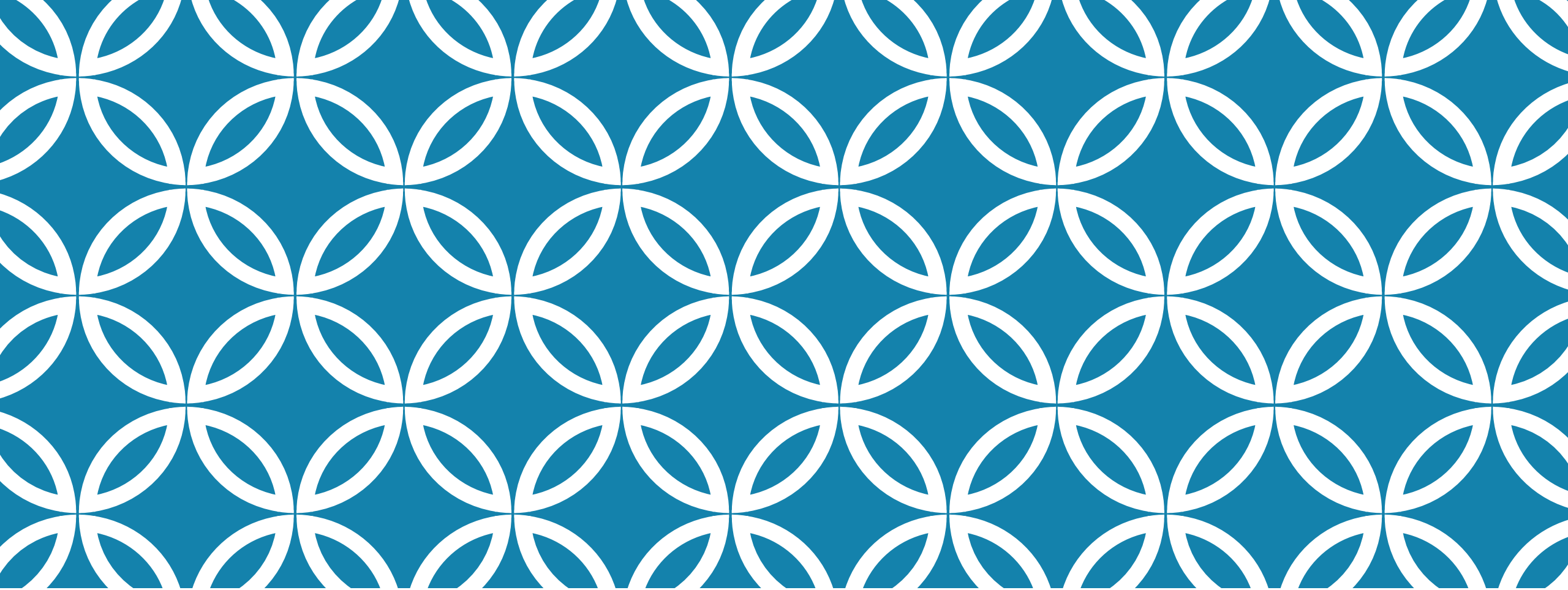


ASSOCIATION & CAUSATION

Dr. Jose Vincent

TWO TYPES OF ASSOCIATION: REAL AND SPURIOUS

A real association is present if

the probability of occurrence of an event depends upon the occurrence the other events.

Spurious associations refer to non-causal associations due to chance, bias, failure to control for extraneous variables (confounding), etc.

THE RELATIONSHIP BETWEEN COFFEE CONSUMPTION AND PANCREATIC CANCER

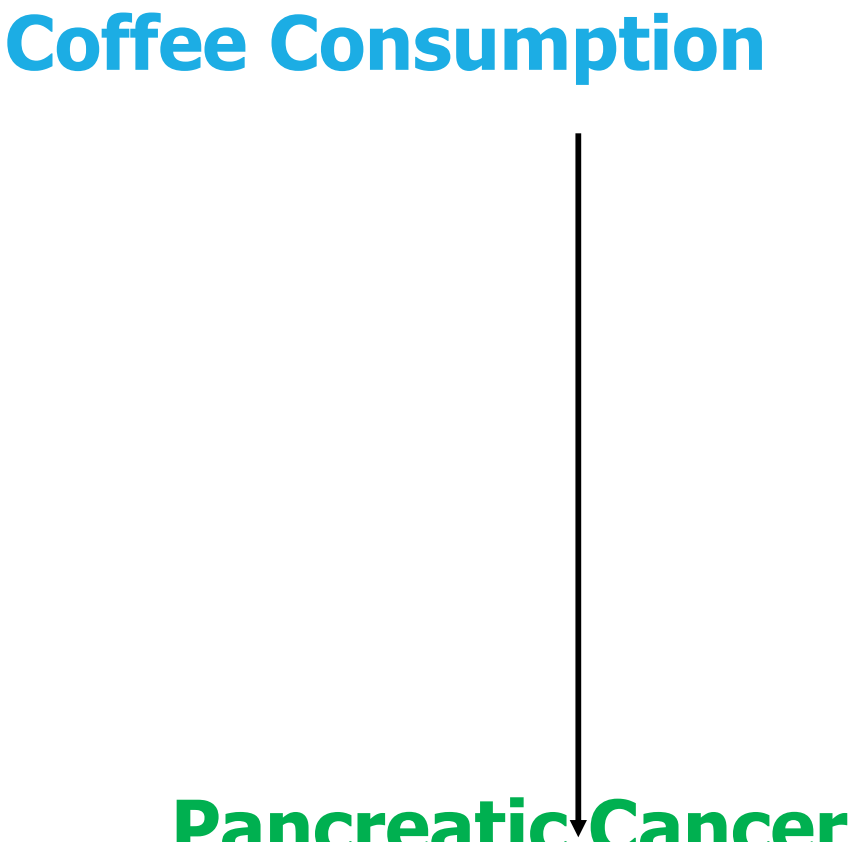
- In 1981, MacMahon et al. reported results from a case-control study of cancer of the pancreas.

- There was an apparent dose response relationship between **coffee consumption** and **cancer of the pancreas.**

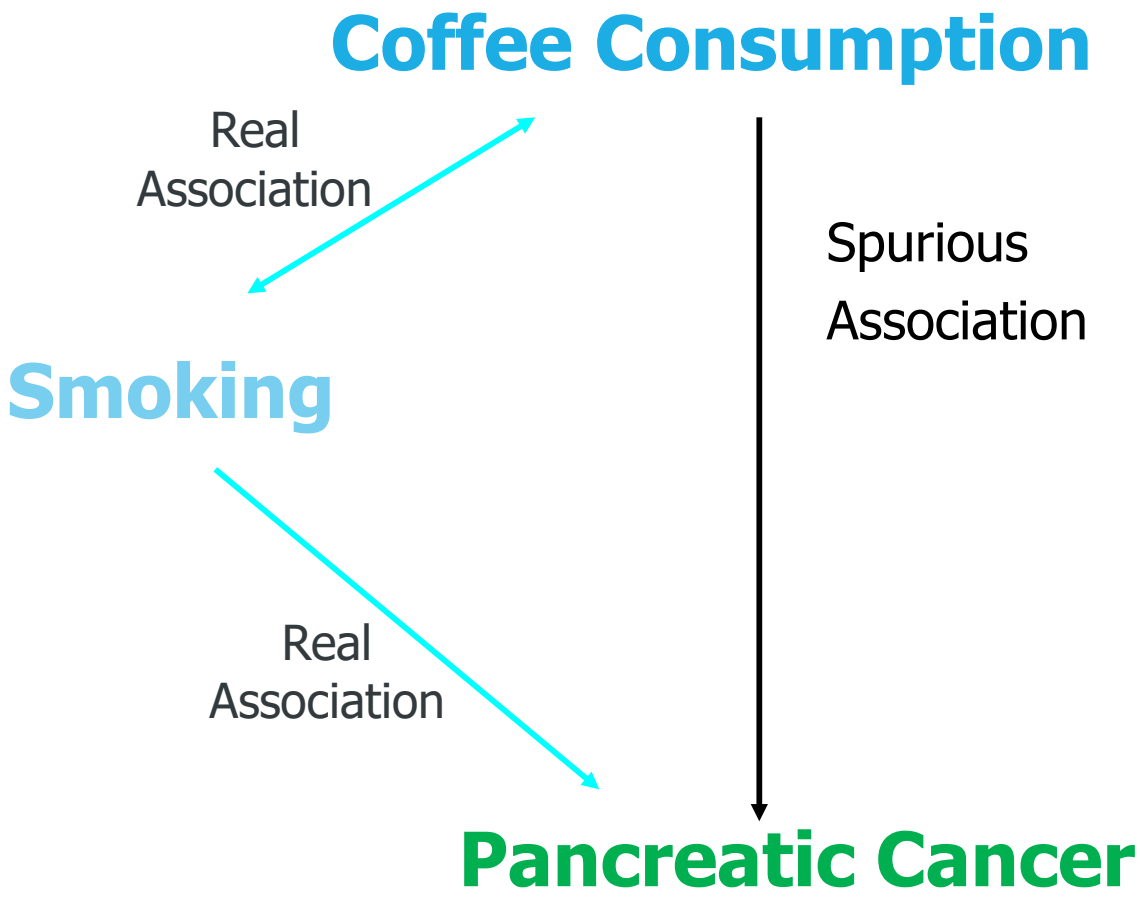
MacMahon B, et al. N Engl J Med 1981 304:630 - 33

Interpreting Associations - Causal and Non-Causal

Causal

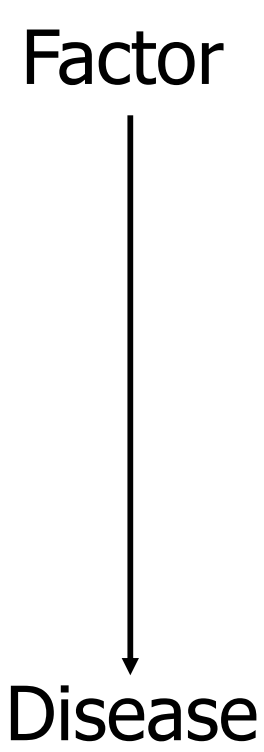


Non-Causal (due to confounding)

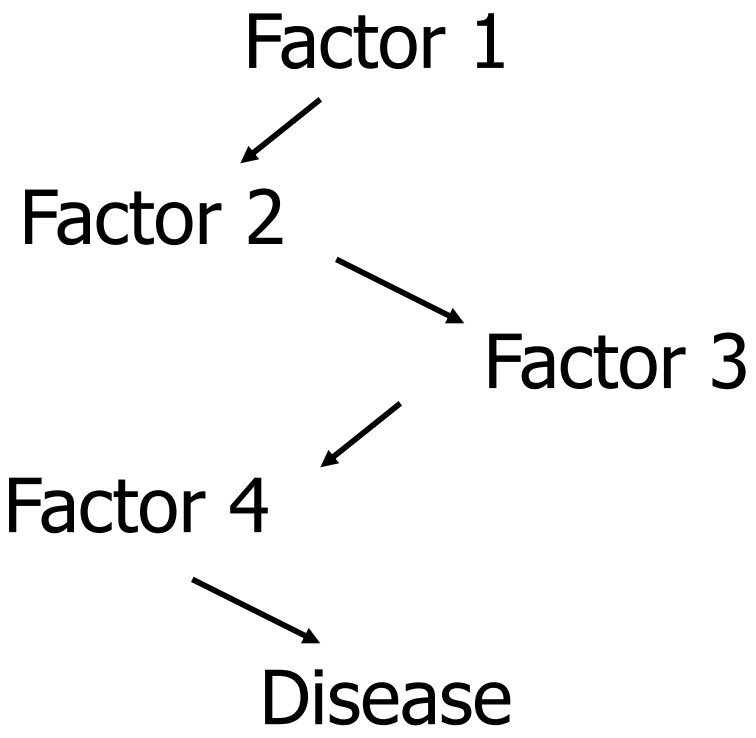


TYPES OF CAUSAL RELATIONSHIPS: DIRECT VS INDIRECT

Direct



Indirect



TYPES OF CAUSAL RELATIONSHIPS: DIRECT VS INDIRECT

Direct

ΔF508 Polymorphism

↓

Cystic Fibrosis

Indirect

Artery thickening

↓

Hemostatic factors

↓

Myocardial infarction

FOUR TYPES OF CAUSAL FACTORS

- Necessary and sufficient
  - Without factor, disease does not develop
  - Example: HIV

- Necessary but not sufficient
  - Example: Development of tuberculosis requires M. tuberculosis and other factors- immunosuppression.
  - Bacteria still necessary, but not sufficient to cause the disease

FOUR TYPES OF CAUSAL FACTORS

- Sufficient but not necessary
  - Factor can produce disease, but not necessary
  - Example: Both radiation exposure and exposure to benzene are sufficient to cause leukemia, but neither are necessary if the other present.
- Neither sufficient nor necessary
  - Complex models of disease etiology
  - Example: High fat diet and heart disease, hypertension, diabetes, certain kinds of cancer

UNDERSTANDING CAUSALITY

- Let's say you have determined:
  - there is a real association

- NOW have your proven CAUSALITY?

NINE GUIDELINES FOR JUDGING WHETHER AN ASSOCIATION IS CAUSAL

- Temporal relationship
- Strength of association
- Dose response relationship
- Replication of the findings
- Biologic plausibility
- Consideration of alternate explanations
- Cessation of exposure
- Specificity of the association
- Consistency with other knowledge

TEMPORAL RELATIONSHIP

- Exposure to the factor must have occurred before the disease developed.
- Easiest to establish in a cohort study
- Length of interval between exposure and disease very important
  - If the disease develops in a period of time too soon after exposure, the causal relationship is called into question.

Asbetos and Lung Cancer

Well - established temporal relationship

Asbestos — Latent period of 10 - 20 yrs — Lung Cancer

New Study

Asbestos — Latent period of 3 yrs — Lung Cancer

In this case, the latent period is not long enough for lung cancer to develop if caused by exposure.

STRENGTH OF ASSOCIATION

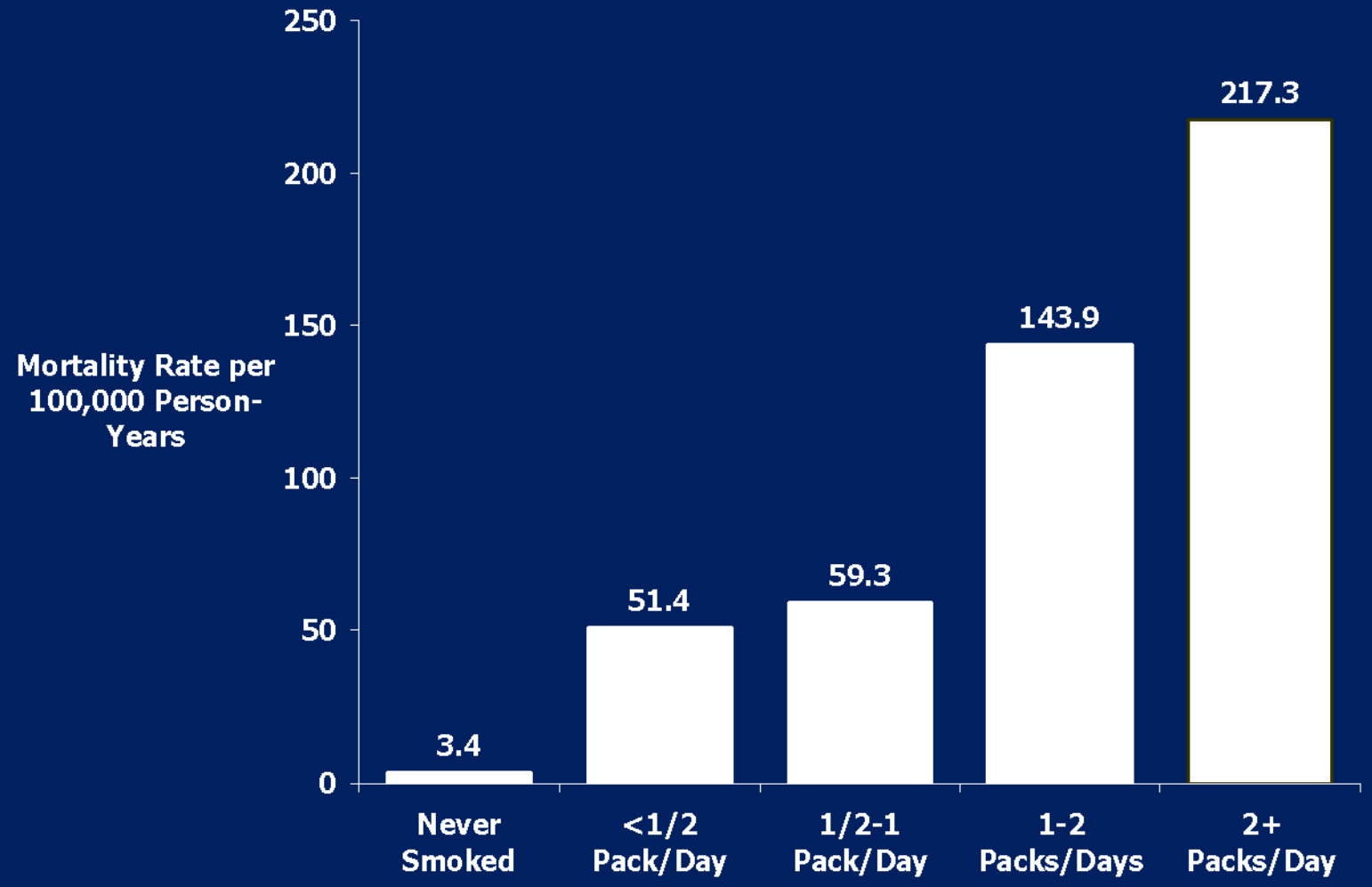
- The larger the relative risk or odds ratio, the higher the likelihood that the relationship is causal.

- However, care must be taken to examine confidence intervals and sample size.
  - For example, if the confidence interval is wide (e.g., 1.8 - 22.6), an OR of 12.0 is less strong because we are less confident of the strength of the odds ratio.

DOSE-RESPONSE RELATIONSHIP

- With increasing dose, there is increasing risk of disease.
- This is not considered necessary for a causal relationship, but does provide additional evidence that a causal relationship exists.

Figure 13-18. Age-standardized death rates due to well-established cases of bronchogenic carcinoma



Adapted from Hammond EC, Horn D: JAMA 166:1294-1308, 1958.)

REPLICATION OF THE FINDINGS

- If there is a true causal relationship between exposure and disease, the expectation is that we would see the association consistently in other (NOT necessarily all) subgroups of the population.

BIOLOGIC PLAUSIBILITY

- Consistency of epidemiologic plausibility with existing biologic knowledge.
- Requires knowledge of the biologic etiology of disease

CONSIDERATION OF ALTERNATE EXPLANATIONS

- If the investigators did not consider possible **confounders and effect modifiers**, the association is less likely to be causal.

- Requires a knowledge of the literature and known risk factors for the disease.

CESSATION OF EXPOSURE

- Upon elimination or reduction of exposure to the factor, the risk of disease declines.

- Example: Emphysema is not reversed with the cessation of smoking, but its progression is reduced.

SPECIFICITY OF THE ASSOCIATION

- The weakest of the criteria (should probably be eliminated)
- Specific exposure is associated with only one disease.
- This is used by tobacco companies to argue that smoking is not causal in lung cancer.
  - Smoking is associated with many diseases.
- If anything, may provide support for a causal relationship, but does not negate if not present.

CONSISTENCY WITH OTHER KNOWLEDGE

- If a relationship is causal, the findings should be consistent with other data.

- If lung cancer incidence increased as cigarette use was on the decline, we would have to be able to explain how this was consistent with a causal relationship (How?!?)

Associations are observed
Causation is inferred

It is important to remember that these criteria provide evidence for causal relationships.

All of the evidence must be considered and the criteria weighed against each other to infer the causal relationship.