Research designs & bias in environmental epidemiology

1. challenges
2. designs
   - traditional
   - non-traditional
3. biases

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Environmental epidemiology: challenges

1. long latency
2. exposure measurement error
3. rare diseases
4. low-level exposure
5. small effect size

notion of "more probable than not"

Morgenstern & Thomas, EHP 1993

calculation of RR in cohort study

	Age (years)								Death rate (deaths/ person-yrs)
	20	30	40	50	60	70	80	90	
5 exposed subjects			1	1	1	1	1		5/200
5 unexposed subjects				1	1	1	1	1	5/250

exposed person-yrs = 20+30+40+50+60 = 200
unexposed person-yrs = 30+40+50+60+70 = 250

$$RR = \frac{5/200}{5/250} = 1.25$$

Environmental epidemiology: designs

A problem:

A public health worker in Turkey has been impressed by the large number of cases of mesothelioma in the region.

How can this impression be moved to a more intellectually (scientifically?) rigorous level?

types of study designs in environmental epidemiology

traditional

- case series
- "ecological"
- cross-sectional
- case-control
- cohort

non-traditional

- time series
  - & case-crossover
- panel
- quasi-experimental (ie, natural experiment)
- gene-environment interaction
- intervention?

Advantages of case series reports

- May identify new occupational or environmental hazard
  - *e.g., (besides asbestos and mesothelioma), vinyl chloride and angiosarcoma of the liver*
- Can lead to intervention

Limitations of case series reports

- Only anecdotal information
  "the plural of 'anecdote' is not 'data'"
- May be a spurious cluster
  (Nassim Nicholas Taleb's "Fooled by Randomness")

"Ecological" study design

Approach

- correlate disease rates with geographical distribution of "exposure"

Example

- compare rates of mesothelioma of Turkish towns with environmental asbestos to those of other towns

Hasanoglu HC, et al. Int Arch Occup Environ Health 2005

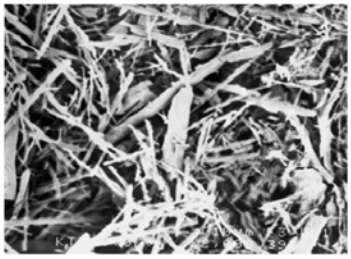

Fig. 2 Scanning electron micrograph of tremolite asbestos taken from the wall of a house (2,000× maginification)

Hasanoglu HC, et al. Int Arch Occup Environ Health 2005

Fig. 1 The map shows the towns of Malatya province and its location in Turkey at the *right bottom*. The well-known areas of environmental asbestos exposure in Guzelyurt are labeled in *bold*

Hasanoglu HC, et al. Int Arch Occup Environ Health 2005

"Ecological" study design

Hasanoglu HC, et al. Lung cancer and mesothelioma in towns with environmental exposure to asbestos in Eastern Anatolia. Int Arch Occup Environ Health 2005.

areas	mesothelioma cases (in 5 yrs)	population	incidence rate/100,00/yr
Arguvan, Hekimhan	7	52,004	2.7
rest of Malatya province	2	771,517	0.1

"Ecological" study design

Hasanoglu HC, et al. Lung cancer and mesothelioma in towns with environmental exposure to asbestos in Eastern Anatolia. Int Arch Occup Environ Health 2005.

areas	lung cancer cases (in 5 yrs)	population	incidence rate/100,00/yr
Arguvan, Hekimhan	29	52,004	11.2
rest of Malatya province	111	771,517	2.9

is there a problem?

"Ecological" study design

Main limitations

- no information on other risk factors for the disease (e.g., for lung cancer = age, smoking, occupational exposures)
- potential misclassification of people's actual exposures

Cross-sectional design

Approach:

Describe/compare prevalence of some feature (e.g., disease/symptoms or physiological/imaging abnormality) typically by level of exposure

A "survey" or "slice in time" without regard to exposure or health outcome

Example:

Compare chest x-ray abnormalities in Turkish towns with environmental asbestos compared to other towns

Cross-sectional design

Coplu L, et al. An epidemiological study in an Anatolian village in Turkey environmentally exposed to tremolite asbestos. J Environ Pathol Toxicol Oncol 1996.

Approach

Questionnaires and chest x-rays for all > 20 yrs old in village of Kureysler.

Findings

18% had pleural plaques and/or calcification c/w asbestos exposure.

Cross-sectional design

Coplu L, et al. An epidemiological study in an Anatolian village in Turkey environmentally exposed to tremolite asbestos. J Environ Pathol Toxicol Oncol 1996.

Interpretation

This is an example of a **descriptive** cross-sectional study in that it describes features of a population, but has no comparison group(s).

More valuable if study included comparisons* with other communities.

*[to give the authors credit, they state that chest x-ray screening in other communities detected no pleural abnormalities, but no details are provided.]

Advantages of cross-sectional studies

- Good for less adverse outcomes (symptoms, physiological measures, imaging)
- Statistical power often good
- Direct contact with population sample (e.g., workers) permits additional individual-level data to be collected on:
  - other risk factors of the outcome
  - modifying factors [use of PPE, etc.]

Limitations of cross-sectional studies

- Very susceptible to selection bias (e.g., migration between jobs/regions influenced by health status).
  - Access only "survivor" population (e.g., workers most affected may have quit = "**healthy worker effect**").
- Whether exposure precedes the outcome (temporality) may be unclear.

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Time Series Studies

- Compare day-to-day changes in exposure with total event numbers in an area
- Group-level design: Total event counts are the outcome and a representative measure of exposure is the population exposure
- a short-term exposure effect design

the exposure

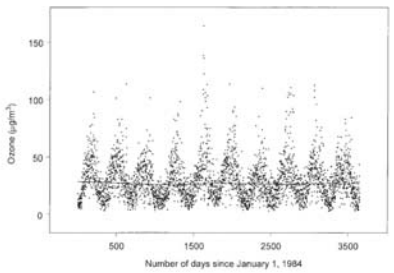


FIGURE 2. Scatterplot of daily concentrations of ozone, Montreal, Canada, 1984–1993. The solid line is the locally weighted regression smooth representing the long-term trend in the data (span of 50% of the data).

Goldberg M et al. Am J Epidemiol. 2001;154:817-26.

the endpoint

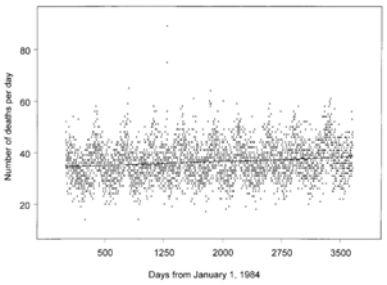
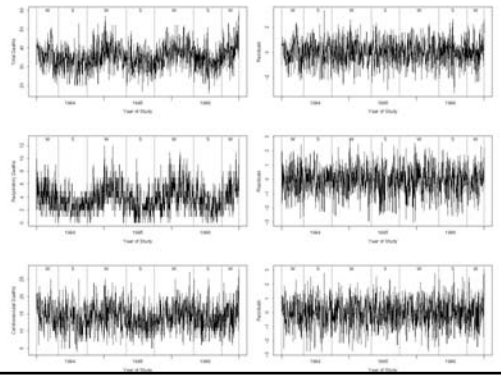


FIGURE 1. Scatterplot of daily number of nonaccidental deaths, Montreal, Canada, 1984–1993. The solid line is the locally weighted regression smooth representing the long-term trend in the data (span of 50% of the data). The total number of days in the time series is 3,653.

What would happen if you looked at the correlation between the two (ie, daily ozone and death counts?)

Goldberg M et al. Am J Epidemiol. 2001;154:817-26.

removing long-term temporal trends

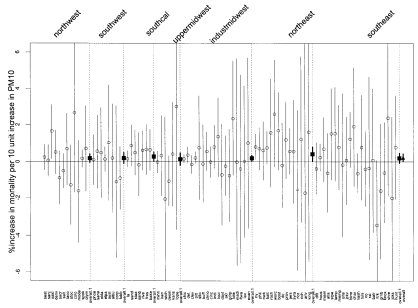


How is the Analysis Done?

- Aim: To relate daily event counts to daily exposure concentrations, adjusting for season and weather confounders
  - Disease model for daily event counts Y_t :

    $\log(E(Y_t)) = f_1(\text{time}) + f_2(\text{weather}) + \alpha(\text{DOW}_t) + \beta(x_t)$
  - β is the parameter of interest for exposure x_t
  - f_1, f_2 are smooth functions
    - Nonparametric smooth → GAM model
    - Parametric smooth → GLM model

NMMAPS: the essential (multi-city) air pollution time series study:
short-term PM_{10} mortality associations in 88 US cities



Dominici, Am J Epidemiol 2002

Time Series Study Designs

- Strengths
  - Data are typically easy to obtain
  - Individual-level factors are controlled by design
  - Generally good statistical power
- Challenges
  - Analytically complex
  - Exposure measurement error that differs for different exposures can complicate interpretation

Case-Crossover Studies

- Concept: The perfect control would be the case under a different exposure scenario (remember time machines)
- For transient exposures and outcomes with abrupt onset, each subject used as their own control
- Harvey Checkoway reviewed on March 27

Referent Time (control) Selection

- Critical in avoiding bias
- Might also want to match for temporal trends (day of week, month, season, etc.)

- Need to have rough understanding of timing so that select referent window outside of induction time or wash-out time

Panel studies

Longitudinal study where subjects (typically well-characterized) are followed (and measured) repeatedly over time

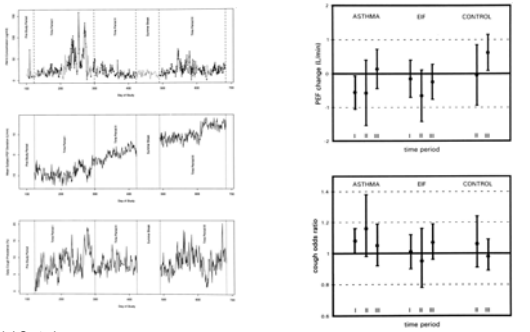
A variant of the repeated measures design except many more measurements than is typical of repeated measures

Example:

n=188 children ages 6-13 followed for 18 months with daily measurement of symptoms and peak flow

Vedal S et al. Acute Effects of Ambient Inhalable Particles in Asthmatic and Non-asthmatic Children. Am J Respir Crit Care Med 1998;157: 1034-433.

Panel studies: example



Vedal S et al.
Am J Respir Crit Care Med 1998; 157: 1034-1043

Panel studies

Advantages:

1. each subject their own control (so, no need to control for individual characteristics – potential confounders)
2. can get measured endpoints (and lots of them)

Disadvantages:

1. requires lots of resources to recruit and follow-up
2. analytically complex (eg, time trends need to be controlled)

Quasi-experimental design (natural experiment)

Takes advantage of an unnatural intervention that is not randomized.

Examples:

1. pre-post study of water fluoridation comparing rate of dental caries in neighboring communities (Morgenstern & Thomas, 1993)
2. steel-mill strike reducing community air pollution levels (Utah Valley)

A steel mill strike in the Utah Valley:
a natural experiment on PM and hospitalizations

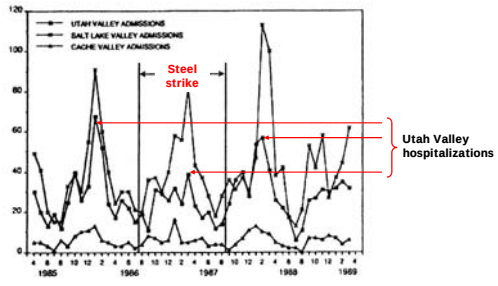


Fig. 3. Monthly bronchitis and asthma admissions for all ages in Utah, Salt Lake, and Cache valleys, April 1985–1989.

Pope CA. Arch Environ Health 1991; 46: 90-7.

Quasi-experimental design (natural experiment)

Advantages:
1. controls for many potential confounders
2. often easy to carry out

Disadvantages:
1. since not really experimental, confounding is still a possibility

Environmental epi intervention design

Example:
Romieu I et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. Am J Respir Crit Care Med 2002; 166:703-9.

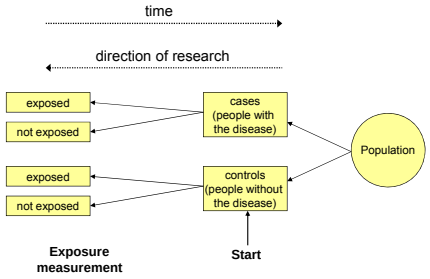
- Randomly assigned Vit E and Vit C to 158 asthmatic children in Mexico City to assess differential response to air pollution
- Finding: lung function declined in association with increases in ozone and PM in the placebo group but not the treatment group

Case-control design

Approach
Compare past exposure of persons with disease *(cases)* with exposure of persons free of disease *(controls)*.

Example
Compare history of residence in Turkish towns with high environmental asbestos in those with and without mesothelioma.

Design of case-control study



Advantages of case-control design

- relatively quick and inexpensive
- good for rare diseases or diseases with a long latency period
- can examine more than one exposure simultaneously

Limitations of case-control design

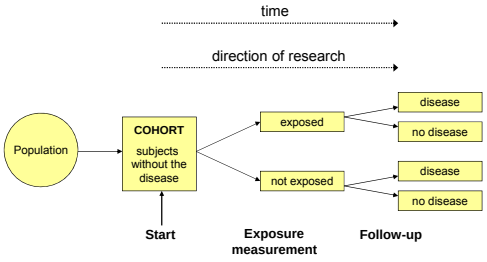
- inefficient if exposure is rare
- direct computation of incidence rates is not possible
- possible to confuse the temporal relationship between the exposure and the outcome
- particularly prone to bias (especially selection and recall [“information”] bias)

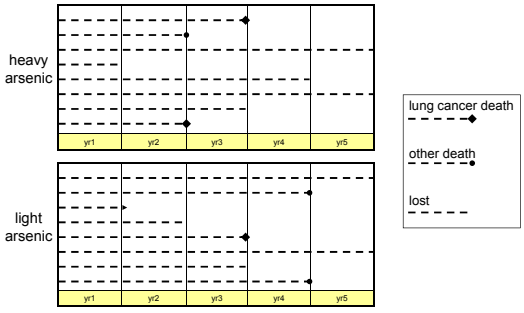
Cohort design

Approach
Compare rate of new disease in a well-defined population cohort according to degree of exposure.

Example
Compare mesothelioma rates in cohort of people from Turkish towns with varying degrees of environmental asbestos.

Design of cohort study





incidence rate (IR)	= (# cases)/(person-yrs)
IR (exposed)	= 2/25 = 0.080
IR (unexposed)	= 1/27 = 0.037
IR ratio (IRR)	= 2.16 = RR

Advantages of cohort studies

- good when rare exposure
- when prospective, less chance of exposure information bias
- time relationship clear (especially if prospective)
- can examine more than one outcome
- directly measures incidence of outcome in exposed and unexposed (if internal comparison)

Limitations of cohort studies

- not good for rare diseases
- relatively costly and time-consuming (especially if prospective)
- if retrospective, often need records and the availability/quality of information may be a problem
- loss to follow-up may cause bias