

Ecological Studies

Seattle Epidemiology and
Biostatistics Summer Session
June, 2004

What is an ecological study?

- *Groups* are units of study
- A family of designs, including:
 - Intervention studies: group-randomized trials
 - Observational studies: cohort, cross-sectional, longitudinal, etc.

Examples

Exposure	Outcome
Prevalence of guns in households	Mortality rate from homicide
% of women with a mammogram in last 5 years	Case fatality rate from breast cancer
Neighborhood income inequality	Mortality rate from drug overdoses

Levels of measurement

Level	Example(s)
Individual	Age, gender, smoking status
Group	
Aggregated	Mean age, % females, prevalence of smoking
Integral	Community size, population density, whether smoking legal in public buildings

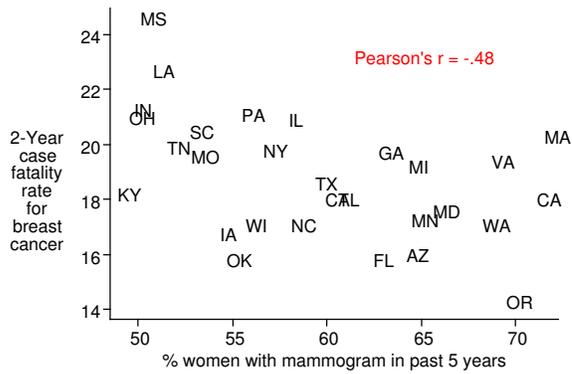
Reasons to study group-level associations

- As proxy for individual-level associations
 - Expedient strategy when group-level, but not individual-level, data available
 - Almost always done with pre-existing data, sometimes involving linkage by investigators of 2+ data sources
- For their own sake

Measures of effect in ecological studies

- **Correlation coefficient:** commonly used, but hard to compare with other study designs or to interpret from a public-health viewpoint
- **Slope:** from regression model of disease incidence on exposure prevalence or level
- Relative risk (*RR*) and attributable risk (*AR*)

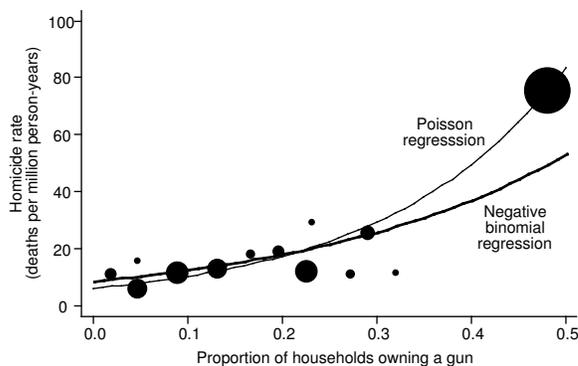
Mammography and breast cancer case fatality



RR and AR in ecological studies

1. Use regression to model disease incidence from exposure prevalence
2. Use regression results to predict disease incidence in a *fully exposed* population (call it R_1) and in a *fully non-exposed* population (call it R_0)
3. Estimate $RR = R_1/R_0$ and $AR = R_1 - R_0$

Gun ownership and homicide rates



Pitfalls in inferring individual-level associations

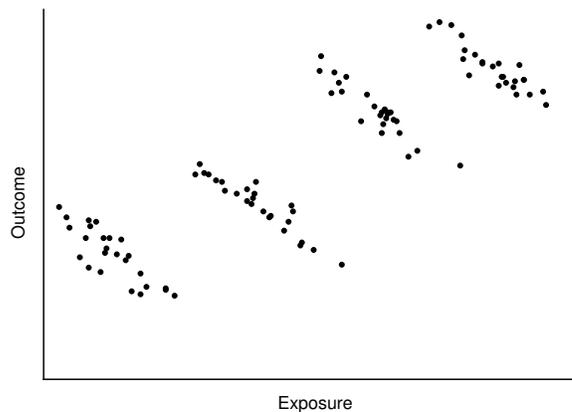
- Potential for *ecological fallacy*
- Weird effects of measurement error: non-differential misclassification can bias measures of excess risk away from the null
- Susceptibility to confounding from either individual-level or group-level characteristics

Example of the ecological fallacy

Pop.	Exposure prevalence	Disease incidence		Total
		Exposed? Yes	Exposed? No	
X	.20	11.7	23.3	$(.20)(11.7) + (.80)(23.3) = 21.0$
Y	.34	16.9	33.7	$(.34)(16.9) + (.66)(33.7) = 28.0$

- Exposure prevalence is greater in Y, and so is disease incidence—a *positive* exposure-disease association
- Yet *within* either population, disease incidence is lower among exposed persons—a *negative* exposure-disease association

Graphical view of ecological fallacy



The ecological fallacy (cont.)

- **Group-level association may not accurately reflect the corresponding individual-level association**
- Ecologic fallacy a form of *cross-level bias*
- Rarely possible to know when such a bias is present

When *group-level* associations are of main interest

- One person's exposure status can affect risk in another: e.g., smoke alarms
- Exposure an intrinsically group-level factor: e.g., a policy
- Example:
 - Is a 0.08% maximum blood alcohol concentration (BAC) law associated with lower motor-vehicle crash mortality?
 - Some states have such a law; others do not
 - Adoption of the law is recent in some states

Results of .08% law evaluation

Law	Adjusted* rate ratio	(95% CI)
.08% BAC law	0.97	(0.96 – 0.98)
Zero-tolerance	0.96	(0.95 – 0.97)
Admin. revocation	0.95	(0.94 – 0.96)
Sobriety checkpoints	1.02	(1.01 – 1.03)
Mandatory jail after 1st DUI	1.02	(1.01 – 1.03)
Primary seat belt law	0.93	(0.92 – 0.94)
Secondary seat belt law	1.01	(1.00 – 1.03)

*For all other laws shown

(Source: *Am J Epidemiol* 2003; 157:131-40)

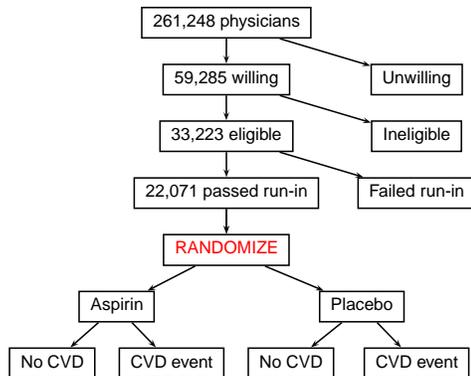
Multi-level analysis

- Disease risk = f (individual factors, family factors, community factors, . . . , national factors)
- Has great theoretical appeal
- Poses several methodological challenges for study design, data analysis, interpretation

Randomized Trials

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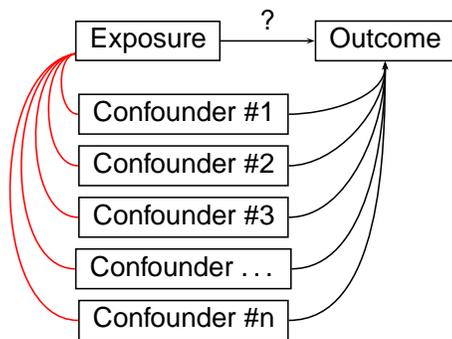
Example: Physicians Health Study



Special strengths of randomized trials

- Protect against confounding, even by factors that may be unknown or difficult to measure
- Provide sound basis for statistical inference
- Enable blinding

How randomized trials prevent confounding



Randomization breaks the red links

Research situations favoring randomized trials

- Exposure a *modifiable* factor over which individuals willing to relinquish control
- Legitimate uncertainty about effects of alternative strategies on relevant outcome
- Outcome(s) of interest reasonably common and not long delayed, unless potential benefits important enough to justify a large or long study

Parachutes and “gravitational challenge”



“Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials.”

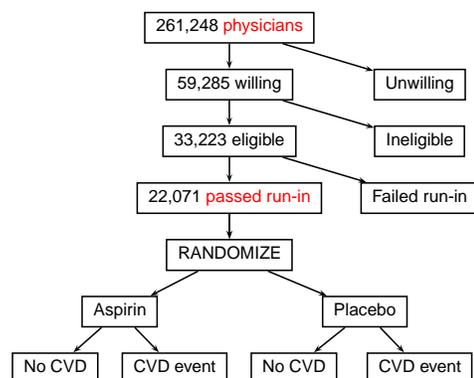
(Source: *BMJ* 2003; 327:1459–61)

Trial Objectives

Efficacy vs. effectiveness

- **Efficacy:** how well an experimental intervention *can* work under near-ideal conditions
- **Effectiveness:** how well an experimental intervention *does* work in the “real world”
- Efficacy a necessary, but not sufficient, prerequisite for effectiveness

Physicians Health Study revisited



Example of an *effectiveness* trial

Intervention: Brief visit with MD for safety advice; discounts on safety equipment (stair gates, smoke alarms, socket covers, etc.)

Control: Usual care

Eligibility: Any family registered with study MD and with a child <5 years old (165/169 such families recruited)

(Source: *BMJ* 1998; 316:1576–9)

Treatment Arms

Common options in 2-arm trials

- Experimental group
 - Idea for intervention usually precedes mounting of a trial
 - Form taken may differ for efficacy vs. effectiveness trials
- Comparison group
 - Nothing
 - Placebo
 - Specific alternative intervention
 - “Usual care”

Examples of placebos

Experimental	Placebo
Aspirin for CVD prevention	Inactive drug that looks and tastes similar
Acupuncture for pain after oral surgery	Needles placed at "inactive" locations
Arthroscopic knee surgery for osteoarthritis	Sham arthroscopic surgery

Enrollment of Study Subjects

Considerations in setting eligibility criteria

- Benefits and risks to subjects
- *Internal* validity of trial: will it reach the correct conclusion for subjects actually enrolled?
 - Data quality
 - Compliance
 - Dropout
 - Statistical power: probability of experiencing a key outcome
- *External* validity of trial: how generalizable will results be?

Randomization

Randomization

- *Random* ≠ haphazard; it has a precise technical meaning
- Each participant has a known probability of receiving a given intervention
- Actual assignment determined by a formal chance process and cannot be predicted
- Deterministic allocation methods are *not* random—e.g.:
 - Alternate assignment
 - By day of week
 - By medical record number
 - By date of birth

Three issues in randomization

- **Sequence generation:** process used to assign participants to treatment arms
- **Allocation concealment:** steps taken to hide randomization sequence from those who refer or enroll participants into trial
- **Implementation:** who does what—specifically, how sequence-generation function is separated from subject-enrollment function

Simple randomization

	<u>Study ID</u>	<u>Random number</u>	<u>Treatment group</u>
• Assign a random number between 0 and 1 to each study ID	1	0.81422	E
	2	0.90634	E
	3	0.32979	C
• If random number ≥ 0.5 , assign to Experimental	4	0.05449	C
	5	0.32959	C
	6	0.06776	C
• Otherwise, assign to Control	7	0.72420	E
	8	0.29415	C

Blocked randomization: blocks of size 2

	<u>Study ID</u>	<u>Block</u>	<u>Random number</u>	<u>Treatment group</u>
• Each pair of subjects becomes a <i>block</i>	1	1	0.81422	C
	2	1	0.90634	E
• Within each block, assign subject with larger random number to Experimental	3	2	0.32979	E
	4	2	0.05449	C
	5	3	0.32959	E
	6	3	0.06776	C
• Assign remaining subjects to Control	7	4	0.72420	E
	8	4	0.29415	C
	

Remarks about randomization

- Not costly, time-consuming, or difficult to do properly
- Randomization list can usually be completed in advance, before any participants are enrolled, as long as it is kept adequately concealed

Allocation concealment

- **Adequate** methods
 - Central randomization
 - Numbered and coded containers
 - Serially marked, sealed, opaque envelopes
- **Inadequate** methods
 - Alternate assignment
 - Allocation based on an identifier
 - Allocation by date of birth or date of entry

(Source: *JAMA* 1995; 273:408–12)

Data Collection

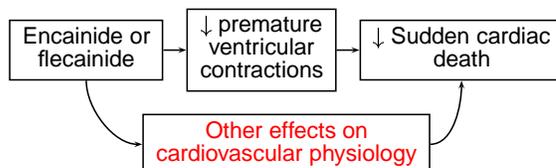
Types of outcomes

- Primary vs. secondary
 - **Primary**: of main importance, and on which sample-size or power calculations were based
 - **Secondary**: of less importance, and for which trial may or may not have good statistical power
- Intermediate vs. final
 - **Intermediate**: outcomes expected to occur early along the causal pathway from intervention to . . .
 - **Final**: ultimate health outcomes that the experimental intervention is intended to influence

Uses and misuses of intermediate outcomes

- Can help test causal model on which experimental intervention is based
 - If trial shows benefit on final outcomes, benefit in intermediate outcomes can provide confirmatory evidence as to mechanism
 - If *no* benefit on final outcomes is found, intermediate outcomes can help distinguish between an incorrect causal model vs. failure in implementation
- Risky to rely on as a surrogate for final outcomes

Pitfall of surrogate outcomes: CAST



Group	Cardiac arrest		Death	
	No.	Rate	No.	Rate
Active drug ($n = 730$)	33	4.5%	56	7.7%
Placebo ($n = 725$)	9	1.2%	22	3.0%

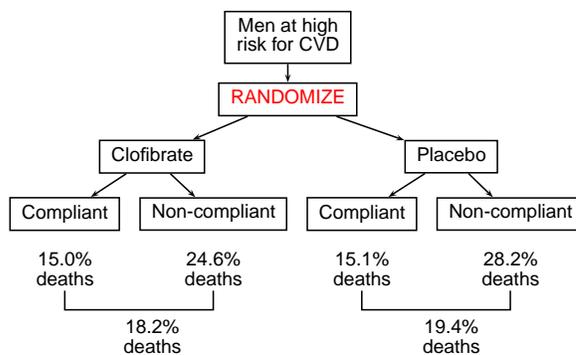
Who is blinded?

- Participants*
- Staff who assess outcomes*
- Clinicians responsible for care of participants
- Statisticians (!)

* Usually meant by “double-blind”

Analysis

A lesson from the Coronary Drug Project



The intent-to-treat principle

- **Keep the groups formed by random assignment intact in the analysis**
 - Balancing property of randomization applies only to those groups
 - Re-formulating the comparison groups discards the key advantage of the randomized design
- To extent that intended treatment \neq treatment received, differences in outcomes between arms are attenuated

Why to pay attention to subgroup comparisons

- Almost certainly person-to-person variation in response to interventions
- Subgroup differences = effect modification
Overall treatment effect may be a poor summary of effects that vary among strata
- Each subgroup association deserves to be evaluated on its own merits, using usual guidelines for causality

Why *not* to pay attention to subgroup comparisons

- Often not specified in advance
 - May be offered up to rescue an otherwise negative study
 - Like betting on a horse after race is over
- Multiple subgroups → multiple tests of significance → \uparrow Pr(Type I error)
- Trials not usually powered to detect subgroup differences → \uparrow Pr(Type II error)
- Tests for heterogeneity across subgroups typically have low power

Probably reasonable advice on subgroups

- Specify any important subgroup hypotheses in advance
- Limit number of subgroup hypotheses
- Use tests of interaction to reduce multiple-comparisons problem
- Interpret post-hoc subgroup differences with great caution

Variations on randomized trial design

- Sequential trials
- Factorial trials
- Randomization within a person
 - Of body parts
 - Crossover studies
 - “N-of-1” trials
- Group-randomized trials

Introduction to Epidemiologic Methods — Summer, 2004
Discussion Questions: Randomized Trials

The questions below refer to the following article:

The Multicentre Aneurysm Screening Study Group. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002; 360:1531–9.

1. Was the trial blinded?
2. How was allocation concealment achieved?
3. The trial's primary outcome measure was AAA-related mortality.
 - (a) What was the advantage of using cause-specific mortality rather than all-causes mortality as the primary outcome? What disadvantage was there, if any?
 - (b) Three patients in the intervention group died of a ruptured AAA between randomization and their first scheduled screening appointment. It can certainly be argued that those deaths could not have been prevented by screening that had not yet taken place. Should those deaths have been excluded? Why or why not?
 - (c) Were deaths of patients who had undergone elective AAA surgery considered AAA-related deaths, even if rupture of an aneurysm was not the mechanism of death?
4. Some patients in the invited group ended up not being screened, while some in the control group evidently were screened and got elective surgery. Would it not have been better to compare those who actually *were* screened with those who were not screened?