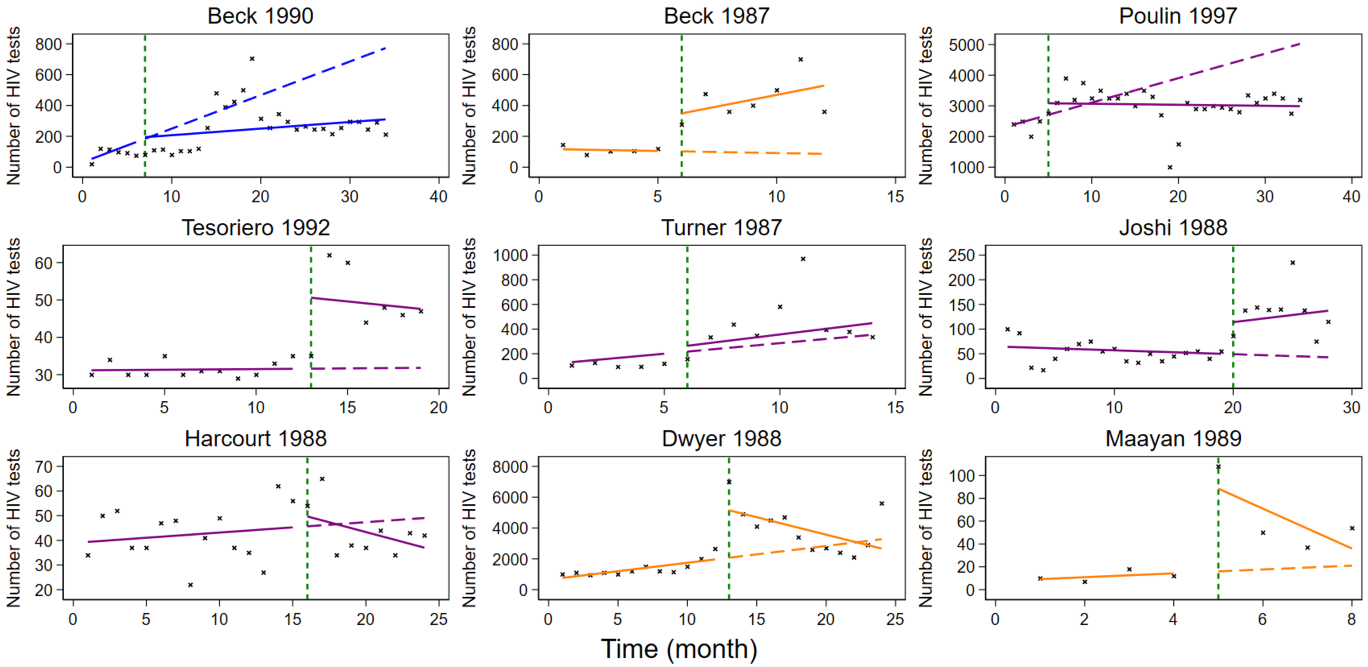
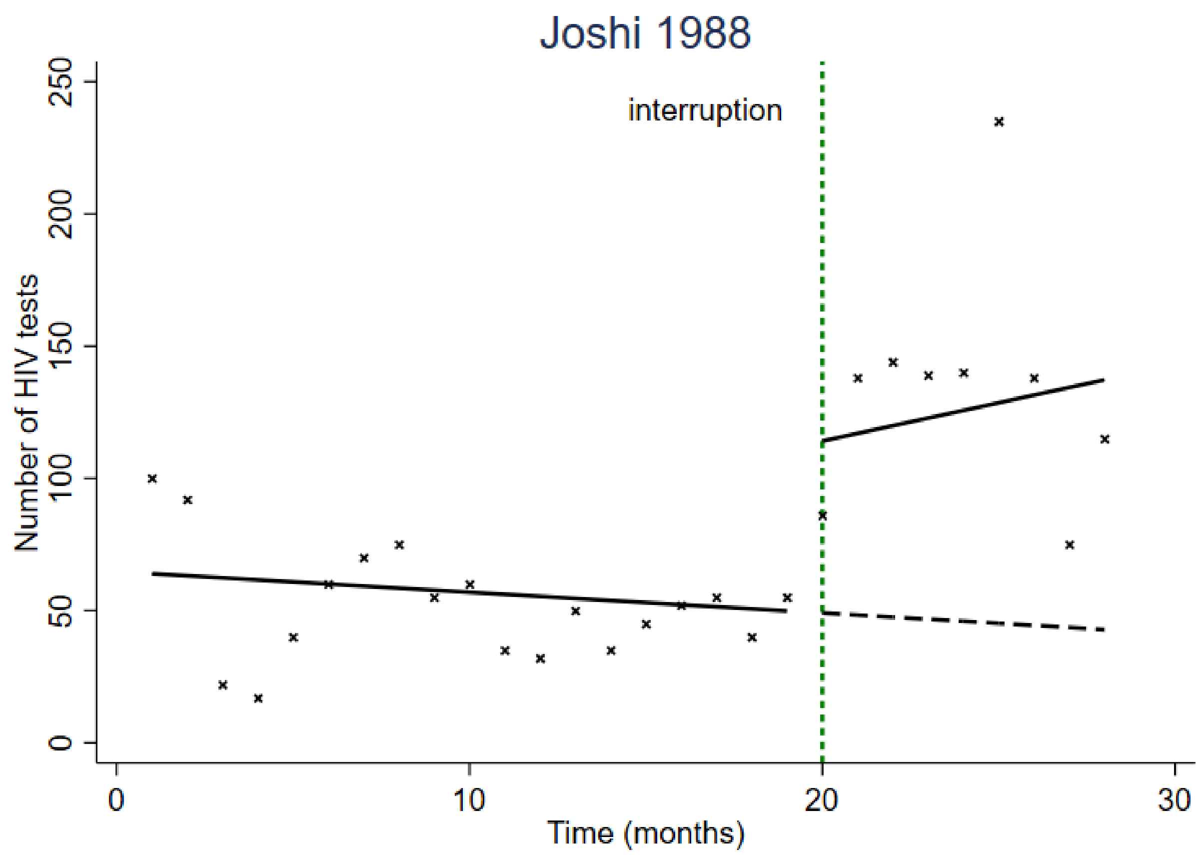


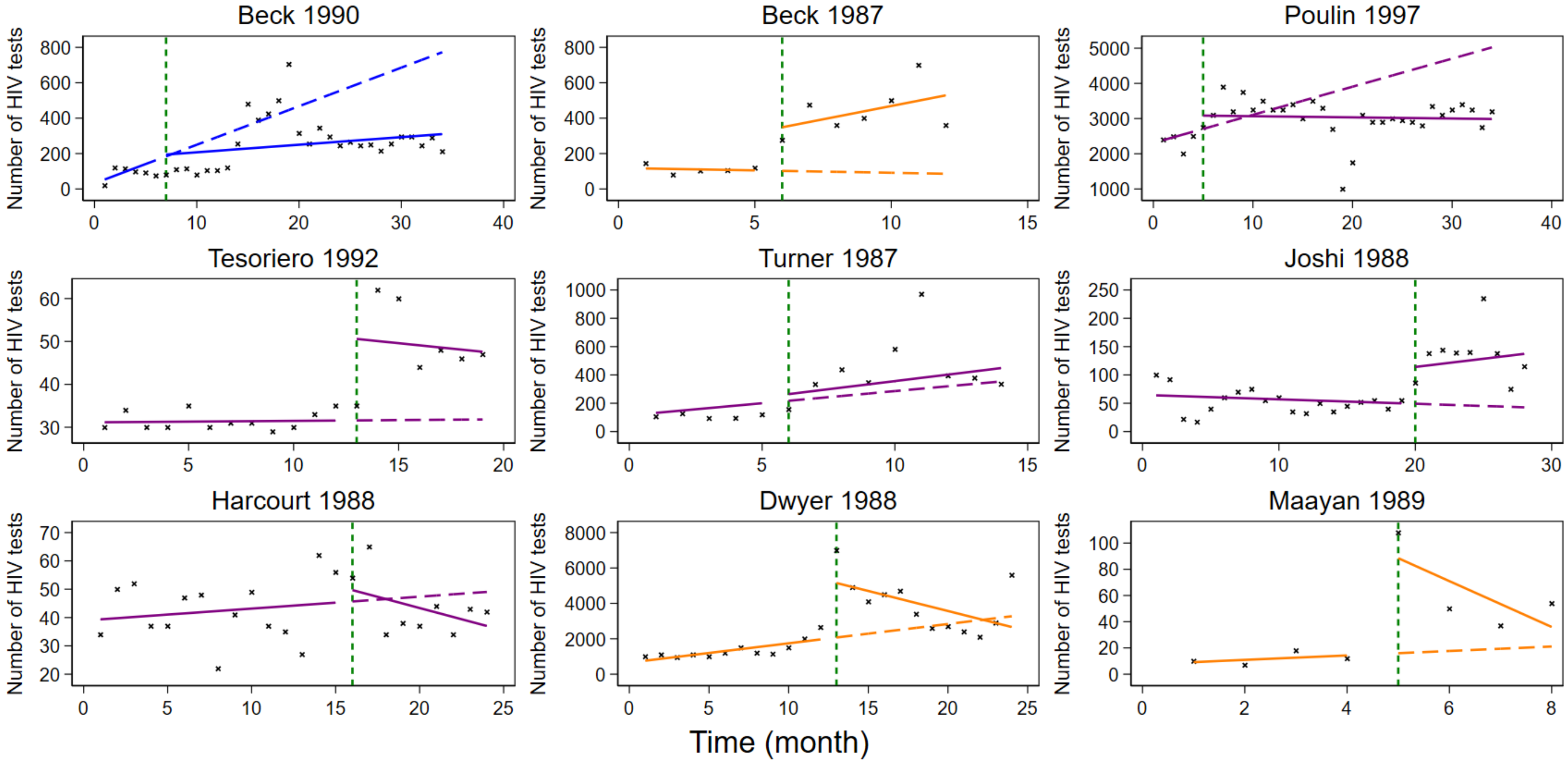
- Interruption: mass media campaign to increase HIV testing, introduced in month 20
- Outcome: number of HIV tests
- Time: 28 monthly datapoints



Obtaining estimates of the effect measures of interest

Long-term level-change at ?? timepoint

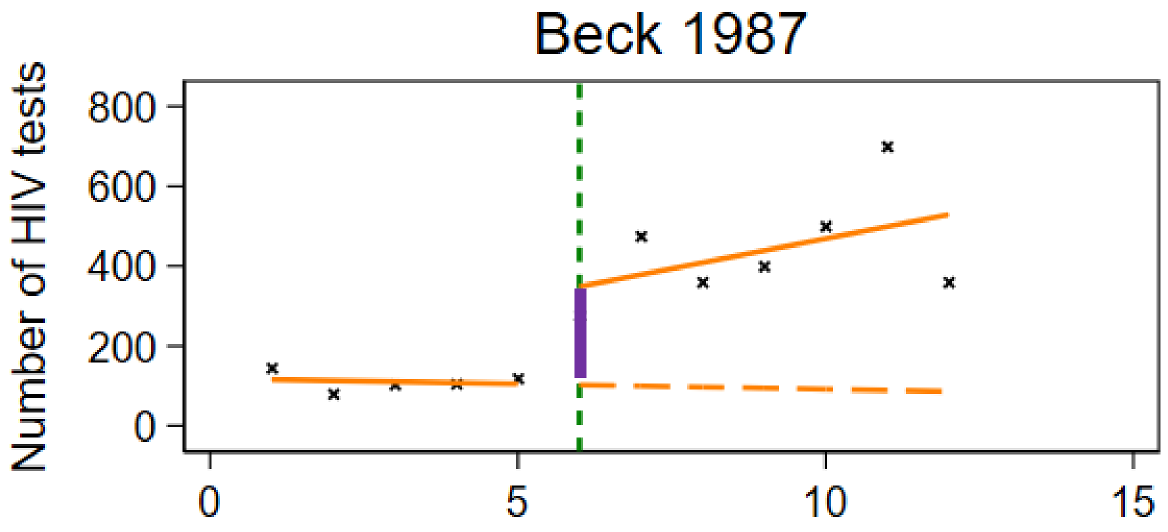
- **What effect measures are possible for a given ITS study?**



Obtaining estimates of the effect measures of interest

- **What effect measures are possible for a given ITS study?**

Long-term level-change at ?? timepoint – 12-months?
Projecting beyond the number of datapoints?



Obtaining estimates of the effect measures of interest

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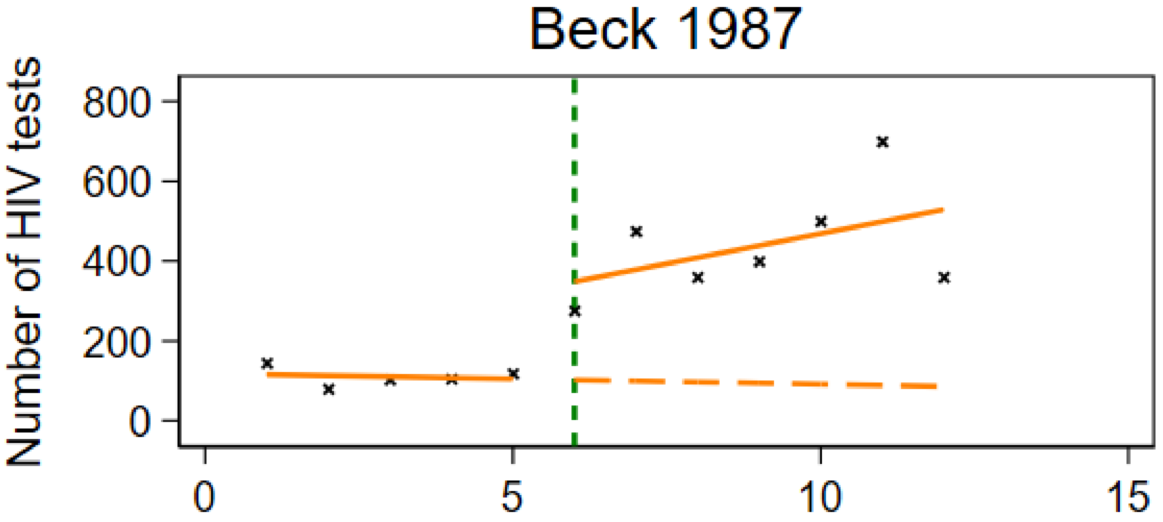
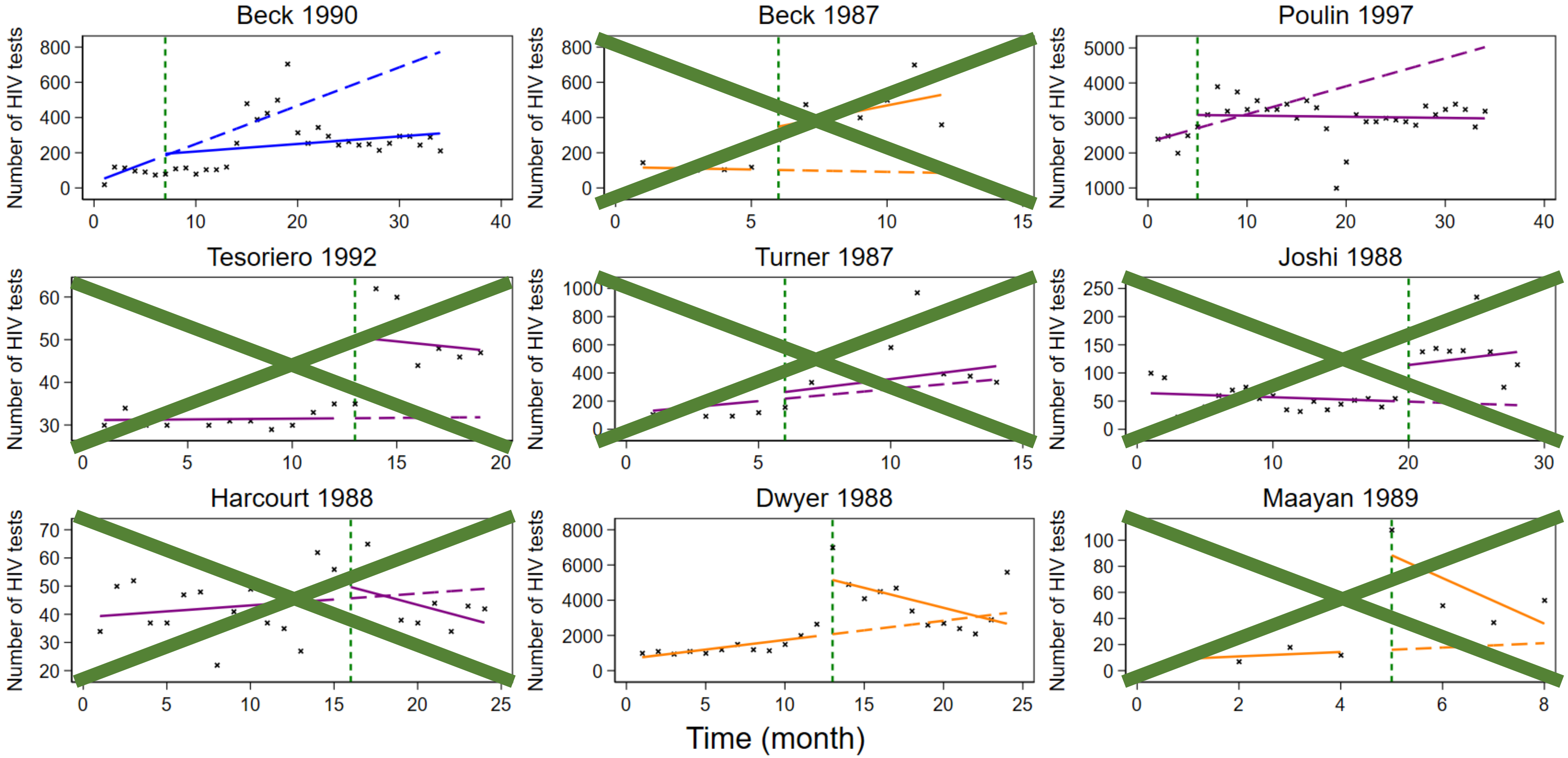


Obtaining estimates of the effect measures of interest

- **What effect measures are possible for a given ITS study?**

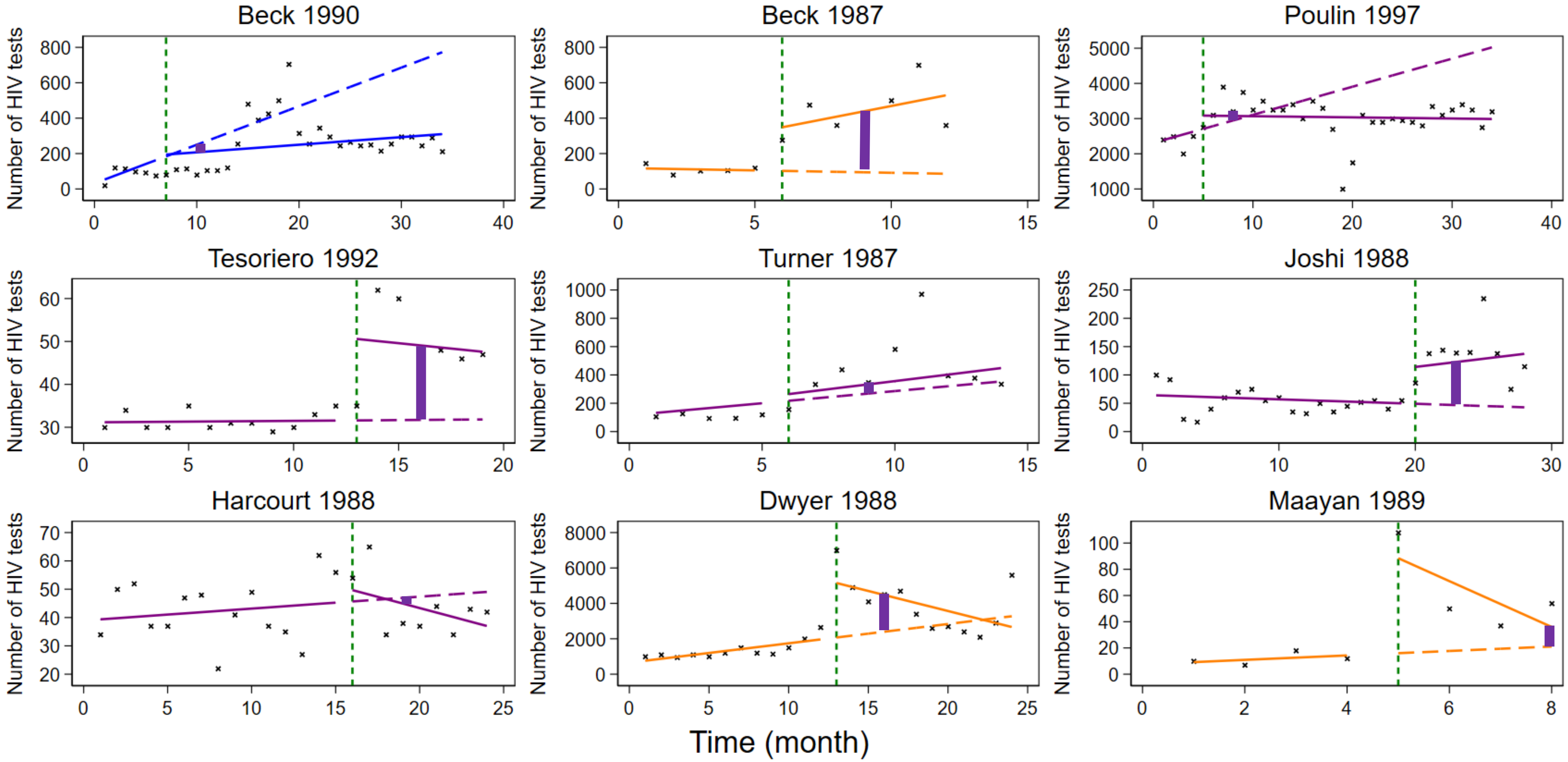
Long-term level-change at ?? timepoint – 12-months?
Exclude ITS that don't have at least 12 months of data?



Obtaining estimates of the effect measures of interest

- **What effect measures are possible for a given ITS study?**

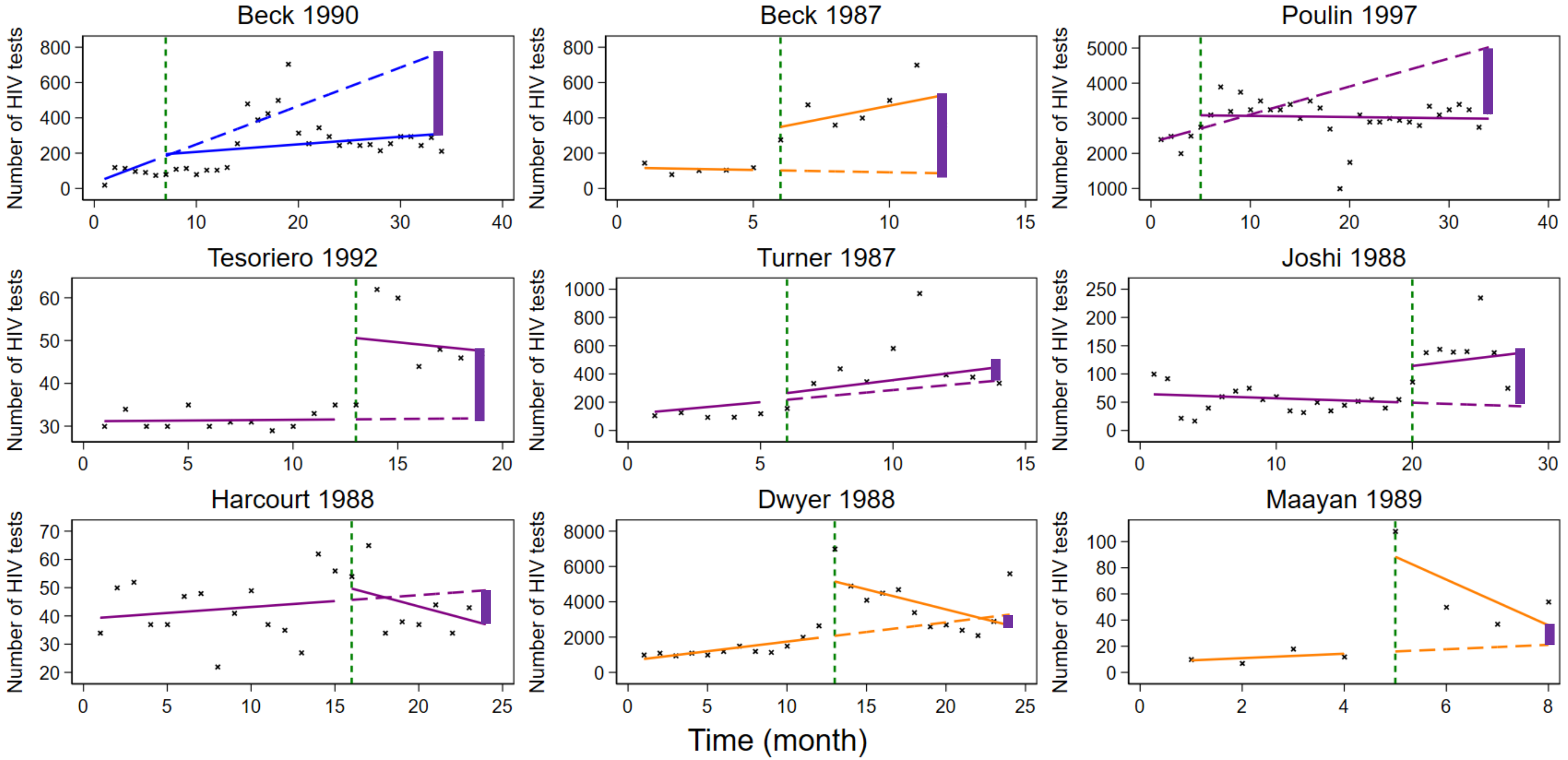
Long-term level-change at ?? timepoint – 4-months?
Timepoint common to all series?



Obtaining estimates of the effect measures of interest

- **What effect measures are possible for a given ITS study?**

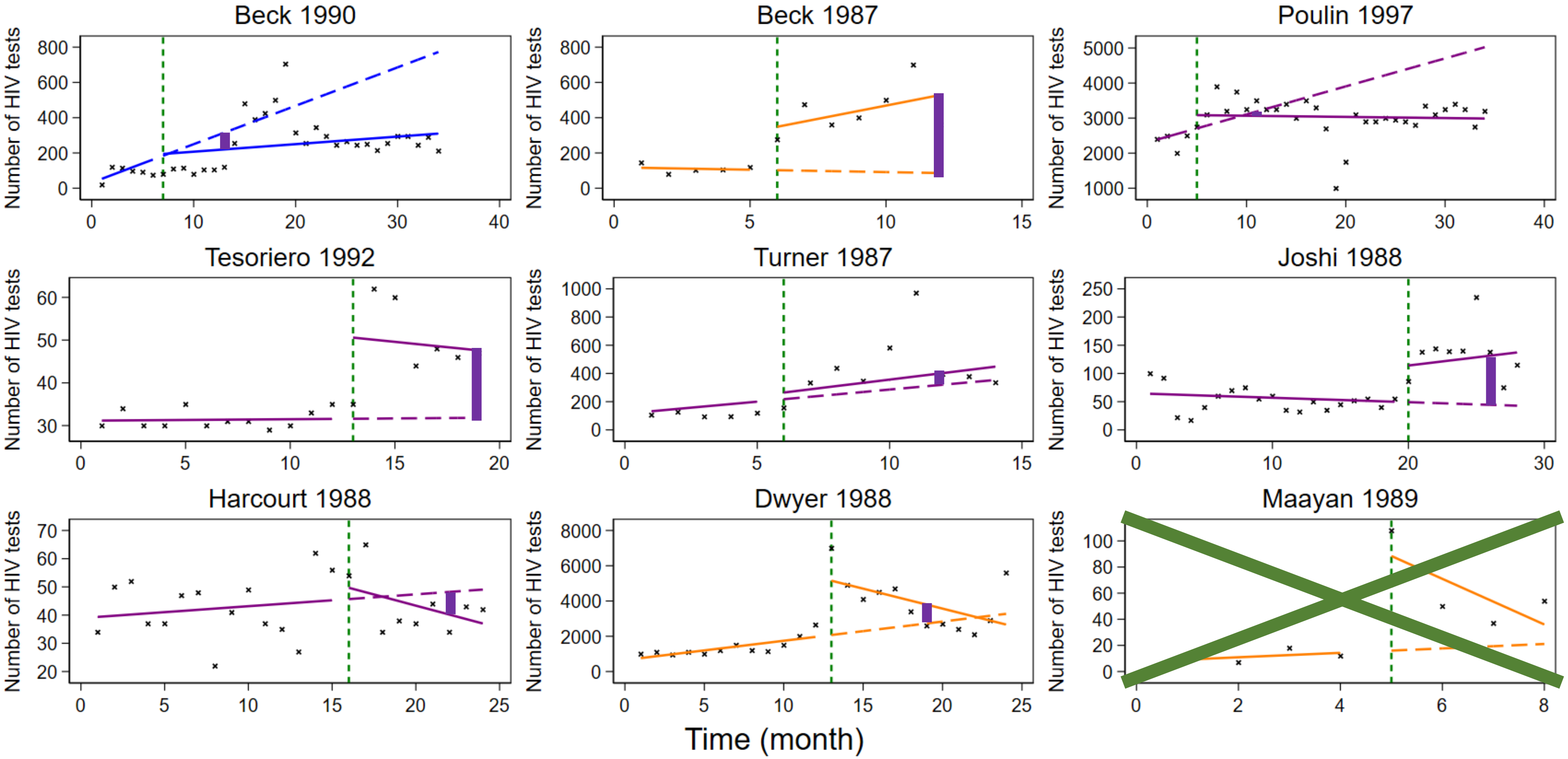
Long-term level-change at ??
Calculate the effects at the end of follow-up?



Obtaining estimates of the effect measures of interest

- **What effect measures are possible for a given ITS study?**

Long-term level-change at ??
Calculate the effects at the latest, most common follow-up?
At 6-months post-interruption?



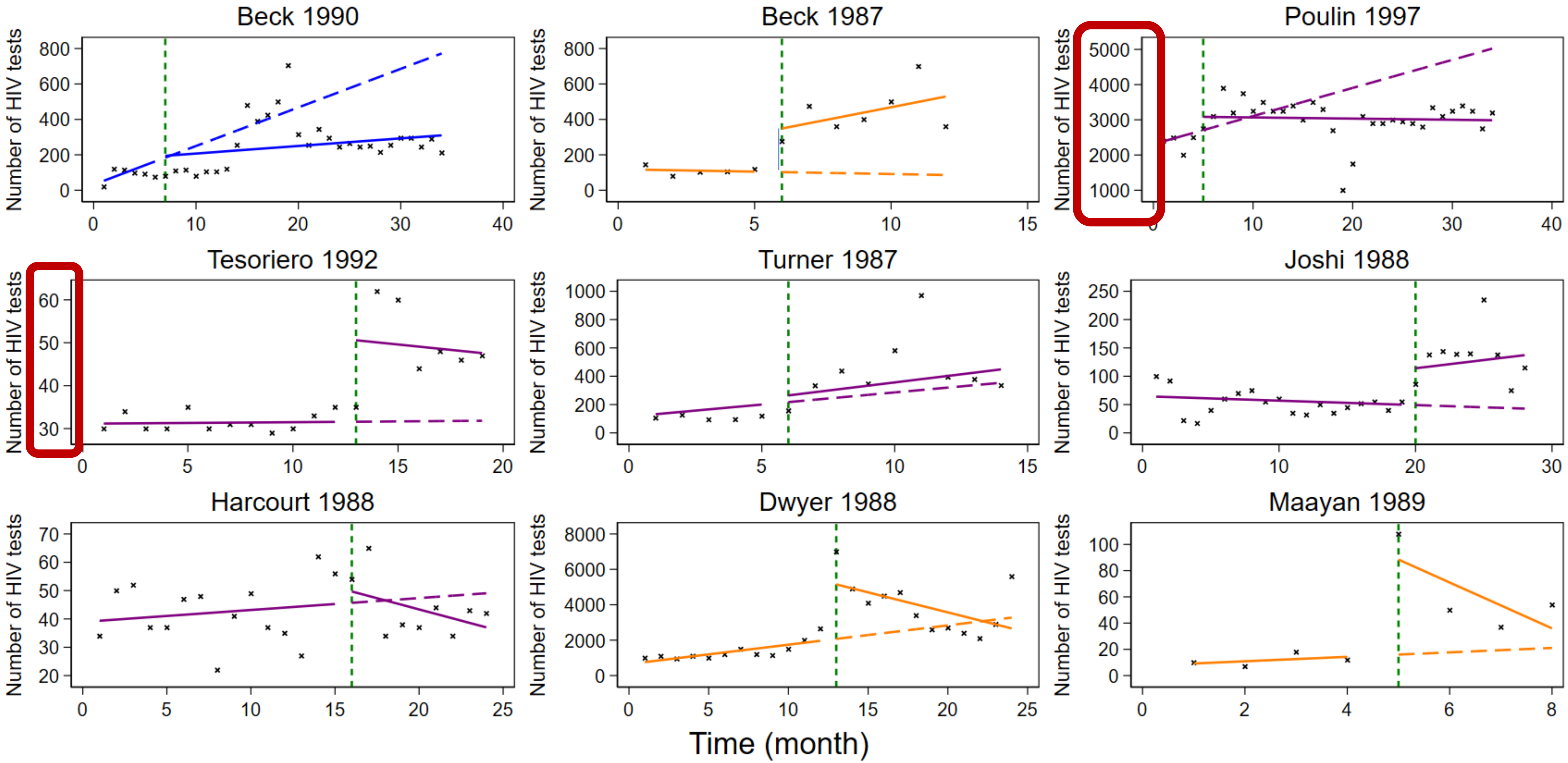
Meta-analysis

- Obtaining estimates of the effect measures of interest
- **Standardisation**
- Selecting the meta-analysis methods
- Retrieving and interpreting the meta-analytic results

Meta-analysis

- Obtaining estimates of the effect measures of interest
- **Standardisation**
  - **Of the outcome**
  - **Of the unit of time**
- Selecting the meta-analysis methods
- Retrieving and interpreting the meta-analytic results

Standardisation of the outcome



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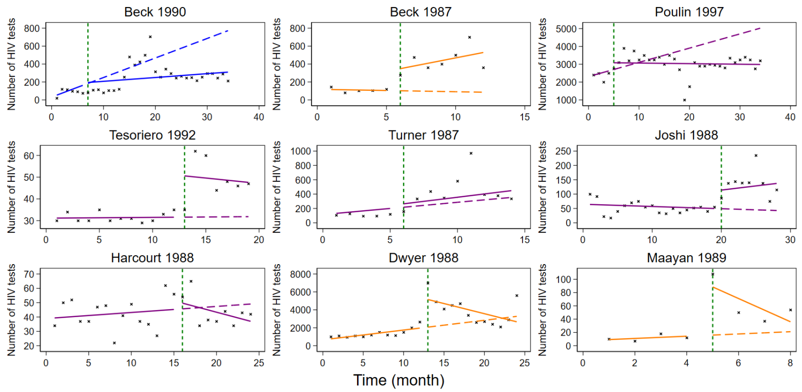
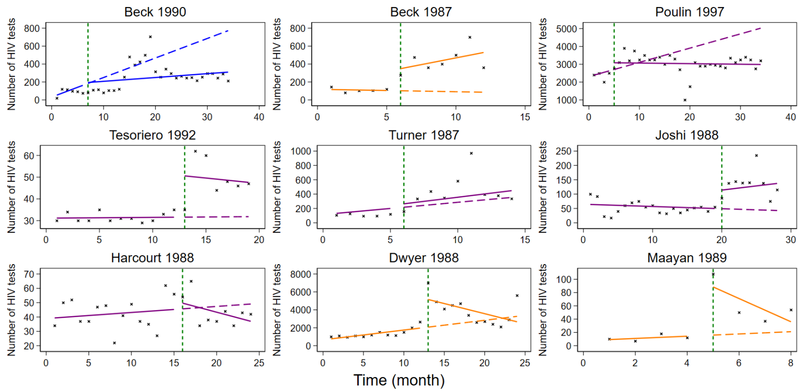


- Standardised by the
  - standard deviation of the raw data in the pre-interruption segment
  - standard deviation of the raw data in the entire series
  - RMSE (root mean square error) of the model fit to the pre-interruption segment
  - RMSE of the model fit to the full ITS (i.e. including both pre- and post-interruption segments)

Standardisation of the outcome



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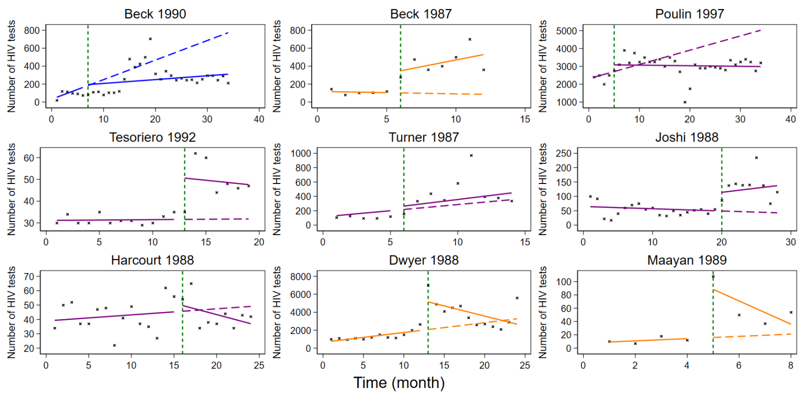

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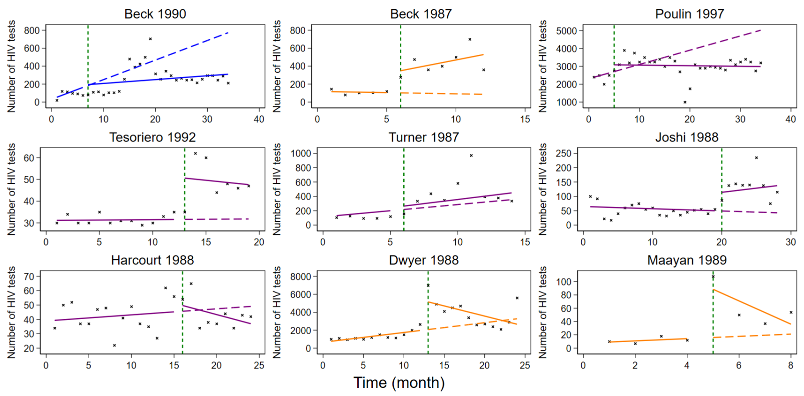
Does not account for trends

Standardisation of the outcome



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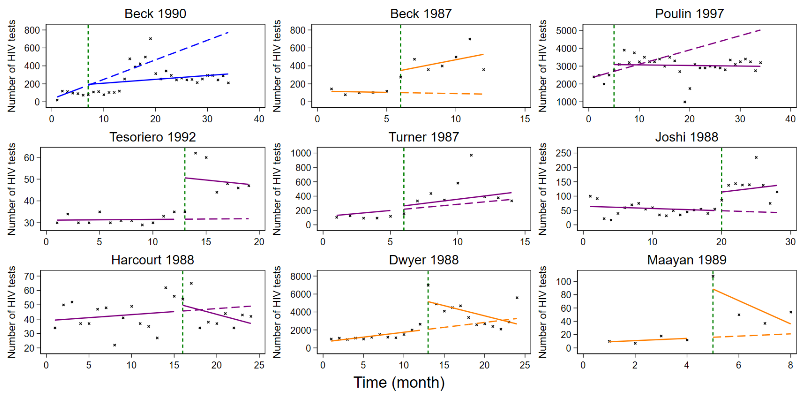
Does not account for trends

Accounts for trends

Standardisation of the outcome



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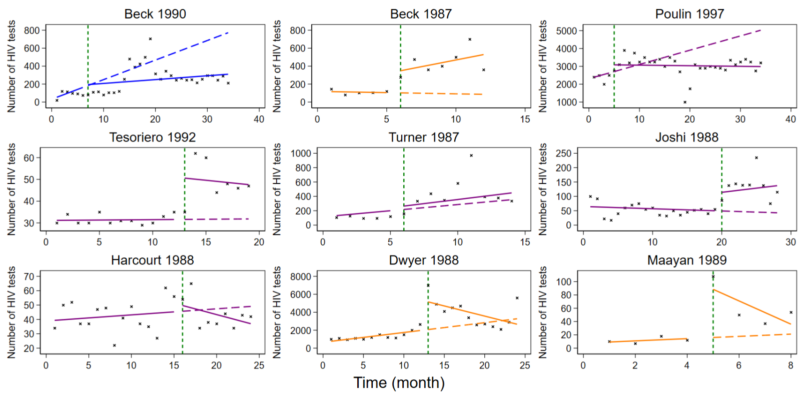
Does not use all available data

Standardisation of the outcome



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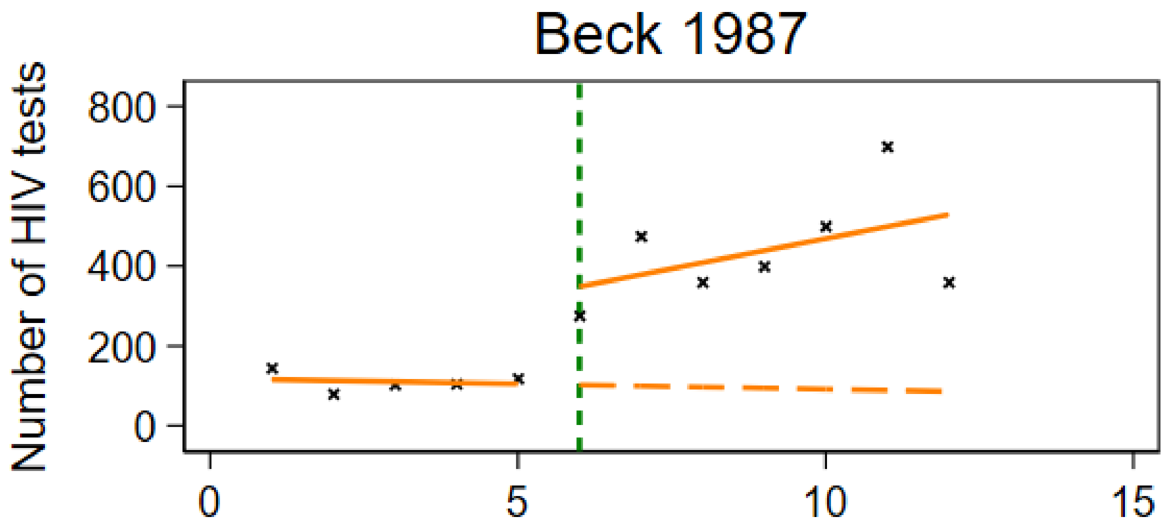
  - **RMSE of the model fit to the full ITS (i.e. including both pre- and post-interruption segments)**

Does not use all available data

Assumes the standard deviation is the same in the pre- and post-interruption segments

Standardisation of the outcome

- Number of HIV tests are very variable across the series
- Standardise by the RMSE of the model fit to the full ITS (i.e. including both pre- and post-interruption segments)



Standardisation of the outcome

- Number of HIV tests are very variable across the series
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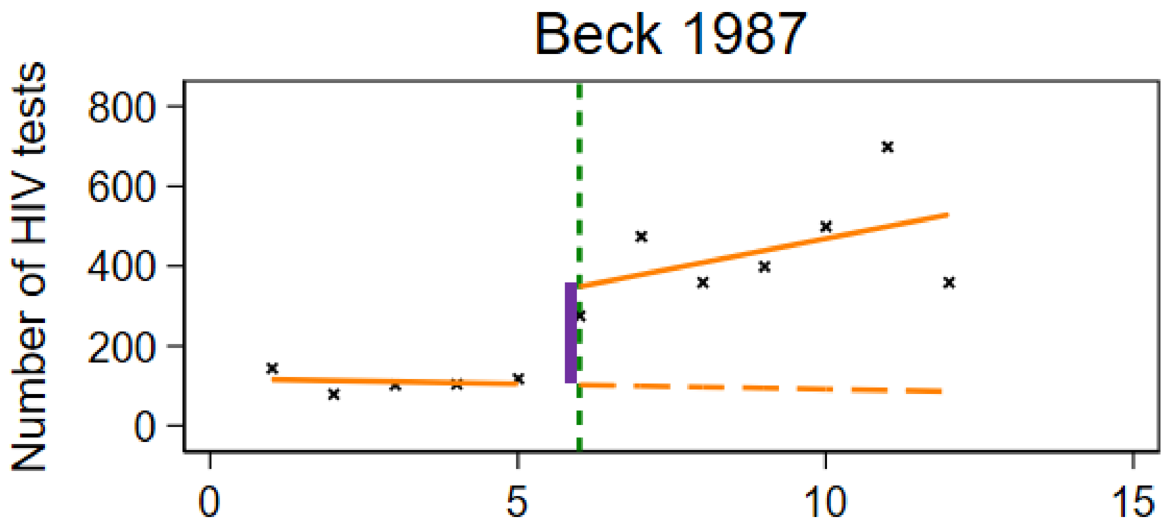
$$\text{Standardised level\_change} = \frac{\text{raw level\_change}}{\text{root mean square error}}$$



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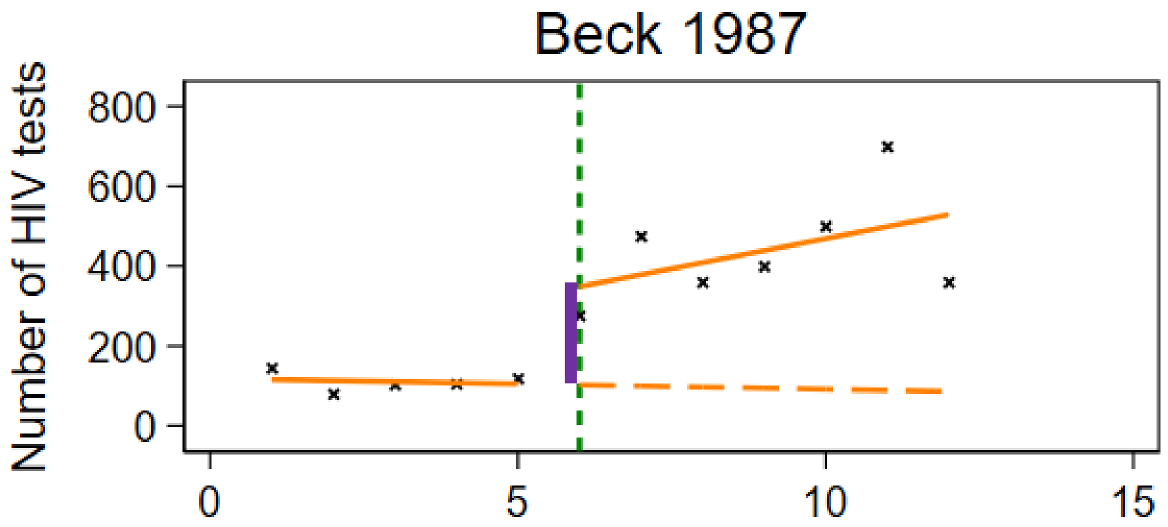
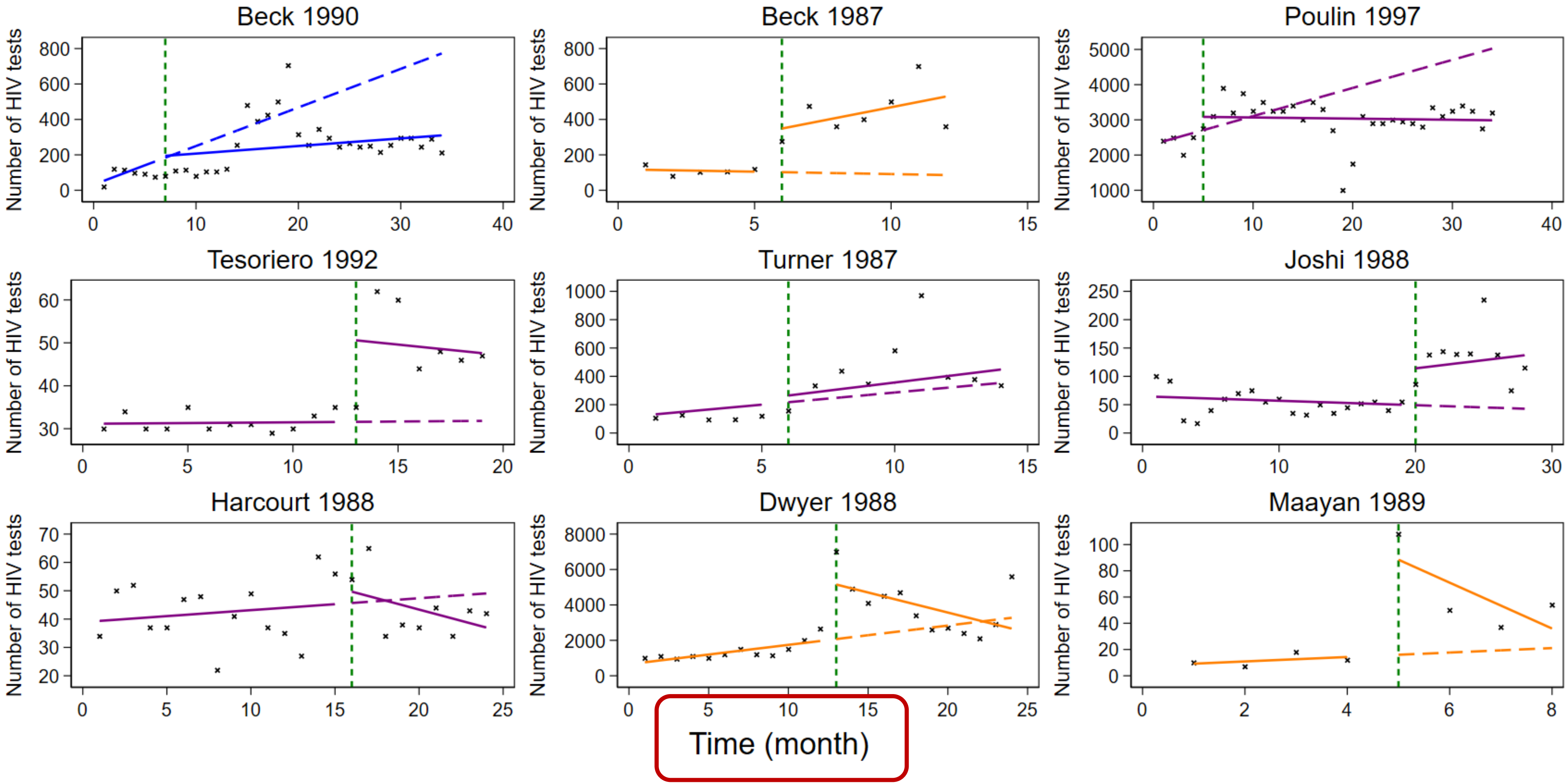
$$\text{Standardised level\_change} = \frac{\text{raw level\_change}}{\text{root mean square error}} = \frac{246.2}{106.42} = \mathbf{2.31}$$

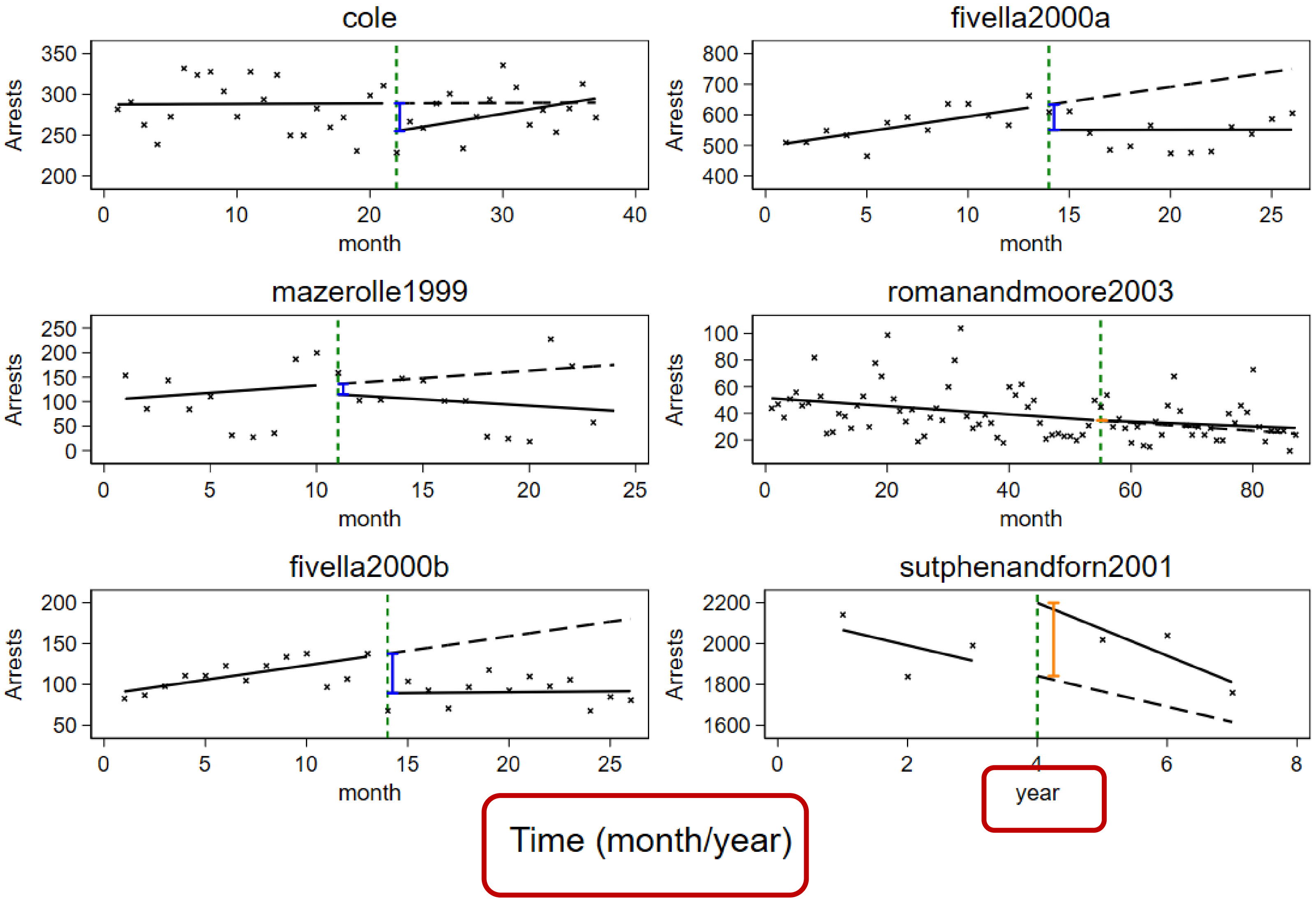


Standardisation of time



Standardisation of time

- Time scale has important implications for the interpretation of the effects
- Ways to standardise:
  - Source monthly data from ITS study authors
  - Aggregate monthly datapoints into yearly datapoints
  - Convert the slope-change effect from years to months (or vice versa)
    e.g., a decrease of 120 arrests per year becomes a decrease of 10 arrests per month



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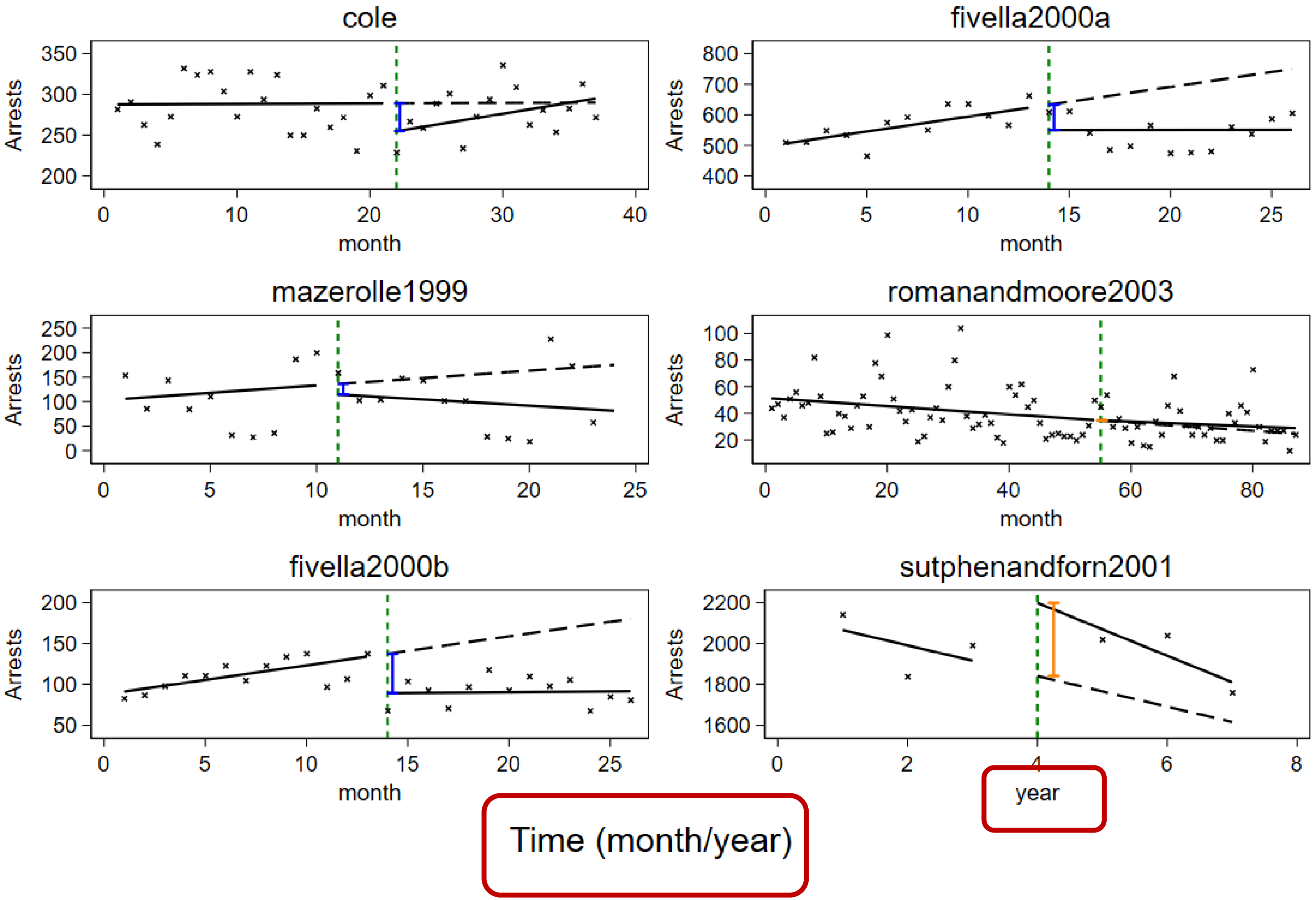

Meta-analysis

- Obtaining estimates of the effect measures of interest
- Standardisation
  - Of the outcome
  - Of the unit of time
- **Selecting the meta-analysis methods**
- Retrieving and interpreting the meta-analytic results

Selecting meta-analysis methods

- Meta-analysis model
  - Random-effects model more plausible model in the context of combining results from ITS studies (due to likely diversity in, for example, populations and interruptions)
- Between-study variance estimator
  - Recommendations suggest REML slightly better than DL (Veroniki 2016)
- Confidence interval method
  - HKSJ slightly better than WT
- Simulation study suggests (Korevaar 2023)
  - Reasonable confidence interval coverage for the meta-analysis effect was obtained irrespective of the combination of ITS analysis method and meta-analysis method
  - ITS analysis method is important for validly estimating heterogeneity

McKenzie, J. E., Beller, E. M., and Forbes, A. B. (2016) Introduction to systematic reviews and meta-analysis. Respirology, 21: 626– 637. doi: 10.1111/resp.12783.

Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, Kuss O, Higgins JP, Langan D, Salanti G. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016 Mar;7(1):55-79. doi: 10.1002/jrsm.1164. Epub 2015 Sep 2. PMID: 26332144; PMCID: PMC4950030.

Korevaar E, Turner SL, Forbes AB, Karahalios A, Taljaard M, McKenzie JE. Evaluation of statistical methods used to meta-analyse results from interrupted time series studies: A simulation study. Res Synth Methods. 2023 Nov;14(6):882-902. doi: 10.1002/jrsm.1669. Epub 2023 Sep 20. PMID: 37731166; PMCID: PMC10946504.

Meta-analysis

- Obtaining estimates of the effect measures of interest
- Standardisation
  - Of the outcome
  - Of the unit of time
- Selecting the meta-analysis methods
- **Retrieving and interpreting the meta-analytic results**

Back transforming standardised effects to the original scale

- Standardised meta-analytic effect
  - An ***increase in the number of HIV tests by 1.80 standard deviations*** immediately following the mass media campaigns compared to if the campaigns had not been introduced. The 95% confidence interval indicated that plausible estimates could range from an increase of 0.73 standard deviations to an increase of 2.88 standard deviations.

Rescale / Re-express on a more interpretable scale →

- Rescaled meta-analytic effect
  - An ***increase of 543 HIV tests*** immediately following the mass media campaigns compared to if the campaigns had not been introduced. The 95% confidence interval indicated that plausible estimates could range from an increase of 218 tests to an increase of 868 tests.

Back transforming standardised effects to the original scale

- Standardised meta-analytic effect
  - An ***increase in the number of HIV tests by 1.80 standard deviations*** immediately following the mass media campaigns compared to if the campaigns had not been introduced. The 95% confidence interval indicated that plausible estimates could range from an increase of 0.73 standard deviations to an increase of 2.88 standard deviations.

Rescale / Re-express on a more interpretable scale

→

Multiply by the median RMSE across the studies meta-analysed

- Rescaled meta-analytic effect
  - An ***increase of 543 HIV tests*** immediately following the mass media campaigns compared to if the campaigns had not been introduced. The 95% confidence interval indicated that plausible estimates could range from an increase of 218 tests to an increase of 868 tests.

Meta-analysis
Extensions and complexities

- Control series
- One-stage meta-analysis
- Risk of bias

Meta-analysis
Extensions and complexities

- **Control series**
- One-stage meta-analysis
- Risk of bias

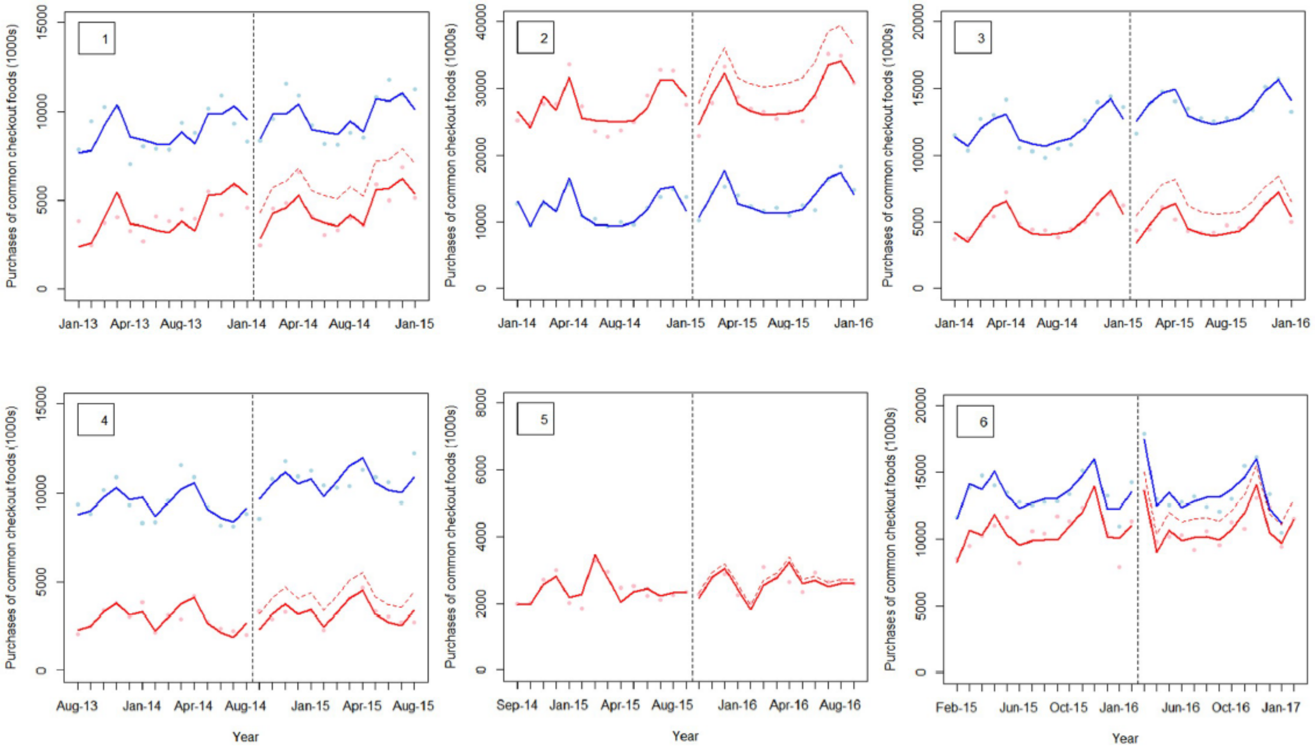

Fig 2. Interrupted time series models: Association between checkout food policy implementation and purchases of common checkout foods. 'Best fit' comparison group. Panel number indicates intervention store number as used elsewhere. Vertical black dotted line = time of implementation. Red line = intervention store, red dotted line = counterfactual, blue line = comparison store.

https://doi.org/10.1371/journal.pmed.1002712.g002

Ejlerskov KT, Sharp SJ, Stead M, Adamson AJ, White M, Adams J (2018) Supermarket policies on less-healthy food at checkouts: Natural experimental evaluation using interrupted time series analyses of purchases. PLoS Med 15(12): e1002712. https://doi.org/10.1371/journal.pmed.1002712

Meta-analysis
Extensions and complexities

- Control series
- **One-stage meta-analysis**
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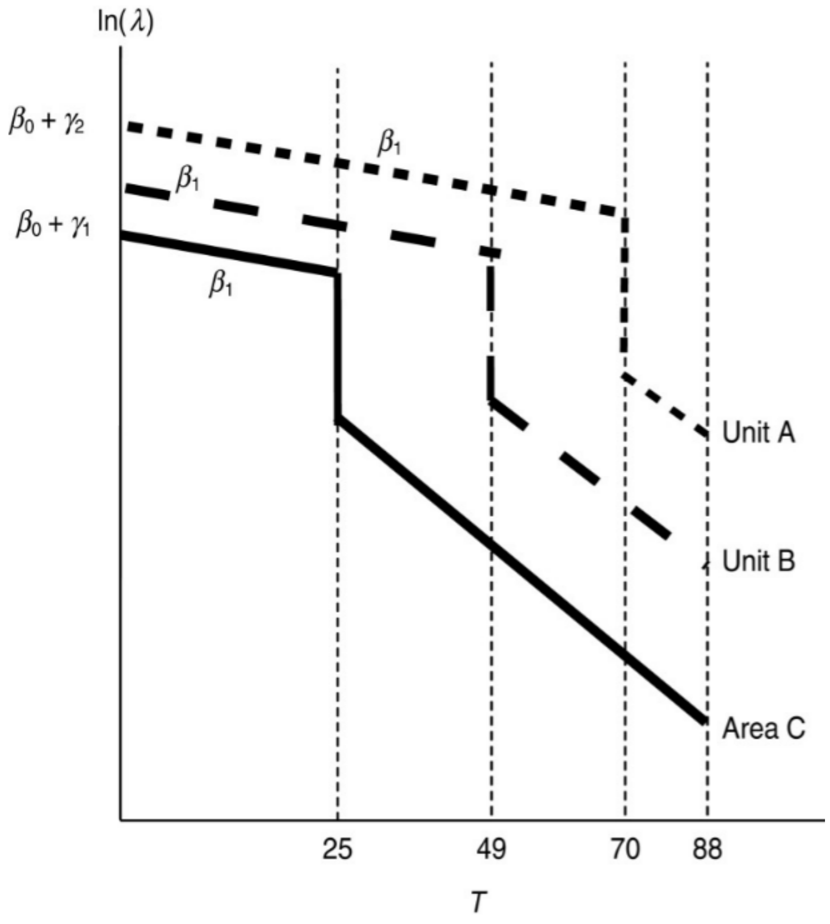

Figure 3 from Gebski V, Ellingson K, Edwards J, Jernigan J, Kleinbaum D. Modelling interrupted time series to evaluate prevention and control of infection in healthcare. Epidemiol Infect. 2012 Dec;140(12):2131-41. doi: 10.1017/S0950268812000179. Epub 2012 Feb 16. PMID: 22335933; PMCID: PMC9152341.

Meta-analysis
Extensions and complexities

- Control series
- One-stage meta-analysis
- **Risk of bias**

Chapter 25: Assessing risk of bias in a non-randomized study

Jonathan AC Sterne, Miguel A Hernán, Alexandra McAleenan, Barnaby C Reeves, Julian PT Higgins

Sterne JAC, Hernán MA, McAleenan A, et al. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, et al. (eds) Cochrane Handbook for Systematic Reviews of Interventions. Cochrane, www.training.cochrane.org/handbook (2022).

Key information to report for your meta-analysis of ITS studies

- **Design**
  - **Each ITS study’s design characteristics**
    - **Number of datapoints, time point of the interruption, time interval of each datapoint**
  - **How many ITS study’s are included in the meta-analysis**
- **Analysis methods**
  - **ITS analysis methods used for each ITS study**
    - **Model structure**
    - **Effect measures of interest and how they are calculated**
    - **Accounting for features of time series data (autocorrelation)**
  - Meta-analysis methods used
    - Fixed-effect vs random-effects
    - Between-study variance estimator
    - 95% confidence interval method
- Results
  - Effect measure
  - Effect estimate
  - 95% confidence interval
  - Between-study variance
  - Prediction intervals if random-effects is used

ELSEVIER

Check for updates

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REVIEW

Methodological systematic review recommends improvements to conduct and reporting when meta-analyzing interrupted time series studies

Elizabeth Korevaar[a], Amalia Karahalios[b], Simon L Turner[a], Andrew B Forbes[a], Monica Taljaard[c,d], Allen C Cheng[a,e], Jeremy M Grimshaw[c,d,f], Lisa Bero[g], Joanne E McKenzie[a,*]

Summary

- Reanalysis of data from ITS studies if often possible, making meta-analysis of results from ITS studies a possibility
- This should be considered more frequently in reviews examining public health and policy interventions where ITS studies may be the only available evidence.
- In reviews including ITS studies, there is a need for:
  - Statistical expertise - lots of ITS and meta-analysis methods
  - Content expertise - to understand the most appropriate ITS models to fit, and methodological features that may introduce bias
- Interpreting meta-analysis results of ITS studies requires careful interpretation

Questions on meta-analysis of ITS?

- Obtaining estimates of the effect measures of interest
- Standardisation
- Selecting the meta-analysis methods
- Retrieving and interpreting the meta-analytic results

Questions on anything we've said today?

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We will run a workshop at GES

Introduction to analysis and meta-analysis of interrupted time series studies with continuous outcomes
Workshop Session E9 Thursday, Sep 12, 2024 14:00 - 15:30 Hall D4

Questions on anything we've said today?

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