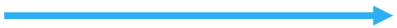
Lecture 7: From association to causation

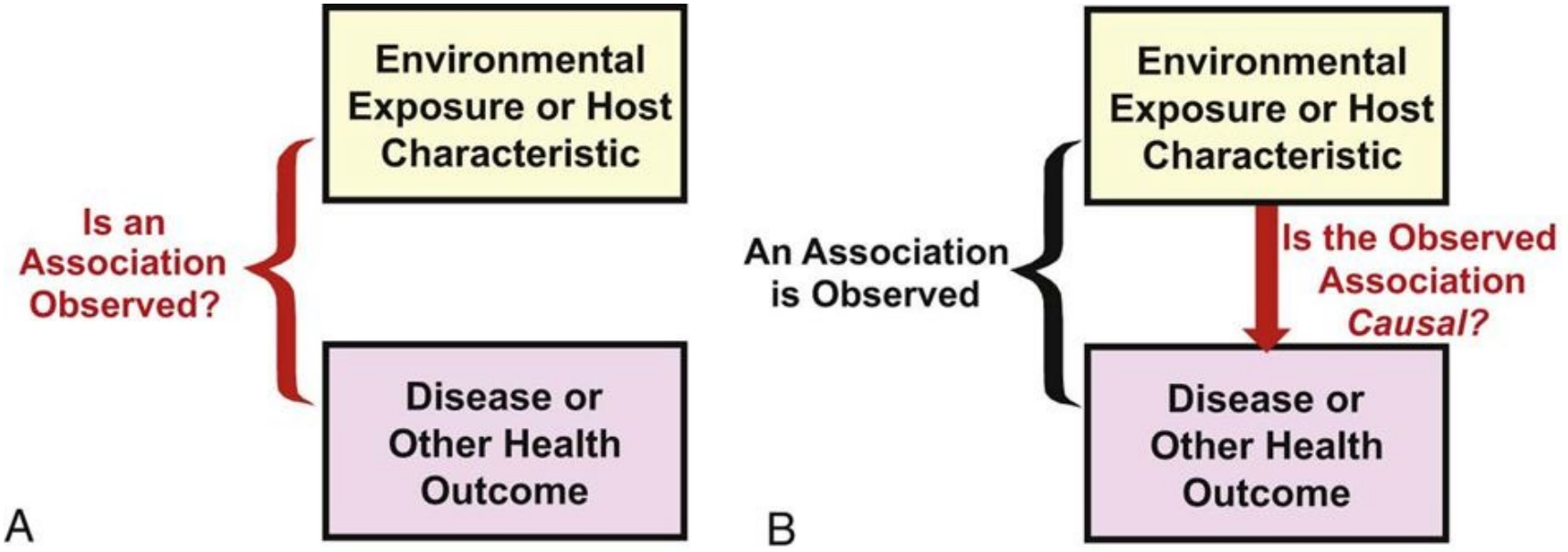
Lecture prepared by Dr. Hailey Banack, PhD

Causality

Exposure X  Outcome Y

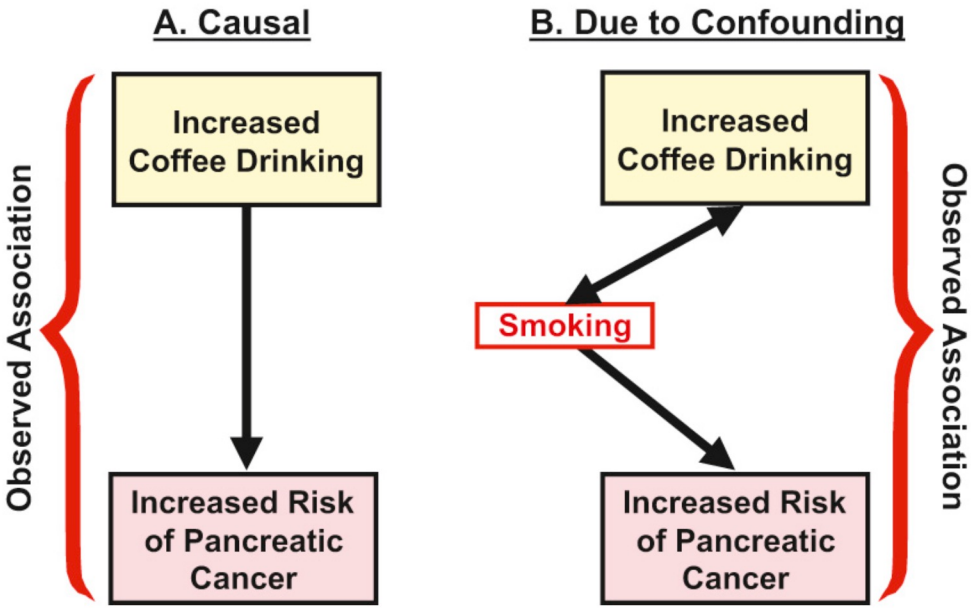
Epidemiologists often attempt to identify etiologic (causal) relationships between exposure and outcome

Causal inference: deciding that the evidence is sufficient to conclude that exposure X *causes* outcome Y


Environmental Exposure or Host Characteristic
Is an Association Observed?
Disease or Other Health Outcome
A
Environmental Exposure or Host Characteristic
An Association is Observed
Is the Observed Association Causal?
Disease or Other Health Outcome
B

Types of Associations

- Spurious associations- false/erroneous relationships that are due to chance or bias but not a causal relationship
- True (causal) associations- causal relationship between exposure and outcome



How can we determine if observed associations reflect causal relationships?

Let’s take a step back.

What is a cause?

Understanding causation

- Early life experiences contribute to our understanding of causation
  - Crying baby = parental response
  - Flipping switch= light bulb on

What is a cause?

"Cause of a disease event is an event, condition or characteristic that preceded the disease event and without which the disease event either would not have occurred at all or would not have occurred until some other time."

[Rothman & Greenland, 1998]

Conceptual Models

1. Bradford Hill guidelines
2. Sufficient-component cause model
3. Counterfactual model

Bradford Hill Guidelines

- In 1965, Sir Austin Bradford Hill proposed a series of guidelines for progressing from an observed association to a "…verdict of causation."
- Adapted from the U.S. Surgeon General's 1964 report on smoking and health.

Hill's Causal Guidelines

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy

Example

Human Papillomavirus (HPV) and Cervical Cancer

- 40+ types of HPVs that are easily transmitted
- Very high percentage of people will be infected at some point
- Most go away within 1-2 years, some persist
- HPV 16 and 18 are responsible for about 70% of cases of cervical cancer

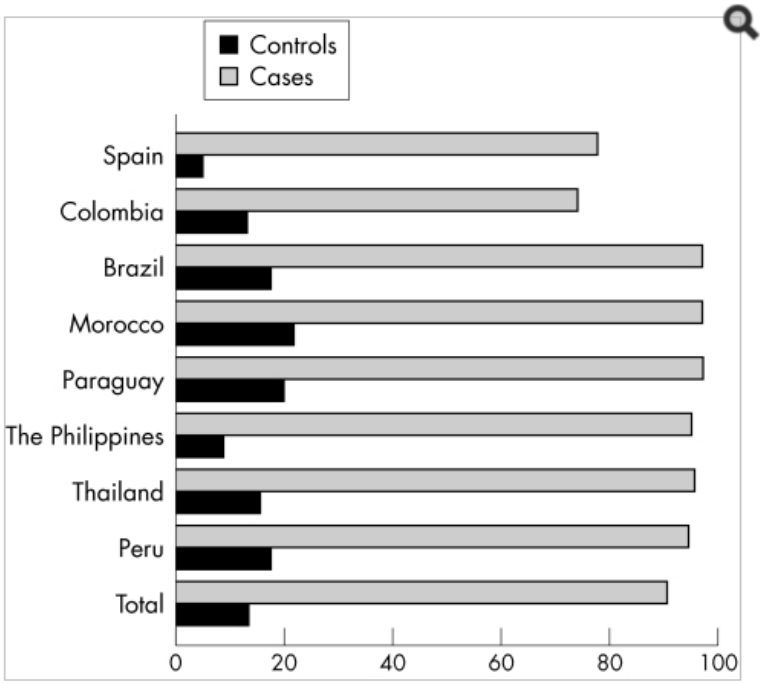
GARDASIL®
Human Papillomavirus Vaccine
Types 6,11,16,18

CDC; Gazdar et al., 2002

Strength

This criterion implies that the greater the magnitude of the association between a proposed cause and effect the greater the likelihood that the relationship is causal.

The strength of association between HPV and cervical cancer is considered one of the strongest for a human cancer. Recent studies have shown that HPV (all types combined) is present in >90% of cervical cancers



Prevalence of human papillomavirus (HPV) DNA in cases and controls in the IARC multicentre case–control study.[24–30]

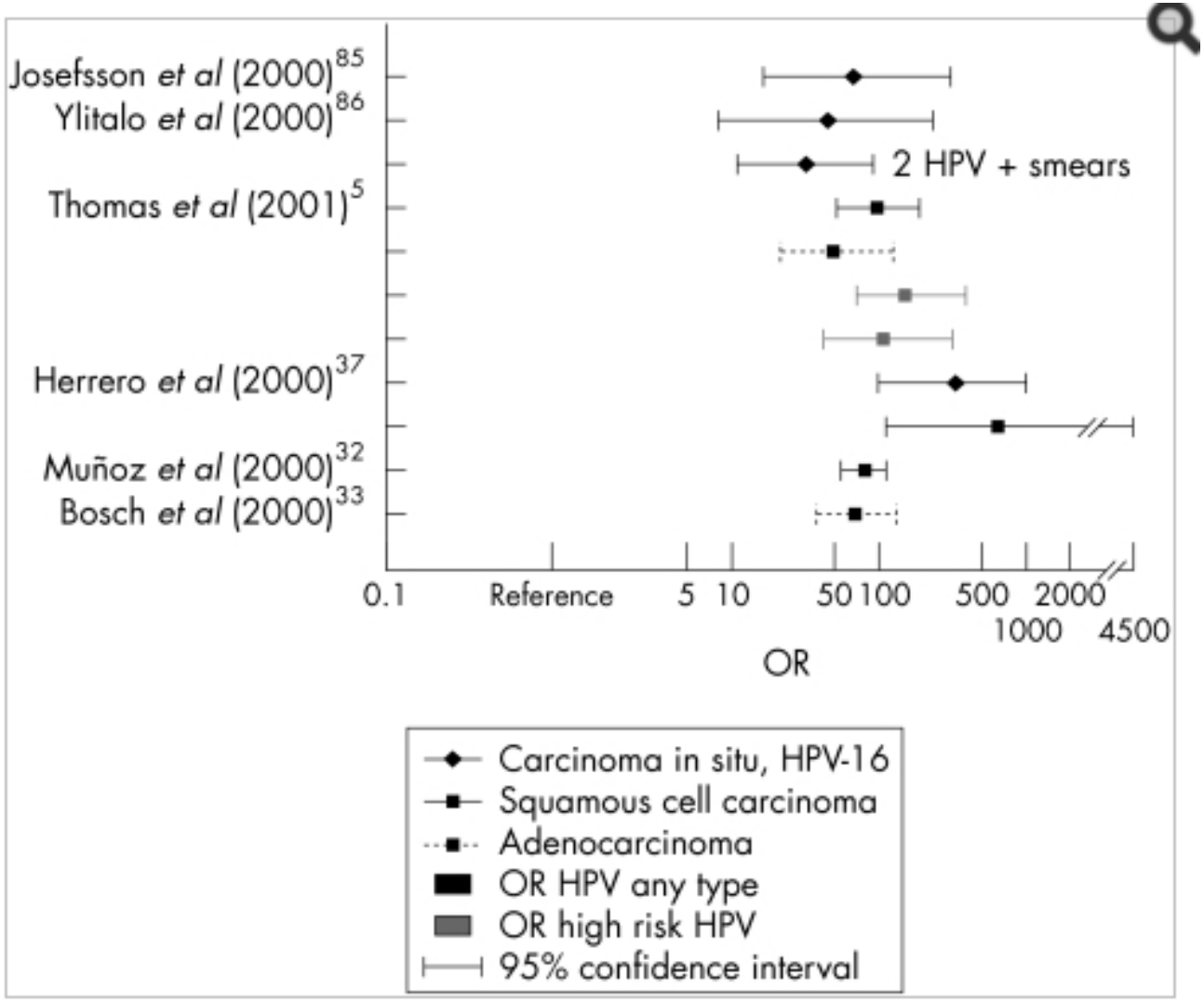
		HPV DNA prevalence (%)		
	No. studies	Controls	Cases	OR (95% CI)
Squamous	9	13.4	90.7	83.3 (54.9 to 105.3)
Adeno and mixed	6	15.4	91.9	68.7 (36.2 to 130.5)

J Clin Pathol. 2002 Apr; 55(4): 244–265

Consistency

Repeated observations of the relationship by different persons, under different circumstances, and at different times lends support to the idea of causality.

The presence of HPV in cervical cancer is consistent among a large number of studies, regardless of the HPV testing system used. There are no published studies with negative observations that challenge the association of HPV and cervical cancer.



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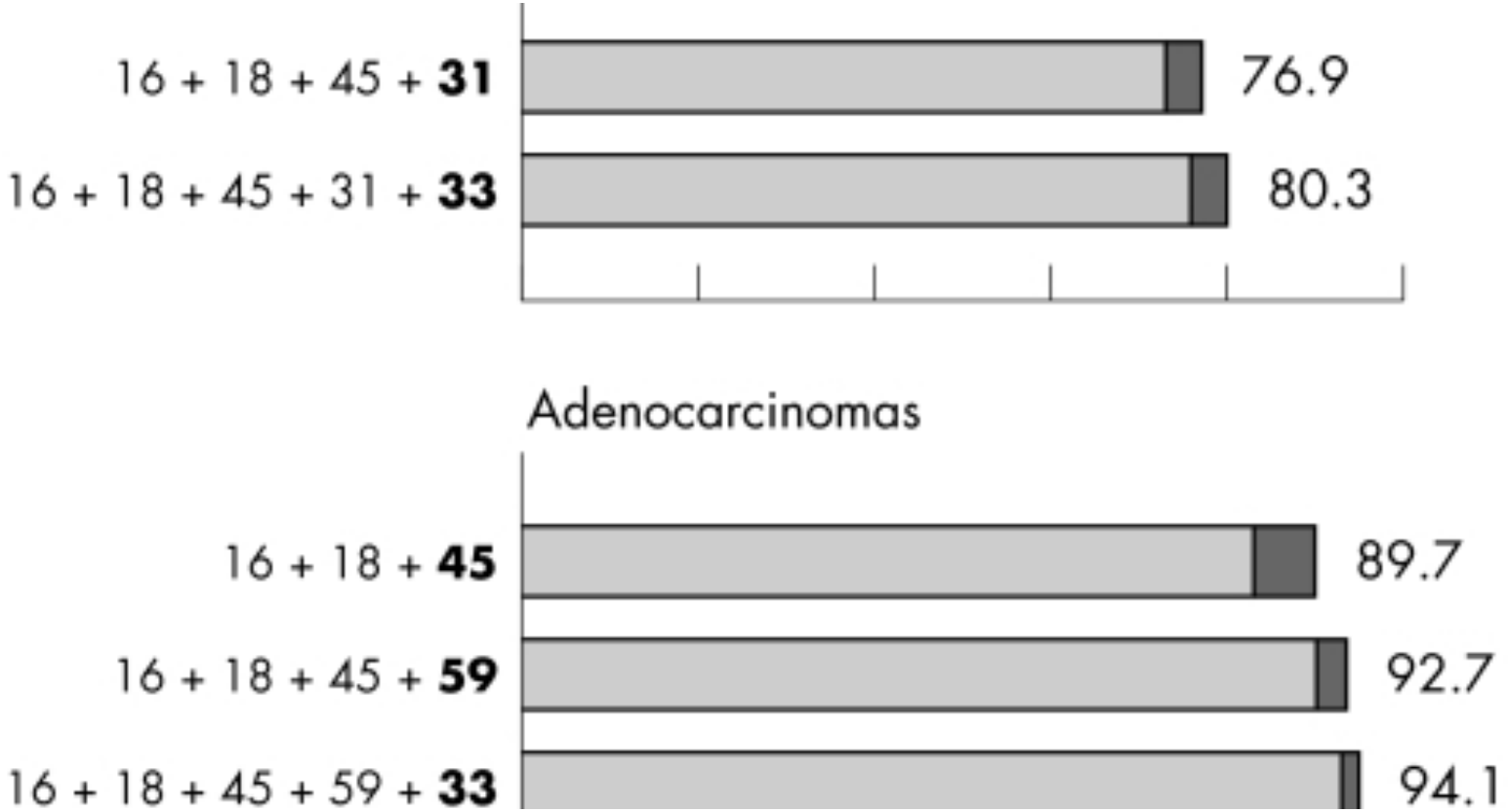
Specificity

The notion of specificity suggests that a relationship is more likely to be causal if the exposure is related to a single outcome rather than multiple outcomes.

Specific cancers are related to the presence of HPV. HPV type is also important in the development of specific cancers. HPV is present in the tumour cells.



Cumulative prevalence of human papillomavirus (HPV) types in cervical cancer.

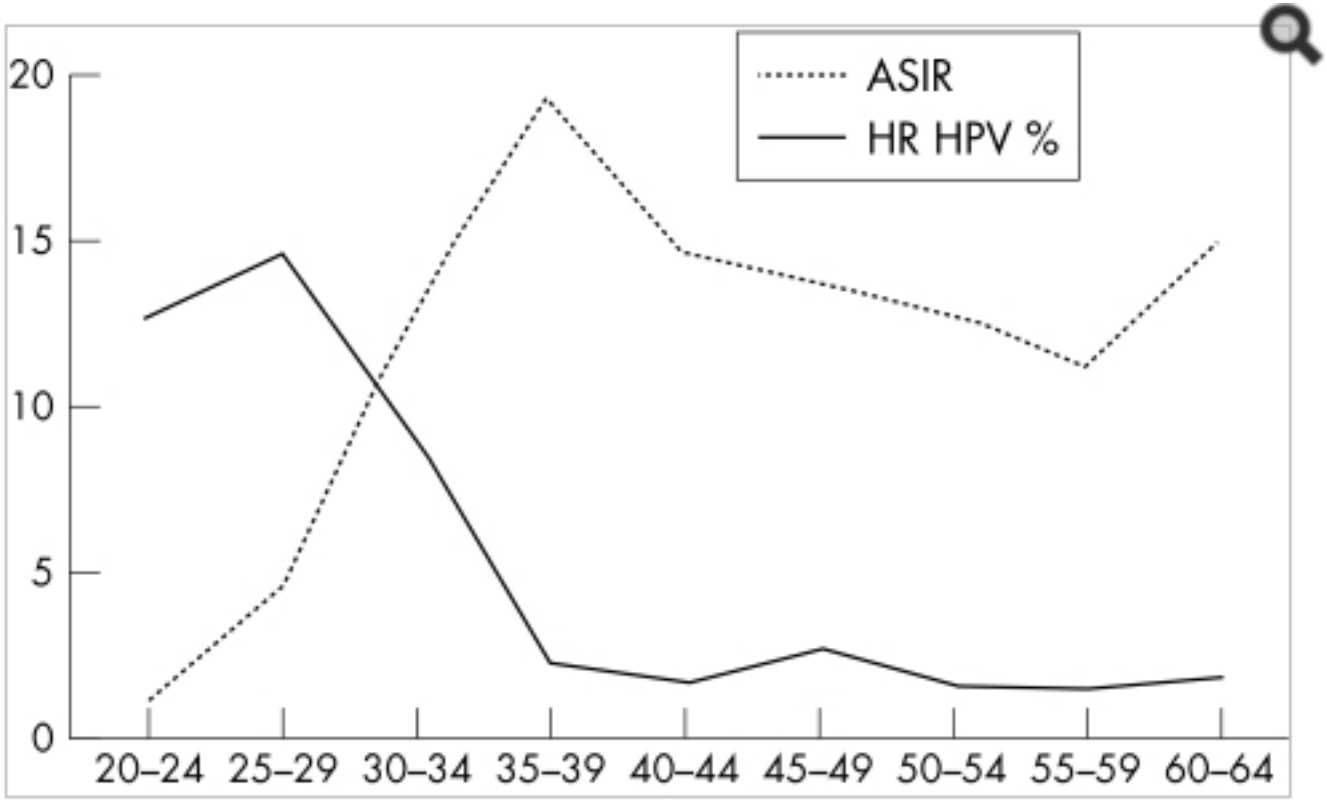
About 15 HPV types are involved in over 95% of the cervical cancer cases.

J Clin Pathol. 2002 Apr; 55(4): 244–265

Temporality

Temporality implies that the cause precedes the effect.

HPV infections precede pre-cancerous cervical lesions and cervical cancer by years to decades



Age specific prevalence (%) of high risk (HR) human papillomavirus (HPV) DNA in 3700 women entering a screening program and age specific incidence rate (ASIR) of cervical cancer in the Netherlands.

J Clin Pathol. 2002 Apr; 55(4): 244–265

Biological Gradient (dose-response)

A dose-response relationship implies that as the dose of an exposure increases so does the risk of disease

Early studies show that cervical cancer is associated with high viral loads

Plausibility/Coherence

Plausibility: “It will be helpful if the causation we suspect is biologically plausible.”

HPV is a powerful carcinogen that immortalizes human keratinocytes *in vitro*. There are no animal models in which a sexually transmitted PV produces cervical cancer. HPV is present in cervical cancer, where it expresses the oncogenic proteins E6 and E7 that inactivate the host regulatory proteins p53 and RB, respectively.

Coherence: “…the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease…”

The association does not conflict with what is known about the natural history of cervical cancer development

Experimental Evidence

Evidence from randomized trials may bolster confidence in causal interpretation. However, you could never do a randomized trial of a harmful exposure (like HPV).

In vitro and *in vivo* evidence supports a causal role for HPV in the development of cervical cancer

Natural Experiments

RESEARCH CMAJ

Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study

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Abstract

Background: Suboptimal human papillomavirus (HPV) vaccine coverage in some jurisdictions is partly attributed to fears that vaccination may increase risky sexual behaviour. We assessed the effect of HPV vaccination on clinical indicators of sexual behaviour among adolescent girls in Ontario.

Methods: Using Ontario's administrative health databases, we identified a population-based cohort of girls in grade 8 in the 2 years before (2005/06 and 2006/07) and after (2007/08 and 2008/09) implementation of Ontario's grade 8 HPV vaccination program. For each girl, we then obtained data on vaccine receipt in grades 8 and 9 and data on indicators of sexual behaviour (pregnancy and non–HPV-related sexually transmitted infections) in grades 10–12. Using a quasi-experimental method known as regression discontinuity, we estimated, for each outcome, the risk difference (RD) and relative risk (RR) attributable to vaccination and to program eligibility.

Results: The cohort comprised 260 493 girls, of whom 131 781 were ineligible for the program and 128 712 were eligible. We identified 15 441 (5.9%) cases of pregnancy and sexually transmitted infection and found no evidence that vaccination increased the risk of this composite outcome: RD per 1000 girls –0.61 (95% confidence interval [CI] –10.71 to 9.49) and RR 0.96 (95% CI 0.81 to 1.14). Similarly, we found no discernible effect of program eligibility: RD per 1000 girls –0.25 (95% CI –4.35 to 3.85) and RR 0.99 (95% CI 0.93 to 1.06). The findings were similar when outcomes were assessed separately.

Interpretation: We present strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls. These results suggest that concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating at a young age.

Analogy

Analogous relationships may make the association under investigation more plausible

Other DNA tumour viruses can induce cancers in humans, and species-specific papillomaviruses can induce cancers in animals

Criticism of Hill's Criteria

Strength	Depends on presence of other component causes. Strong ≠ unbiased
Specificity	A single exposure can have many effects. Specificity is considered rare and unnecessary for causation
Dose-Response	Gradient can be the result of bias (e.g birth order and Downs)
Plausibility, Coherence, Consistency, Analogy	Can be subjective, often based on prior/subjective beliefs "Hindsight is 20/20" Vague
Exp't Evidence	Not always possible to obtain, trial data can still be biased/misleading

Temporality is necessary

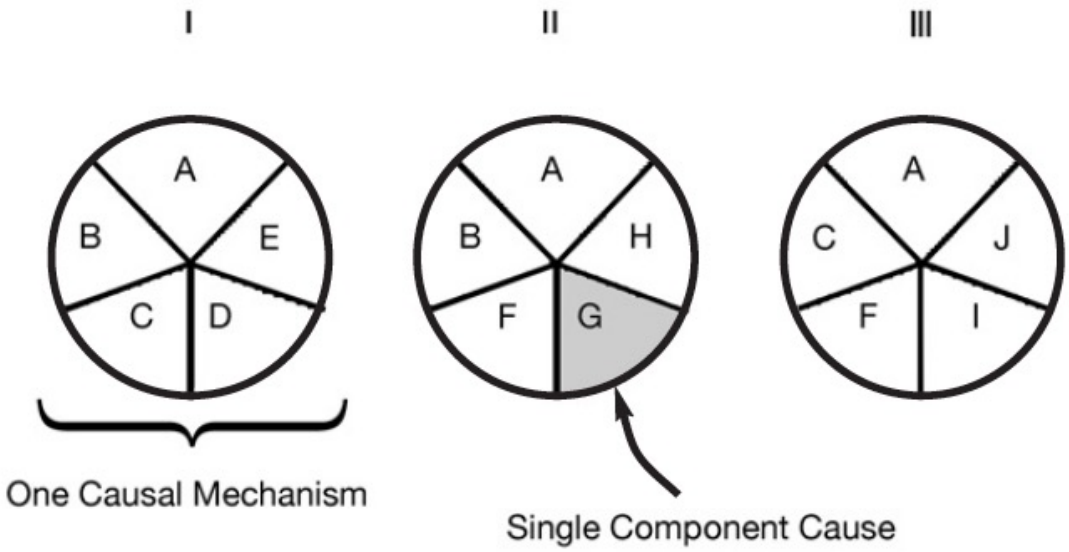
Temporality is the only criteria included in the list that is absolutely necessary for establishing causality.

- Can be difficult to determine
  - Does poverty lead to poor health or does poor health lead to poverty?

Sufficient-Component Cause Model

- General conceptual model for causation developed in 1976 by Ken Rothman
- Conditions necessary to cause (and prevent) disease in a single individual and for the epidemiological study of the causes of disease among groups of individual
- Emphasizes multi-causality

Causal Pies

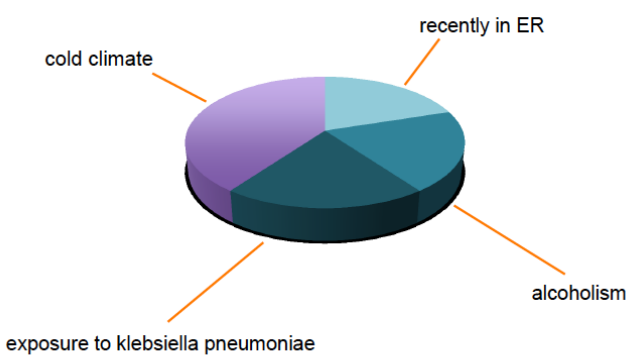


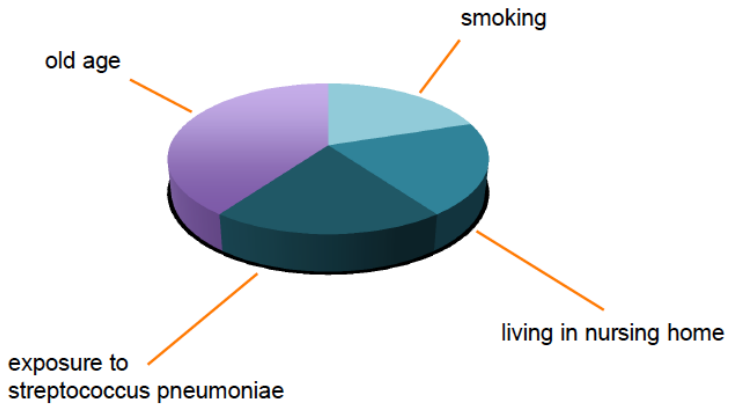
Each individual instance of disease – each case – occurs through a single causal mechanism, also referred to as a sufficient cause. A sufficient cause is the minimum set of component causes necessary to cause disease.

Multi-causality: A given disease can be caused by more than one causal mechanism.

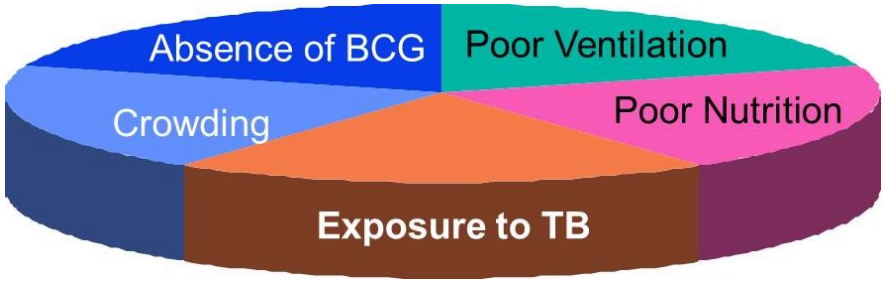
Multi-Causality Example 1

Pneumonia



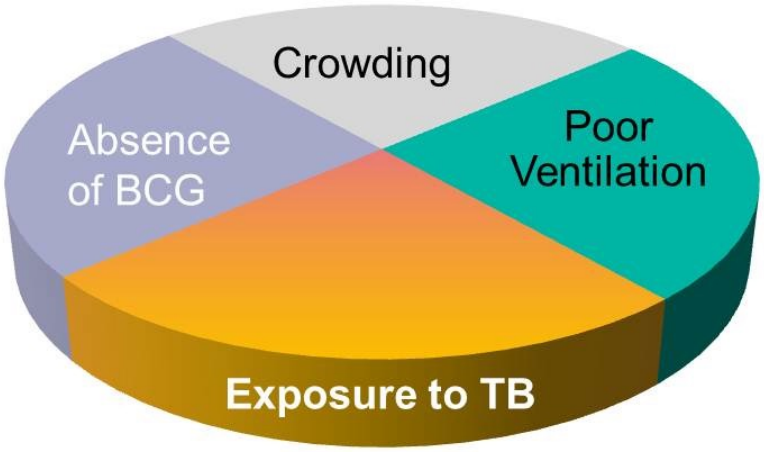


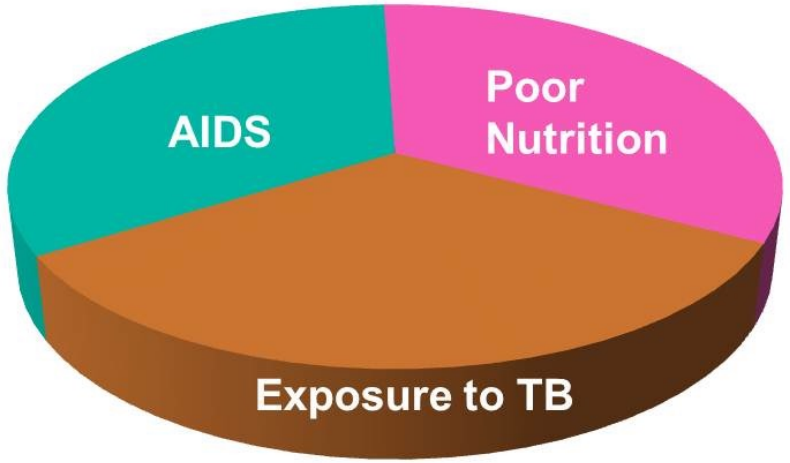
Multi-causality Example 2



TB

Necessary cause:_____





Strength of Causes

- With respect to an individual case of disease, every component cause was necessary to the occurrence of that case.
- Therefore, in an individual case there is no such thing as a strong or weak component cause.
- The relative strength of a component cause is defined by the proportion of cases in the population in which factor X is a component
  - *e.g., smoking is considered a strong cause because it plays a role in a large proportion of cases of lung cancer*

Strength of Causes

The proportion of cases in which a specific component cause plays a role may change across populations and over time

- Lead paint, fetal alcohol spectrum disorder, developmental delays
- Smoking, wildfires, asthma exacerbations

The relative strength of a cause is not a biologically stable characteristic.

Disease Occurrence

- The completion of a sufficient cause is synonymous with the biologic occurrence of the outcome

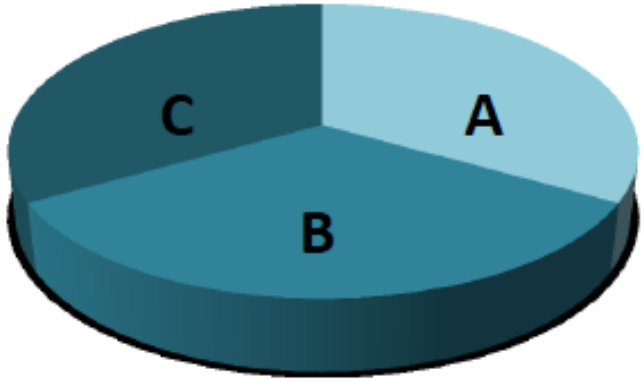
- The components of a sufficient cause do not need to act simultaneously; they can act at different times.

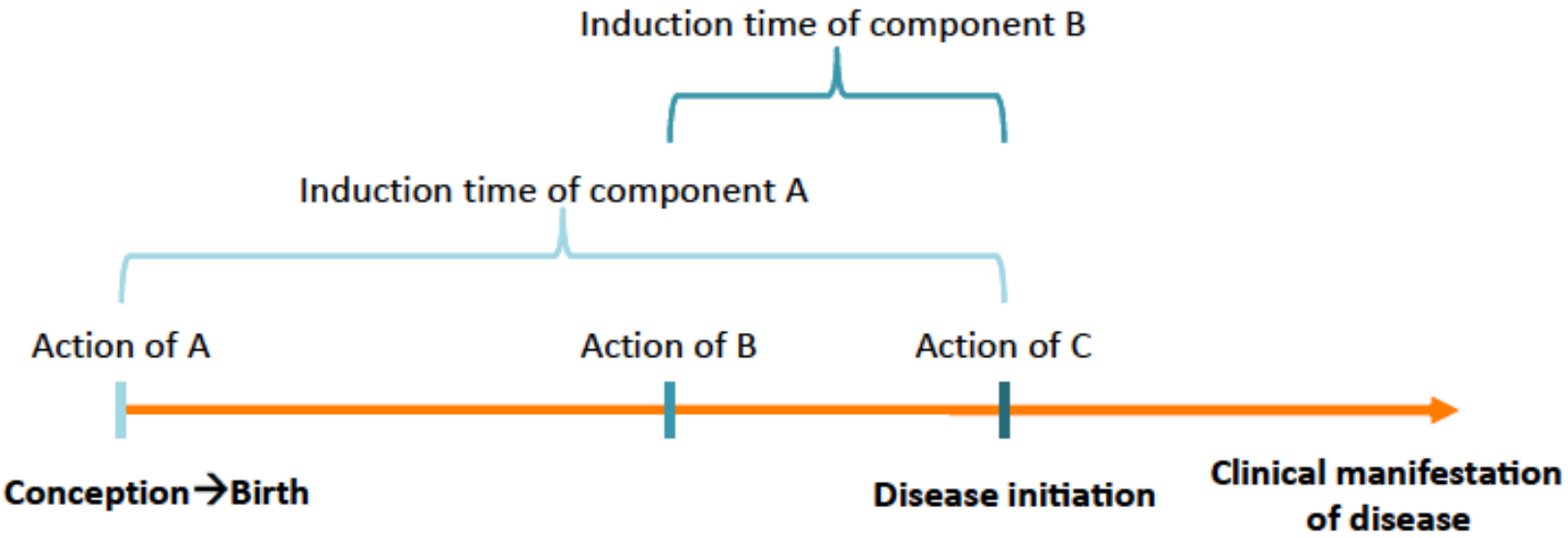
  e.g., the transition to a malignant cancer within a single cell marks the biologic onset of the cancer.

Induction Period

- Component causes can act at different time points.
- Disease occurs at the time the final component cause acts and the sufficient cause completed.
- The time period between the action of a single component cause and the completion of a sufficient cause, the occurrence of disease, is called the induction period.
- Early-acting component causes (“initiator”) have a long induction period and late-acting components (”promoter”) short induction period.

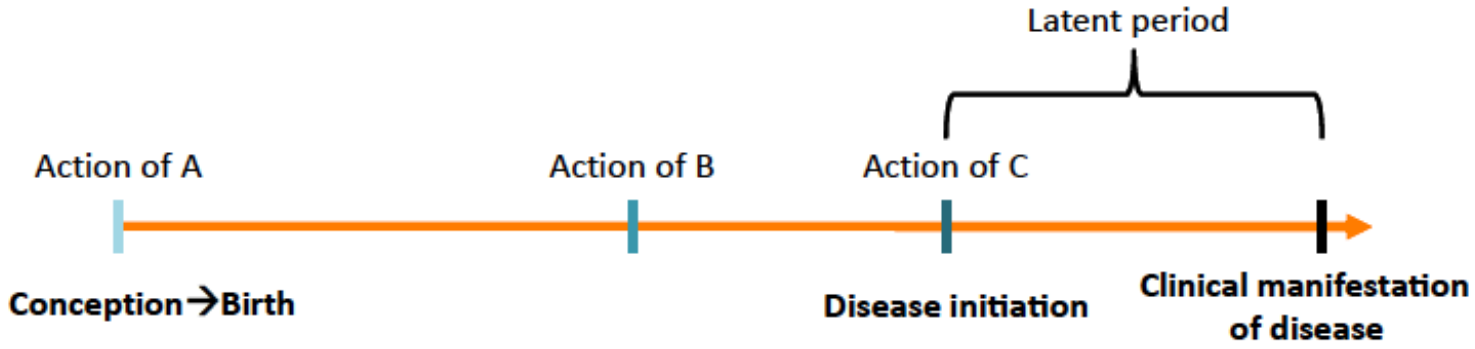
Induction time over the life course





Latent Period

The time interval between the action of the final component (marking disease occurrence) and the detection of disease is called the latent period



A. Koski, 2014

Counterfactual Model

"If this one experience or exposure did not happen to an individual, how would it impact that person's health outcome today?"

Of course, this is an impossible question to answer.

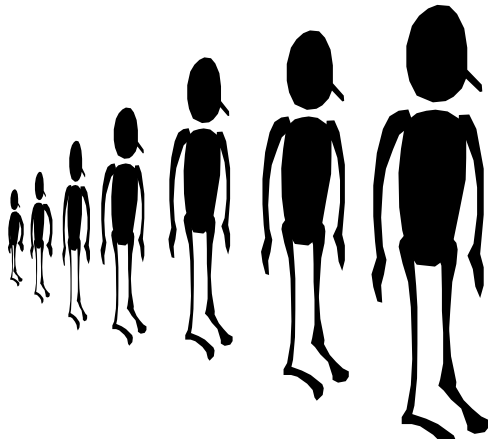
You can't observe the outcome for a *single* population under *two different* exposure conditions for the *exact same* period of time.

Counterfactual Model

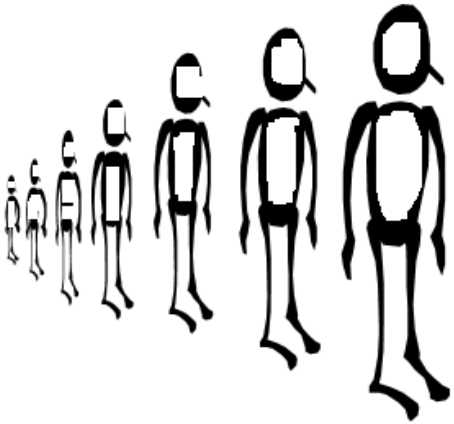
Treatment A is said to have a causal effect on an individual's outcome, Y, if the outcome had the individual been treated differs from the outcome had the individual not been treated:

$$Y^{A=1} \neq Y^{A=0}$$

Within the counterfactual model, individual causal effects are defined as a contrast of two outcome values, one observed (factual) and the other unobserved (counterfactual).

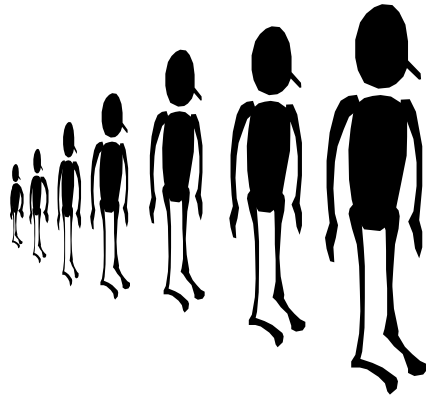


Exposed Group

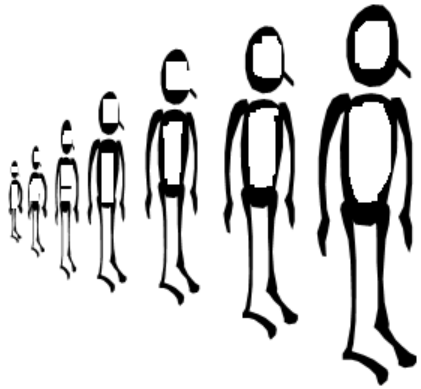


Counterfactual Group

Maldonado & Greenland, Int J Epi 2002;31:422-29

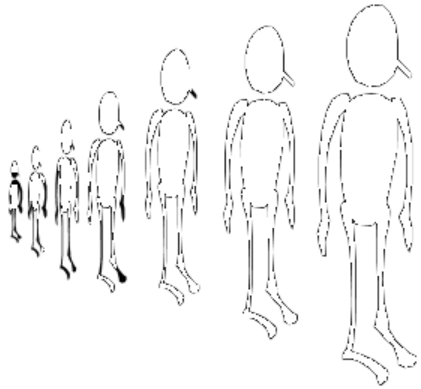


Exposed Group



Unexposed Group

(Counterfactual)



Unexposed group

(Substitute)

Causal Effects

A causal effect cannot be measured directly because counterfactuals are **unobservable**

- This is the fundamental problem of causal inference
- Must choose a substitute population for the counterfactual
  - Need this substitute to be as similar as possible to the observed population
- Validity of the estimates depends on the validity of the substitution

Assumption: Exchangeability

The substitutes used as comparison group are said to be **exchangeable** if their response to the exposure are the same the exposed [treated] group.

If we have exchangeable groups, the observed actual outcomes for the substitute control group will be **identical** to the unobserved, **potential outcomes** of the exposed group had they not been exposed.

Application

The counterfactual model provides a general framework for designing and analyzing etiologic studies.

- It pushes researchers to be very precise in their definition of treatment/exposure and the causal effect being estimated.
- Causes generally thought of as factors that can potentially be modified
- Makes assumptions explicit

Association

- Is the outcome more likely in people with a particular exposure?
- **Statistical relationship** between exposure and outcome
- Variables can be associated without a causal relationship

Causation

- A causal effect defines a comparison of the exposed and unexposed groups (one of which is hypothetical)
  - Assuming theoretically everyone is simultaneously treated and untreated
- The exposure produces the outcome

  Can be harmful e.g, exposure to asbestos

  Can be preventive e.g., not wearing a seatbelt

Null hypothesis significance testing

- Inferential approach for testing experimental factor against a hypothesis of no effect (null hypothesis) based available data
- "*p*-value is the probability under a specified statistical model that a statistical summary of the data (e.g., mean difference between groups) would be equal to or more extreme than its observed value
- P-value is a widely used metric to set a level of significance
  - If p-value <0.05=statistically significant result

This is incorrect → you cannot conclude there is no difference or no association because a p-value is >0.05

Example: side effects of NSAIDS

"results were statistically non-significant, one set of researchers concluded that exposure to the drugs was "not associated" with new-onset atrial fibrillation (the most common disturbance to heart rhythm) and that the results stood in contrast to those from an earlier study with a statistically significant outcome"

What were their results? Risk ratio = 1.20 (95% CI: 1.03-1.48; p=0.091)

Prior results? RR= 1.20 (95% CI: 1.03-1.33; p=0.0003)

Association

Contrast

Conflating effect size and sample size

- P-values conflate the magnitude of an effect with sample size and are thus uninformative
  - A very small effect ***can*** produce a small *p*-value if the sample size is large enough (high precision)
  - A large effect ***can*** produce large *p*-values if the sample size is small (low precision)
  - Identical estimated effects will have different *p*-values if the precision of the estimates differs.

Q: Why do so many colleges and grad schools teach $p = 0.05$?

A: Because that's still what the scientific community and journal editors use.

Q: Why do so many people still use $p = 0.05$?

A: Because that's what they were taught in college or grad school.

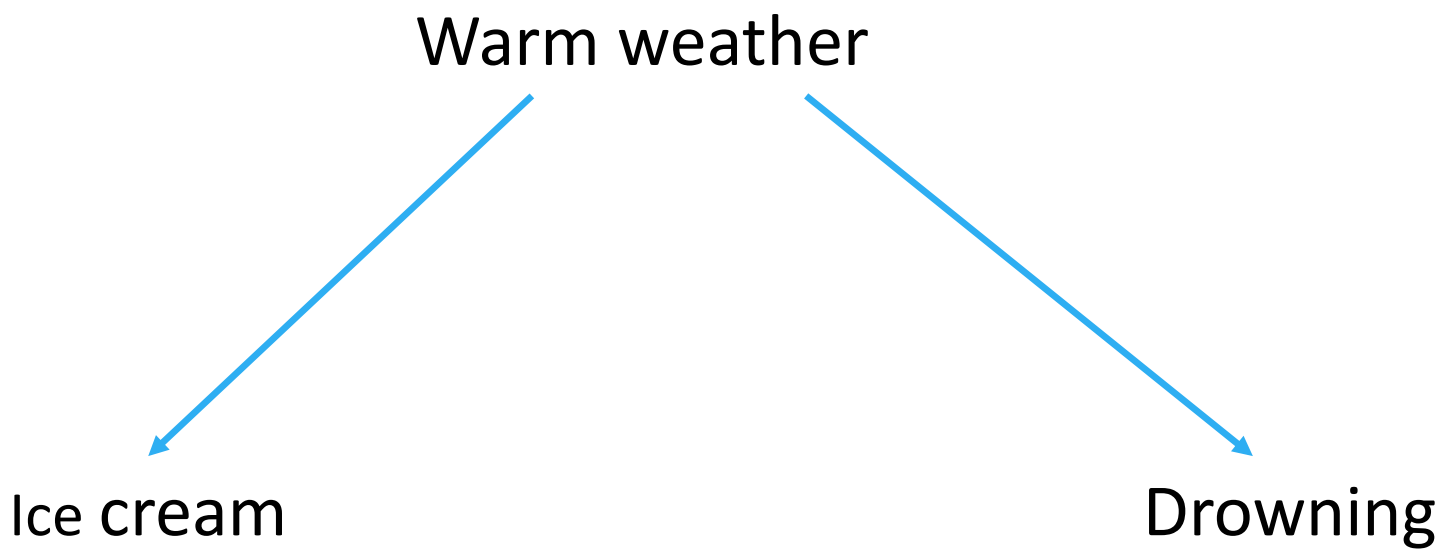
We teach it because it's what we do; we do it because it's what we teach."
-George Cobb

It's time for change!

Association ≠ causation

- Study reports relationship between ice cream and drowning deaths

Directed Acyclic Graphs



Non-causal associations

- 3rd variable "explains" the relationship between exposure and outcome
  - This variable is called a confounder

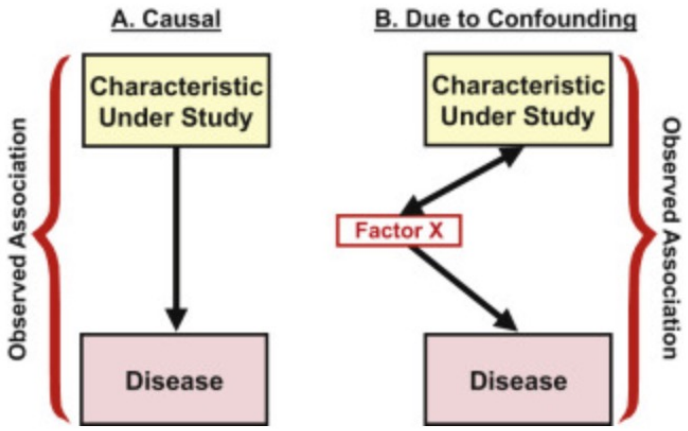


Fig. 14.4

Types of associations.

Example:
Coffee and Pancreatic Cancer

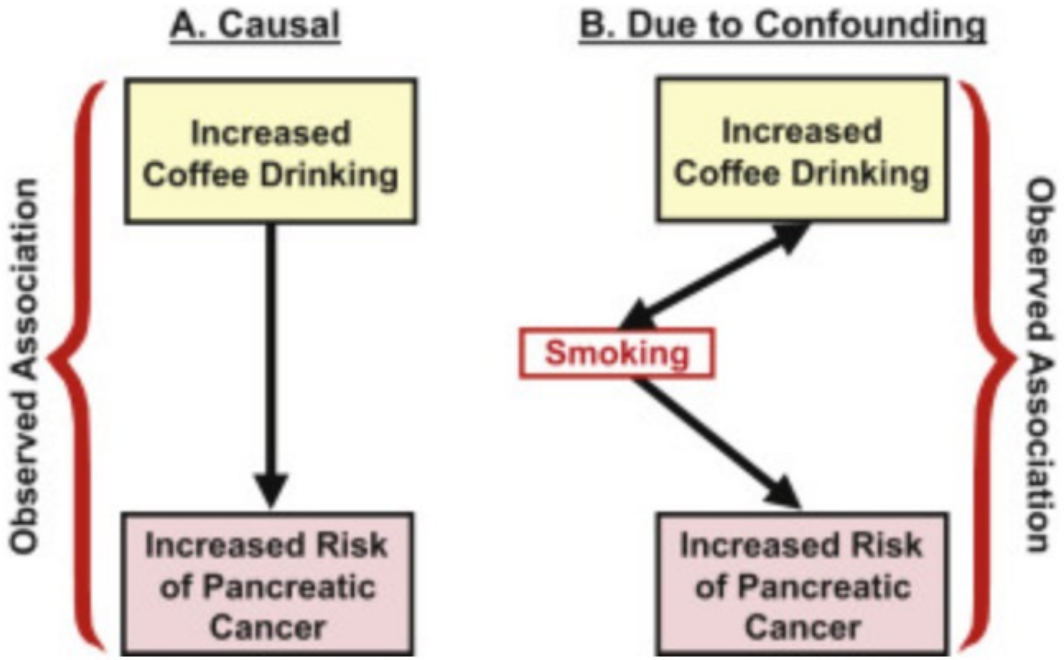


Fig. 14.5

Directed Acyclic Graphs (DAGs)

- Graphical representation of causal effects between variables
  - Arrows indicate a causal relationship
  - Absence of an arrow indicates no causal relationship

Situation 1: causal relationship between X and Y

Situation 2: no causal relationship between X and Y

X Y