Overview of Key Ozone Epidemiology Literature

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Ozone Webinar

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Epidemiology

- The study of the causes, distribution, and control of disease in populations
- Realistic exposure conditions
- Doesn't require extrapolation of results from animals
- Sometimes sufficient to causation
- Individual studies may have limitations that can affect the interpretation of results

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Types of Epidemiology Studies

Observational Studies

- Ecological
- Cluster analysis
- Case study/series
- Cross-sectional
- Case-control
- Cohort
- Panel
- Time-series
- Case-crossover

Experimental Studies

- Controlled exposure
- Clinical trial

Reviews

- Literature review
- Meta-analysis
- Weight-of-Evidence

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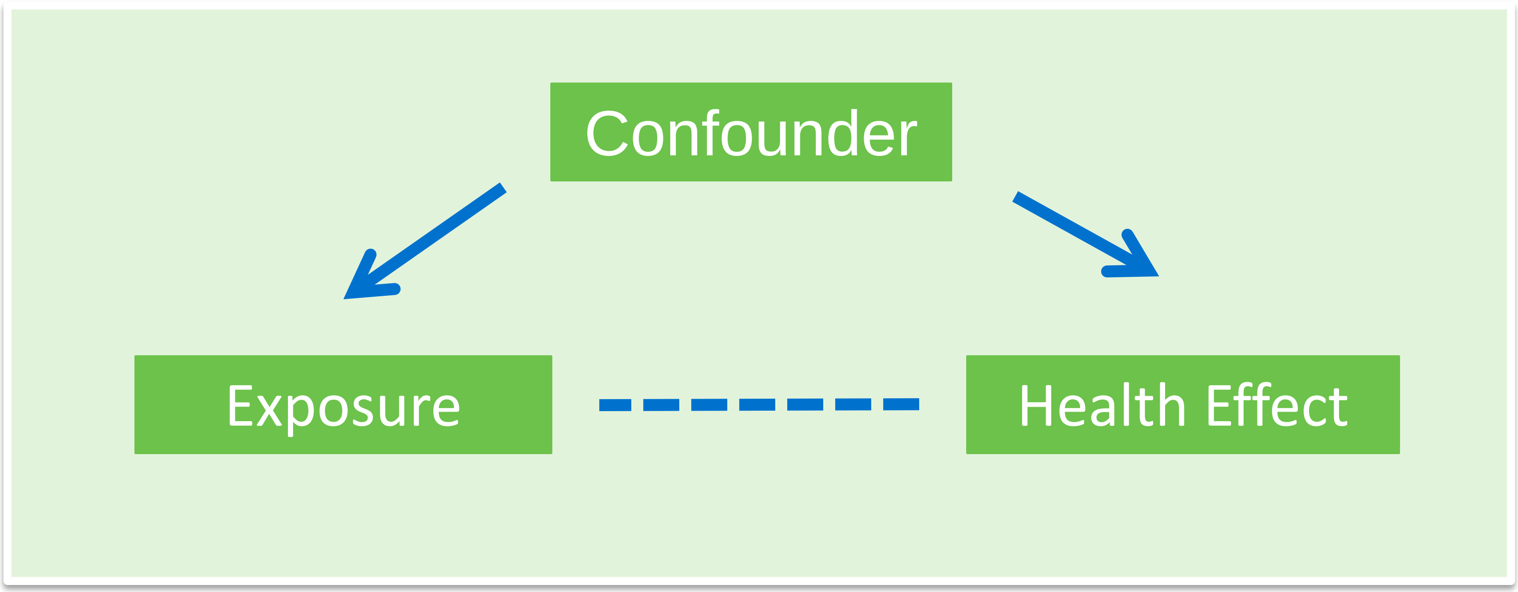
Confounding

A **confounder** is a factor associated with both the exposure and the health outcome, but is not in the causal pathway of interest (*e.g., other exposures, age*)



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Confounding Example

Pollen

Ozone

Respiratory morbidity

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Dealing with Confounding

Design phase

- "Match" or restrict participants on potential confounders
- Collect information on potential confounders

Analysis phase

- Conduct stratified analysis
- Account for confounder in statistical model

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Other Limitations in Ozone Epidemiology Studies

- Exposure measurement error – central ambient monitoring sites provide community-wide averages
- Model misspecification
- Model selection bias
- Publication bias
- Heterogeneity

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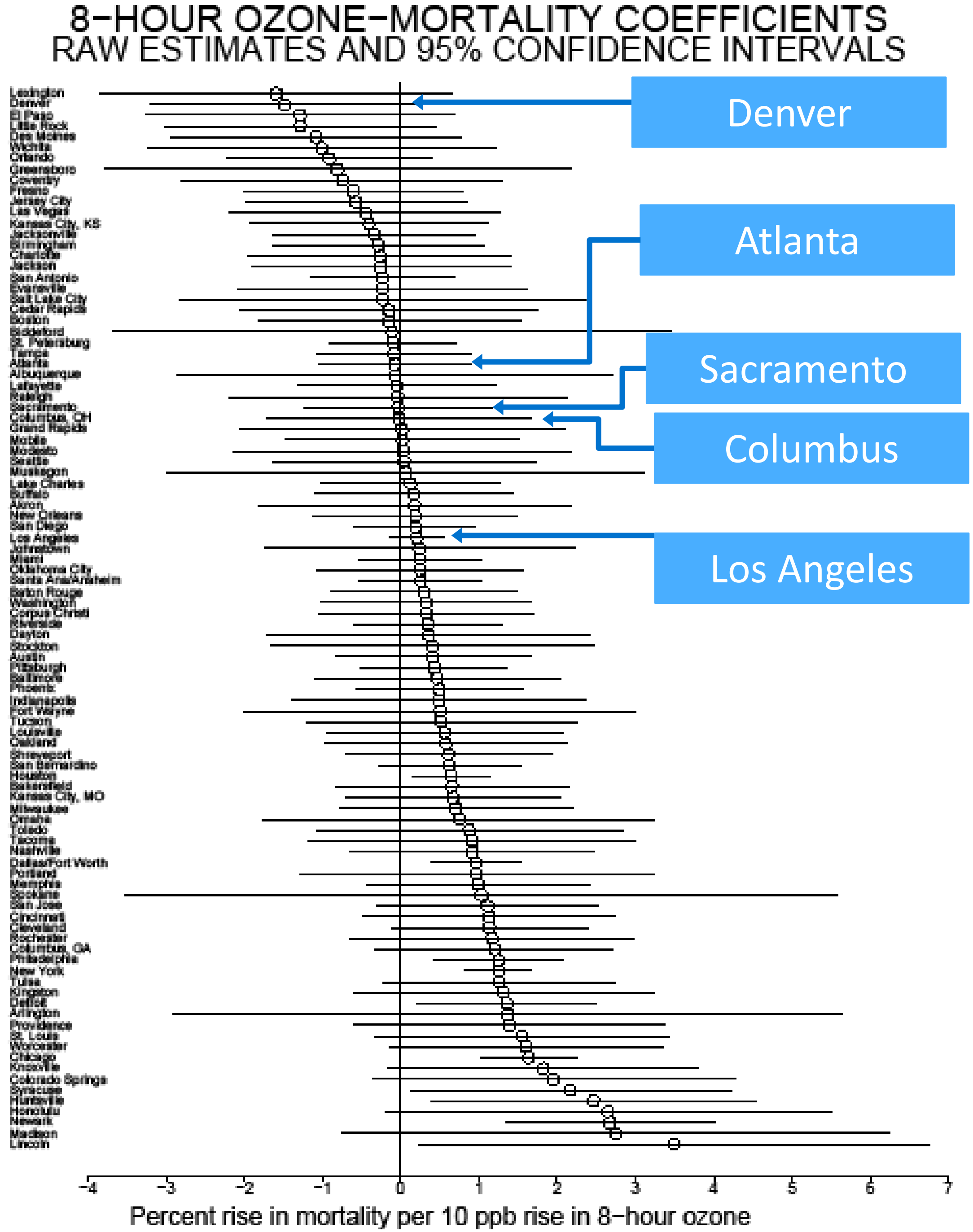
Heterogeneity

- Risks not statistically significant in vast majority of cities.
- “Protective” effects in some cities indicate causal association unlikely.
- Between-city heterogeneity remains unexplained



Smith *et al.* (2009)

Ozone Epidemiology Study Designs

- Short-term exposure (hours, days, or weeks)
  - Time-series studies
  - Case-crossover studies
  - Panel studies
- Long-term exposure (months, years)
  - Longitudinal cohort studies
- One time point
  - Cross-sectional studies

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Time-series Studies

- Aggregate estimates of exposure and health
  - Central site monitors and existing databases
- <u>Population-average</u> rates of acute health events
  - Hospital admissions (HA), emergency department (ED) visits, death rates

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Time-series Studies

Strengths

- Can assess health status in a large population over many years
- Efficient use of resources
- Captures temporal ozone concentration variability
- Insensitive to time-invariant subject characteristics
    - Smoking history
    - Socio-economic status

Limitations

- Confounding by time-varying factors
    - Temperature
    - Respiratory infection epidemics
    - Outdoor pollen and other aeroallergens
    - Temporal trends
- Ecological in nature
- Exposure measurement error

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Case-crossover Studies

- Individual-level exposure estimates
  - Central site monitors often used
  - Case period *vs.* control period
- Individual-level acute health events
  - Administrative data often used: hospital admissions (HA), emergency department (ED) visits

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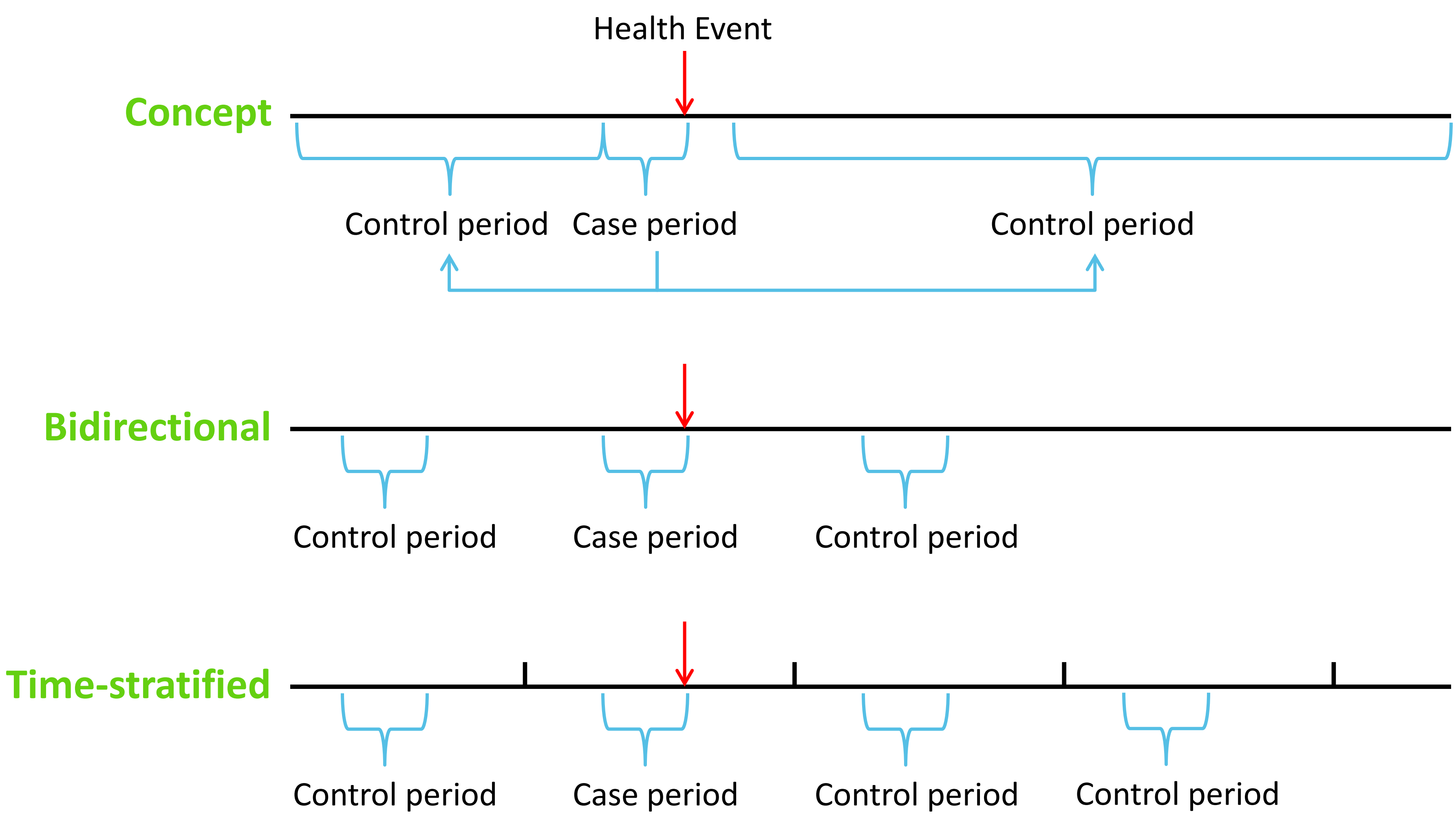
Case-crossover Studies



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Case-crossover Studies

Strengths	Limitations

• Can use existing databases
• Can make individual-level causal inference
• Inherently controls for temporal trends
• Captures temporal ozone concentration variability
• Insensitive to time-invariant subject characteristics
  ▪ Smoking history
  ▪ Socio-economic status
	• Confounding by time-varying factors
	  ▪ Temperature
	  ▪ Respiratory infection epidemics
	  ▪ Outdoor pollen and other aeroallergens
	  ▪ Outdoor activities
	• Exposure measurement error

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Panel Studies

- Repeatedly assess health status of individual subjects
- Time-varying ozone exposure
  - Central-site monitoring or personal exposure
- Commonly used to investigate lung function and asthma symptoms

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Panel Studies

Strengths	Limitations

• Subjects serve as their own controls
• Individual-level outcome data
• Captures health outcomes that resolve in a short time frame
	• Self-reported outcomes (*e.g.*, symptoms, lung function)
	• Challenging to account for missing data
	• Compliance can be low
	• Confounding by time-varying factors
	  ▪ Temperature
	  ▪ Respiratory infection epidemics
	  ▪ Outdoor pollen and other aeroallergens
	  ▪ Outdoor activities

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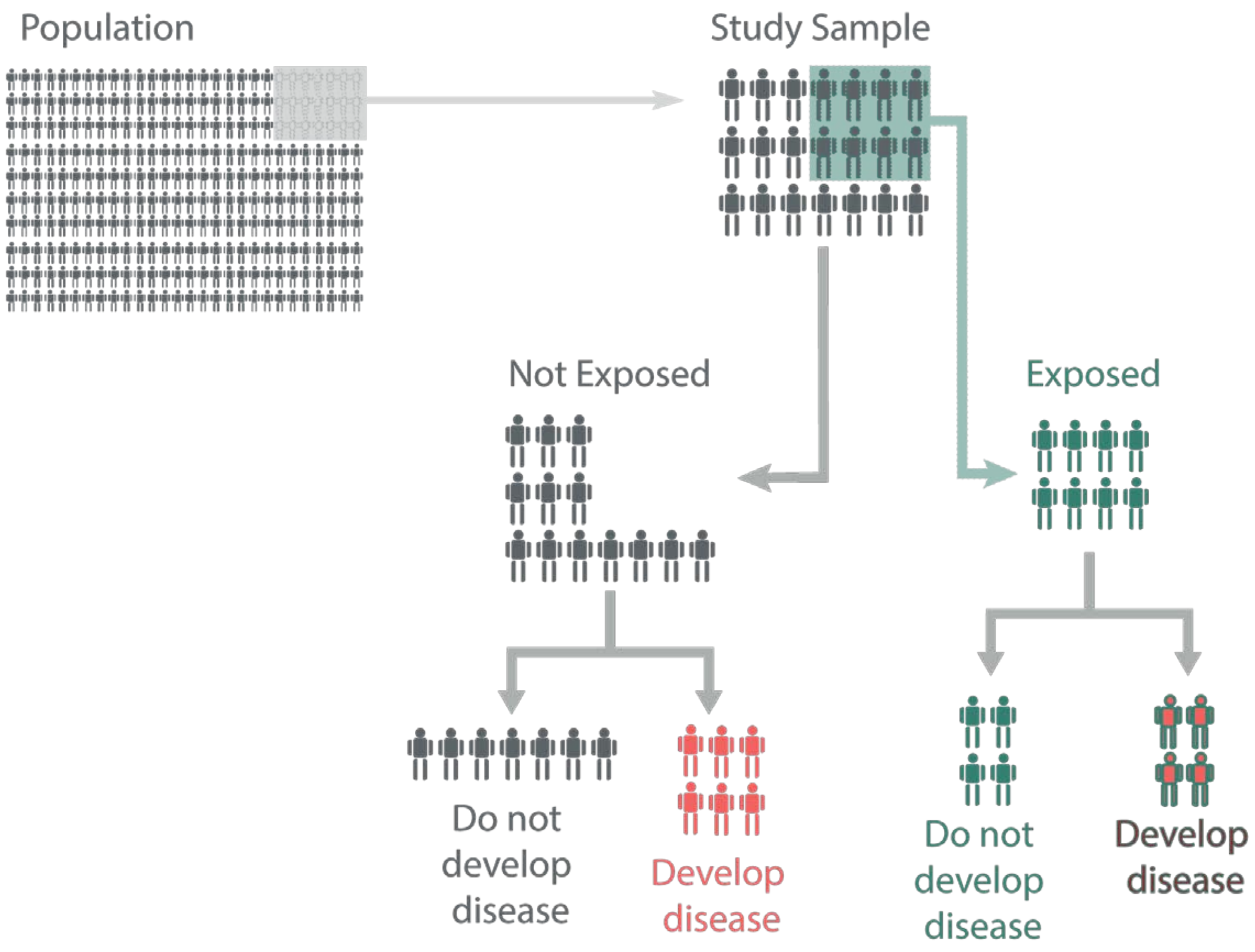
Longitudinal Cohort Studies



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Longitudinal Cohort Studies

Strengths
• Less bias in risk factor data • Can evaluate several diseases • Yields incidence rates and relative risks • Can control for individual-level characteristics

Limitations

• Large sample size, long follow-up period
• Problem with attrition
• Changes in methods and classifications over time
• Costly
• Exposure measurement error
• Confounders
  ▪ Measurement error
  ▪ Proxy measures

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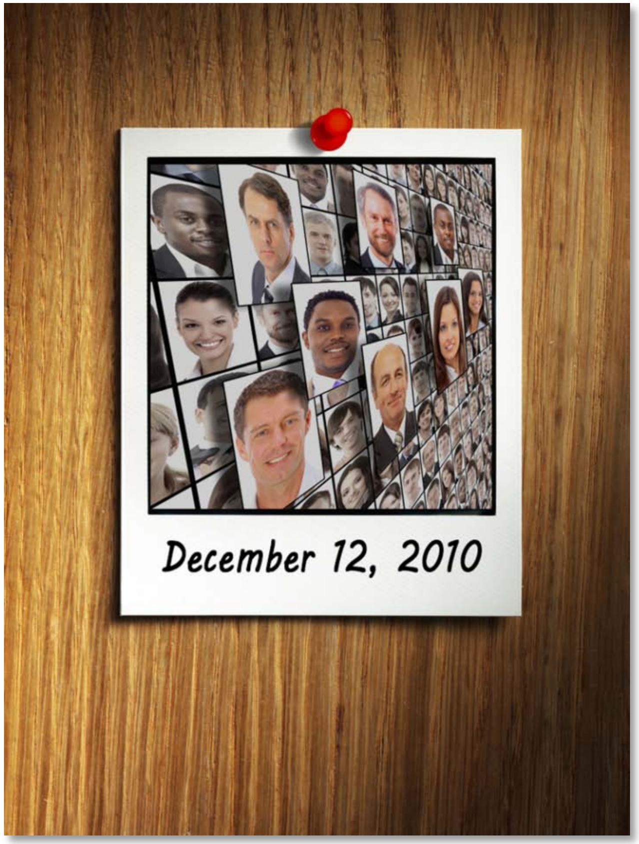
Cross-sectional Studies

- Exposure status and disease status are measured at one point in time or over a short period. No follow-up.
- Comparison of disease prevalence among exposed and non-exposed (*e.g.*, asthma prevalence)



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Cross-sectional Studies

Advantages	Disadvantages
• Relatively inexpensive, little time to conduct • Can look at many risk factors and outcomes • Results often generalizable	• Exposure and disease measured at same time • Only see longer-lasting cases

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Health Endpoints Evaluated in Ozone Studies

Short-term ozone exposure (hours, days, weeks)	Long-term ozone exposure (months, years)
• Respiratory effects • Cardiovascular effects • Mortality	• Respiratory effects • Cardiovascular effects • Reproductive and developmental effects • Central nervous system effects • Cancer • Mortality

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Strickland *et al.* (2010) – Pediatric Asthma or Wheeze ED Visits

Rate Ratios (95% CIs) for IQR Increases in 3-day Moving Average Ozone, Atlanta, Georgia (1993-2004)		
	Warm Season (May-October)	**Cold Season (November-April)**
Base Model	1.082 (1.043–1.123)	1.044 (0.992–1.098)
No URI Control	1.106 (1.066–1.147)	1.062 (1.010–1.118)
Time-series	1.071 (1.025–1.119)	1.013 (0.953–1.077)
Case-crossover	1.092(1.049–1.137)	1.053 (0.996–1.113)
Bi-monthly windows	1.058 (1.014–1.104)	1.019 (0.961–1.113)
Lag -1 Pollution	1.015 (0.991–1.039)	1.004 (0.973–1.036)

Source: Table 4; Strickland, MJ; Darrow, LA; Klein, M; Flanders, WD; Sarnat, JA; Waller, LA; Sarnat, SE; Mulholland, JA; Tolbert, PE. 2010. "Short-term associations between ambient air pollutants and pediatric asthma emergency department visits." *Am. J. Respir. Crit. Care Med.* 182(3):307-316.

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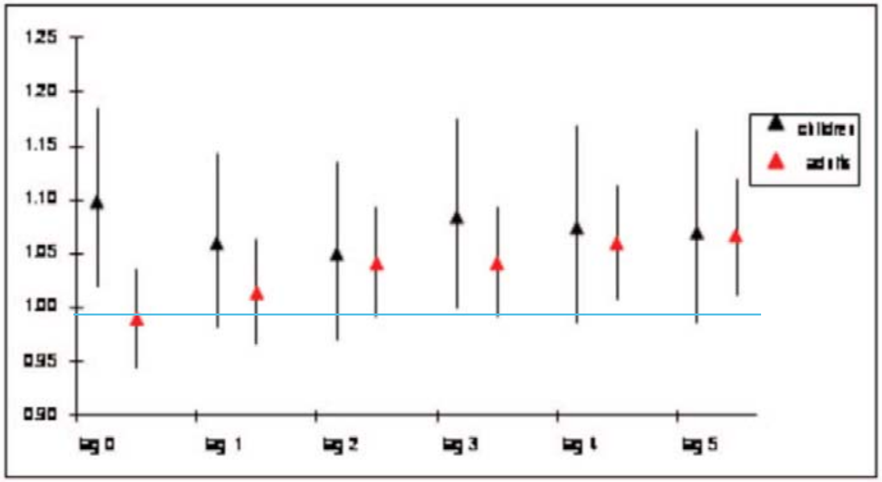
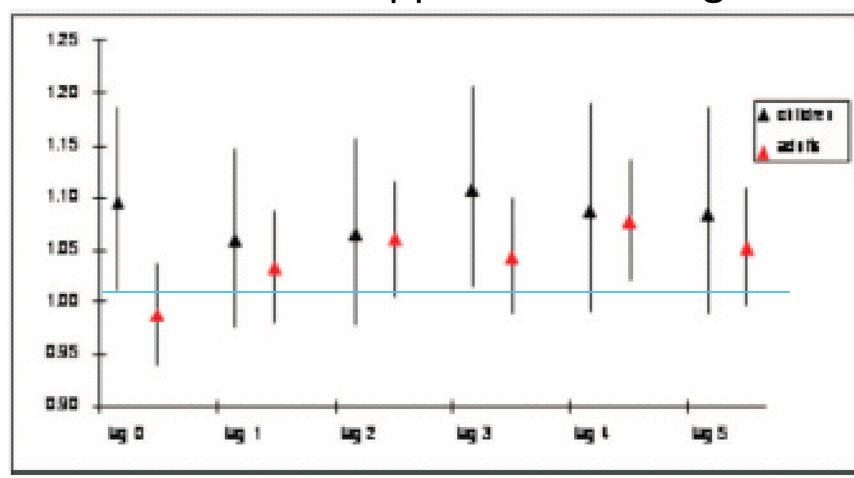
Mar and Koenig (2009) – Asthma ED Visits in Seattle, Washington



Risk assoc with 10 ppb max 1-hr avg ozone

Risk assoc with 10 ppb max 8-hr avg ozone



Mar, TF; Koenig, JQ. 2009. "Relationship between visits to emergency departments for asthma and ozone exposure in greater Seattle, Washington." *Ann. Allergy Asthma Immunol.* 103:474-479.

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Katsouyanni *et al.* (2009) – Air Pollution and Health: A European and North American Approach

Association between all-cause mortality and 40 ppb increase in 1-hr max ozone		
Location	Percent Change	95% CI
Europe	1.66	0.47-2.94
Canada	5.87	1.82-9.81
US	3.02	1.10-4.89

Katsouyanni, K; Samet, JM; Anderson, HR; Atkinson, R; Le Tertre, A; Medina, S; Samoli, E; Touloumi, G; Burnett, RT; Krewski, D; Ramsay, T; Dominici, F; Peng, RD; Schwartz, J; Zanobetti, A. October 29, 2009. "Air Pollution and Health: A European and North American Approach (APHENA)." HEI Research Report 142. 132p. [209-6475]

Zanobetti and Schwartz (2008) – Short-term Ozone and Mortality

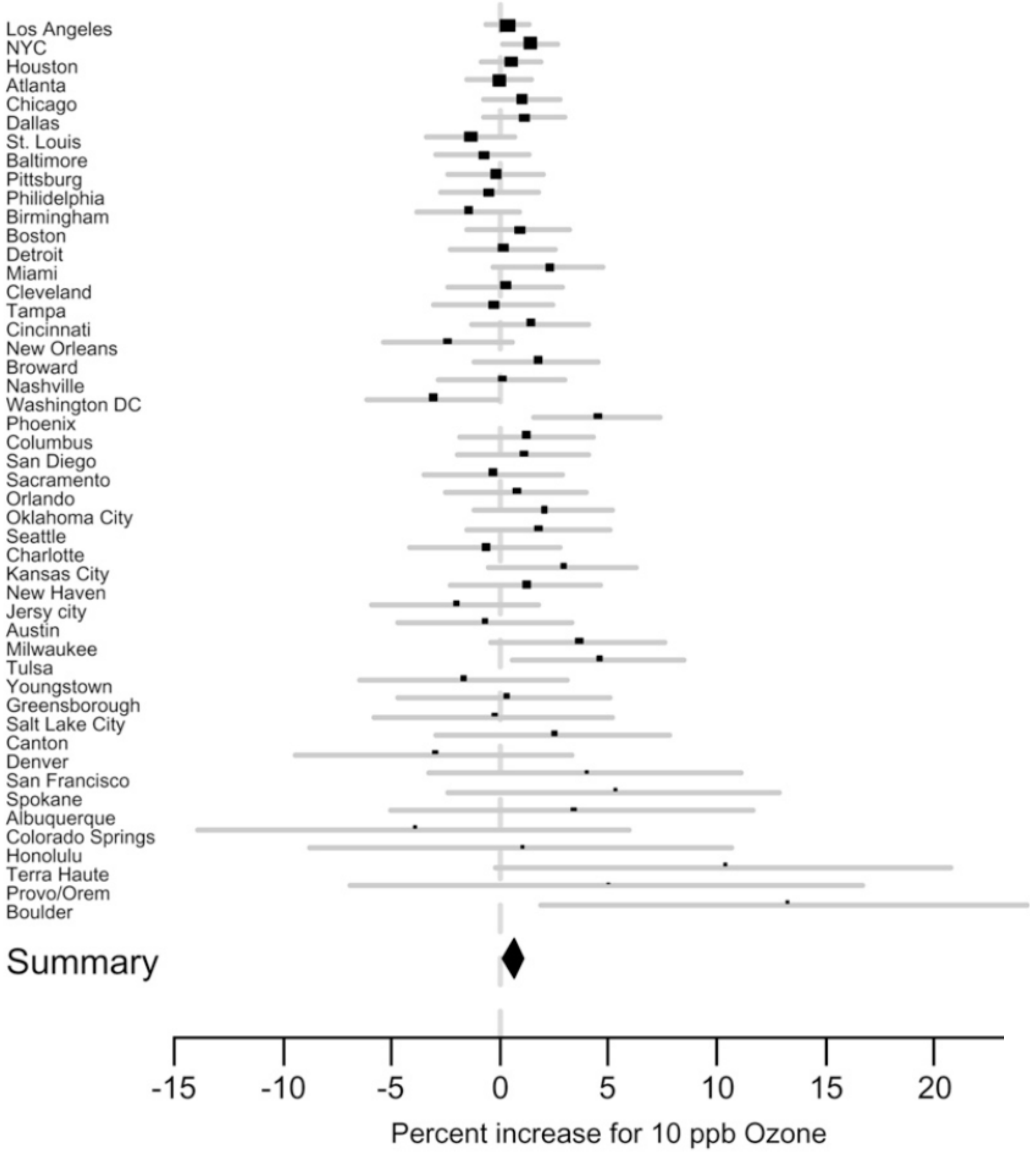

Figure 1. Effect of a 10-ppb increase in 8-hour ozone on mortality overall and by city, during the June–August months. The results are sorted by the confidence interval amplitude.

Zanobetti, A; Schwartz, J. 2008. "Mortality displacement in the association of ozone with mortality: An analysis of 48 cities in the United States." *Am. J. Respir. Crit. Care Med.*177(2):184-189.

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Jerrett *et al.* (2009) – Long-term Ozone Exposure and Respiratory Mortality

Relative risk (95% CI) of death due to 10-ppb change in ambient ozone conc.	
Cause of Death	Ozone and $PM_{2.5}$
Any cause	0.989 (0.981, 0.996)
Cardio-pulmonary	0.992 (0.982, 1.003)
Respiratory	1.040 (1.013, 1.067)
Cardiovascular	0.983 (0.971, 0.994)
Ischemic Heart Disease	0.973 (0.958, 0.988)

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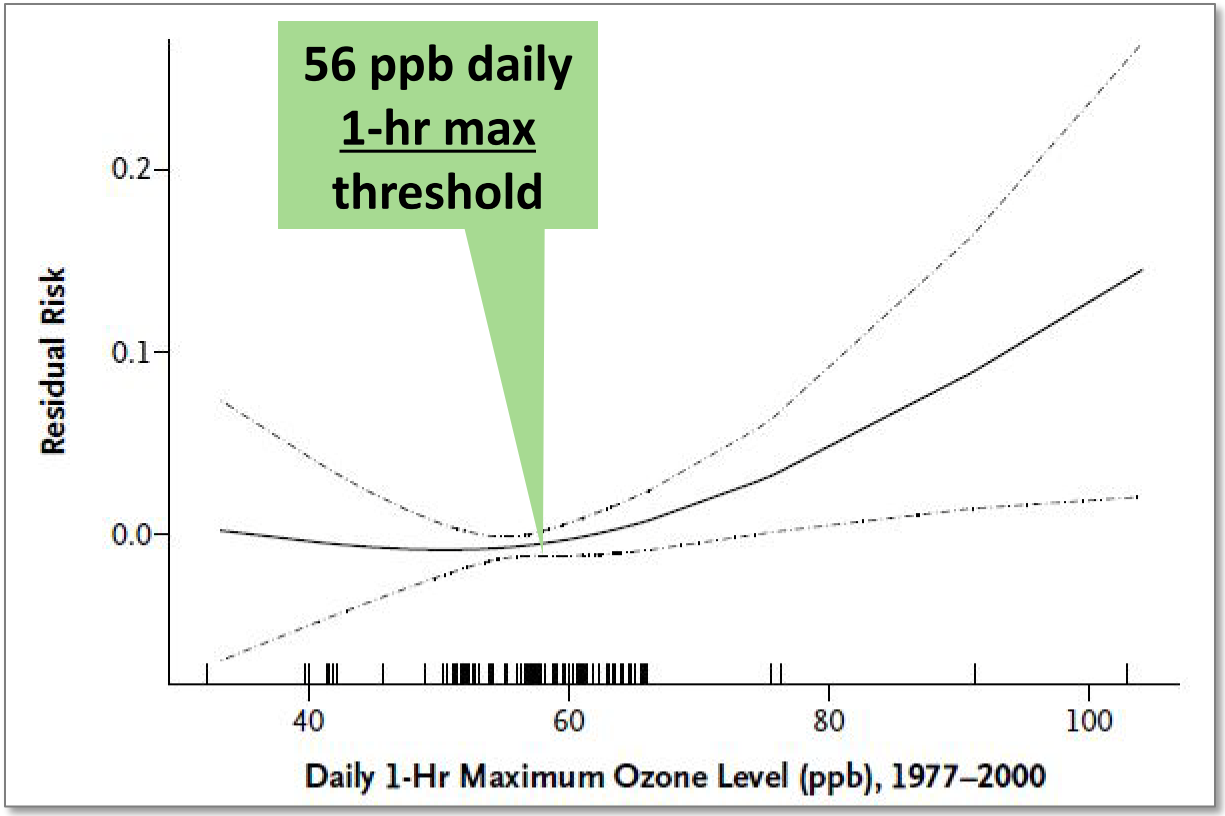
Jerrett *et al.* (2009) – Long-term Ozone Exposure and Respiratory Mortality



Jerrett, M; Burnett, RT; Pope, CA; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. 2009. "Long-term ozone exposure and mortality." *N. Engl. J. Med.* 360(11):1085-1095.

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Questions?

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