CoCare Society

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Interrupted time-series (ITS) regression

Yoonhee Kim, PhD

Department of Global Environmental Health
Graduate School of Medicine
The University of Tokyo

Japan Science and Technology Agency

Key references

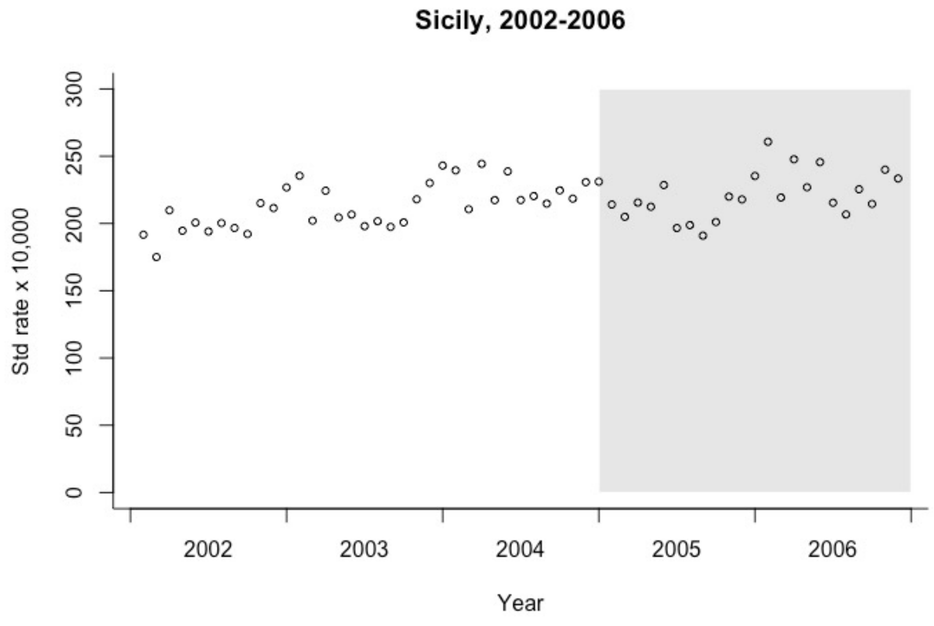
- Bernal, J. L., et al. (2017). "Interrupted time series regression for the evaluation of public health interventions: a tutorial." Int J Epidemiol **46**(1): 348-355.

- Bernal, J. L., et al. (2021). "Corrigendum to: Interrupted time series regression for the evaluation of public health interventions: a tutorial." Int J Epidemiol **50**(3): 1045-1045.

Interrupted time seires (ITS) design

- Used for evaluating effectiveness of public health interventions at a population level over a specific time period.
- ‘interrupted’ means an intervention at a known time point
  - e.g., Indoor smoking ban in Jan 2005, Italy
- Evaluation of ‘natural experiments’

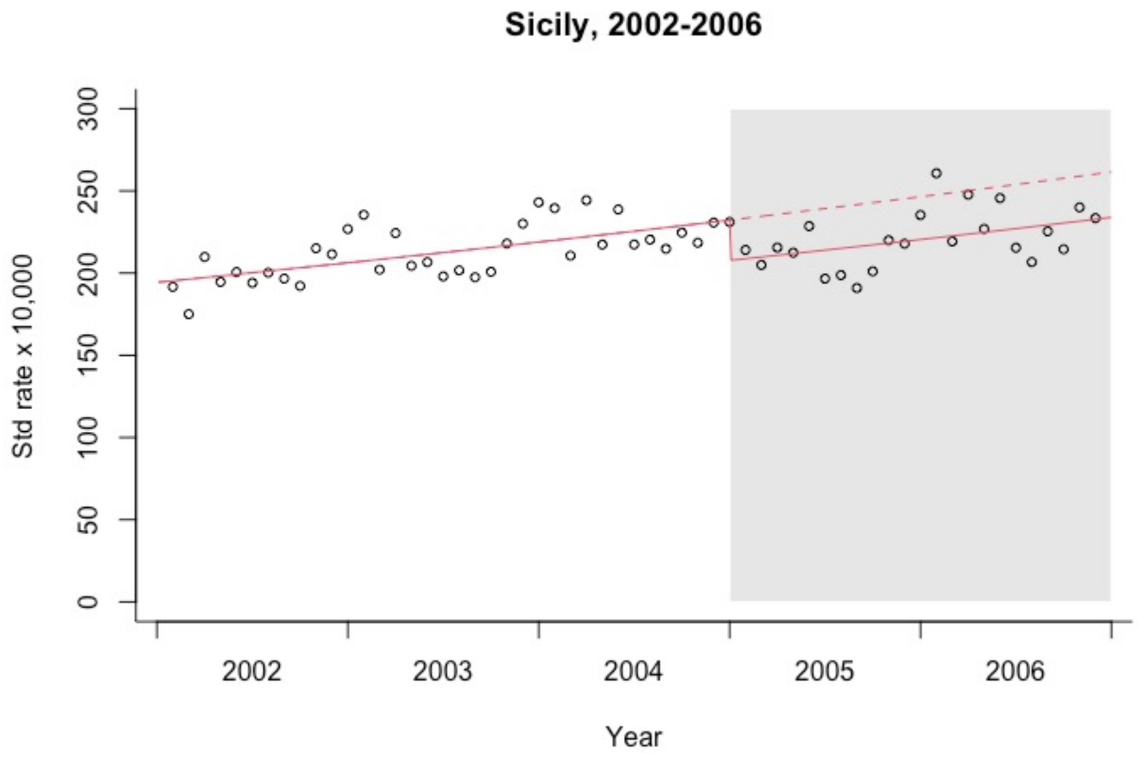
- Cohort and case-control studies
  - Less useful as intervention studies
- Randomized controlled trials (RCTs)
  - Not always possible at the population level



Hospital admissions for Acute Coronary Events among aged 0-69 years

Counterfacual scenario

- A hypothetical scenario as if the intervention was not implemented and the trend continues unchanged
  - The ‘expected’ trend, in the absence of the intervention
- Compared with any change occurring in the post-intervention period
  - Many points lie below the counterfactual dotted line
  - A decrease in Acute Coronary Events admissions after the smoking ban?



Introductory guidelines for an ITS analysis

- Step 1: Is an ITS design appropriate?
  - The intervention
  - The outcome
- Step 2: Proposing the impact model
  - Choose the most appropriate impact model as a priori based on literature
- Step 3: Descriptive analysis
- Step 4: Regression analysis
- Step 5: Addressing methodological issues
  - Seasonality, time-varying confounders, over-dispersion, autocorrelation, etc.
- Step 6: Model-checking and sensitivity analysis

Step 1: Is an ITS design appropriate?

- The intervention
  - Clearly defined time period before and after the intervention
  - Possible to know when the intervention began?
  - A gradual roll-out → consider a gradual (slope) change

- The outcome
  - Various forms (e.g., counts, continuous or binary variables)
  - Best with short-term outcomes to show the change immediately after an intervention or after clearly defined lag
  - ACE vs. lung cancer (less appropriate)

Data requirements

- Sequential outcome measurements before and after an intervention
- Power
  - Accurate and sufficient time points to show underlying trends
  - Equally distributed data points
- Routine data with a long time seires –most appropriate
- Data quality
  - Validity and reliability

Step 2: Selecting the most appropriate impact model

- Decide it *a priori* based on
  - Existing literature
  - Knowledge of the intervention
  - Intervention mechanism on the outcome

- Examples ------------------>>>>>>>
  a) Level change
  b) Slope change
  c) Level and slope change
  d) Slope change following a lag
  e) Temporary level change
  f) Temporary slope change leading to a level change

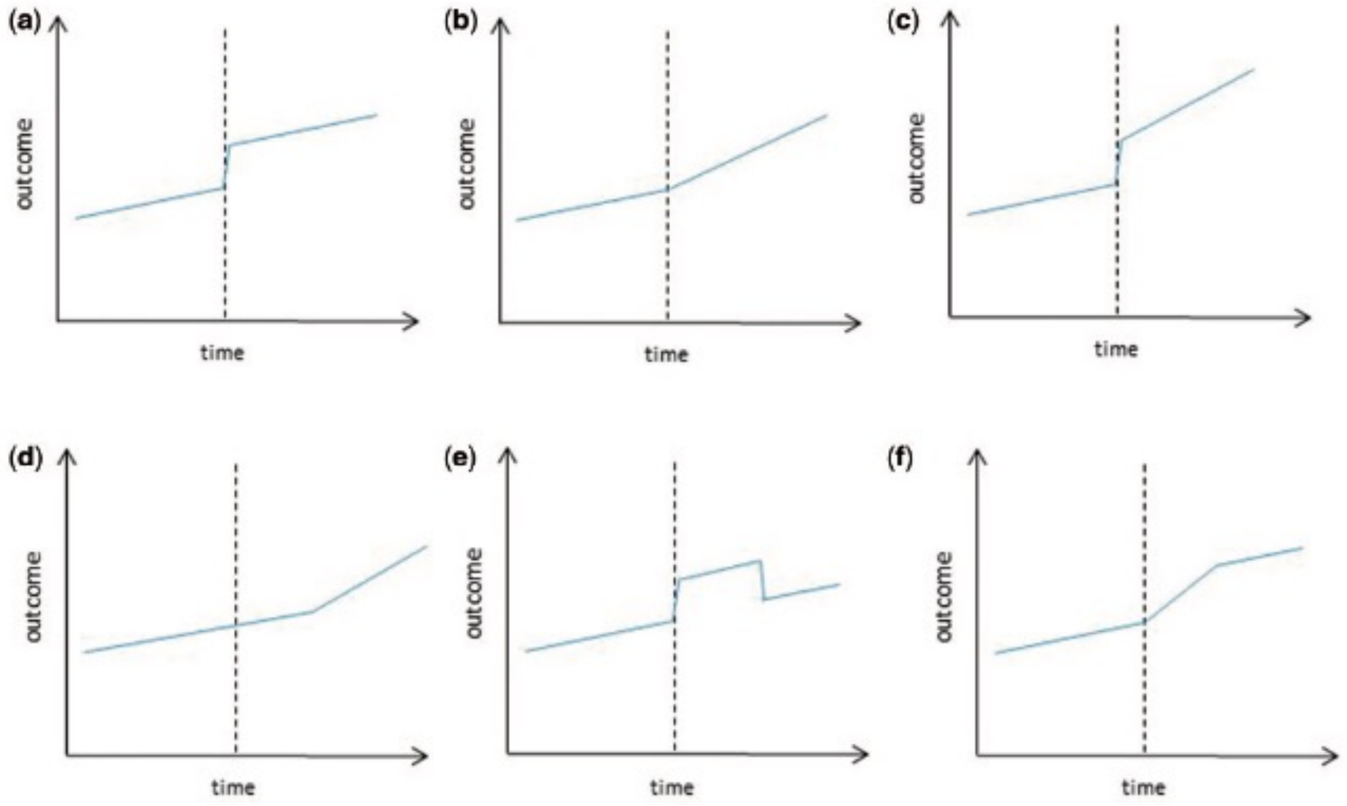


Figure 2 Examples of impact models used in ITS

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

Step 3: Descriptive analysis

- Time series plots
  - Underlying trend to see whether a linear model is appropriate
  - Seasonal patterns to see whether there was a seasonal trend
  - Outliers

- Summary statistics
  - Simple comparisons before and after the intervention
  - Comparisons between outcome and time-varying confounders

Step 4: Regression analysis

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 (T - T_0) X_t + \varepsilon_t$$

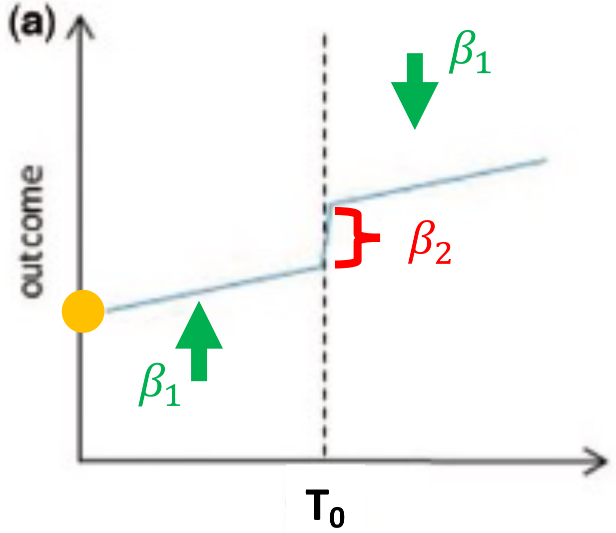
T represents the time (e.g., month or year) over the study period

T_0 represents the time at the beginning of the intervention

X_t represents a dummy variable; coded 0 for the pre-intervention and coded 1 for the post-intervention

Y_t represents the outcome at time t

(A) Level change



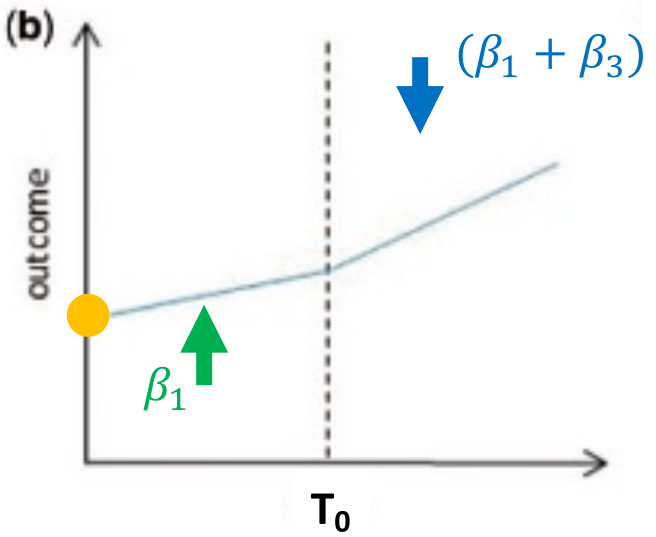
$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \varepsilon_t$$

β_0 represents the baseline level (i.e., the intercept in pre-intervention, X_t=0)

β_1 represents the change in outcome associated with a time unit increase (i.e., the slope for the time in pre-intervention and post-intervention)

β_2 represents **the level change following the intervention** (i.e., the difference in the two expected means of outcome on the two slopes [pre-intervention and post-intervention for each])

(B) Slope change



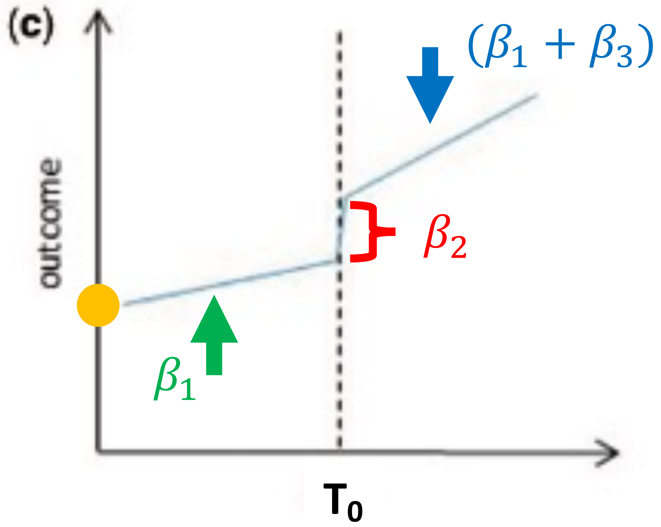
$$Y_t = \beta_0 + \beta_1 T + \beta_3 (T - T_0) X_t + \varepsilon_t$$

β_0 represents the baseline level (i.e., the intercept in pre-intervention, X_t=0)

β_1 represents the change in outcome associated with a time unit increase (i.e., the slope for the time in pre-intervention, X_t=0)

β_3 represents **the slope change following the intervention** (i.e., the difference in the two estimated slopes for the time between pre-intervention and post-intervention)

(C) Level and slope change



$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 (T - T_0) X_t + \varepsilon_t$$

β_0 represents the baseline level (i.e., the intercept in pre-intervention, X_t=0)

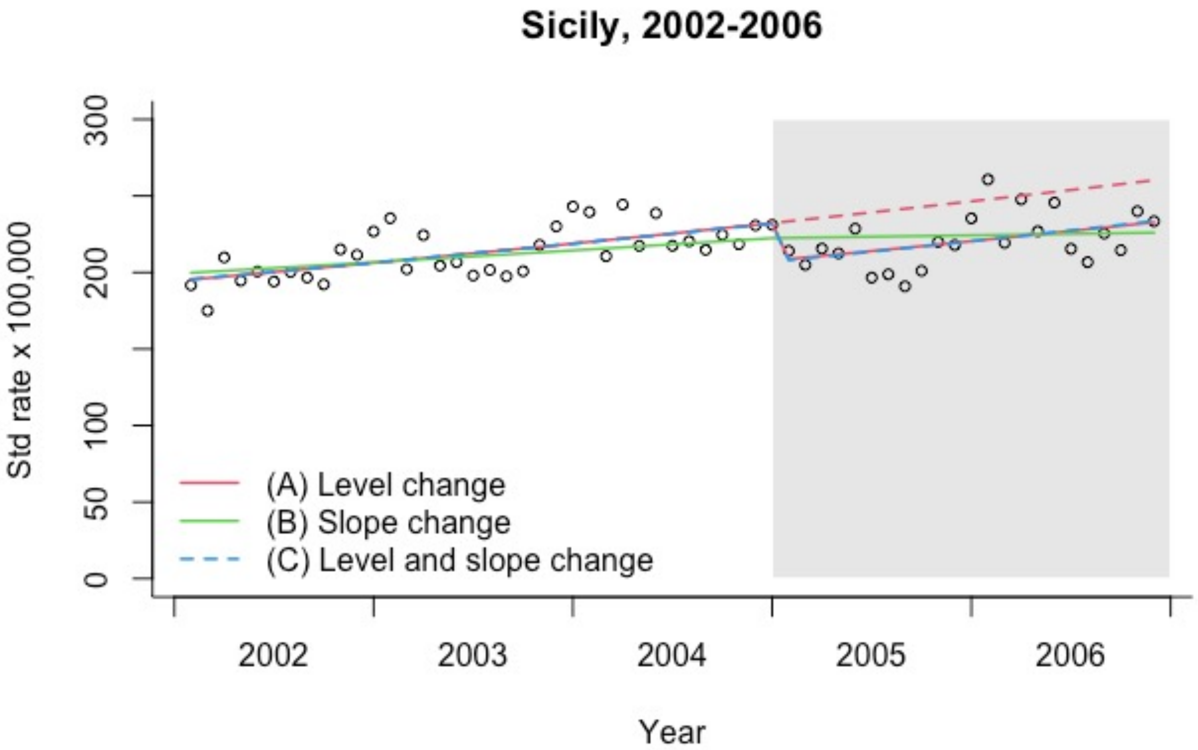
β_1 represents the change in outcome associated with a time unit increase (i.e., the slope for the time in pre-intervention, X_t=0)

β_2 represents **the level change following the intervention** (i.e., the difference in the two expected means of outcome on the two slopes [pre-intervention and post-intervention for each] at the specific time point, T=T_0)

β_3 represents **the slope change following the intervention** (i.e., the difference in the two estimated slopes for the time between pre-intervention and post-intervention)

Example data: Indoor smoking ban in Sicily, Italy

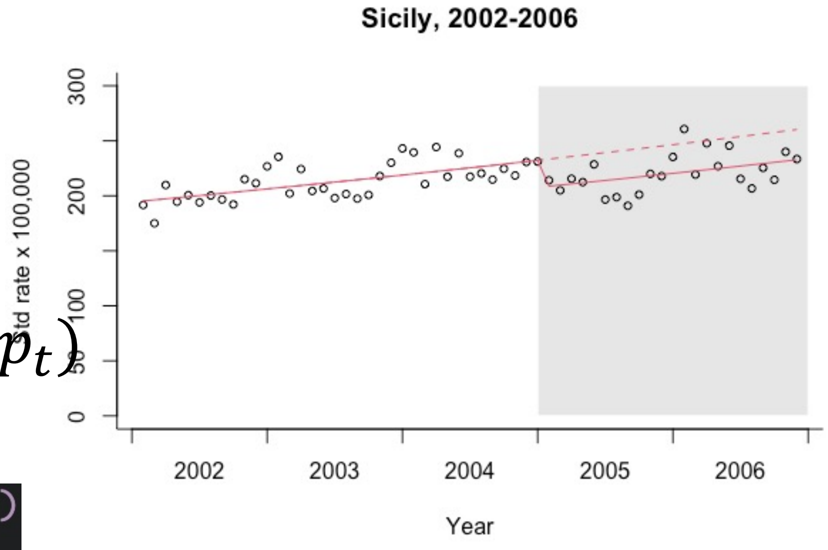
- Monthly time-series data
  - from Jan 2002 to Dec 2006 (t = 1 … 59)
- The intervention was implemented in January 2005 (t = 37)
  - Coded 0 for pre-intervention (t = 0 … 36)
  - Coded 1 for post-intervention (t = 37 … 59)
- Outcome
  - Monthly hospital admissions for Acute Coronary Events (ACE) among aged 0-69 years
- Age-standardized population as an offset



Example: (A) Level change

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \varepsilon_t$$

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_2 * smokban_t + \log(pop_t)$$

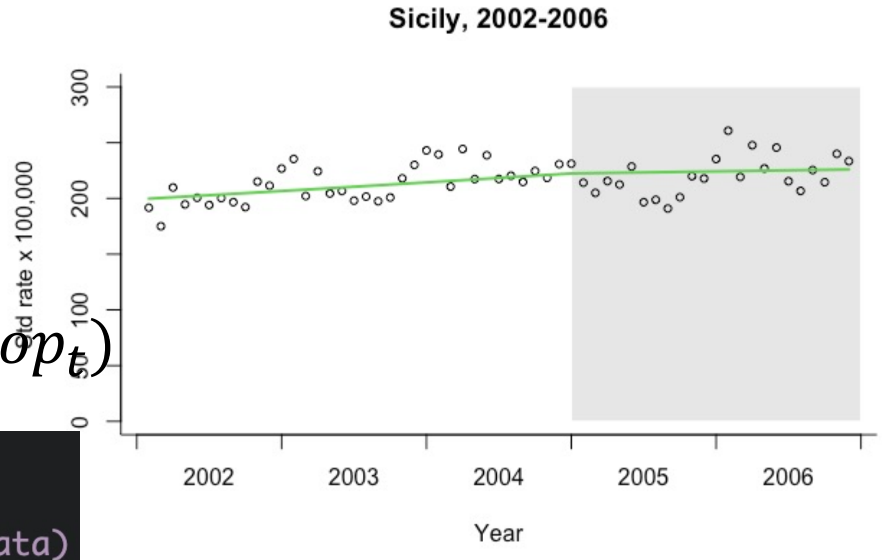



```
> model.a <- glm(aces ~ offset(log(stdpop)) + time + smokban, family=poisson, data)
> ci.exp(model.a)
             exp(Est.)        2.5%       97.5%
(Intercept) 0.001943721 0.001901558 0.001986819
time        1.004957239 1.003974397 1.005941042
smokban     0.894376508 0.864686417 0.925086046
```

Parameter	exp(Estimate) (95% CI)	Note	How to interpret it
$\exp(\beta_0)$	0.002 (0.002, 0.002)	0.00194 x 10^5 = 194	Indicating the expected ACE when time=0 (i.e., intercept)
$\exp(\beta_1)$	1.005 (1.004, 1.006)	RR for the time	Indicating the ACEs increased by 0.5% per the time unit increase (i.e., month)
$\exp(\beta_2)$	0.894 (0.865, 0.925)	RR for the intervention	Suggesting a strong evidence of a reduction in ACEs following the smoking ban, with a decrease of 10.6%

RR=Relative Risk; CI=Confidence Interval

Example: (B) Slope change



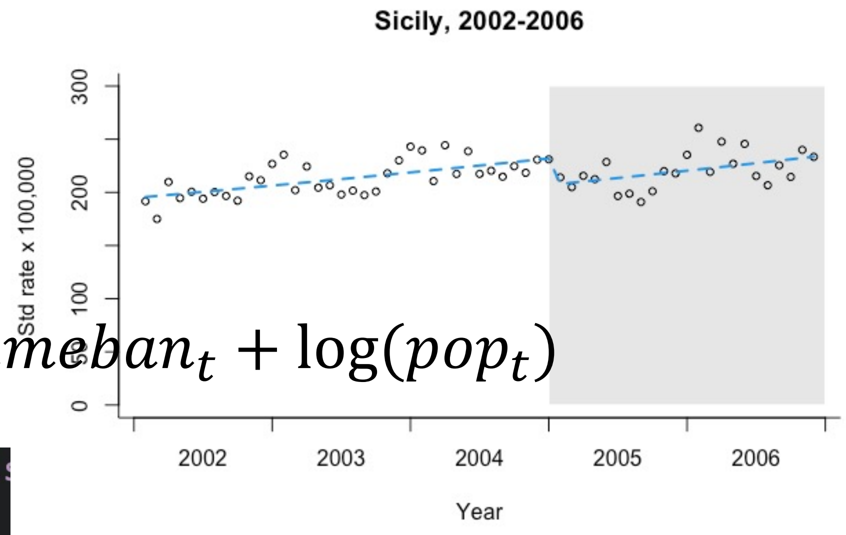
$$Y_t = \beta_0 + \beta_1 T + \beta_3 (T - T_0) X_t + \varepsilon_t$$

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_3 * timeban_t + \log(pop_t)$$

```
> pre.itv <- tail( data$time[ data$smokban == 0 ], 1)
> data$timeban <- ifelse(data$smokban == 0, 0, data$time - pre.itv)
> model.b <- glm(aces ~ offset(log(stdpop)) + time + timeban, family=poisson, data)
> ci.exp(model.b)
              exp(Est.)        2.5%       97.5%
(Intercept) 0.001991694 0.001946777 0.002037648
time        1.003068972 1.002119776 1.004019068
timeban     0.997627792 0.995435598 0.999824814
```

Parameter	exp(Estimate) (95% CI)	Note	How to interpret it
$\exp(\beta_0)$	0.002 (0.002, 0.002)	0.00199 x 10^5 = 199	Indicating the expected ACE when time=0 (i.e., intercept)
$\exp(\beta_1)$	1.003 (1.002, 1.004)	RR for the time before ban	Indicating the ACEs increased by 0.3% per the time unit increase (i.e., month) in the pre-intervention
$\exp(\beta_3)$	0.9976 (0.995, 1.000)	Ratio of $RRs_{[post-pre]}$	Slope change (decreased) following the intervention (p for interaction b/w time and intervention = 0.034)

Example: (C) Level and slope change



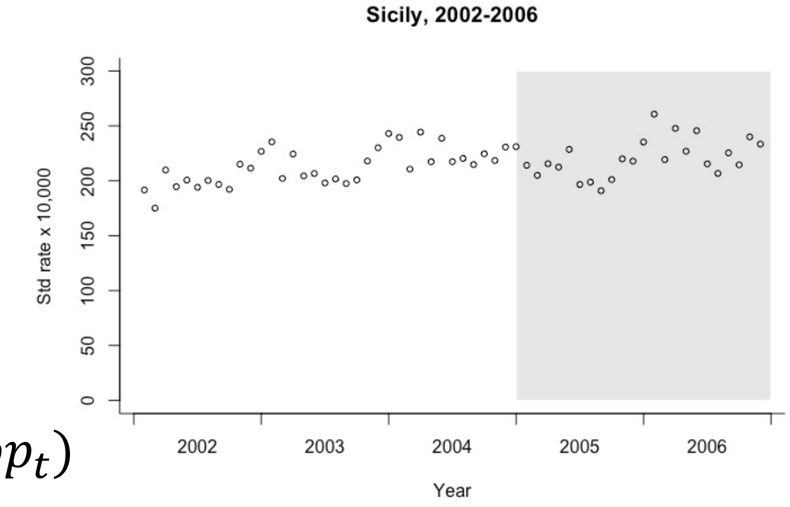
$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 (T - T_0) X_t + \varepsilon_t$$

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_2 * smokban_t + \beta_3 * timeban_t + \log(pop_t)$$

```
> model.c <- glm(aces ~ offset(log(stdpop)) + time + smokban + timeban, family=pois
> ci.exp(model.c)
              exp(Est.)        2.5%       97.5%
(Intercept) 0.001947068 0.001900863 0.001994395
time        1.004866720 1.003756847 1.005977821
smokban     0.892158897 0.860069126 0.925445960
timeban     1.000416932 0.998041365 1.002798154
```

Parameter	exp(Estimate) (95% CI)	Note	How to interpret it
$\exp(\beta_1)$	1.005 (1.004, 1.006)	RR for the time before ban	Indicating the ACEs increased by 0.5% per the time unit increase (i.e., month) in the pre-intervention
$\exp(\beta_2)$	0.892 (0.860, 0.925)	RR for the intervention	Suggesting a strong evidence of a reduction in ACEs following the smoking ban (when time=36 [Dec 2004]), with a decrease of 10.8%
$\exp(\beta_3)$	1.0004 (0.998, 1.003)	Ratio of $\text{RRs}_{[\text{post-pre}]}$	Slope change following the intervention (p for interaction b/w time and intervention = 0.731)

Which model we should select?



(A) Level change

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_2 * smokban_t + \log(pop_t)$$

(B) Slope change

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_3 * timeban_t + \log(pop_t)$$

(C) Level and slope change

$$\log(E(ACE_t)) = \beta_0 + \beta_1 * time + \beta_2 * smokban_t + \beta_3 * timeban_t + \log(pop_t)$$

Model	RR (95% CI) for intervention *(smokban)*	Ratio of RRs (95% CI) for slope *(timeban)*	*p* for interaction	AIC
(A) Level change	0.894 (0.865, 0.925)	NA	NA	**708.0326**
(B) Slope change	NA	0.9976 (0.995, 1.000)	0.034	745.4136
(C) Level and slope change	0.892 (0.860, 0.925)	1.0004 (0.998, 1.003)	0.731	**709.9145**

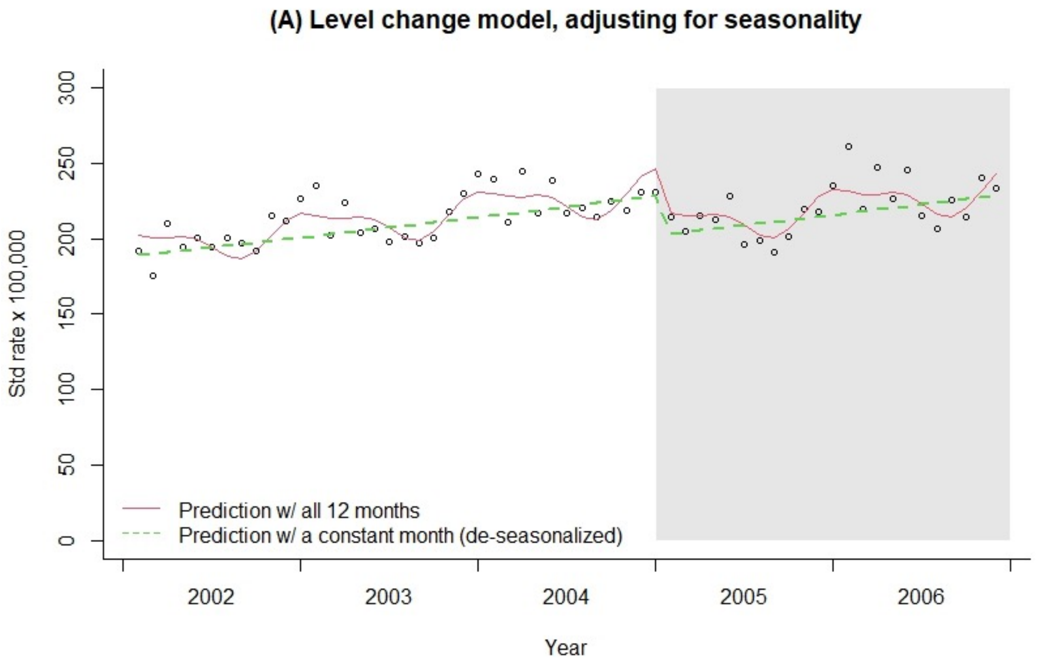
Step 5: Addressing methodological issues

- Seasonality
- Time-varying confounders
- Use of controls and other more complex ITS designs
- Over-dispersion
- Autocorrelation

It needs to be addressed to improve the robustness of the analysis.

Seasonality adjustment

- Seasonality can bias/confound the results.
- An uneven distribution of months before and after the intervention
  - E.g., a higher proportion of winter months
- A higher correlation with neighboring months (i.e., autocorrelation)
- Various ways to control for seasonality and long-term trends
  - Stratified by month (and year)
  - Fourier terms (pairs of sine and cosine functions)
  - Spline functions



Adjustment of time-varying confounders

- Seasonality
- Infectious disease outbreaks
- Weather events

- Other events
  - that occur around the same time as the intervention
  - that potentially influence the outcome
  - e.g., other simultaneous interventions targeting the same outcome (a new test implemented)
  - e.g., other simultaneous interventions targeting risk factors of the outcome (a healthy eating intervention)
  - e.g., natural events that could affect the outcome

Seasonality adjustment & Over-dispersion

Model	Seasonality	Dispersion	RR (95% CI) for intervention	Interpretation
(A) Level change	None	1	0.894 (0.865, 0.925)	A reduction in ACEs following the smoking ban, with a decrease of 10.6% (95% CI = -13.5%, -7.5%)
(A)_1 Level change	Fourier	1	0.885 (0.854, 0.917)	with a decrease of 11.5% (95% CI = -14.6%, -8.3%)
(A)_2 Level change	Fourier	2.26	0.885 (0.839, 0.933)	with a decrease of 11.5% (95% CI = -16.1%, -6.7%)

Summary

- The interrupted time-series (ITS) design is useful to evaluate effectiveness of public health interventions at a population level over a specific time period.
- When selecting an impact mode, it is crucial to consider previous knowledge and intervention's mechanism on the outcome.
- Analyses should be carefully planned with adjustment for seasonality and time-varying confounders to draw the plasible conclusions regarding intervention effectiveness. Interpretation should be approached with caution.
- Relying solely on the data-driven model specification is not recommended.
- It is worth considering methodological extensions.

A previou study using an ITS with DLNM

Research

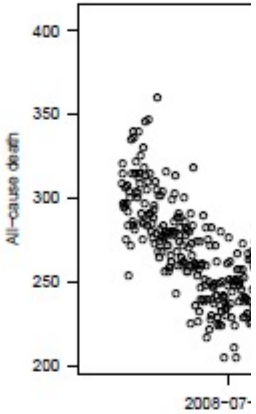
A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP493.

Heat-Related Mortality in Japan after the 2011 Fukushima Disaster: An Analysis of Potential Influence of Reduced Electricity Consumption

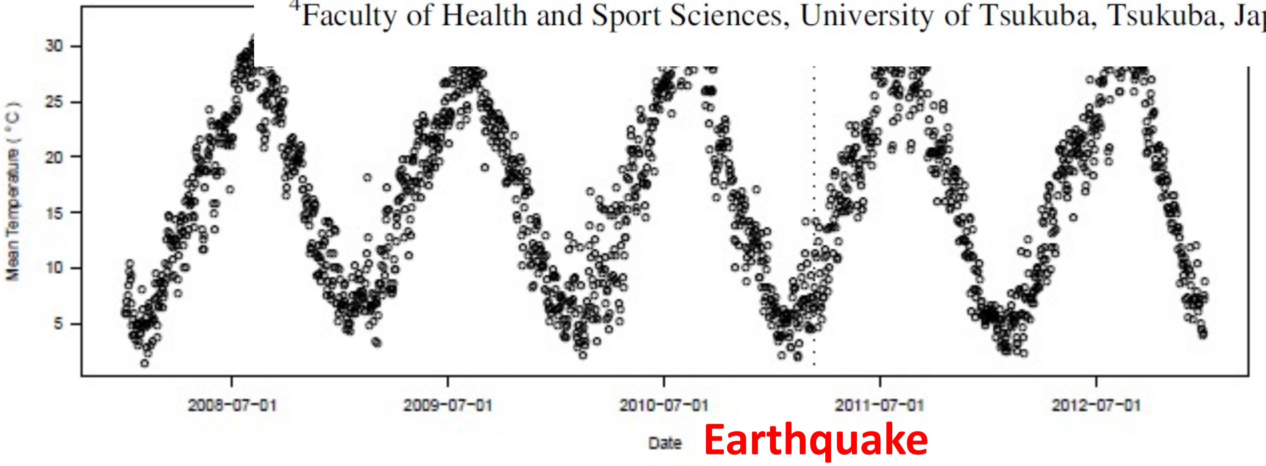
Yoonhee Kim,[1] Antonio Gasparrini,[2,3] Masahiro Hashizume,[1] Yasushi Honda,[4] Chris Fook Sheng Ng,[1] and Ben Armstrong[2]

[1]Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[2]Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, UK
[3]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
[4]Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan

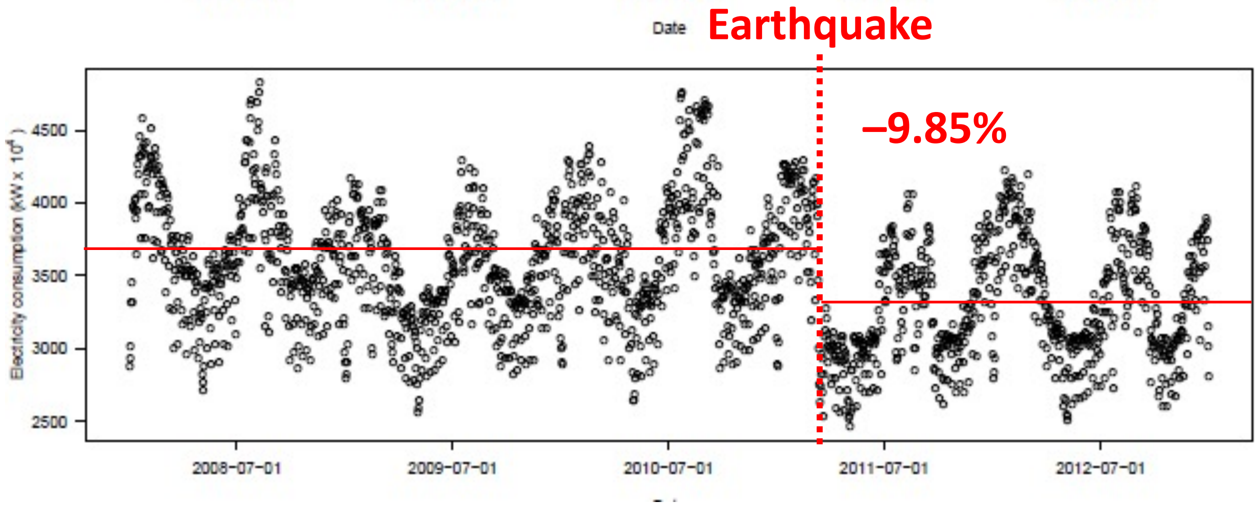
all-cause deaths



mean temperature



Electricity consumption



Time-series data in Tokyo metropolitan area

Characteristic	Before	After
Year	2008-2010	2011-2012
# of days (May-Sept)	459	306
All-cause death	256 (24)	270 (19)
Mean Temperature (ºC)	24.1 (4.1)	24.4 (4.3)
Electricity consumption (kW x 10^4)	3635.8 (471.1)	3277.7 (386.1)

Unit: Daily mean (standard deviation)

Relative Risk (RR) and ratio of RR in two big prefectures

- In Tokyo which is the most populous prefecture in the most-affected area,
  - the cumulative relative risks (RR) after the earthquake were lower than those before.
- In Osaka which is the most populous prefecture in the less-affected area,
  - there was little evidence of changes in the cumulative relative risks (RR) before and after.