

# **Traditional Approaches: Koch's Postulates and the Austin Bradford Hill Criteria for Causality**

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## How Events Can Be Related

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- **Not statistically associated (independent)**
- **Statistically associated**
  - **Noncausally (secondarily) associated**
  - **Causally associated**
    - **indirectly associated**
    - **directly associated**

## Association vs. Causation

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- **Association** refers to statistical dependence between two variables, ie., the degree to which the rate of disease in persons with a specific exposure is either higher or lower than the rate of disease among those without the exposure.
- But the presence of an association in no way implies the observed relationship is one of cause and effect.
- A **causal association** is one in which a change in the frequency or quality of the exposure or characteristic results in a corresponding change in the frequency of the disease or outcome of interest.

## Association vs. Causation

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- **Assessing causality is neither simple or straightforward**
- **Requires a judgment based on the totality of evidence, of which the result of any single study is only a component**
- **Chain of logic, which involves two questions:**
  1. **Is there a valid statistical association in this study?**
  2. **Can this valid association be judged to be one of cause and effect?**

# Framework for the Interpretation of an Epidemiologic Study

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## I. Is there a valid statistical association?

- Is the association likely to be due to chance?
- Is the association likely to be due to bias?
- Is the association likely to be due to confounding?

## II. Can this valid statistical association be judged to be one of cause and effect?

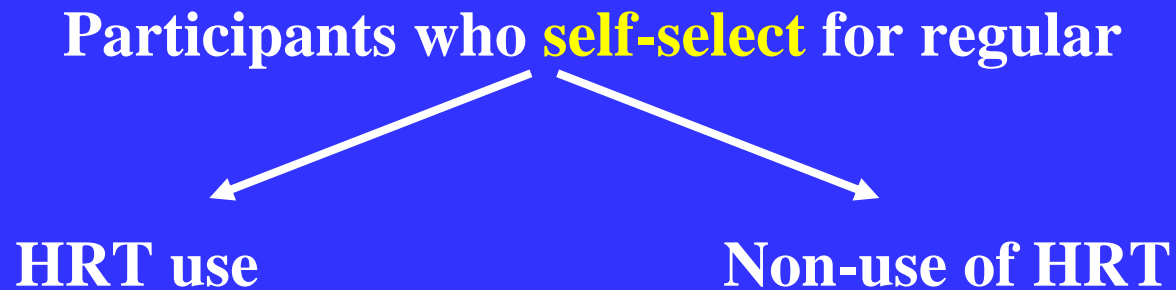
- Need the presence of positive criteria beyond the one study.

# What is an Observational Study?

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In an observational study, such as a cohort study:



are followed over time to see how many develop disease in one group compared to the other group.

## Limitations of Observational Studies of HRT

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- Women who take hormones for an extended time differ from those who don't take hormones in many ways besides hormone use.
- In observational studies, estrogen users were leaner, less likely to smoke, more physically active, more likely to see doctors regularly, and more educated.

*These inherent differences could explain the lower rates of heart disease among hormone users in observational studies.*

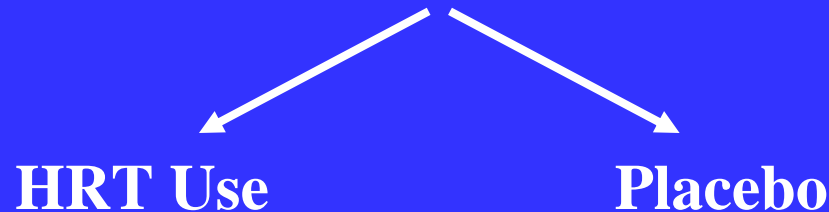
# What Is A Clinical Trial?

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In a randomized, placebo-controlled clinical trial:

Participants who are eligible are **randomly assigned** to:



They are followed over time to see how many develop disease in one group compared to the other group.

*Hormone takers are similar to placebo takers in lifestyle factors, medical and family history and other factors.  
Design will minimize bias and confounding.*

# Historical Development of Theories of Disease Causation

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- Ancient times, illness occurred because of divine retribution for committing sins.
- 4th century BC, Hippocrates introduced idea of imbalance of four body humors (phlegm, yellow bile, blood and black bile) - but also hypothesized imbalances caused by changes in season, air, winds, water and stars, as well as personal habits.
- Mid 1800s, Pasteur, Berkeley and others introduced the germ theory of disease, that specific transmissible pathogens are responsible for disease.

# Historical Development of Theories of Disease Causation

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- Mid to late 1800s, Henle and Koch developed postulates based on germ theory
  1. the microorganism will occur in every case of the disease and can explain the pathology and clinical changes associated with the disease (specificity)
  2. the microorganism must be shown to be distinct from any others that might be found with the disease.
  3. if the microorganism is isolated and repeatedly grown in culture, it will induce a new case of disease in a susceptible animal.

# Historical Development of Theories of Disease Causation

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- Henle and Koch did not consider these rigid criteria for causation
- Issue of specificity works better for infectious diseases than noninfectious diseases (“Aetiology: Koch’s postulates fulfilled for SARS virus”, *Nature* 2004).
- In 1960, concept of “web of causation” emerged in response to chronic diseases, which suggested that occurrence could be explained by many interconnected factors, including host and environment. Fundamental shift incorporating the idea of multiple causes of disease with the possibility of prevention at multiple steps, ie., that don’t need a primary cause or to know the most important or direct of the causal factors.

# Historical Development of Theories of Disease Causation

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- In the 1950s/1960s, new set of criteria proposed, in response to the process of the judgment of causation for smoking and lung cancer in the 1964 Surgeon General's Report.
- Sir Austin Bradford Hill's criteria for assessing causation:
  - Strength of the association
  - Consistency
  - Specificity
  - Temporality
  - Biological gradient
  - Plausibility
  - Coherence
  - Experiment
  - Analogy

# Historical Development of Theories of Disease Causation

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- Like Koch, Hill did not intend these to be used as rigid criteria, rather as guidelines:

“Here then are nine different viewpoints from all of which we should study association before we cry causation . . . None of my nine viewpoints can bring indisputable evidence for or against the case-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or lesser strength, is to help us make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

Hill AB. The environment and disease: association or causation? *Proc Royal Soc Med.* 1965; 48:295-300

# Hill's Criteria for Assessing Causation

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## 1. Strength of the association

- large associations are more likely to be causal: less likely to be accounted for entirely by alternative explanations such as bias and confounding
- but small associations can be causal; just harder to rule out alternative explanations

## 2. Consistency

- judgment of causation enhanced when different investigators using different methodologies in different populations are all seeing similar results: less likely to be all due to error or artifact
- but absence of consistency does not preclude causation, if reasonable explanation for differing study results

### **3. Specificity**

- a cause should lead to a single effect, and vice versa
- so many well-known exceptions that lack of specificity is not considered an argument against causality

### **4. Temporality**

- the cause must precede the disease
- little disagreement, and one basis for prospective cohort studies being felt to provide stronger evidence on causality than case-control studies

### **5. Biological Gradient (ie., dose-response)**

- association more likely to be causal if its strength increases as exposure level increases
- but could be a “threshold effect”; could be curvilinear relationship; could be inability to accurately ascertain exposure level

## **6. Plausibility (ie., biologic credibility)**

- should be existing biologic or social mechanistic model to explain the association
- but could just be beyond our biologic knowledge at this point in time; may require interdisciplinary research

## **7. Coherence (ie., consonance with existing knowledge)**

- related to plausibility; cause-effect interpretation should not conflict with known facts about the natural history of the disease (e.g., temporal pattern, histopathology, animal findings)
- but lack of such evidence doesn't nullify the epidemiologic observations (e.g., species)

## **8. Experiment**

- not a guideline; rather a method for testing a specific causal hypothesis
- if available, well designed and conducted experimental studies provide strong evidence for or against causation - but for the specific, often limited, question that was tested
- but when infeasible and/or unethical to conduct, leaves observational studies to provide most of the data for judging whether association is causal

## **9. Analogy**

- use analogies or similarities between the observed association and other associations
- depends on depth of knowledge at a given time point

## Positive Criteria for Assessing Causality

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- Which are used by epidemiologists today?
  - Weed and Gorelic published in 1996 (*Cancer Epidemiol Biomarkers Prev*) a review of review papers of alcohol and breast cancer: found that investigators selectively used guidelines, excluding some, and altering others. Most commonly considered: bias and confounding; consistency, strength of association, biologic plausibility, and biologic gradient.

# Framework for the Interpretation of an Epidemiologic Study

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## I. Is there a valid statistical association?

- Is the association likely to be due to chance?
- Is the association likely to be due to bias?
- Is the association likely to be due to confounding?

## II. Can this valid statistical association be judged to be one of cause and effect?

- Is there a strong association?
- Is there consistency with other studies?
- Is the time sequence compatible?
- Is there biologic credibility to the hypothesis?
- Is there evidence of a dose-response relationship?

## **Positive Criteria for Assessing Causality**

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- **Weed and Gorelic found that none of the papers claimed causation, but many of the authors made public health recommendations for or against changes in policy or practice.**

## Need for Action . . .

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- In epidemiologic research, causation remains a matter of belief or judgment based on all available evidence. It is neither easy nor objective, and differences of opinion are common. Caution is required.
- But, when does it become prudent to act at a given point in time on the premise that a causal relationship exists rather than await further evidence, knowing that this may precede by years a complete understanding of the disease or its mechanism.
- How do we balance not inappropriately concluding that a trial is not needed because the data are sufficient from the observational studies, versus a trial is not needed because the data from the observational studies are not sufficient to justify.
- How do we safely move forward?

# Summary

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## Framework for assessing statistical association and cause-effect relationships in epidemiology

### A. Is there a valid statistical association?

1. Chance
2. Bias
3. Confounding

### B. If there is a valid statistical association, is it one of cause and effect? Positive criteria:

1. Strength of association
2. Totality of evidence
3. Biologic credibility
4. Dose-response

### C. Generalizability, clinical implications, message

**“All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. This does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. Who knows, asked Robert Browning, but that the world might end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.”**

**(A. Bradford Hill, 1965)**