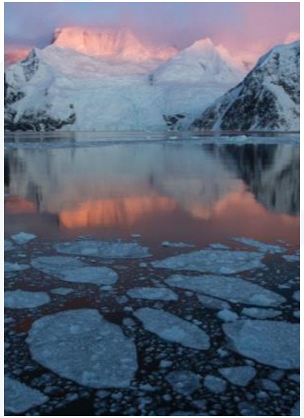
STUDY DESIGNS FOR ACUTE HEALTH IMPACTS OF ENVIRONMENTAL RISK FACTORS

Chen Chen & Lara Schwarz

UC San Diego | SCRIPPS INSTITUTION OF OCEANOGRAPHY

OUTLINE



Section 1:

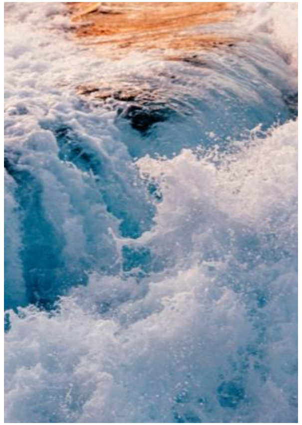
Overview

Section 2:

Considerations in analyzing time-series data

Break!

Coffee, stretch your legs…



Section 3:

Coding time—applications in R

Section 4:

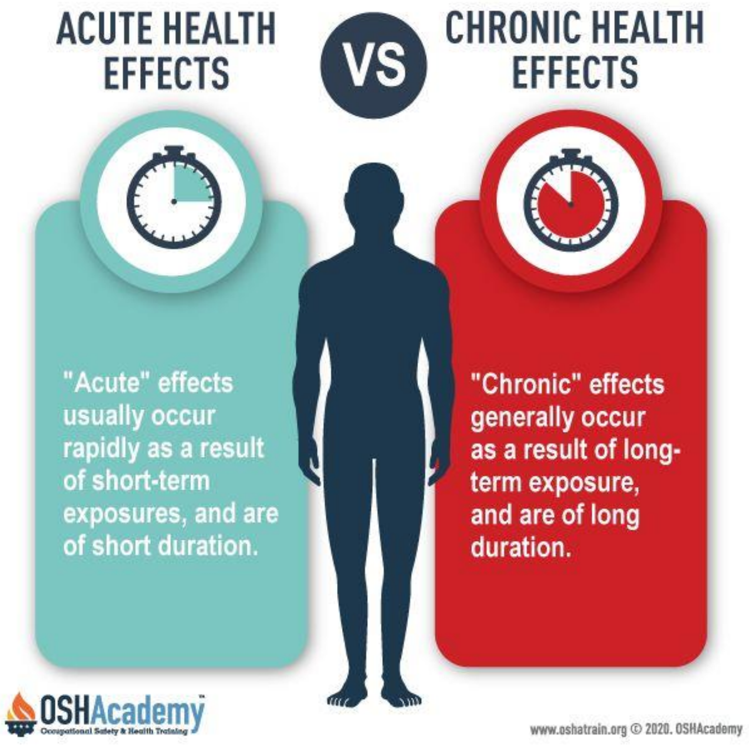
Extended use

OVERVIEW

Useful Island, Antarctic Peninsula. *Credit: Maria Stenzel*

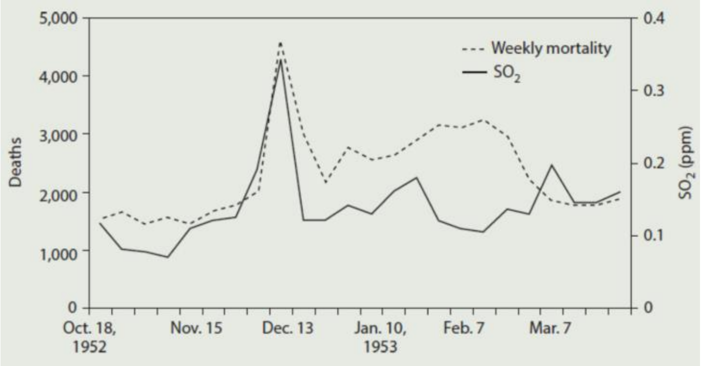
ACUTE EXPOSURE-WHAT DO WE MEAN

- **Acute effect**: Health effects that usually occur rapidly, as a result of short-term exposure
- **Acute exposure:** Short term exposure, in environmental epidemiology, this is usually on time scale of minutes, hours, days, or weeks
  - Can be a "trigger" or the last step in leading from pathophysiology to disease, or the final component cause leading a susceptible person to experience a specific outcome

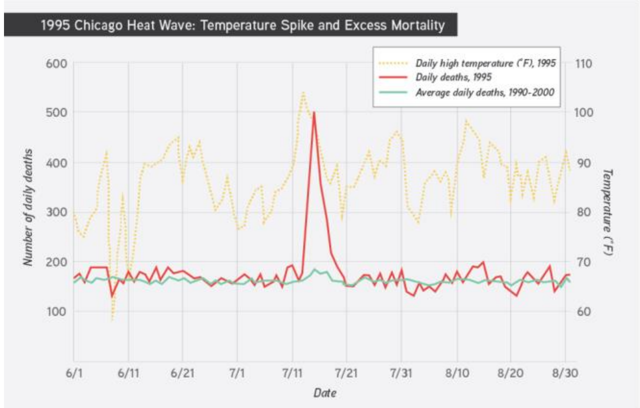


WHY ARE ACUTE ENVIRONMENTAL STRESSORS IMPORTANT TO STUDY

- Acute environmental events which can be studied include (but not limited to):
  - ❖ High air pollution concentrations
  - ❖ Extreme heat or high temperature
  - ❖ Natural disasters such as tornadoes, floods, hurricanes
- Evidence of the effect of acute environmental exposures can be used to inform measures to protect populations during high exposure days
  - ❖ Relevant to regulatory processes and public health action



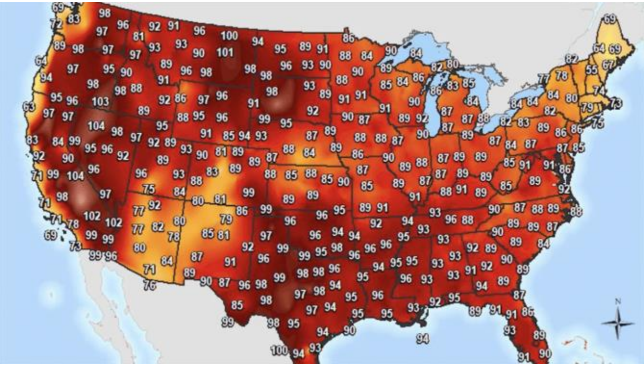
(Mortality and SO_2 levels during the 1952 London Smog, adapted from Bell et al., 2001)



UNIQUE ISSUES OF STUDIES LOOKING AT ENVIRONMENTAL STRESSORS

- Randomized controlled trials are generally unethical in environmental epidemiology

- Effect tends to be small but large populations are affected
  - ❖ We can capitalize on this widespread exposure to study effects
  - ❖ Small risks can have major impact when affecting large populations
    - ❖ Relative vs. absolute scales
  - ❖ More easily generalizable



HOW DO WE STUDY ACUTE EFFECTS? TIME SERIES DATA!

Example of the outcome and exposure time-series in a time-series study (Figure 1 from Bhaskaran et al. 2013)

Date	Exposure (ex: PM2.5)	Outcome (ex: hosp)	Covariates (ex: temp)
1/1/2016	36.4	116	25.4
1/2/2016	42.3	125	26.9
1/3/2016	40.5	123	20.3
1/4/2016	38.7	119	18.5
…	…	…	…

- Continuous sequence of observations of a population, taken repeatedly over time (normally equal intervals)
- Data for time-series include repeated measures for a given area
  - ❖ Number of health events (ex: daily mortality count)
  - ❖ Exposure levels (ex: concentrations of PM)
  - ❖ Covariate information such as weather variables
- Capitalize on day-to-day (or other time scale) variations in risk factor and in mortality or morbidity counts.

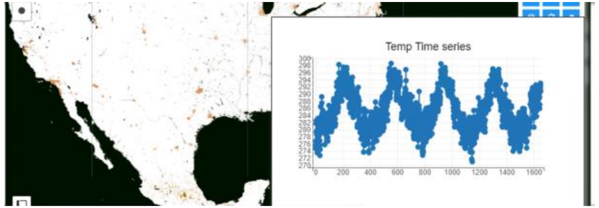
USING TIME SERIES DATA

Data Access

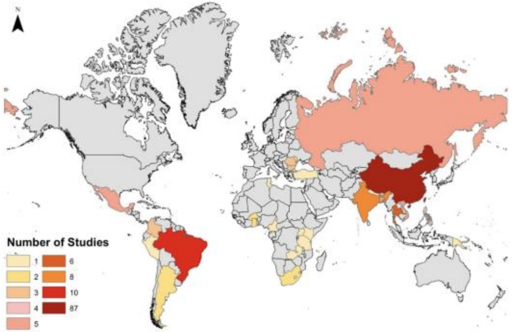
- No need for individual level information
- Confounding by population characteristics is negligible as they are quite stable day to day
- Requires data at a fine temporal scale (ex: daily) for both exposure and outcome

Inference

- Ecological level
- Large scale studies that are generalizable



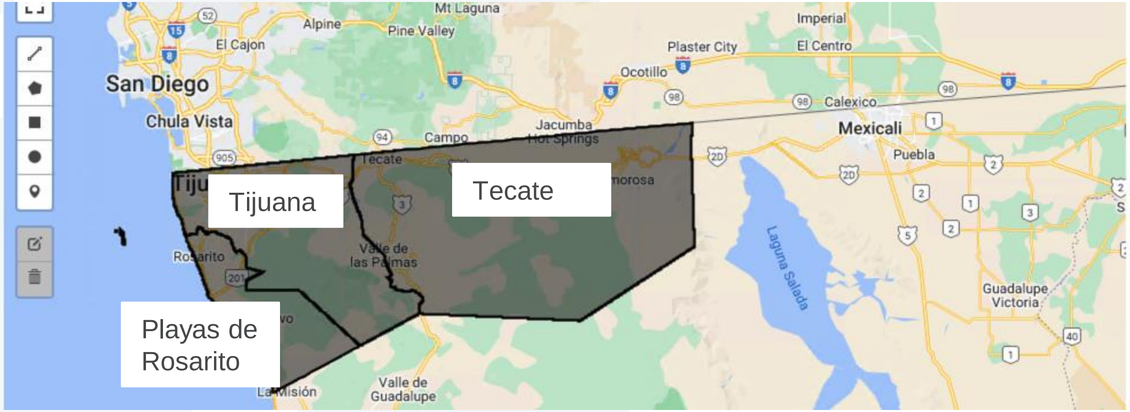
Satellite products make climate data much more accessible on global scale



Heat-related in studies in low and middle income countries. (Figure 3 from Green et al., 2019)

EXAMPLE ON HEATWAVE IMPACTS

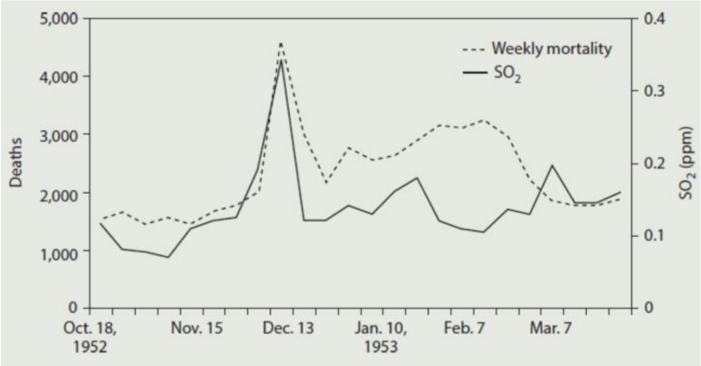
What is the effect of heat waves on hospital admissions in three Baja California municipalities from 2008-2018?



TIME SERIES ANALYSIS

Population-based ecological study design to estimate **short-term** health effects of environmental stressors

- Directly models the association between day-to-day variations of exposure and outcome
- Population-based ecological study: we treat the entire study population as exposed and modeled the association between aggregated health outcomes and aggregated exposure.
- Short-term health effects: acute health impacts of environmental stressors, normally within days or weeks.



(Mortality and SO_2 levels during the 1952 London Smog, adapted from Bell et al., 2001)

TIME SERIES ANALYSIS

Use **Poisson regression with over-dispersion** to model the daily count of health outcome:

- **Poisson regression** models count outcome and assumes independence of events after adjusting for confounders
- **Over-dispersion** allows the variance to deviate from mean in the outcome data (quasi-Poisson regression and negative binomial regression)
- Simplified model:

$$\ln\left(E\left(Y_t^c\right)\right) = \text{offset}\left(\ln\left(Pop_{c,t}\right)\right) + \beta^c X_t^c + confounders$$

  - Y_t^c: number of events on day *t* in city *c*
  - $\text{offset}(\ln(Pop_{c,t}))$: population at risk on day *t* in city *c*
  - X_t^c: level of environmental stressor (or heatwave status) on day *t* in city *c*
  - *Confounders:* examples include long-term and seasonal trends in time
  - β^c: city-specific log incidence rate ratio associated with one unit increase in *X* (or comparing heatwave to non-heatwave days)

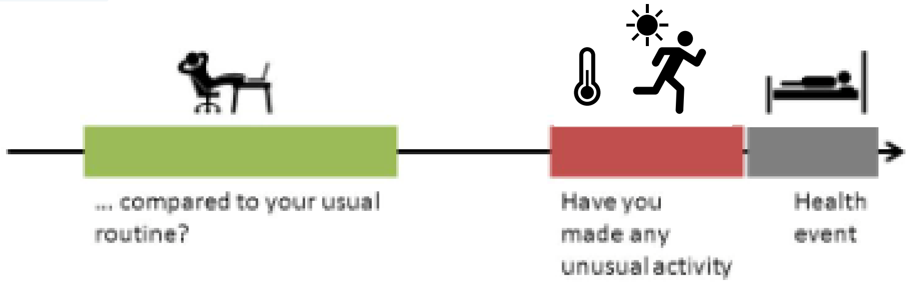
CASE CROSSOVER DESIGN

An innovative combination of crossover trial design and matched case-control design

- Crossover trial design: each patient receives different treatments during different time periods (i.e., patients cross over from one treatment to another during the trial)
- Matched case-control design: select matching controls to cases so that they are similar in confounders to increase efficiency and a matched analysis is generally needed

First proposed by Maclure (1991) to study transient effects on acute health events

- Uses each event or ‘case’ as its own control
- Identifies ‘control’ periods in which the event did not occur
- Control for any time-fixed information for by design when using matching method in analysis



CASE CROSSOVER DESIGN

Depending on the datasets being used, we could categorize case crossover design into

- Individual case crossover design: each case has their distinct individual exposure value
- Aggregated case crossover design: cases within one geographical area use the same exposure for that geographical area (i.e., time-series exposure dataset)—most likely

Analyzed similarly to a **matched case control study** where exposure is compared across case and control (conditional logistic regression)

- The exposure of the case period are compared to exposures in control periods in the same stratum, then averaged across strata
  - In a binary exposure setting, it is the same as estimating ratio of discordant pairs in matched case-control study (Mantel-Haenszel method)

CASE CROSSOVER ANALYSIS

Simplified model for conditional logistic regression:

$$logit(P_{i,k}) = \alpha_i + \beta \times X_{i,k} + confounders$$

- $P_{i,k}$ represents the probability of having the event for period *k* in stratum *i*
- α_i represents intercept for stratum *i*
- $X_{i,k}$ represents the value of environmental stressor *X* (or heatwave status) for period *k* within stratum *i*
- β is the log odds ratio of having the event per unit increase in *X* (or comparing heatwave to non-heatwave days)

Extension: treating each period instead of each event as a case

- Conditional logistic regression with weights equal to number of events for each period
- Conditional Poisson regression

CONSIDERATIONS IN ANALYZING TIME-SERIES DATA

Scripps research in Palau. *Credit: Jennifer Smith*.

OVERVIEW OF CONSIDERATIONS FOR BOTH STUDY DESIGNS

- Estimation of exposure time-series data
  - Time-series analysis: finer or coarser
- Confounding in time-series data
  - Case-crossover: controlled by design + controlled by modeling
  - Time-series analysis: controlled by modeling
- Lag structure
- Pooling of results across geographical units
  - Case-crossover: could skip this step
  - Time-series analysis: multilevel modeling

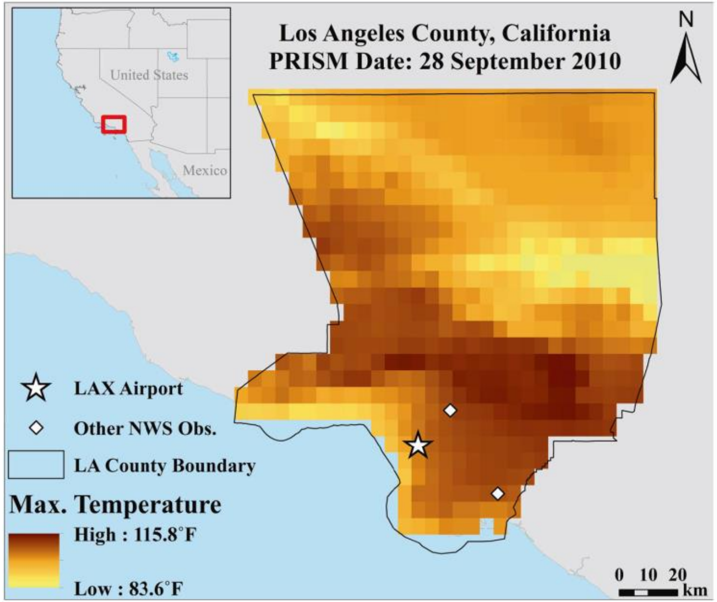
ESTIMATION OF EXPOSURE TIME-SERIES DATA

Exposure data sources:

- Direct measurements from monitoring sites (e.g., weather station)
- Use ensemble model to incorporate indirect info (e.g., satellite and land use data)

In time-series analysis, things to consider in choosing the size of the geographical unit for exposure data aggregation/estimation:

- Maintaining spatial homogeneity of exposure within the unit to approximate population average exposure
  - Population mobility across units
- Having large enough population to satisfy the independence assumption for outcome



Spatial heterogeneity of ambient temperature across Los Angeles county after incorporating indirect info. (Figure 1 from Spangler et al. 2018)

CONFOUNDING IN TIME-SERIES DATA

Temporally stable confounders

- Population composition (e.g., age structure, smoking population)

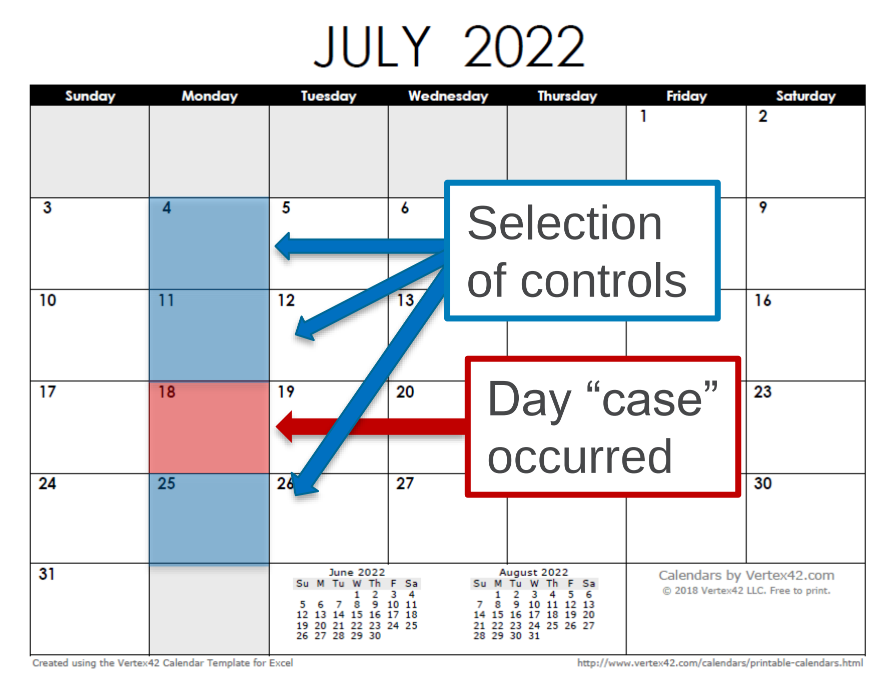
Time-varying confounders

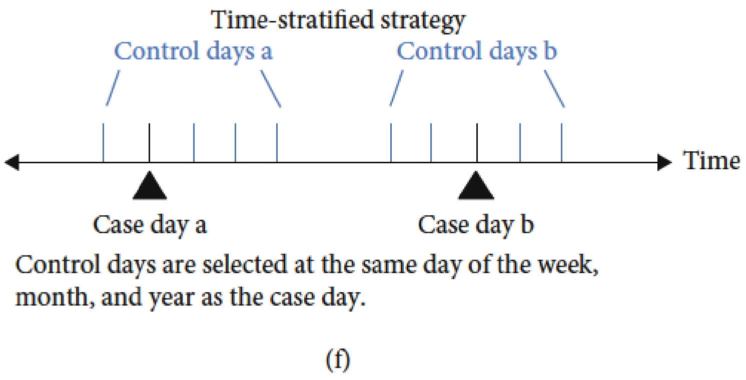
- Day of the week
- Relevant environmental factors (e.g., temperature in studies of air pollution)
- Seasonal trend or long-term pattern (e.g., higher influenza rates and lower temperature in winter)

Types of confounding	Time-series analysis	Case-crossover
Temporally stable confounders	Controlled by design	Controlled by design
Time-varying confounders	Adjusted for in the model	Controlled by design + adjusted for in the model

CASE CROSSOVER DESIGN- SELECTION OF CONTROLS

Time-stratified case crossover design selection of controls





(Figure 1 Wu et al., 2021)

CONTROLLING FOR TIME TRENDS BY DESIGN

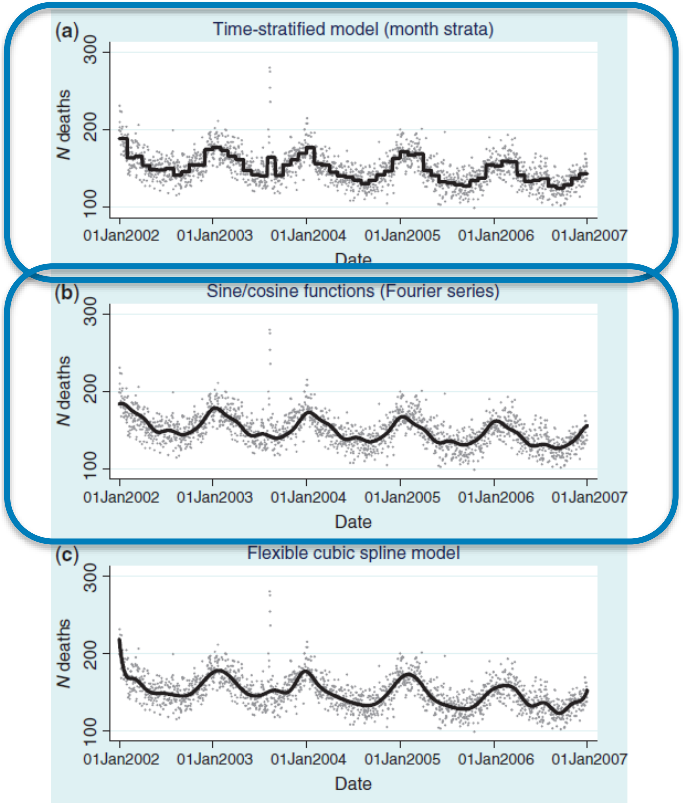
With time-stratified approach, bi-directional selection of controls adjusts for seasonality and time trends by design

- Using the same day of the week to account for behavioral differences between weekdays assuming that activities will be similar on same weekday in a month
- Any time-varying confounder that will differ throughout the month beyond seasonal time trend will still have to be adjusted for in model
  - Ex: humidity in heatwave study, and temperature in air pollution studies

CONTROL FOR TIME TRENDS IN MODEL

Adjustment for time-varying confounders like seasonal trend, long-term pattern and relevant environmental factors

- Fixed-effect model
  - Split the study period into intervals and estimate each interval separately
  - Cons: abrupt change with large number of parameters
- Periodic function of time
  - Use Fourier terms to summarize the seasonal trend
  - Cons: forced the same trend every year

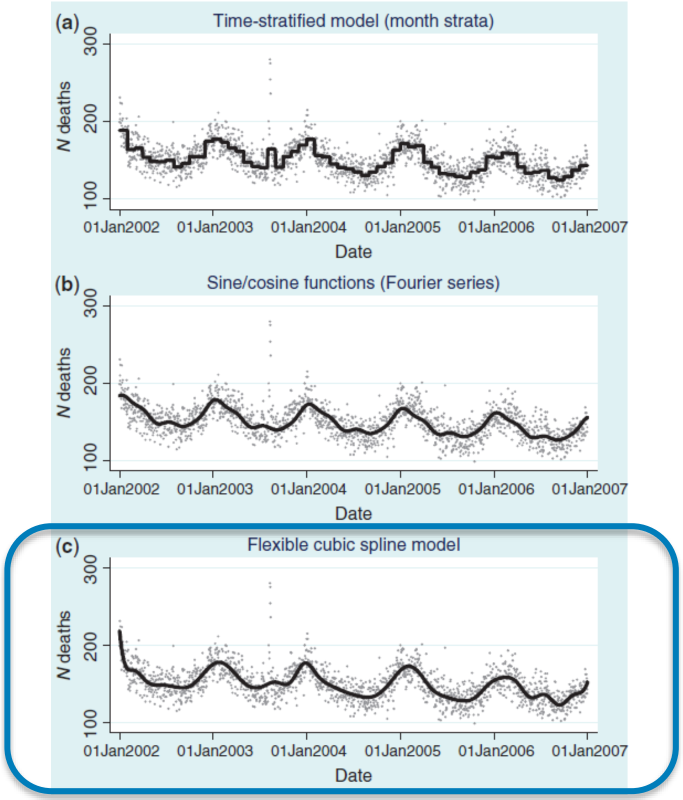


Three ways of modelling long-term pattern (Figure 2 from Bhaskaran et al. 2013)

CONTROL FOR TIME TRENDS IN MODEL

Adjustment for time-varying confounders like seasonal trend, long-term pattern and relevant environmental factors

- ❖ Spline function of time: smoothed polynomial curves
  - ❖ Degree of freedom: chosen *a prior* based on previous knowledge or chosen based on data



Three ways of modelling long-term pattern (Figure 2 from Bhaskaran et al. 2013)

CONTROL FOR TIME TRENDS IN MODEL

Adjustment for time-varying confounders like seasonal trend, long-term pattern and relevant environmental factors

- Spline function of time: smoothed polynomial curves
  - Degree of freedom: chosen *a prior* based on previous knowledge or chosen based on data
  - Simulation study suggested up to 10 degree of freedom per year for time-series analysis of air pollution (Peng et al. 2006)
  - Case-crossover study with time-stratified design is mathematically equivalent to including a spline function with 90 degree of freedom per year (Lu and Zeger 2007)

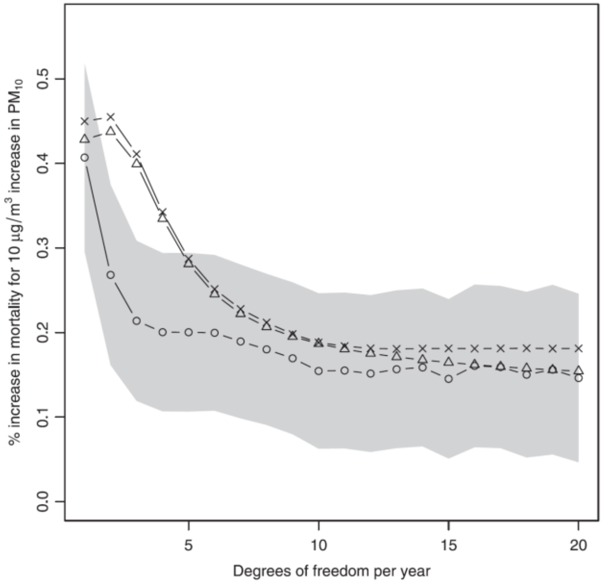


Fig. 3. Sensitivity analysis of the national average estimate of the percentage increase in mortality for an increase in PM_{10} of 10 μg m^{-3} at lag 1: city-specific estimates were obtained from 100 US cities using data for the years 1987–2000 and the estimates were combined by using a hierarchical normal model (○, GLM-NS; △, GAM-R; ×, GAM-S; ■, 95% posterior intervals for the estimates obtained by using GLM-NS)

RR estimates vs. degree of freedom used in adjustment by different spline functions (Figure 3 from Peng et al. 2006)

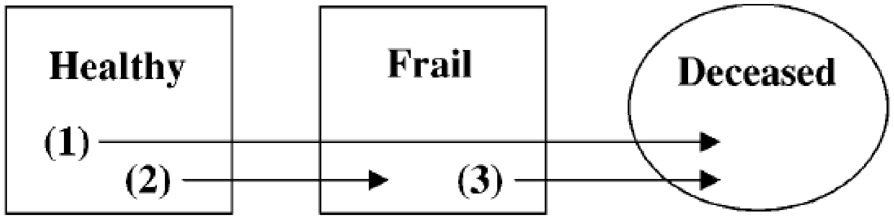
LAG STRUCTURE

What is a short-term exposure?

- Same day vs. multiple days

How long will the effect of a short-term exposure persist?

- Etiological question
- A concern over mortality displacement ("harvesting"):
  - The health impact of short-term exposure to heatwave are solely due to deaths of frail individual, whose deaths are brought forward by a few days, and deprivation of the pool of frail individuals will lead to decreased mortality in later days (Zeger et al. 1999)



Model for mortality among healthy and frail population (Figure 5 from Bell et al. 2004)

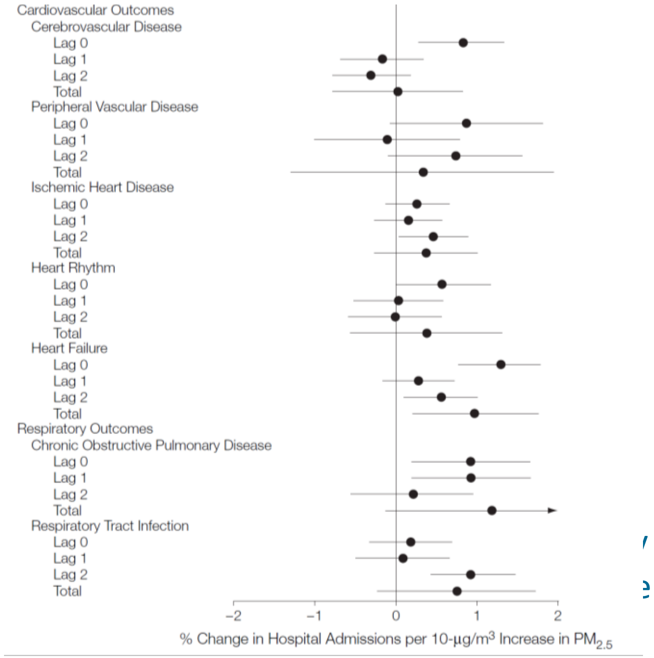
HOW TO CONSIDER LAG STRUCTURE

Existing methods to account for lag structure (applicable to both designs)

- Cumulative effect
  - Moving average of exposure from a few days
- Lagged effect
  - Multiple single-day model with different lag
  - Distributed lag model

Mostly current studies evaluated lag structure up to a week

- Lag structure longer than a week are hard to handle in time-stratified case-crossover design



2000)

Percentage change in hospitalization rate per 10 µg/m^3 increase in $PM_{2.5}$ (Figure 2 from Dominici et al. 2006)

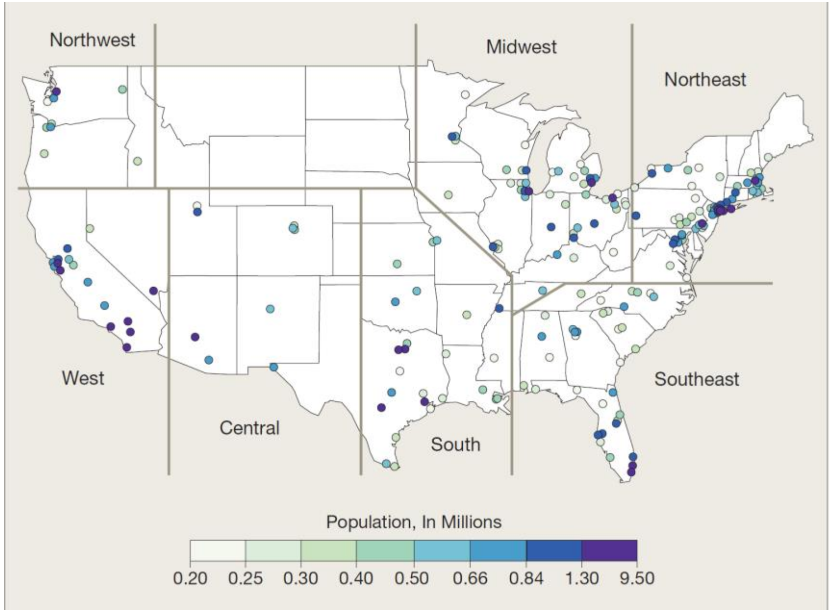
POOLING RESULTS ACROSS GEOGRAPHICAL UNITS

Assuming **the same concentration-response function (i.e. association/effect) in all geographical units**, we could pool results across them to increase precision

- ❖ Time-series analysis: multilevel modeling
  - ❖ Bayesian hierarchical modeling
  - ❖ Meta-analysis with random intercept for each geographical unit
- ❖ Case-crossover design could skip this step
  - ❖ Including all risk sets in one model

What if heterogeneity exists?

- ❖ Effect modification (later section)



Counties included in one study of air pollution (Figure 1 from Dominici et al. 2006)

COMPARISON OF TWO DESIGNS

	Time-series analysis	Case-crossover

*to relax the assumption of equal mean and variance; +there are other options; **many parameters estimated.

WHEN TO USE WHICH DESIGN?

Considerations to decide between case crossover (CC) and time series design (TS):

- Lag structure
  - Is there rationale/interest to study longer lags? -> TS may be more appropriate
- Distribution of outcome
  - Is there a lot of days with 0 outcome? -> CC may be more efficient (aggregation retains more information)
- Flexibility to account for long term trends
  - Are there strong long-term trends that need to be considered? -> Your preference but time stratified CC makes fewer assumptions for long term trends

FIVE-MINUTE BREAK!

Come back at 2:25pm PDT, please

Salton Sea. *Credit: Tyler Huston*

APPLICATION IN R–CODING IT

Southern Ocean. *Credit: San Nguyen*

CODING EXAMPLE: SPLINES

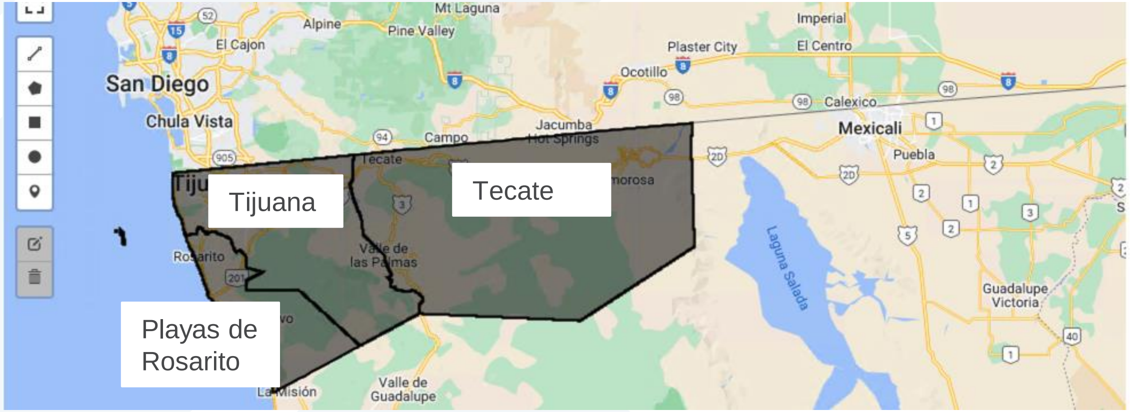
CODING EXAMPLE: TIME SERIES ANALYSIS

CODING EXAMPLE: TIME-STRATIFIED CASE CROSSOVER

YOUR TURN!

RESEARCH QUESTION

What is the effect of heat waves on hospital admissions in three Baja California municipalities from 2008-2018?



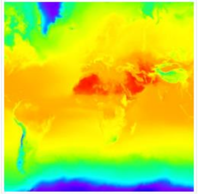
DATASETS

Exposure:

Global daily climate estimates of maximum temperature from ERA5

Heat wave defined at 90th percentile

ERA5 Daily Aggregates - Latest Climate Reanalysis Produced by ECMWF / Copernicus Climate Change Service



Outcome:

Hospital admissions reported by medical units administered by the Mexican Secretary of Health

Daily count computed for each municipality from 2008-2018

GOBIERNO DE MÉXICO

SALUD

SECRETARÍA DE SALUD

INSTRUCTIONS

You will be split in two groups; each will be assigned to apply one of the methods for studying acute health impacts of environmental exposures discussed in this workshop:

Group 1. Time series analysis

Group 2. Time stratified case crossover

You will have 20 mins to apply your assigned approach, we will then come together to compare results and have discussion. Feel free to use R markdowns covered in workshop for reference.

QUESTIONS TO STUDY

1. What is the effect of heat waves on hospital admissions in Northern Baja California (all three Mexican municipalities) overall?
    - For time-series analysis, use 4 degree of freedom per year for the natural cubic spline function of time
2. What is the effect of heat waves for each municipality- Tijuana, Tecate and Playas de Rosarito?
3. Bonus (if you have time): What is the lagged effect of heat waves on hospital admissions the day following a heat wave?

20-minute coding and take a break as you need :)

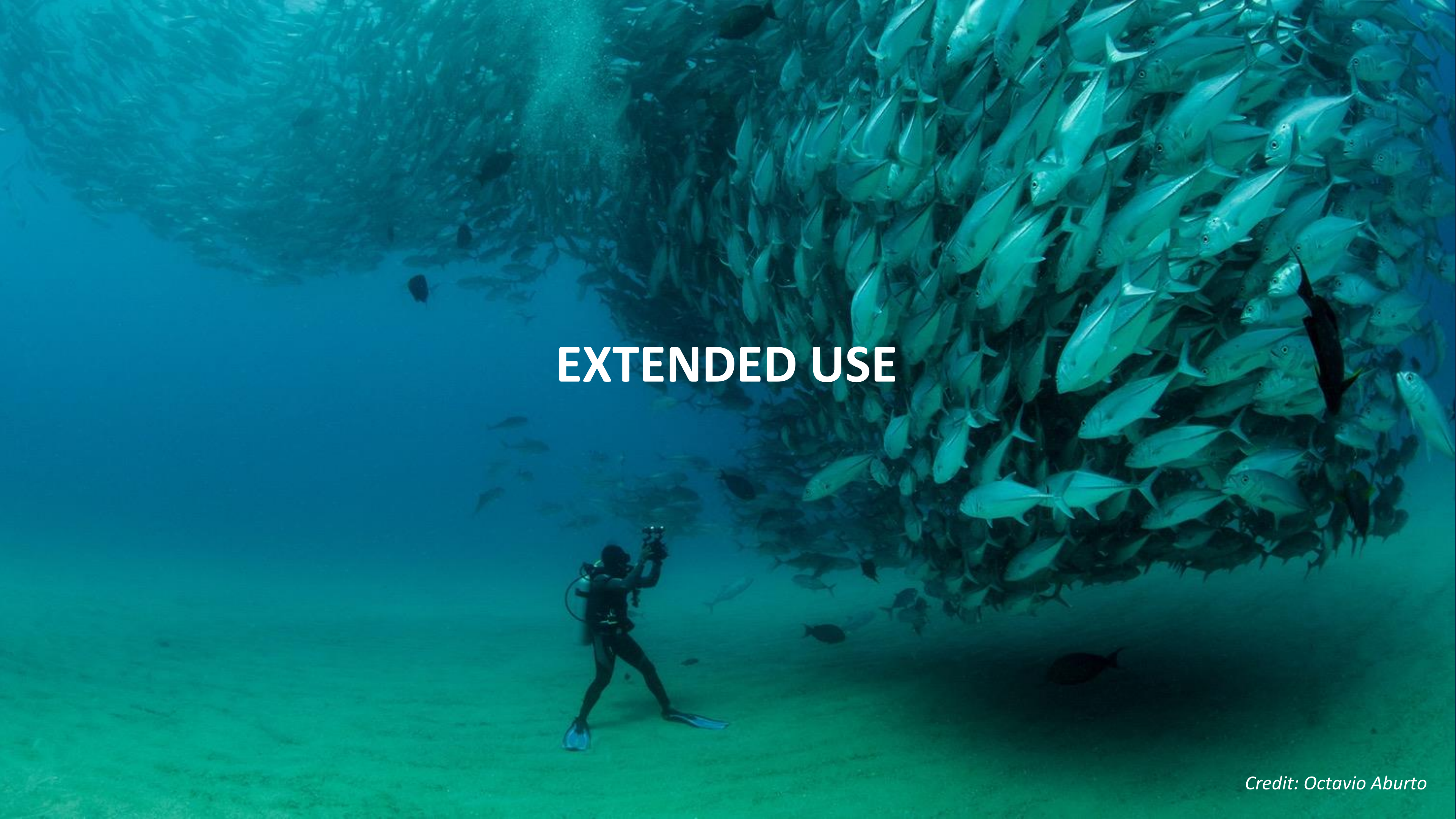
DISCUSSION OF RESULTS

Municipality	Time-series analysis	Time stratified case crossover
Regional		

RESULTS

Municipality	Exposure measure	Time-series analysis	Time stratified case crossover
Tijuana	HW same day	1.035 [1.009, 1.062]	1.037 [1.008, 1.068]
Tecate		1.036 [0.981, 1.094]	1.044 [0.980, 1.112]
Rosarito		1.014 [0.944, 1.090]	1.007 [0.936, 1.083]
Regional		1.034 [1.011, 1.057]	1.035 [1.010, 1.061]
Tijuana	HW lag 1	1.017 [0.992, 1.044]	1.010 [0.983, 1.037]
Tecate		0.976 [0.924, 1.032]	0.976 [0.903, 1.055]
Rosarito		1.081 [1.007, 1.044]	1.031 [0.967, 1.098]
Regional		1.020 [0.972, 1.069]	1.009 [0.986, 1.033]

EXTENDED USE



Credit: Octavio Aburto

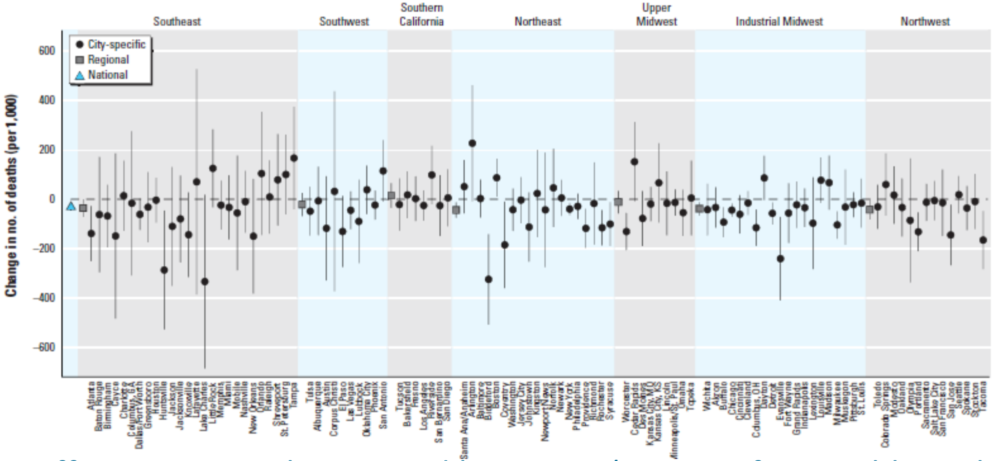
OVERVIEW OF EXTENDED USE

- Effect modification
- Nonlinear concentration-response function
- Alternative study designs

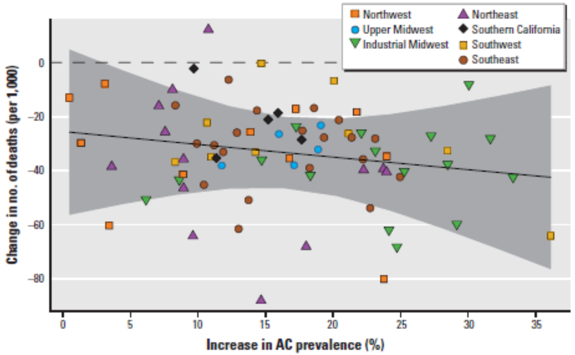
EFFECT MODIFICATION

Allow the effect to vary across:

- Individual-level effect modifiers
  - Subgroup (e.g., age and sex)
  - Method: subset analysis or adding interaction terms of exposure and effect modifier
- Community-level effect modifiers
  - Regions (e.g., Southeast U.S.)
  - Community characteristics (e.g., air conditioning prevalence)
  - Method: subset analysis or meta-regression with effect modifiers



Effect estimates by city and by region (Figure 1 from Bobb et al. 2014)



Effect modification by prevalence of air conditioning (Figure 2 from Bobb et al. 2014)

EFFECT MODIFICATION—ADDITIVE SCALE

- Measure of additive interaction- may be more relevant to understand potential role of intervention/action on decreasing effects

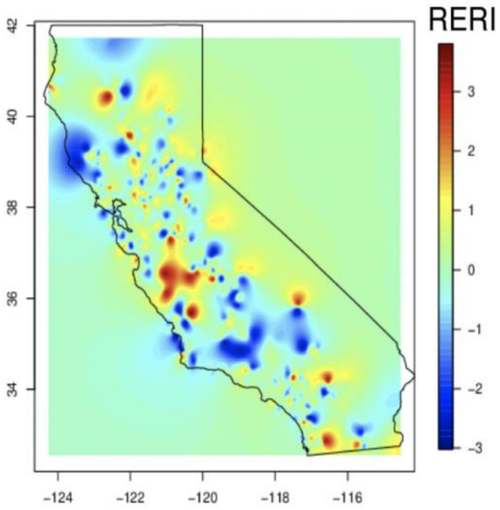
- RERI (relative excess risk due to interaction)- can be used to estimate joint effects of two exposures

$$\text{RERI} = RR_{++} - RR_{+-} - RR_{-+} + 1$$

>0: super-additive interaction (positive)

0: no interaction

<0: sub-additive interaction (negative)

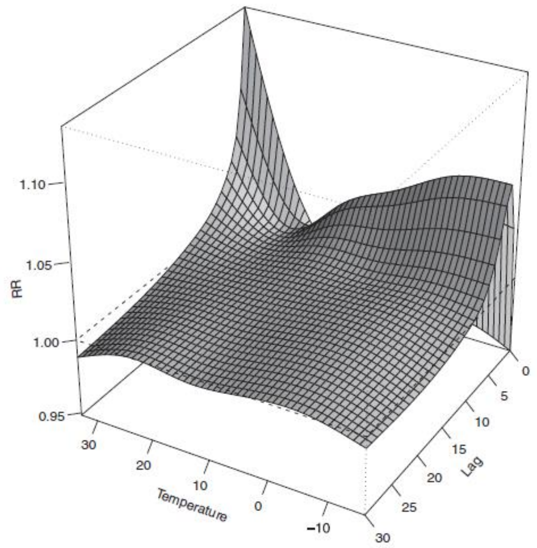


Spatial differences in joint effects of ozone and heat exposure in California (Figure 3 from Schwarz et al., 2021)

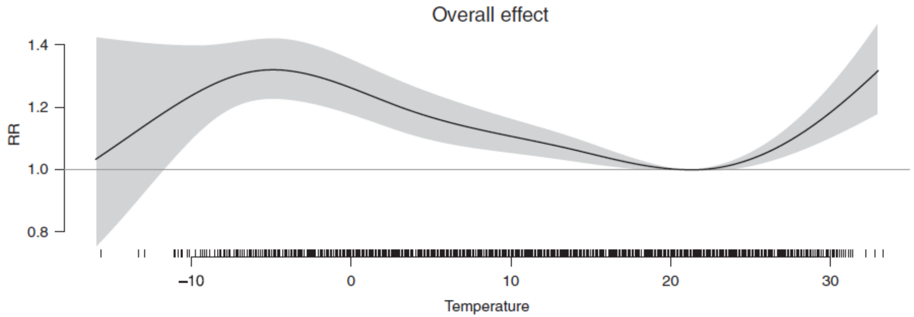
NONLINEAR CONCENTRATION-RESPONSE FUNCTION

Incorporate flexible function of exposure in the model:

- Allow the relationship between exposure and outcome to change along the value of exposure (e.g., exponential, nonlinear)
  - Special case: distributed lag non-linear model (R package *dlnm*), where the lag-response and non-liner concentration-response functions were modeled simultaneously



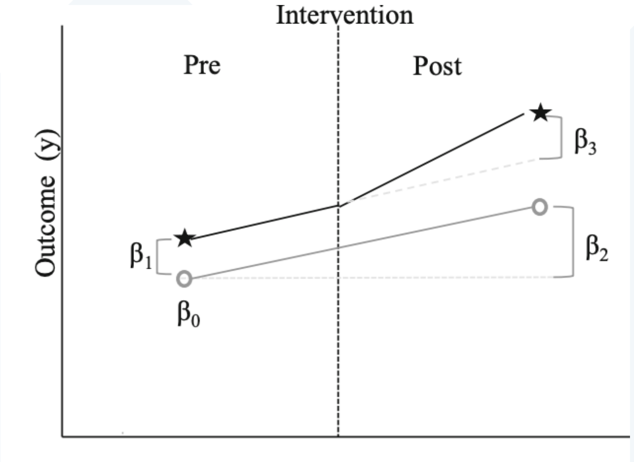
Effect of temperature by temperature and lag (Figure 1 from Gasparrini et al. 2010)



Overall effect of temperature aggregated across lags (Figure 2 from Gasparrini et al. 2010)

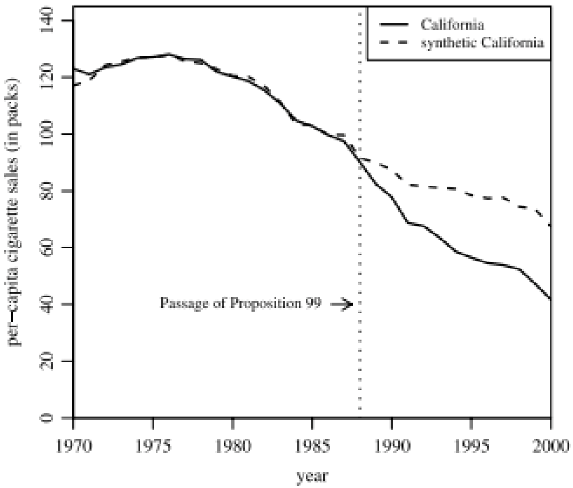
ALTERNATIVE STUDY DESIGNS

Difference-in-differences



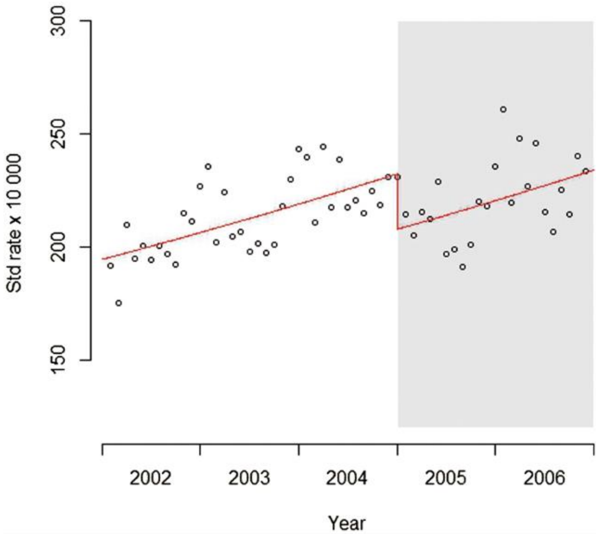
Application of difference in differences to health policy evaluation (Figure 3 from Saeed et al., 2019)

Synthetic control



Trends in per-capita sales: California vs. synthetic California (Figure 2 from Abadie et al. 2010)

Interrupted time series



Interrupted time series applied to smoking ban in Sicily (Figure 3 from Bernal et al., 2017)

Quantifying the impact of changing the threshold of New York City heat emergency plan in reducing heat-related illnesses

Tarik Benmarhnia[1,3], Lara Schwarz[1], Amruta Nori-Sarma[2] and Michelle L Bell[2]

Smoke and COVID-19 case fatality ratios during California wildfires

Lara Schwarz[1,2,*], Anna Dimitrova[3], Rosana Aguilera[3], Rupa Basu[4], Alexander Gershunov[3] and Tarik Benmarhnia[2,3]

ALTERNATIVE STUDY DESIGNS—MATCHED TIME-SERIES

Matched time-series is a good alternative when **exposure is rare,** and it controls for many confounders by design

- Resembles a matched cohort study
- Identify exposed days (e.g., wildfire smoke day)
- Identify non-exposed days for each exposed day as:
  - A few days away from the nearest exposed day
  - Days within a few days of the exposed day in another year or days within the same season at the same location
- Analyzed
  - Using mixed effect model
  - Or using weighted average all non-exposed days based on distance to the exposed day

Cause-Specific Risk of Hospital Admission Related to Extreme Heat in Older Adults

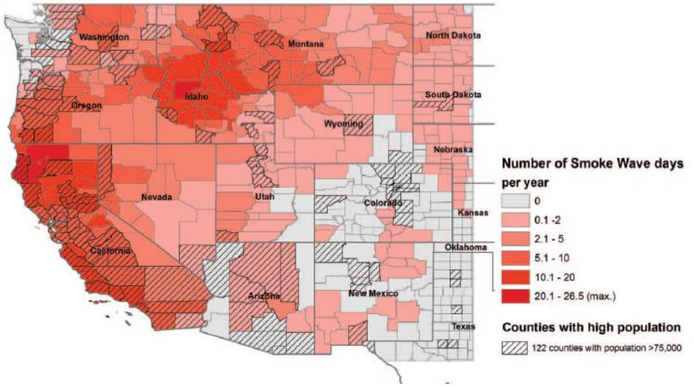
Jennifer F. Bobb, PhD, Ziad Obermeyer, MD, Yun Wang, PhD, and Francesca Dominici, PhD

Spatial variation in the joint effect of extreme heat events and ozone on respiratory hospitalizations in California

Lara Schwarz[a,b,1,2], Kristen Hansen[b,1,2], Anna Alari[c], Sindana D. Ilango[d], Nelson Bernal[e], Rupa Basu[f], Alexander Gershunov[g], and Tarik Benmarhnia[b,g]

Wildfire-specific Fine Particulate Matter and Risk of Hospital Admissions in Urban and Rural Counties

Jia Coco Liu,[a] Ander Wilson,[b] Loretta J. Mickley,[c] Francesca Dominici,[b] Keita Ebisu,[a] Yun Wang,[b] Melissa P. Sulprizio,[c] Roger D. Peng,[d] Xu Yue,[c] Ji-Young Son,[a] G. Brooke Anderson,[e] and Michelle L. Bell[a]



Distribution of exposed days in study (Figure 1 from Liu et al. 2017)

CONCLUSION

- There are various approaches to quantify the acute effects of environmental exposures
  - We focused on two commonly used analyses but there is continued methodological development in this area and many alternatives!
- We hope this will be a good starting point to applying these methods or to identify the best analytical approach for your study question
- There will be further need to continue to study the effects of acute environmental exposures many of which will **be *increasingly prevalent, more extreme and have unprecedented expressions/impacts*** in the context of climate change

THANK YOU!

Lara Schwarz (lnschwar@health.ucsd.edu)
Chen Chen (chc048@ucsd.edu)

UC San Diego | SCRIPPS INSTITUTION OF OCEANOGRAPHY

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