Cause and Effect in Epidemiology

Epidemiology

Cause-Effect

- One of the main objectives of Epidemiology is to identify the cause, or causes, of disease in humans

- Understanding causal effects may lead to
  - New interventions for disease
  - Preventive strategies

Definitions

- A cause is something that brings about a result – Webster
- A cause produces an effect, result, or consequence - American Heritage
- A cause is a factor that induces a change in state of another factor

Definitions

- A philosophical problem
  - Causes cannot be observed
  - Causes can only be inferred

- An inference that one factor exerts influence on another factor. The inference
  - Asserts a predictable relationship between two factors
  - Accounts for the relationship

Approaches to Causality

- Necessary and Sufficient Causes
- Criterion-based Assessments
  - 1964 Report on Smoking and Health
  - 1990 Updated criteria
- Other Approaches

Necessary and Sufficient Causes

- A necessary cause is one that must be present in order for a disease (or condition) to occur
  - M. tuberculosis must be present in all cases of tuberculosis
  - Trisomy 21 must be present for Downs syndrome to develop
  - Antibodies to acetylcholine receptors must be present to develop myasthenia gravis

Necessary and Sufficient Causes

- A sufficient cause is a factor (or set of factors) that inevitably produces disease (or condition) when present
  - Cigarette smoking and lung cancer
  - Radon and lung cancer
  - BRCA 1/2 genotypes and breast cancer

Necessary and Sufficient Causes

- A necessary cause is one that must be present in order for a disease (or condition) to occur

- A sufficient cause is a factor (or set of factors) that inevitably produces disease (or condition) when present

Necessary and Sufficient Causes

- E is a necessary cause: C = 0
- E is a sufficient cause: B = 0
- E is necessary and sufficient: B = C = 0

	Case (D)	Noncase (not D)
Exposed (E)	A	B
Unexposed (not E)	C	D

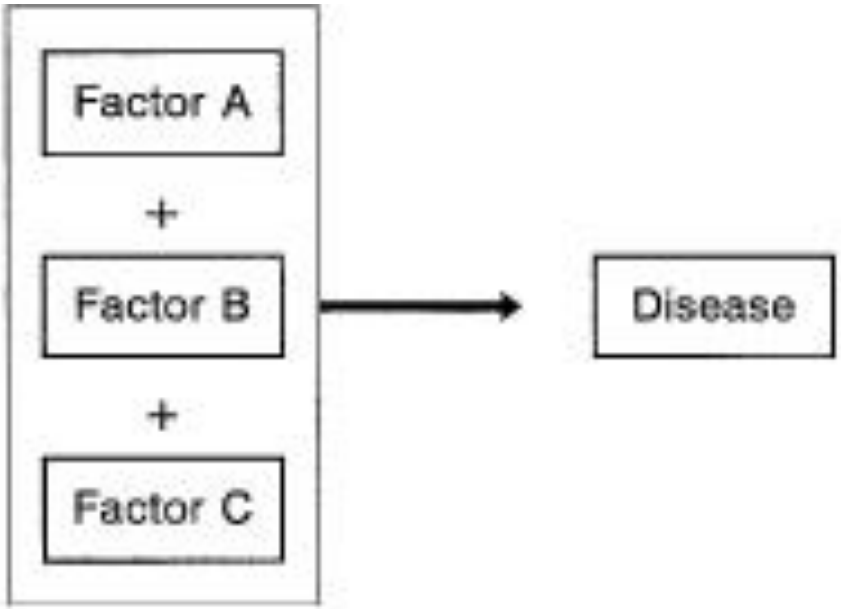
Necessary and Sufficient Causes

A necessary and sufficient cause

Measles is a necessary and sufficient cause of the disease.

Necessary and Sufficient Causes

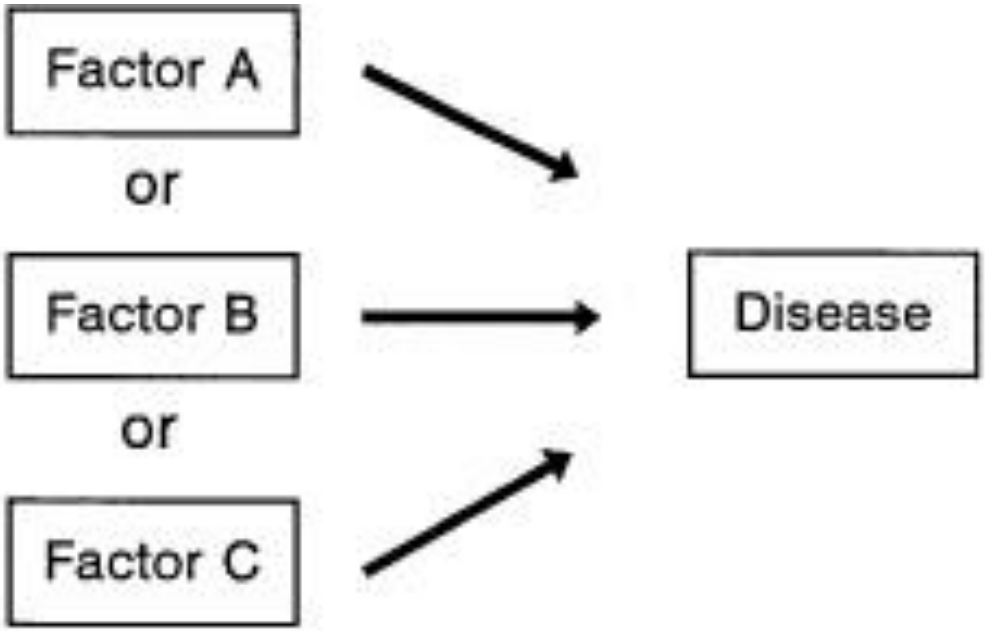
Necessary but not sufficient causes



M. tuberculosis is a necessary but not sufficient cause of tuberculosis

Necessary and Sufficient Causes

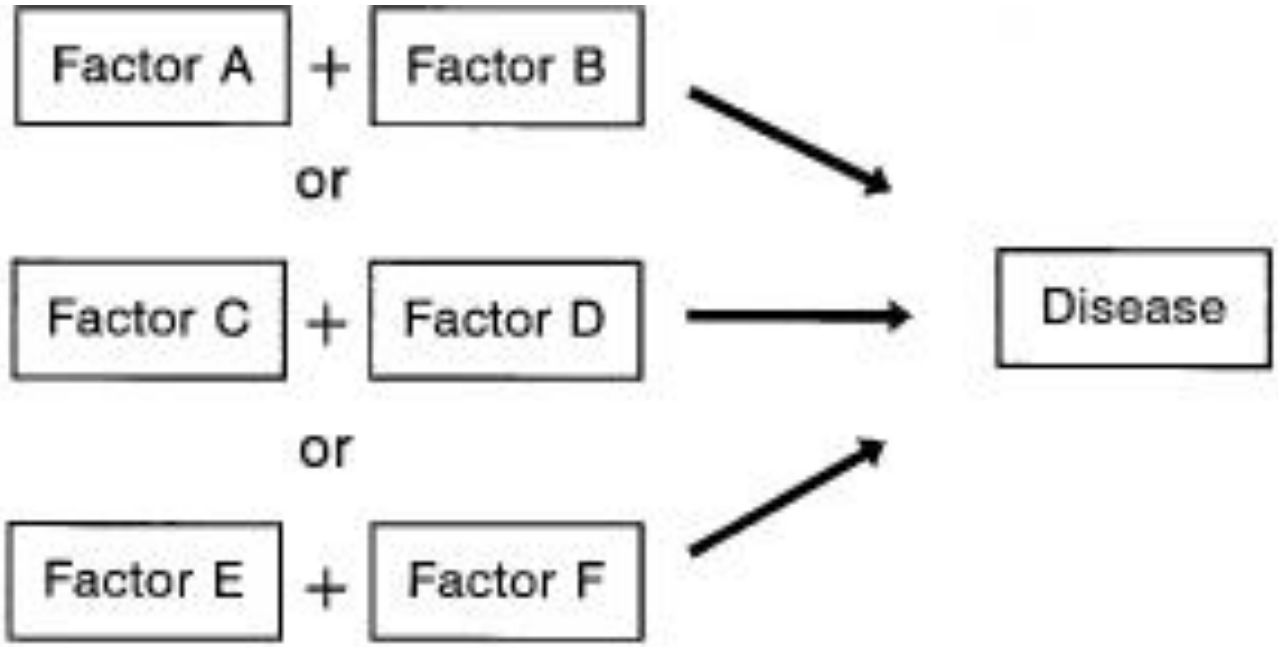
Sufficient but not necessary causes



Cigarette smoking, asbestos, and radon are sufficient but not necessary causes of lung cancer

Necessary and Sufficient Causes

Neither necessary nor sufficient



Criterion-Based Causal Assessment

- Temporality
- Strength of association
- Dose-response patterns
- Replication of findings
- Biologic plausibility
- Cessation of Exposure
- Consistency
- Specificity
- Alternative explanations

Temporality

- The only absolute criterion on the list

- A cause must precede its effect
  - Case-Control studies cannot establish this criterion with certainty
  - Cohort studies and clinical trials establish exposure before disease BY DESIGN

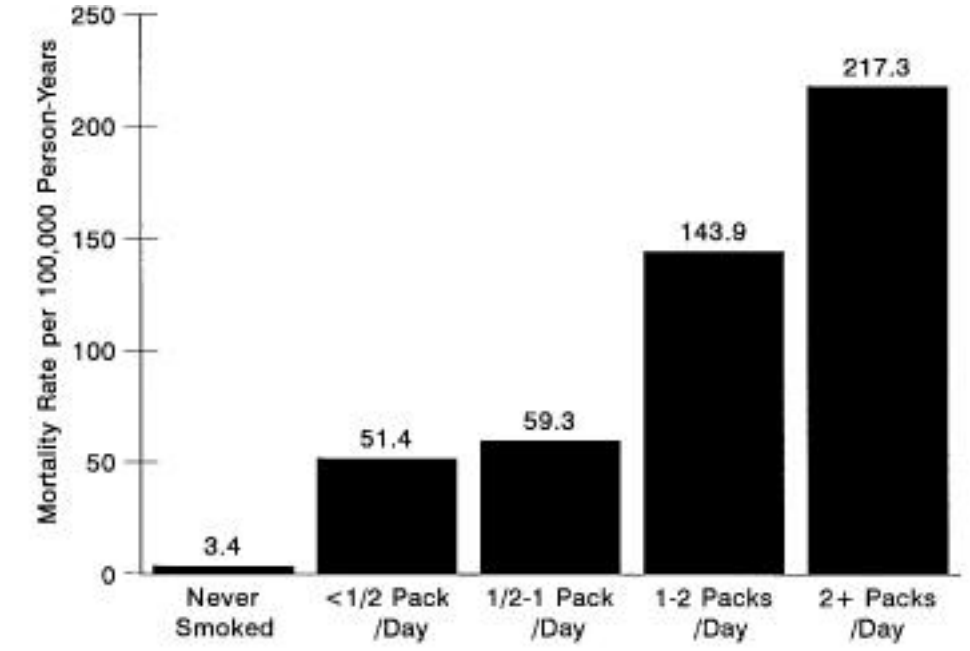
Strength of Association

- The larger the relative risk or odds ratio, the more likely the relation is to be causal

- Examples
  - RR = 10 (95% CI 8.2 – 11.9)
    - One would need a large unrecognized bias or confounder to nullify the effect of the exposure
  - RR = 1.2 (95% CI 0.99 – 1.9)
    - It is more likely that an unrecognized bias of confounder could nullify the result

Dose-Response Patterns

- The greater the exposure, the greater the observed effect
- Absence of dose-response does not rule out causal relationship



Replication of Findings

- The replication of findings in independent studies enhances argument for causality

- If the factor is a cause, we expect consistency of findings
  - Different designs
  - Different populations
  - Among sub-groups

Biologic Plausibility

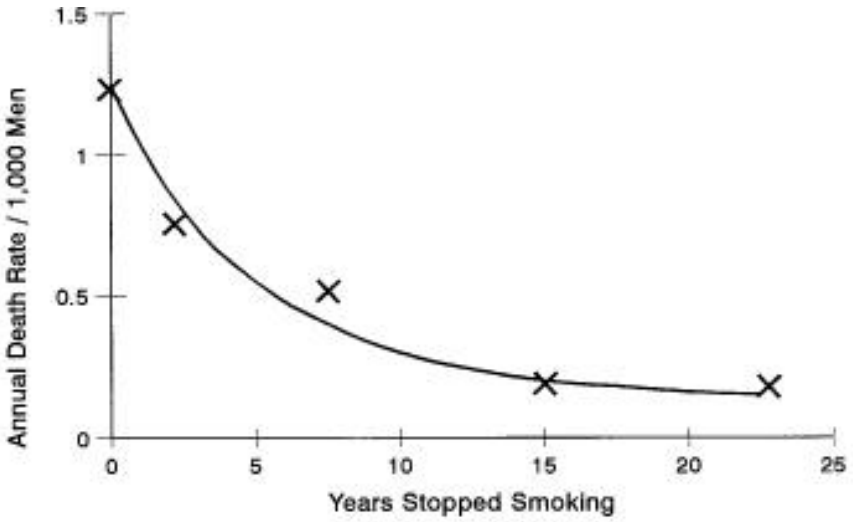
- Biologic mechanism proposed to explain the observed association(s)
  - Carcinogen induces mutation in stem cell which then divides unregulated
  - The immune response to tuberculosis induces more HIV replication, leading to a reduced CD4+ T cell count

- Animal models and laboratory experiments contribute to our understanding of mechanisms and enhance causal relations

Cessation of Exposure

- Risk of disease decreases after cessation of exposure

- Applies when exposure exerts continual influence on disease
  - May not apply if exposure induces a cascade of events



Coherence

- The findings are coherent
  - Studies show internal validity
  - Studies have external validity
  - Findings do not conflict with what is known about the natural history and biology of the disease.
    - Consistent with general body of knowledge in the field
    - If inconsistent, an explanation is needed

Specificity

- A cause leads to a single effect, not multiple effects

- Weak criterion
  - Often one cause $\rightarrow$ multiple effects
    - Cigarette smoking causes lung cancer, atherosclerosis, emphysema
    - That it is not a specific cause does not nullify its role as a causal exposure for all of these diseases.

- When found, it may be a useful criterion

Alternative Explanations

- For any research finding, the result may be due to
  - Chance
  - Bias
  - Confounding
  - Alternative theory
    - E.g., Some lung cancer occurs in people who never smoked, there must be other exposures of interest
    - Impossible to exclude all alternative explanations

Helicobacter pylori and Duodenal Ulcers

- **Temporal** Relationship
  - H. pylori is linked to chronic gastritis
  - 11% progress to develop duodenal ulcers over 10 years
  - In a retrospective cohort study, 34/321 patients with H. pylori 10 years earlier developed duodenal ulcers, whereas only 1/133 without H. pylori developed ulcers

Helicobacter pylori and Duodenal Ulcers

- **Strength** of Association
  - H. pylori is found in at least 90% of patients with duodenal ulcers
  - In an Australian population without ulcers, H. pylori has never been found
- Dose-Response Relationship
  - Density of organisms per mm of gastric mucosa is higher in patients with duodenal ulcers compared to those without duodenal ulcers

Helicobacter pylori and Duodenal Ulcers

- **Replication** of Findings
  - Many studies have validated these findings
- Biologic Plausibility
  - H. pylori has binding sites on antral cells
  - H. pylori indices mediators of inflammation
  - H. pylori infected mucosa is susceptible to damage by acid environment

Helicobacter pylori and Duodenal Ulcers

- **Cessation** of Exposure
  - Eradication of H. pylori heals duodenal ulcers
  - Relapse of duodenal ulcers is lower in people treated with antibiotics compared to H_2 blockers
- **Specificity** of Association
  - Prevalence of H. pylori in patients with duodenal ulcers is 90 – 100%
  - However, found also in a few asymptomatic persons

Helicobacter pylori and Duodenal Ulcers

- **Coherence**
  - Prevalence is similar between men and women
  - Incidence of duodenal ulcers decreasing in industrialized countries as living conditions improved
- **Alternative** Explanations
  - Stomach acid used to be the etiology of duodenal ulcers
  - Cigarette smoking has been associated with ulcers
  - Both of these explanations are address with the H. pylori hypothesis

Revised Causal Criteria

- Stage I – Categorize the quality of the evidence by its source
  - Clinical Trials > Cohort > Case-Control> Time-Series > Case Series
    - This ranking of quality is controversial
  - For each design, compare the completed study with the IDEAL study for that design
    - e.g., Randomized clinical trial with or without blinding
    - e.g., Cohort study with questions about whether disease was adequately excluded at the time of enrollment

Revised Causal Criteria

- Stage II – Apply guidelines for evaluating the evidence of a causal relationship
  - Major Criteria
    - Temporal relationship
    - Biologic plausibility
    - Reproducibility
    - Alternative explanations addressed
  - Minor Criteria
    - Dose-response relationship
    - Strength of association
    - Cessation effects

Revised Causal Criteria

- Grading of the internal validity of individual studies
  - Cohort Studies
    - Initial assembly of comparable groups
    - Exclusion of occult disease
    - Maintenance of comparable groups
    - Valid, reliable measurements applied equally to all groups
    - Definitions of exposure and outcome clear
    - Analysis appropriate

Advanced Topics in Causality

- Sufficient cause and component cause
- Counterfactual basis of causal arguments
- Bayesian approaches to causal effects
- Statistical Inference
- Causal vs. association statistical modeling
- Philosophical basis of causality

Bias
Confounding
Interaction

Study Validity

- Internal validity
  - The degree to which the observed results of the study are true.
  - Inferences are correct regarding the participants in the study
- External Validity
  - Generalizability of the result
  - Inferences are correct regarding the population at risk

Study Validity
An Approach

The observed results occurred because:

- Chance
  - Random error
- Bias
  - Systematic error
  - Confounding
- Truth

If the role of chance is small, if bias can be reasonably excluded, and if confounding is addressed, then the study is internally valid

Bias

- Bias is any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease

- Bias is a systematic error in inference

- Bias is a systematic error in the design or conduct of a study

Bias

- Sources of Error
  - Random error
    - Chance
    - Variation that is equally likely to distort the result in one direction or the other.
- Systematic Error
  - Selection Bias
  - Information Bias

Bias

- Selection Bias
  - The process of recruiting and enrolling participants into the study distorts the relationship between the exposure and the outcome
  - The relation between exposure and outcome is different for those who participate and those who would be eligible for the study but do not participate. Rothman
- Information
  - Systematic errors in measurement
  - Misclassification
    - Differential
    - Non-differential

Selection Bias

- Self-selection bias
  - Healthy (or diseased) people may seek out participation in the study
- Referral bias
  - Sicker patients are referred to major health centers
- Diagnostic bias
  - Diagnosis of outcome associated with exposure
- Non-response bias
  - Response, or lack of it, depends on exposure
- Differential loss to follow-up
  - Exposed (or unexposed) group followed with different intensity
- Berkson's bias
  - Hospitalization rates differ for by disease and presence/absence of the exposure of interest

Information Bias

- Data collection bias
  - Bias that results from abstracting charts, interviews or surrogate interviews
- Recall bias
  - Disease occurrence enhances recall about potential exposures
- Surveillance or detection bias
  - The exposure promoted more careful evaluation for the outcome of interest
- Reporting bias
  - Exposure may be under-reported because of attitudes, perceptions, or beliefs

Information Bias

Misclassification

- Non-differential
  - Error in assessing exposure or disease is similar between study groups
  - Measure of effect tends toward 1
- Differential
  - Error in assessing exposure (or disease) differs in different study groups
  - May increase or decrease measure of effect

Information Bias

- Non-differential Misclassification
  - Hypothetical Case-Control study

	D	D̄	
E	60	40	
Ē	40	60	
	100	100	

OR = 60*60/40*40 = 2.25

Percent Exposure Misclassification: 20% 20%

	D	D̄	
E	48	32	
Ē	52	68	
	100	100	

OR = 48*64/36*52 = 1.96

Information Bias

- Differential Misclassification
  - Hypothetical Case-Control study

	D	$\bar{D}$	
E	60	40	
$\bar{E}$	40	60	
	100	100	

OR = 60*60/40*40 = 2.25

Percent Exposure Misclassification: 5% 20%

	D	$\bar{D}$	
E	57	32	
$\bar{E}$	43	66	
	100	100	

OR = 48*64/36*52 = 2.74

Bias

- Approaches to bias
  - Random error –
    - Repeat measurements
  - Systematic error
    - Careful planning of measurements
    - Formal assessments of validity
    - Regular calibration of instruments
    - Training of data collection personnel

Confounding

The Idea:

Confounding is a confusion of effects.

Definition:

The apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect.

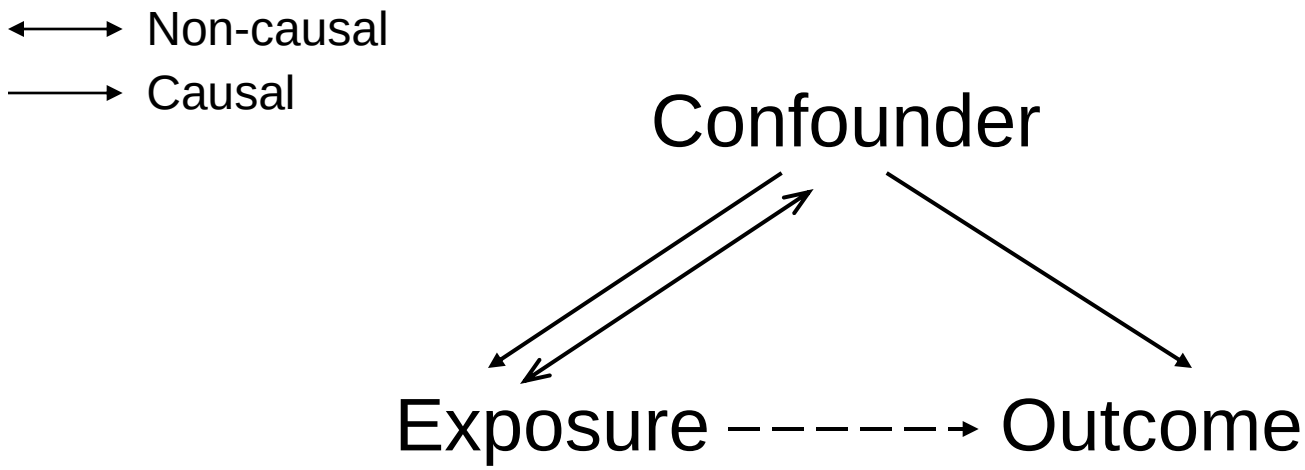
Confounding

Properties of a Confounder:

- A confounding factor must be a risk factor for the disease.
- The confounding factor must be associated with the exposure under study in the source population.
- A confounding factor must not be affected by the exposure or the disease.

  The confounder cannot be an intermediate step in the causal path between the exposure and the disease.

Confounding



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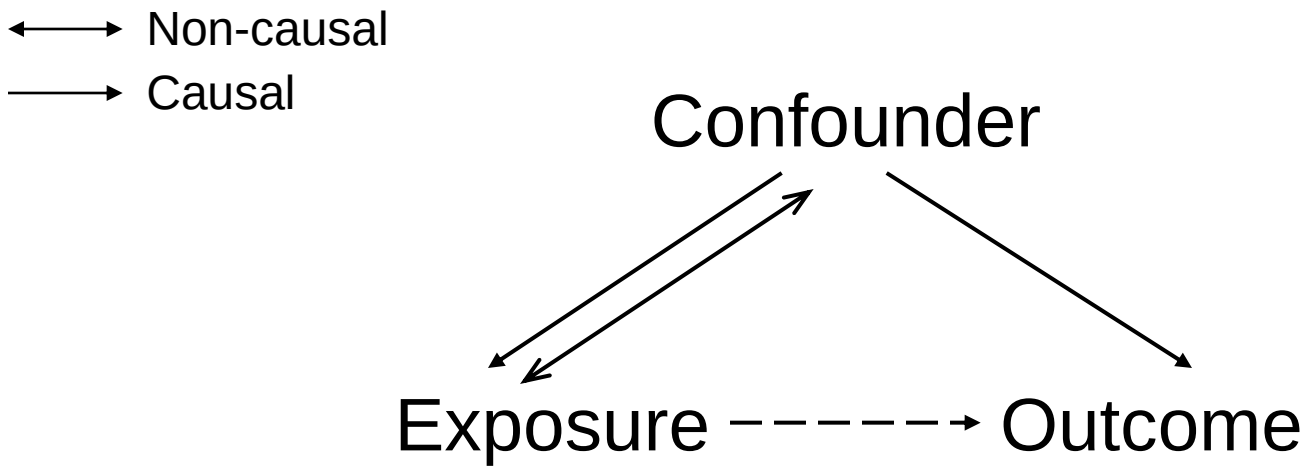
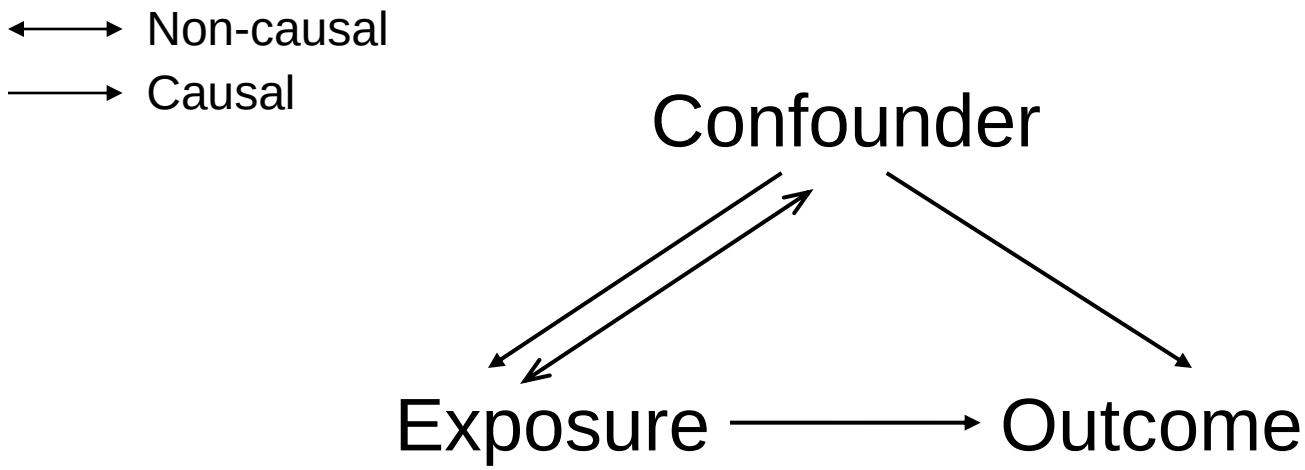


Birth order ⟶ **Down Syndrome**

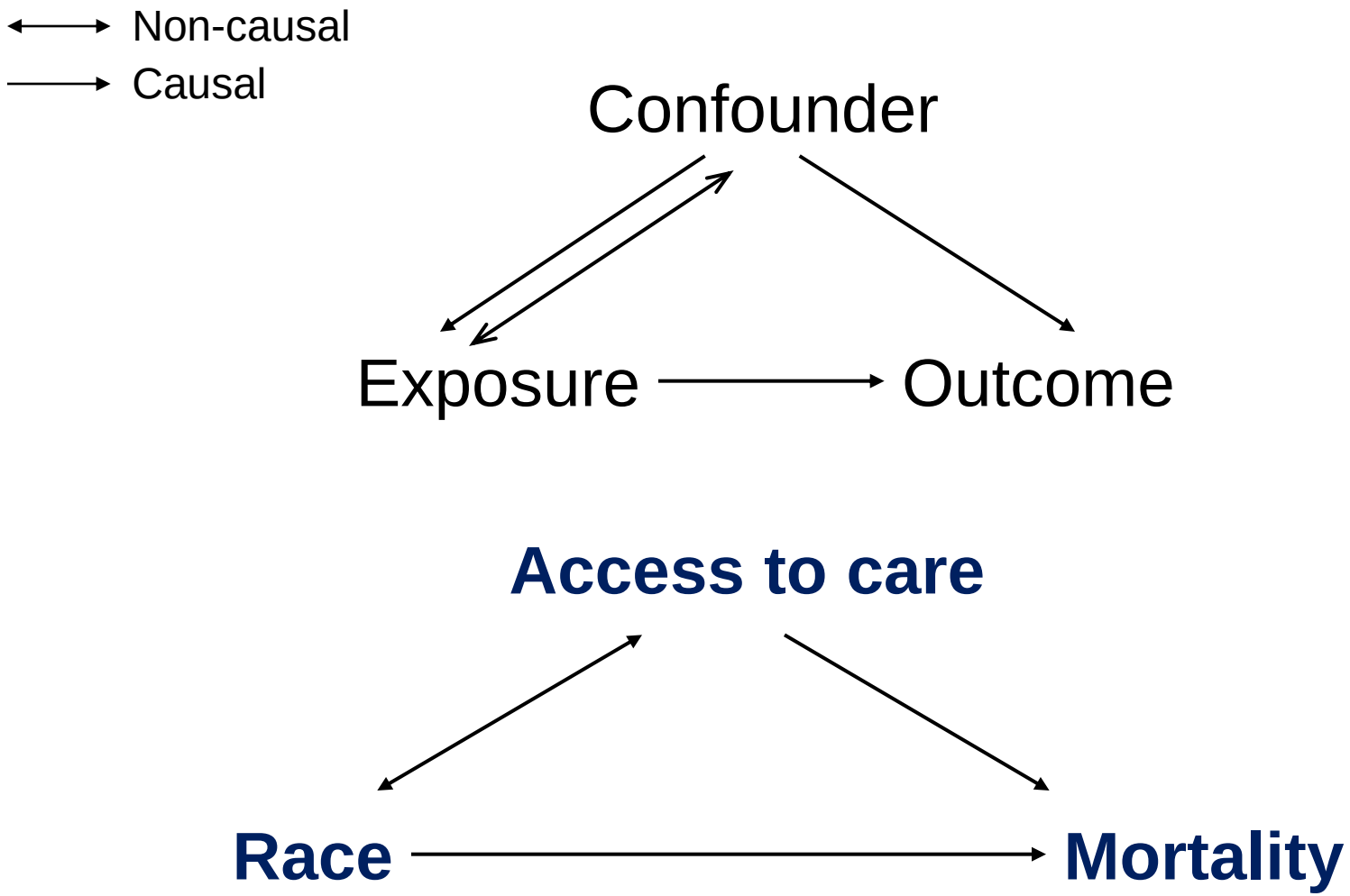
Confounding



Maternal Age

Birth order → **Down Syndrome**

Confounding



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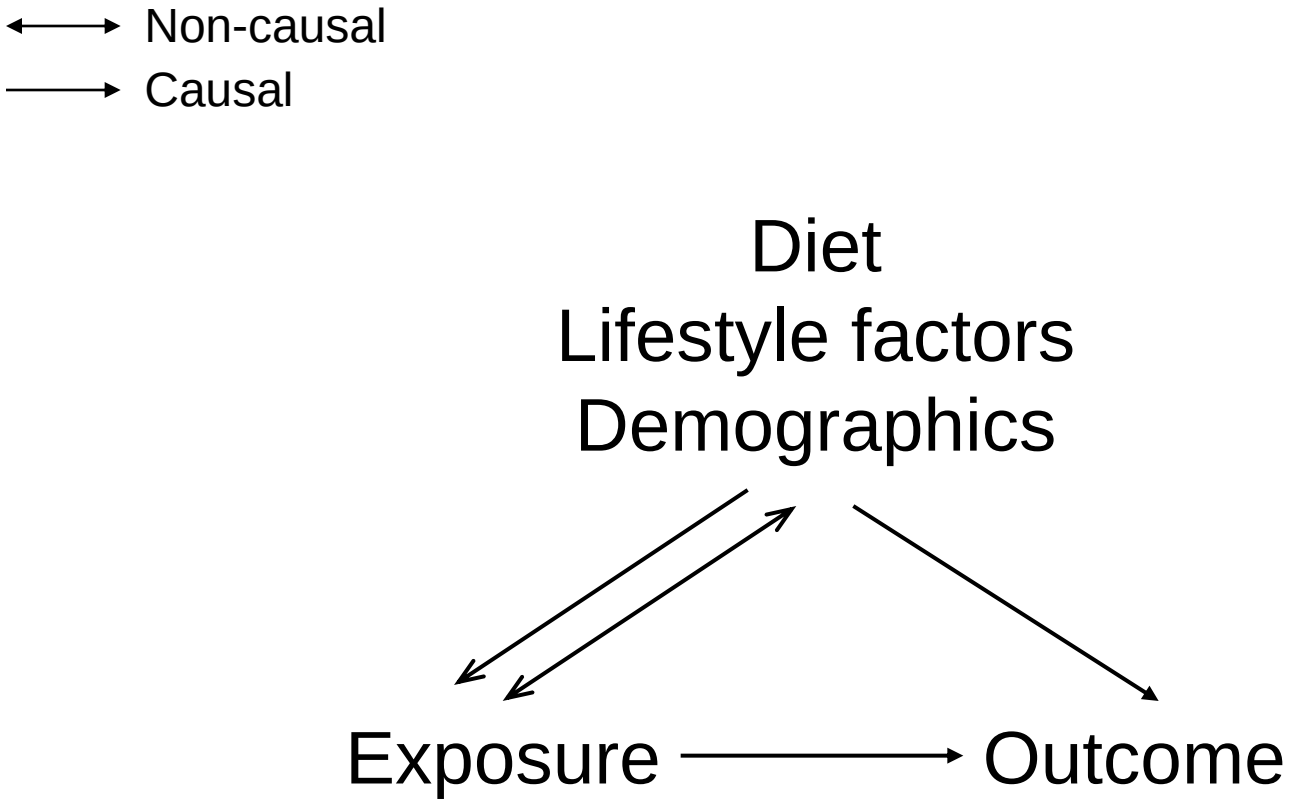
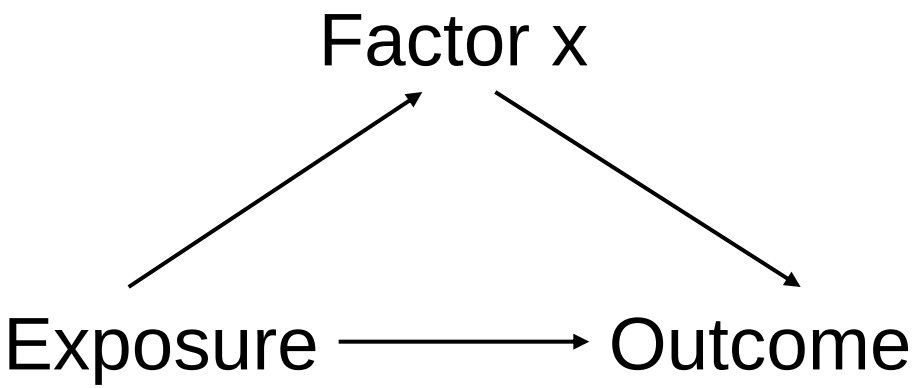


Confounding

Non-causal

Causal



Factor x is an intermediate effect (or in the causal pathway) between exposure and disease.

It is NOT a confounder.

Confounding

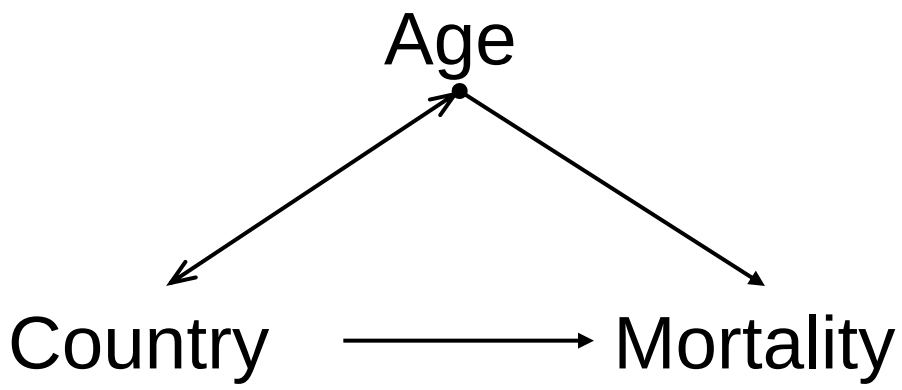
- Sources of confounding
  - Randomized clinical trials
    - Random differences between groups
    - Randomized clinical trials reduce confounding effect by balancing known and unknown confounding factors
  - Observational Studies
    - Random differences between groups
    - Factors associated with the exposure of interest

Country of Residence and Mortality

Country	Mortality (per 1000)
Costa Rica	3.8
Venezuela	4.4
Mexico	4.9
Canada	7.3
U.S.	8.7

Confounding

Ecologic study to determine whether country of residence is associated with mortality.



Non-causal

Causal

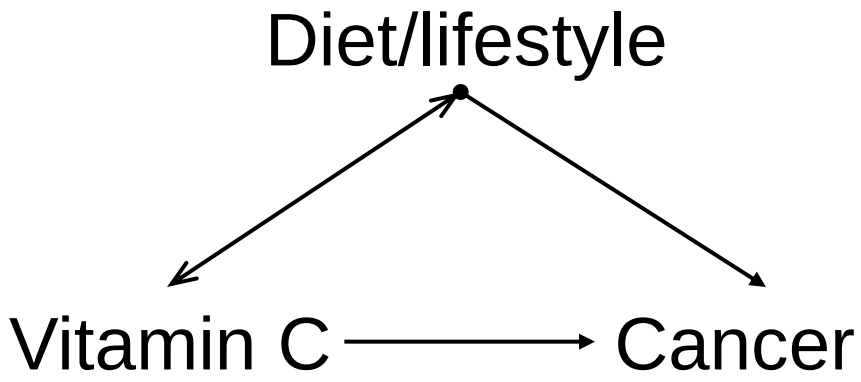
Average age may be different among countries.

Country of Residence and Age-Adjusted Mortality

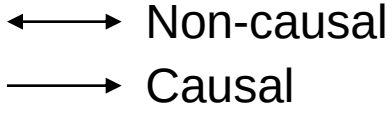
Country	Adjusted Mortality (per 1000)
Costa Rica	3.7
Venezuela	4.6
Mexico	5.0
Canada	3.2
U.S.	3.6

Confounding

Case-control study to determine whether vitamin C intake is associated with colon cancer.



People who take vitamin C may eat a healthier diet and live a healthier lifestyle



Confounding

- Design
  - Restriction
  - Matching
    - Individual matching
    - Group matching
  - Randomization
- Analysis
  - Stratified analysis
  - Adjustment
    - Age-adjustment
    - Regression analysis

Confounding

- Detection
  - Biologic model or underlying theory should allow you to specify potential confounders in advance of study/analysis
  - Assess for confounding in a systematic way
    - Known or potential confounding factors
    - Other factors not previously known to be confounding factor

Stratified Analysis

	D	$\bar{D}$	
E	a	b	a+b
$\bar{E}$	c	d	c+d
	a+c	b+d	

$OR_c = ad/bc$

$OR_a = f(OR_1, OR_2)$

Stratum 1	D	$\bar{D}$	
E	e	f	e+f
$\bar{E}$	g	h	g+h
	e+g	f+h	

$OR_1 = eh/fg$

2	D	$\bar{D}$	
E	i	j	i+j
$\bar{E}$	k	l	k+l
	i+k	j+l	

$OR_2 = il/kj$

Confounding

$OR_c = ad/bc$

$OR_a = f(OR_1, OR_2)$, Mantel-Haenszel procedure

If $OR_c = OR_a$ → no evidence for confounding

If $OR_c \neq OR_a$, → evidence for confounding

Stratified Analysis: Confounding

	D	$\bar{D}$	
E	30	18	48
$\bar{E}$	70	82	152
	100	100	200

$OR_c = ad/bc = 1.95$

$OR_a = f(OR_1, OR_2) = 1.0$

Age < 40	D	$\bar{D}$	
E	5	8	13
$\bar{E}$	45	72	117
	50	80	130

$OR_1 = eh/fg = 1.0$

Age ≥ 40	D	$\bar{D}$	
E	25	10	35
$\bar{E}$	25	10	35
	50	20	70

$OR_2 = il/kj = 1.0$

Stratified Analysis: No Cofounding

	D	$\bar{D}$	
E	200	800	1000
$\bar{E}$	50	950	1000
	250	1750	2000

$OR_c = ad/bc = 4.75$

$OR_a = f(OR_1, OR_2) = 4.9$

Stratum 1	D	$\bar{D}$	
E	160	240	400
$\bar{E}$	40	360	400
	200	600	800

$OR_1 = eh/fg = 6.0$

2	D	$\bar{D}$	
E	40	560	600
$\bar{E}$	10	590	600
	50	1150	1200

$OR_2 = il/kj = 4.2$

Stratified Analysis

	D	$\bar{D}$	
E	30	18	48
$\bar{E}$	70	82	152
	100	100	200

$OR_c = ad/bc = 1.95$

$OR_a = f(OR_1, OR_2) = 1.0$

Age < 40	D	$\bar{D}$	
E	5	8	13
$\bar{E}$	45	72	117
	50	80	130

$OR_1 = eh/fg = 1.0$

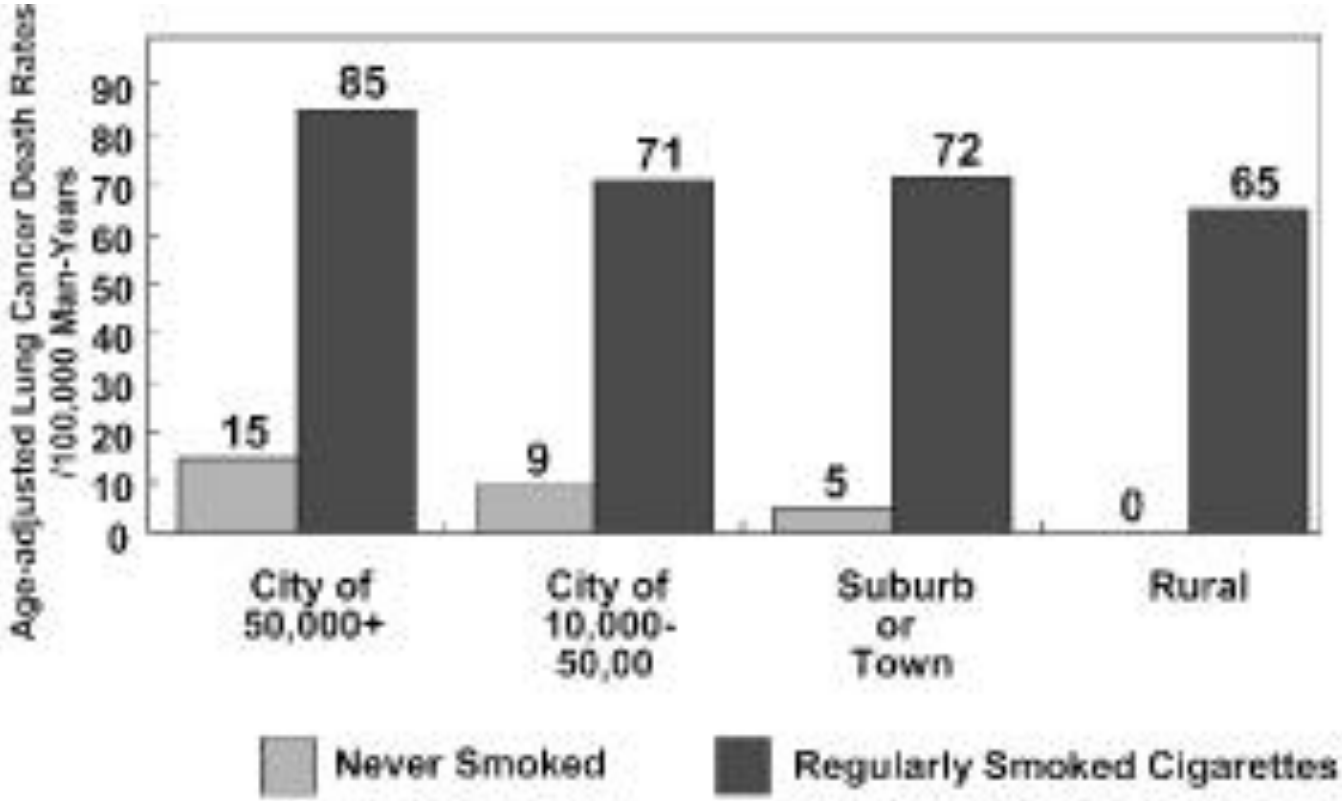
Age ≥ 40	D	$\bar{D}$	
E	25	10	35
$\bar{E}$	25	10	35
	50	20	70

$OR_2 = il/kj = 1.0$

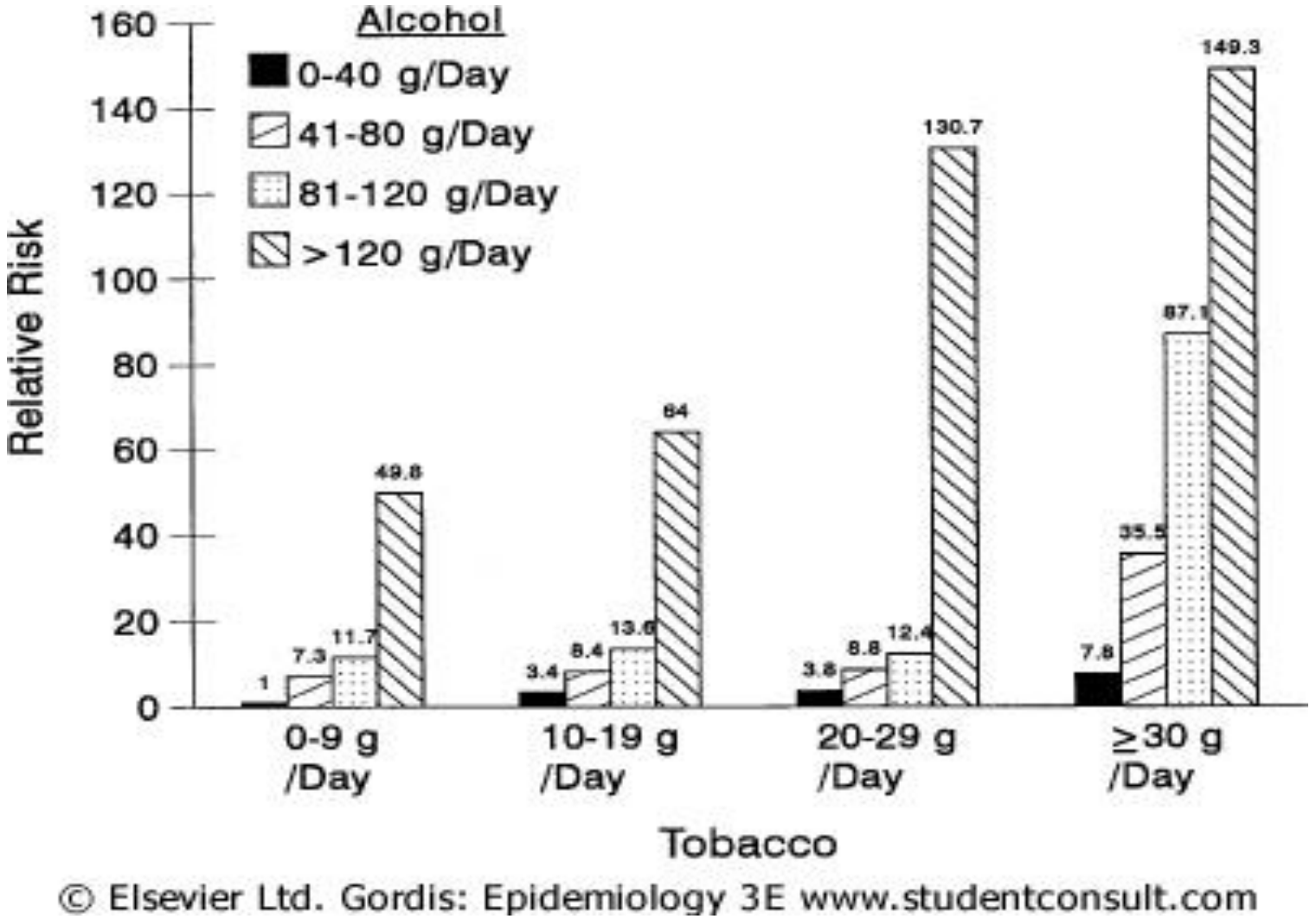
Confounding

- Analytic Criteria for Confounding
  - The crude estimate of effect differs from the adjusted estimate of effect
- Steps to assess confounding
  - Calculate crude measure of effect (RR, OR)
  - Stratify and calculate stratum-specific measures of effect
  - Perform a statistical test for heterogeneity of effects across stratum – test for interaction
  - If effects are similar, calculate an adjusted measure using Mantel Haenszel procedures
  - Compare the crude and adjusted measures
    - ORc = ORa then no confounding
    - ORc ≠ ORa then confounding

Age-Adjusted Lung Cancer Rates by Urban-Rural Setting and Smoking Status: Example of Stratification



Esophageal Cancer Stratified by Smoking and Drinking Behaviors



Confounding

- Advanced Topics
  - Adjustment using regression analysis
  - Residual confounding
    - Categories of confounder too broad
    - Unaccounted for confounders
  - Types of confounding
    - Positive
    - Negative
    - Qualitative
  - Statistical issues
  - Conditional confounding
  - Time-dependent confounding

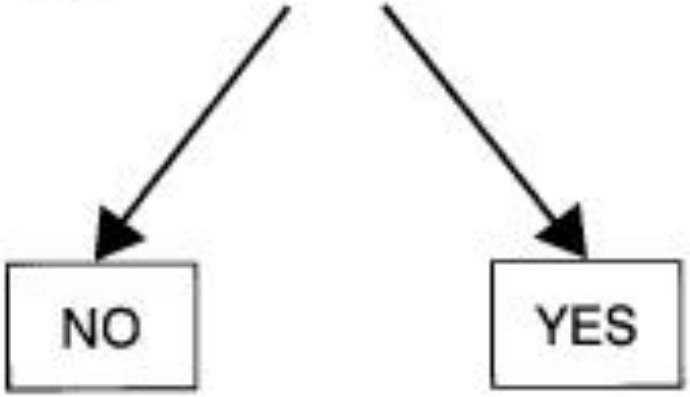
Interaction

- Definition

  “Interaction is present when the incidence rate of disease in the presence of two or more risk factors differs from the incidence rate expected to result from their individual effects.” -- MacMahon

Approach to Interaction

1. Is there an association?
2. If so, is it due to confounding?
3. Is the association equally strong in strata formed on the basis of a third variable?



Interaction

	D	$\bar{D}$	
E	a	b	
$\bar{E}$	c	d	

$OR_c = ad/bc$

$OR_1 \neq OR_2$

Stratum 1	D	$\bar{D}$	
E	e	f	e+f
$\bar{E}$	g	h	g+h
	e+g	f+h	

$OR_1 = eh/fg$

2	D	$\bar{D}$	
E	i	j	i+j
$\bar{E}$	k	l	k+l
	i+k	j+l	

$OR_2 = il/kj$

Stratified Analysis

	Lung CA	Control
Smoking	200 (80%)	436 (46%)
no smoking	50 (20%)	514 (54%)

Crude RR = 3.55

Asbestos

	Lung CA	Control
Smoking	90 (82%)	100 (45%)
No smoking	20 (18%)	120 (55%)

RR = 3.32

No asbestos

	Lung CA	Control
Smoking	70 (50%)	230 (32%)
No smoking	70 (50%)	500 (68%)

RR = 1.90

Interaction

- Test for interaction
  - Heterogeneity in measures of association within a stratum
  - OR1 ≈ OR2, then no interaction
  - OR1 ≠ OR2, then interaction
- Statistical tests for heterogeneity
  - Mantel-Haenszel chi square test
  - Woolf test
- If interaction is present,
  - present OR_1 and OR_2, separately
  - OR_c has no intrinsic meaning

Interaction / Effect Modification

- Additive Model
  - The effect of one factor is added to the effect of another factor
  - Is the disease incidence (risk difference) among people who are exposed to both Factor A and Factor B different from that which we would expect if those people experienced the independent contributions of both factors?

Interaction
Additive Model

Disease Rates

Factor A

Factor B	Absent	Present
Absent	3.0	9.0
Present	15.0	?

Factor A

Factor B	Absent	Present
Absent	3.0	9.0
Present	15.0	21.0

Risk Difference

Factor A

Factor B	Absent	Present
Absent	0	6.0
Present	12.0	18.0

Interaction / Effect Modification

- Multiplicative Model
  - Effect of two factors is multiplicative
  - Is the disease incidence (relative risk) among people who are exposed to both Factor A and Factor B different from that which we would expect if those people experienced the independent contributions of both factors?

Interaction
Multiplicative Model

Disease Rates

Factor B \ Factor A	Absent	Present
Absent	3.0	9.0
Present	15.0	?

Factor B \ Factor A	Absent	Present
Absent	3.0	9.0
Present	15.0	45.0

Relative Risks

Factor B \ Factor A	Absent	Present
Absent	1.0	3.0
Present	5.0	15.0

Deaths from Lung Cancer* with and without Smoking and Asbestos Exposure: Interaction under Additive Model

Smoking	Asbestos Exposure	
	No	Yes
No	11.3	58.4
Yes	122.6	601.6

* Deaths per 100,000 population

Relative Risks of Oral Cancer by Alcohol and Smoking Exposures: Multiplicative Model of Interaction

Alcohol	Smoking	
	No	Yes
No	1.00	1.53
Yes	1.23	5.71

Risk Ratios for Oral Cancer Stratified by Alcohol and Smoking Exposures

Alcohol (oz/d)	Cigarette Equivalents per Day			
	0	< 20	20 - 39	≥ 40
0	1.00	1.52	1.43	2.43
< 0.4	1.40	1.67	3.18	3.25
0.4 – 1.5	1.60	4.36	4.46	8.21
> 1.5	2.33	4.13	9.59	15.50

2.33 * 2.43 = 5.66 << 15.50,
Evidence for Multiplicative Interaction, but no upper bounds for highest categories

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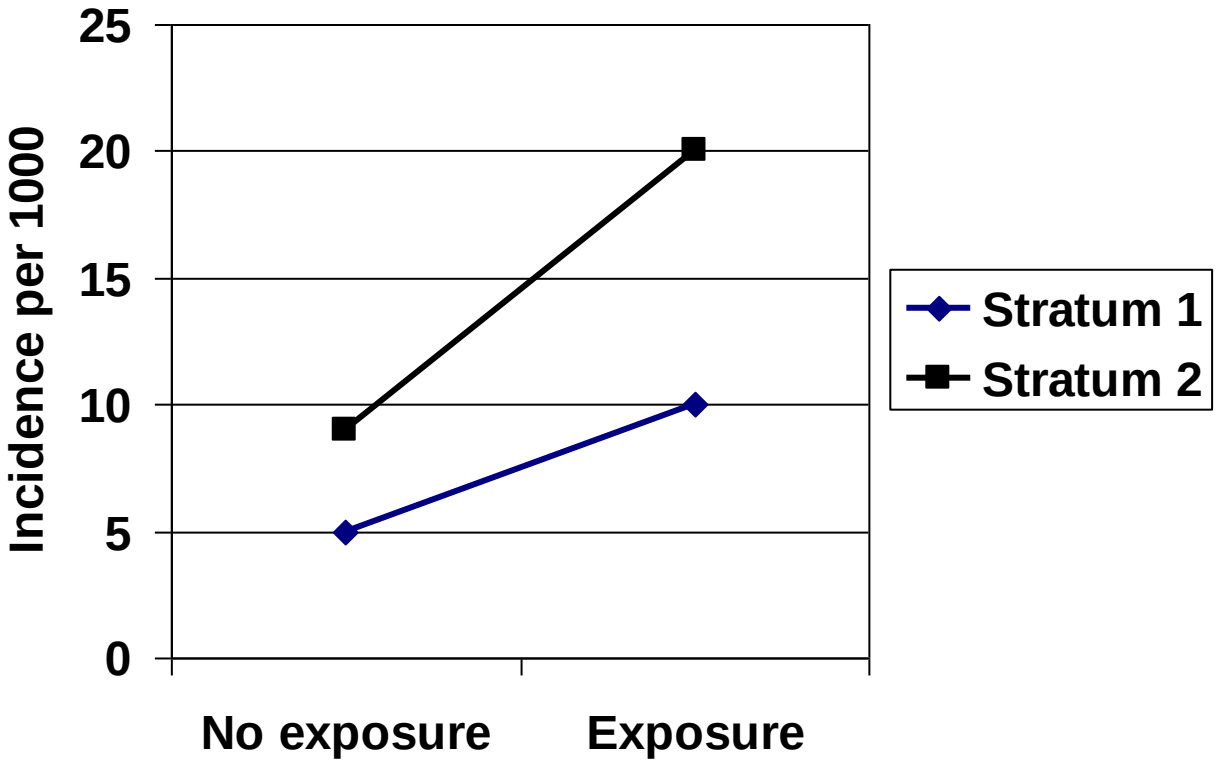
1.60 * 1.43 = 2.29 < 4.46,
Still evidence for multiplicative interaction

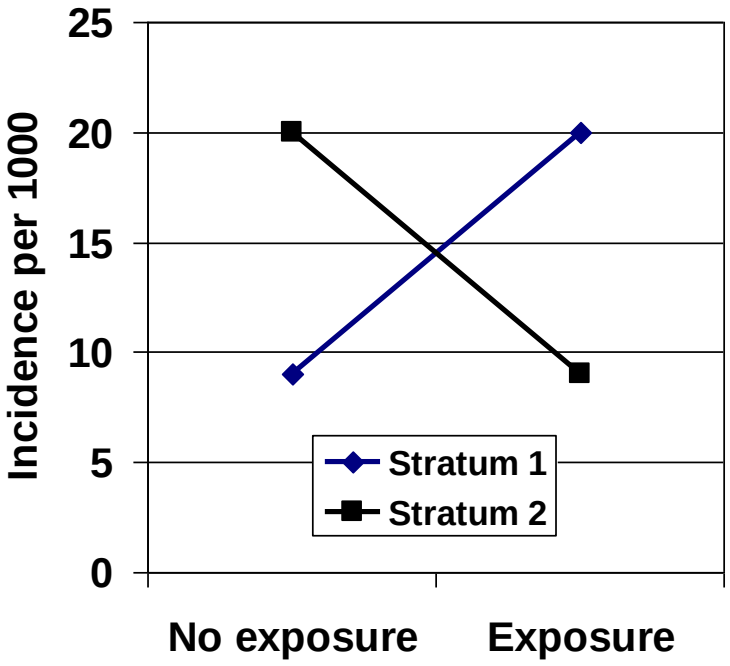
Interaction / Effect Modification

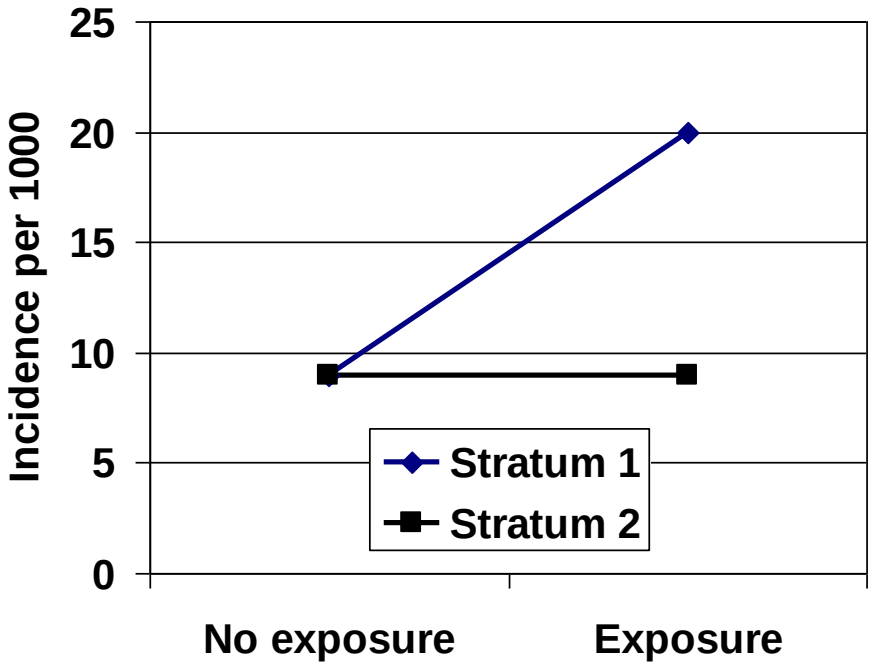
- Positive interaction (synergism)
  - Observed effect > expected effect
- Negative interaction (antagonism)
  - Observed effect < expected effect
- Quantitative interaction
  - Stratum 1 ≠ Stratum 2, but both go in same direction
    - Crude RR = 4.5
    - Stratum 1 RR = 2.3 and Stratum 2 RR = 3.4
- Qualitative interaction
  - Stratum 1 ≠ Stratum 2, but go in opposite directions from crude RR
    - Stratum 1 RR = 0.5 and Stratum 2 RR = 5.6
  - Stratum 1 ≠ Stratum 2, but no effect in one strata and an effect in the other strata
    - Stratum 1 RR = 1.0 and Stratum 2 RR = 3.5

Quantitative Interaction



Qualitative Interaction





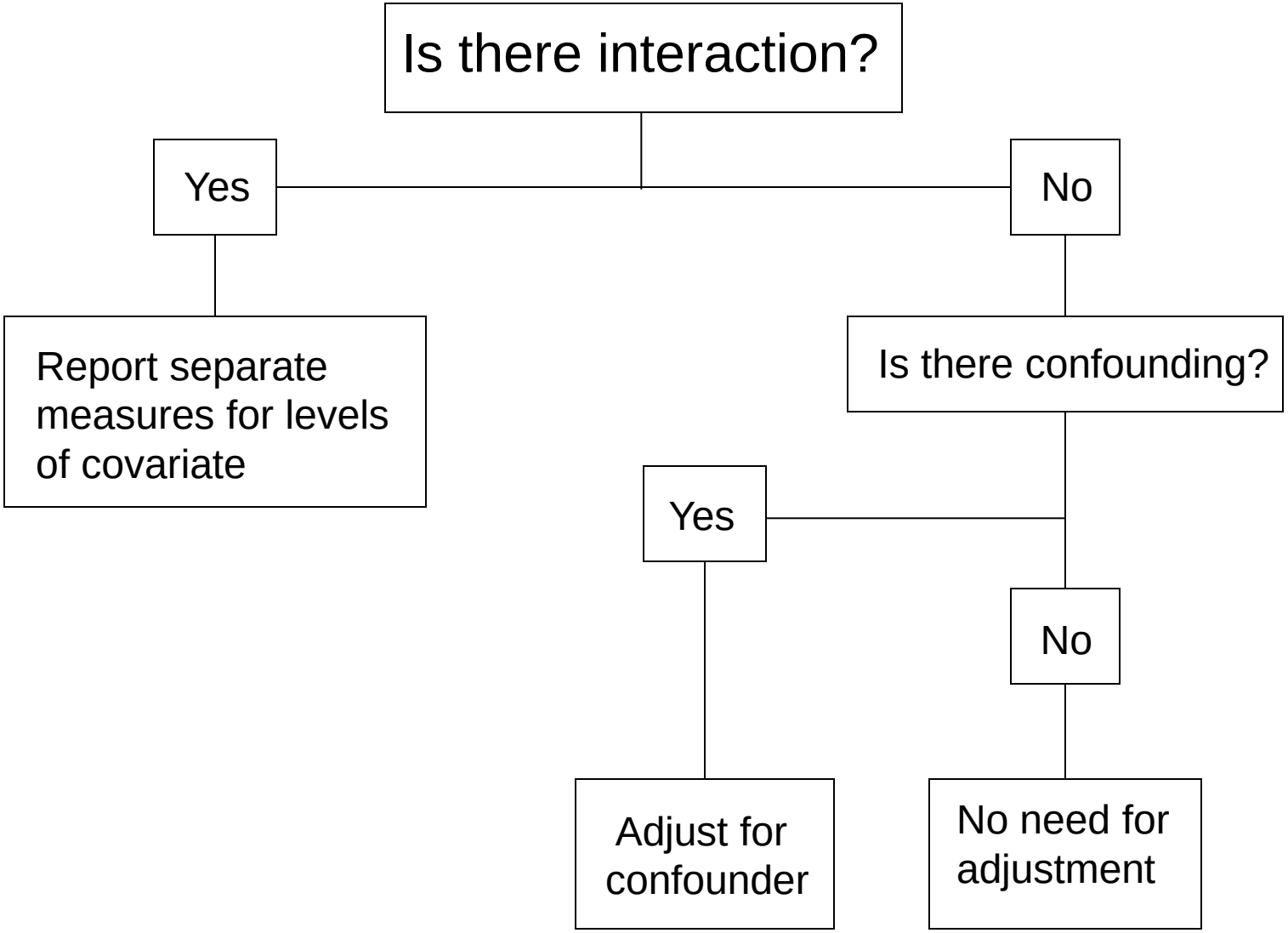
Interaction / Effect Modification

- Test for interaction
  - Heterogeneity in measures of association within a stratum
  - Stratum 1 ≈ Stratum 2, then no interaction
  - Stratum 1 ≠ Stratum 2, then interaction
- Statistical tests for heterogeneity
  - Mantel-Haenszel chi square test
  - Woolf test
- If interaction is present,
  - Present stratum specific risk estimates, separately
  - Crude estimate has no intrinsic meaning

Interaction

- Depends on how one defines no interaction
  - Additive versus multiplicative model
  - Model dependent
    - Must specify which model when discussing interaction
  - Interaction is a characteristic of the observed data, which is assumed to reflect population
    - Conclusion about population also model dependent
    - Public health – additive interactions
    - Etiologic research – multiplicative interactions

Approach to Interaction and Confounding



Confounding

- Analytic Criteria for Confounding
  - The crude estimate of effect differs from the adjusted estimate of effect
- Steps to assess confounding
  - Calculate crude measure of effect (RR, OR)
  - Stratify and calculate stratum-specific measures of effect
  - Perform a statistical test for heterogeneity of effects across stratum – test for interaction
  - If effects are similar, calculate an adjusted measure using Mantel Haenszel procedures
  - Compare the crude and adjusted measures
    - ORc = ORa then no confounding
    - ORc ≠ ORa then confounding