ASSOCIATION & CAUSATION IN EPIDEMIOLOGICAL STUDIES

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Association and Causation

Which of these foods will stop cancer? (Not so fast)

- Cancer patients always ask what to eat to reduce their chances of dying from the disease.
- Diet messages are everywhere:
  - NCI: Eat 5 to 9 fruits and vegetables a Day for Better Health
  - Prostate Cancer Foundation has anticancer diet
- Will dietary changes make a difference.
- It is more difficult than expected to discover if diet affects cancer risk.
- Hypotheses are abundant, but convincing evidence remains elusive (hard to prove).

September 27, 2005 – New York Times - By GINA KOLATA

What is the question?

- Does the exposure lead to an increase (or decreased) risk of disease?
- Is the exposure causal (or protective)?
- Some problems:
  - We observe **associations**
  - We infer (guess, speculate, reach to a conclusion) **causes.**

Descriptive studies

↓

Identify disease problem in community

↓

Relate to environment & host factor

↓

Suggest an etiological hypothesis

↓

Analytical & experimental studies

↓

Test the hypothesis derived for observed **RELATIONSHIP** b/w suspected cause & disease

ASSOCIATION

- **Definition**: the concurrence of two variables more often than would be expected by chance.
- **Types of Associations:**

1. **Spurious Association**
2. **Indirect Association**
3. **Direct (causal) Association**
   1. **One to one causal association**
   2. **Multi-factorial causation**.

Association or not?

- A researcher in his observational study found that the average serum homocysteine among patients of IHD was 15 mcg/dl (Normal=10-12 mcg/dl)!

Implication

- Can we say that
  - Hyperhomocystenemia causes IHD?
- Hypothesize that
  - Hyperhomocystenemia **may** have a role in etiology of IHD.
- For final proof there has to be a ‘comparison’.
- Comparison would generate another summary measure which shows the extent of ‘Association’ or ‘Effect’ or ‘risk’ (RR, OR, P-value, AR)

Cause

- Cause defined as “anything producing an effect or a result”. [Webster]
- Cause in medical textbooks discussed under headings like- “**etiology**”, “**Pathogenesis**”, “**Mechanisms**”, “**Risk factors**”.
- Important to physician because it guides their approach to three clinical tasks- **Prevention, Diagnosis & Treatment.**

Etiology of a disease

- ✓ **The sum of all factors contribute to the occurrence of a disease**

- ✓ **Agent factors +Host factors +Environmental factors = Etiology of a disease**

- ✓ **The factor which can be modified, interrupted or nullified is most important.**

Factors for disease causation

- **Sufficient factors**: one that inevitably produces disease (the presence of the factor always result in disease).

  Example: Rabies virus for rabies

- **Necessary factors**: without which disease does not occur, but by itself, it is not sufficient to cause disease (the disease will not occur without the presence of the factor)

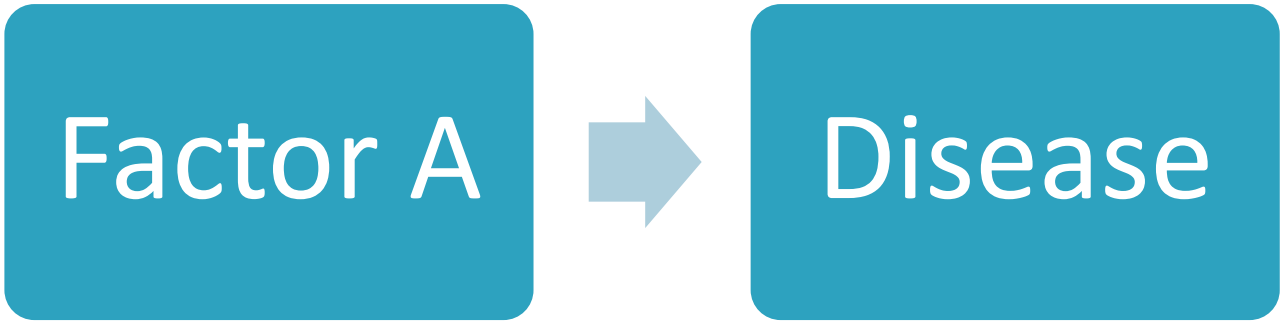
  Example: Mycobacterium TB for TB

Types of Causal Relationships

- **Four types possible:**
  - Necessary & sufficient
  - Necessary, but not sufficient
  - Sufficient, but not Necessary
  - Neither Sufficient nor Necessary

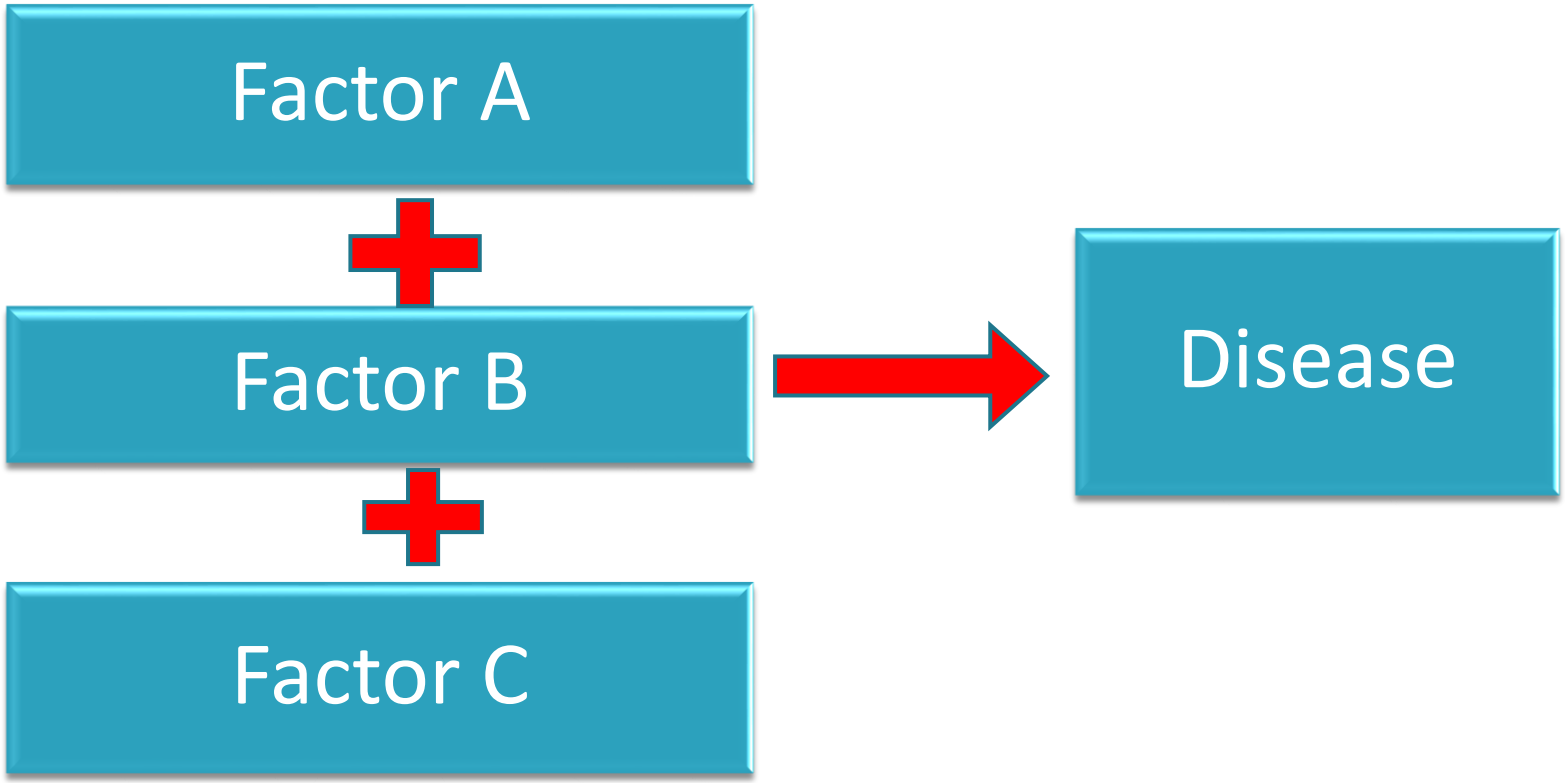
I. Necessary & Sufficient

- Without that factor, the disease never develops (factor is necessary)
- and in presence of that factor, the disease always develops (factor is sufficient).
- Rare situation.



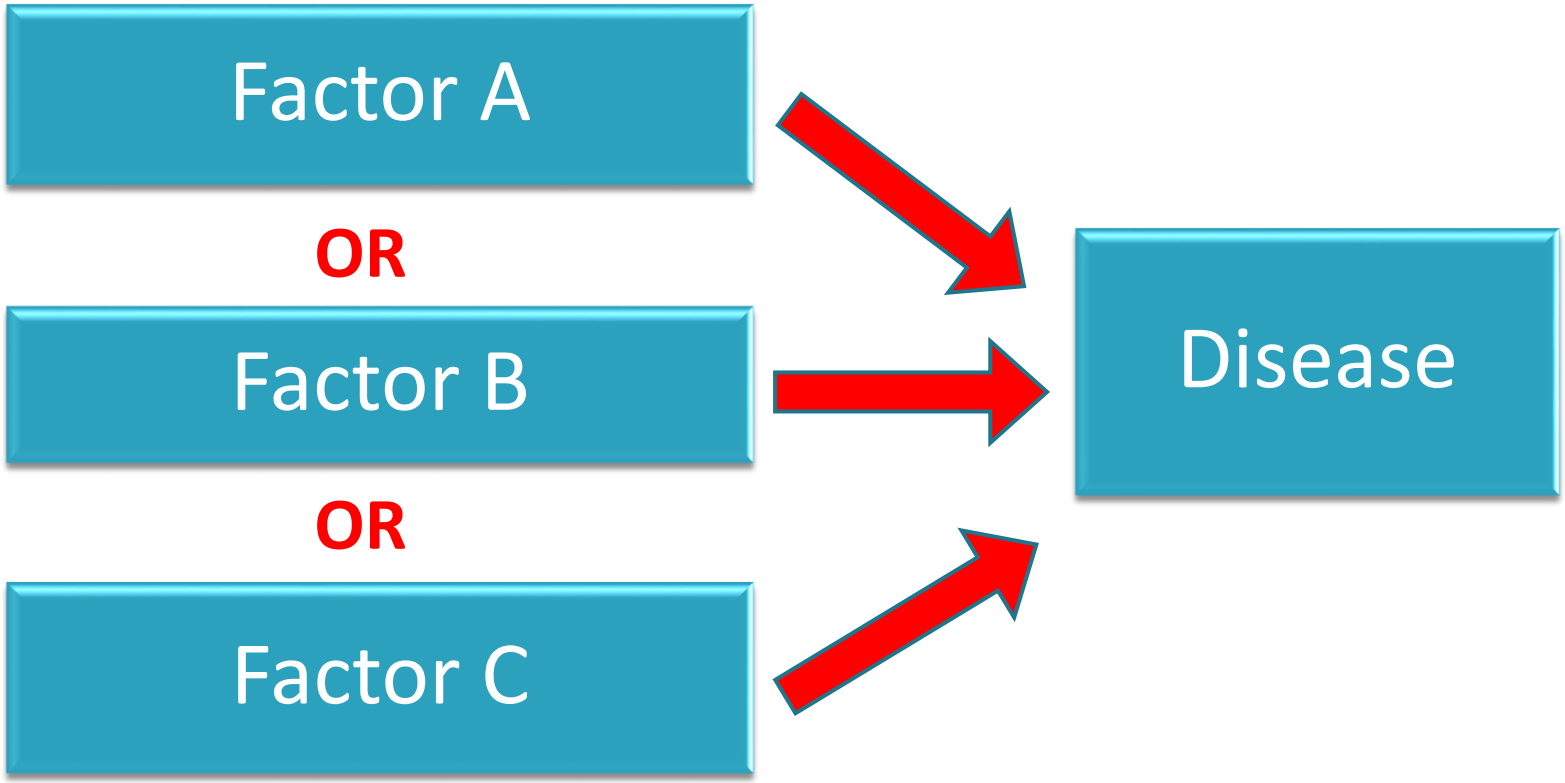
II. Necessary, but not Sufficient

- Multiple factors are required, often in specific temporal sequence (cancer, initiator then promoter)



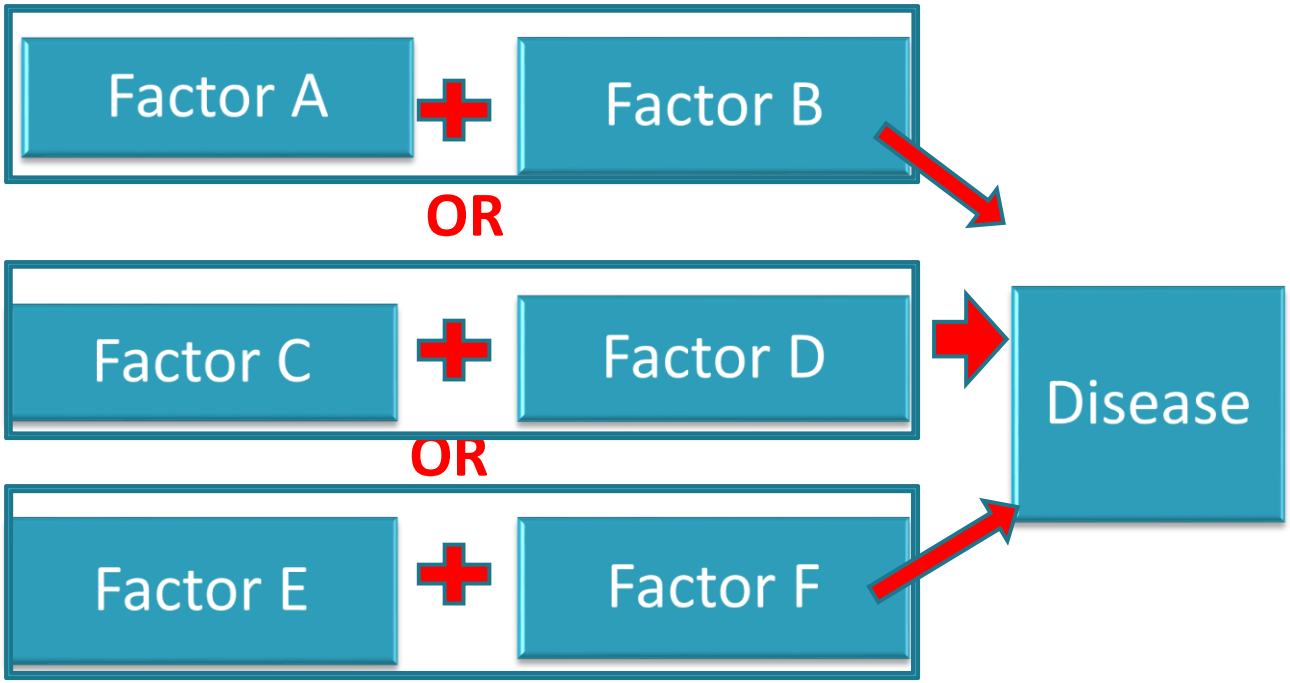
III. Sufficient, but not Necessary

- Factors independently can produce the disease.
- Either radiation or benzene exposure can each produce leukemia without the presence of the other.



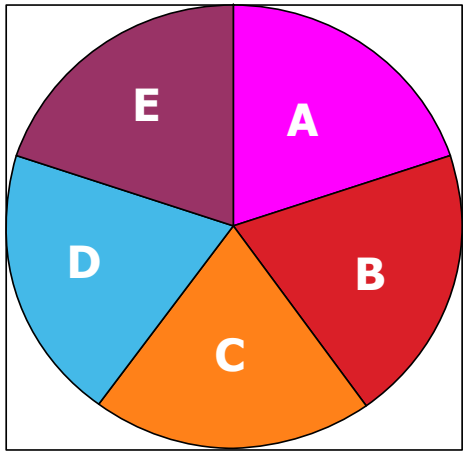
IV. Neither sufficient nor Necessary

- More complex model.
- Probably most accurately represents causal relationships that operate in most chronic diseases

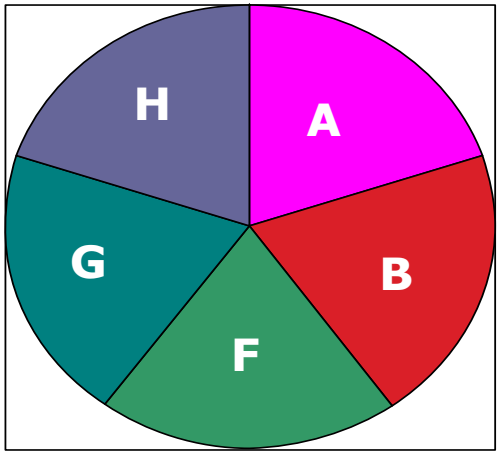


Necessary / Sufficient

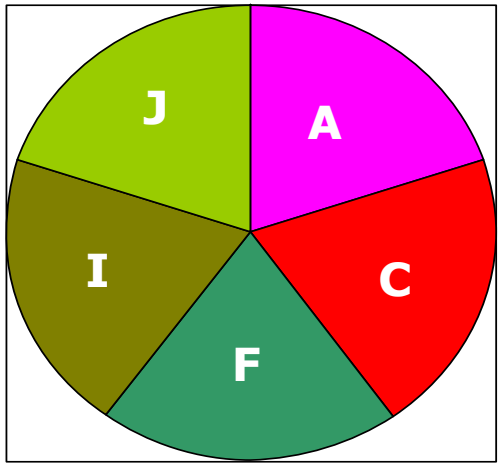
Disease Not Present



Disease Present



Disease Present

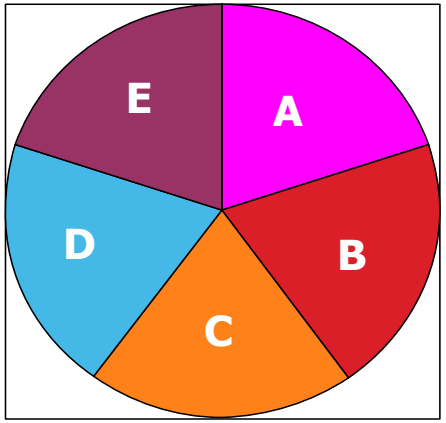


"A" is necessary – it appears in each sufficient causal complex

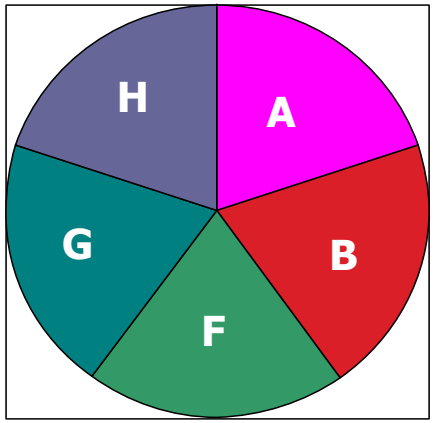
"A" is not sufficient –

Alternate Sufficient Sets for Breast Cancer

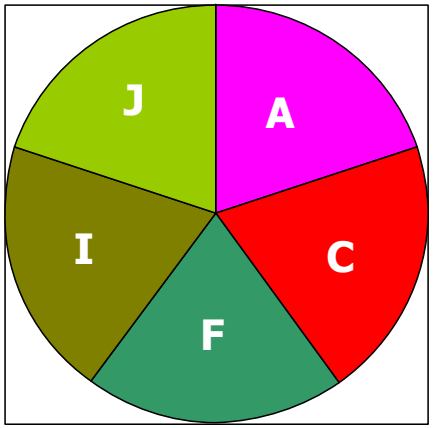
No Breast Cancer



Breast Cancer Present
- Hereditary Set



Breast Cancer Present
- Non Hereditary Set



- Only women with “A” and “F” causal components develop breast cancer
- “A” could be an environmental component that unless is present with “F”, a host susceptibility component, does not cause disease
- In the Hereditary Set, components such as BRCA1 and/or BRCA2 mutations are present
- In the Non Hereditary Set, other environmental or host factors are present.

Example….

- A researcher in his observational study found the presence of *Helicobacter pylori in* patients of duodenal ulcer!

- **Can we say that**
  - H.pylori causes duodenal ulcers?
- **Hypothesize that**
  - H.pylori **may** have a role in etiology of duodenal ulcers.
- For final proof there has to be a ‘comparison’.
- Comparison would generate another summary measure which shows the extent of ‘Association’ or ‘Effect’ or ‘risk’

Process of establishing a “Cause & Effect” or “Exposure & Outcome” relationship

- Needs a research on the lines of ‘hypothesis testing’
- final establishment of an “exposure - outcome” relationship consists of a sequence of steps as follows :
- **Step 1**: ensure that the results of the study are accurate and not “spurious”.
  - Correct methods?
  - Validity, reliability preserved?
  - Bias?

Process of establishing a “Cause & Effect” or “Exposure & Outcome” relationship

- **Step 2a:** do statistical results indicate association?- p value/ 95% CI.
- **Step 2b**: if not significant p value, may be b/c of low power of the study (smaller sample size)-

  The investigator should suggest additional studies using large sample (or else, a ‘meta - analysis’ type of study), rather than straightaway dismissing the ‘exposure - outcome’ association as non - causal.

Process of establishing a “Cause & Effect” or “Exposure & Outcome” relationship

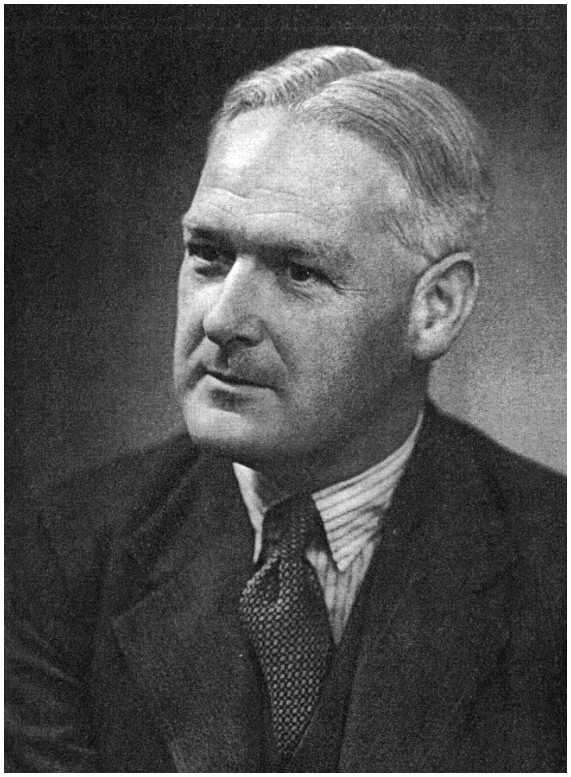
- **Step 3**: if statistically significant –evaluate as to whether this relationship is due to ‘indirect relationship’ with a third variable (confounder).

Process of establishing a “Cause & Effect” or “Exposure & Outcome” relationship

- **Step 4**: if confounder excluded- now test this postulated “causal” relationship on the following **criteria of “causal association**”

Sir Austin Bradford Hill, 1965

- *In what circumstances can we pass from [an] observed association to a verdict of causation? Upon what basis should we proceed to do so?*



Guidelines for judging whether an association is causal

Sir Austin Bradford Hill criteria

- **Most Important criteria**
  1. **Temporality:** cause precedes effect
  2. **Strength of association**: large relative risk
  3. **Consistency**: repeatedly observed by different persons, in different places, circumstances, and times

Guidelines for judging whether an association is causal

- **Additional supportive criteria**
  4. **Biological gradient (dose response):** larger exposures to cause associated with higher rates of disease. And reduction in exposure is followed by lower rates of disease (reversibility).
  5. **Biological plausibility**: makes sense, according to biologic knowledge of the time.
  6. **Experimental evidence.**
  7. **Other criteria: Analogy** (cause & effect relationship already established for a similar exposure or disease), **specificity** (one cause lead to one effect) and **coherence**.

1. Strength of association

- Definition:
  - The larger the magnitude of association the more likely the exposure affects the risk of developing the disease.
- Why Important?:
  - Quantify how much the exposure increases the risk of disease. The larger the risk – the less chance of errors
- Epidemiologic Measures:
  - Risk ratios, risk differences
- Example:
  - RR of lung cancer in smokers vs. non-smokers = 9
  - RR of lung cancer in heavy vs. light smokers = 20
  - Mortality from scrotal caner among chimney sweeps compared to others = 200

2. Consistency

- Definition: The association is observed repeatedly in different persons, places, times, and circumstances.
- Why Important? If association is observed under different circumstances, with different samples and study designs, the more likely it is to be causal.
  - **Smoking associated with lung cancer in 29 retrospective and 7 prospective studies (Hill, 1965)**

3. Specificity

- Definition: The extent to which one exposure is associated with one outcome or disease.
- Why important?: Be certain that you identify the particular agent, or cause, that results in a particular outcome.

3. Specificity

- A single factor can cause several diseases (e.g., smoking associated with increased risk of lung cancer, small birth weight babies, etc.).
- Also, a single disease can be caused by many factors (e.g., heart disease).
- Bradford-Hill: Specificity should be used as evidence in favor of causality, not as refutation against it.
- **Example:**
  - Smoking associated with lung cancer, as well as other conditions (lack of specificity)
  - Lung cancer results from smoking, as well as other exposures.

4. Temporality

- Definition: The factor that is hypothesized to cause the disease must precede it in time.
- Why important?: A factor can co-occur with a disease and not cause it. In some cases, a factor might actually result from a disease.
- R.E. Epidemiology: Study design: Prospective cohort studies designed so that we know the exposure precedes the outcome.

5. Biological Gradient

- Definition: A "Dose Response" association. Persons who are exposed to greater amounts of a risk factor show increasingly higher "rates" of disease.
- A dose-response relationship provides support for causality, but the lack of this relationship does not mean lack of causality.
- **Example:**
  - Lung cancer death rates rise with the number of cigarettes/day smoked.
  - The 16 year risk of colon cancer was similar among women in each of the 5 levels of dietary fiber intake, from lowest to highest (Fuchs et al.,1999).

6. Biological Plausibility

- Definition: Knowledge of biological (or social) model or mechanism that explains the cause-effect association.
- Epidemiologic studies often identify cause-effect relationships before a biological mechanism is identified
  - E.g. In the mid 19th century when a clinician recommended hand washing by medical students & teachers before attending obstetric units, his recommendations were dismissed by medical fraternity as "doesn't stand to reasoning"
  - E.g., John Snow and cholera; thalidomide and limb reduction defects).

Bradford-Hill noted that biological plausibility cannot be "demanded".

7. Coherence

- Coherence - On the other hand, 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.

8. Experiment

- Definition: Investigator-initiated intervention that tests whether modifying the exposure through prevention, treatment, or removal, results in less disease.
- Why Important?: Most epidemiologic studies are observational.
- RE. Epidemiology: Randomized clinical trials are closest to experiments in epidemiology.

9. Analogy

- Definition: Has a similar cause-effect association been observed with another exposure and/or disease?
- Why Important?: Important for generating hypotheses for the cause of newly-observed syndromes.

From Association to Causation