

# ERIC Notebook

Sept/Oct 2001

Issue 19



Michel Ibrahim, MD, PhD  
Director of Education  
Program

Lorraine Alexander, DrPH

Carl Shy, MD, DrPH

Sandra Deming, MPH  
Graduate Research Asst.

[www.sph.unc.edu/courses/eric](http://www.sph.unc.edu/courses/eric)



Ron Horner, PhD  
ERIC Director

Beth Armstrong,  
ERIC program manager

<http://hsrd.durham.med.va.gov/ERIC/>

The ERIC Notebook is funded by the Department of Veterans Affairs (DVA), Veterans Health Administration (VHA), Cooperative Studies Program (CSP), to promote the strategic growth of the epidemiologic capacity of the DVA.

## Causality

The primary goal of the epidemiologist is to identify those factors that have a causal impact on disease development, thereby providing a target for prevention and intervention. At first glance, causality may appear to be a relatively simple concept to define. However, adequately distinguishing causal agents from non-causal agents is not an easy task, from an epidemiological perspective. Unfortunately, there is no elementary parameter that can be measured to provide a definitive answer when determining causality. Rather, there is a series of criteria that have been developed and refined over the years that now serve as the guideline for causal inference. The most important point to remember is that causality is not determined by any one factor; rather it is a conclusion built on the preponderance of the evidence.

Hill (1965) is credited with identifying the nine factors that constitute the current standard for determining causality. In his article, Hill expanded upon criteria that had previously been set forth in the report *Smoking and Health* (1964) by the United States Surgeon General. Below is a discussion of the nine criteria defined by Hill to be utilized in the determination of causality.

### Criteria for determining causality

#### **Strength of Association:**

Strength of association between the exposure of interest and the outcome is most commonly measured via relative risks and odds ratios. Hill believed that causal relationships were more likely to demonstrate strong associations than were non-causal agents. The relationship between smoking and lung cancer is a perfect example where the odds ratios and relative risks are in the 20 to 40 range when comparing smokers to non-smokers. However, OR's and RR's that suggest weak associations should not be taken as an indication of non-causality. This is particularly true when the outcome of interest is

common. An example of a common outcome that exhibits a weak association with smoking is cardiovascular disease (CV). Yet even with a weak association, evidence supports the casual nature between smoking and the development of CV disease. Furthermore, one should not assume that a strong association alone is indicative of causality, as the presence of strong confounding may erroneously lead to a strong causal association.

#### **Consistency of Data:**

This tenant refers to the reproducibility of results in various populations and situations. Consistency is generally used to rule out other explanations for the development of a given outcome. It should also be noted that a lack of consistency does not negate a causal association as some causal agents act only in the presence of other co-factors. In general, the greater the consistency among the data, the more likely a causal association.

#### **Specificity:**

For causality, specificity can be thought of as a single exposure or agent before responsible for a single outcome. However, this criterion has been proven to be invalid in a number of instances, with smoking being the primary example. Evidence clearly demonstrates that smoking does not lead solely to lung carcinogenesis, but to a myriad of other clinical disorders ranging from emphysema to heart disease. Additionally, there are more than one causes of lung cancer. There are certain situations where this 1 to 1 relationship exists, such as with certain bacterium and the disease they cause which is strongly suggestive of a causal influence. Tuberculosis is a good example. However, the lack of specificity should not be taken as evidence against causality.

**Temporality:**

This criterion has been identified as being the most likely to be the *sine qua non* for causality. For an agent to be causal, its presence must precede the development of the outcome. Lack of temporality rules out causality. An example found in the literature is the relationship between atrial fibrillation (AF) and pulmonary embolism. Current wisdom supports that pulmonary embolism causes atrial fibrillation, however more recent evidence and plausible biological hypothesis suggest that the reverse could be true. Determining the proper course of care may hinge upon discovering if pulmonary emboli can indeed precede and thus perhaps cause the development of atrial fibrillation.

**Dose-Response:**

The presence of the dose-response relationship between and exposure and outcome provides good evidence for a causal relationship, however, its absence should not be taken as evidence against such a relationship. Some diseases do not display a dose-response relationship with a causal exposure. They may demonstrate a threshold association where a given level of exposure is required for disease initiation, and any additional exposure does not effect the outcome.

**Biological Plausibility:**

Support for this criterion is generally garnered in the basic science laboratory. It is not unusual for epidemiological conclusions to be reached in the absence of evidence from the laboratory, particularly in situations where the epidemiological results are the first evidence of a relationship between an exposure and an outcome. However, one can further support a causal relationship with the addition a reasonable biological mode of action, even though hard data may not yet be available.

**Coherence:**

This term represents the idea that for a causal association to be supported, any new data should not be in opposition to the current evidence, that is providing evidence against causality. However, one should be cautious in making definite conclusions regarding causation, since it is possible that conflicting information is incorrect or highly biased.

**Experimental evidence:**

Today's understanding of Hill's criteria of experimental evidence results from many areas: the laboratory, epidemiological studies, preventive and clinical trials. Ideally, epidemiologists would like experimental evidence obtained from a well-controlled study, specifically randomized trials. These types of studies can support causality by demonstrating that "altering the cause alters the effect". It should be noted, however, that randomized clinical trials aren't feasible in many instances, given the length of follow-up time and the numbers of participants needed to adequately answer the question of interest.

**Analogy:**

This is perhaps one of the weaker of the criteria in that analogy is speculative in nature and is dependent upon the subjective opinion of the researcher. For example, we understand that smoking causes lung cancer, therefore we may hypothesize that other types of inhaled smoke would also cause lung cancer. However, as mentioned, this would be speculative and would need to be tested to demonstrate further support for a causal effect. It is also important to remember that the absence of analogies should not be taken as evidence against causation.

**Self evaluation**

**Q1: Out of all the mentioned criteria, the one factor, although not in itself sufficient, that is necessary to demonstrate causality is:**

- a. Dose-response
- b. Temporality
- c. Strength of association
- d. Specificity

**Q2: True or False:**

Just as a strong association between an exposure and outcome is indicative of a causal relationship, a weak association between the two suggests a non-causal relationship.

### Answers to Self Evaluation:

- Q1: B: Temporality.** Causality requires that the causal agent precede the outcome. Thus one must demonstrate that the exposure is present before the outcome occurs. Prospective cohort studies, unlike case-control studies, are one of the best designs for demonstrating temporality.
- Q2: False.** In general, a strong association is indicative of a causal relationship, as is seen between cigarette smoking and lung cancer. However a weak association should not be taken as a non-causal relationship. Weak causal associations may be seen where the outcome of interest is common (such as heart disease) and there are numerous causal pathways suggested.

### Suggested reading on the topic:

Hill AB. The environment and disease. association or causation? *Proc R Soc Med* 58:295-300, 1965.

United States Department of Health, Education, and Welfare. *Smoking and health: Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Washington, D.C Government Printing Office, 1964 PHS Publ. No. 1103.

Ridgway D. The logic of causation and the risk of paralytic poliomyelitis for an American child. *Epidemiology & Infection.* 124(1):113-20, 2000.

Mengersen KL. Merrilees MJ. Tweedie RL. Environmental tobacco smoke and ischaemic heart disease: a case study in applying causal criteria. *Int Arch of Occup & Env Health.* 72 Suppl:R1-40, 1999.

Flegel KM. When atrial fibrillation occurs with pulmonary embolism, is it the chicken or the egg? *CMAJ.* 160(8):1181-2, 1999.

Weed DL. On the use of causal criteria. *Int J of Epidemiology.* 26(6):1137-41, 1997.

ERIC NOTEBOOK IS PRODUCED BY THE EDUCATIONAL ARM (MICHEL A. IBRAHIM, MD, PHD, DIRECTOR) OF THE EPIDEMIOLOGIC RESEARCH AND INFORMATION CENTER AT DURHAM, NC (RON HORNER, PHD, DIRECTOR)

**If you are not currently receiving ERIC Notebook and would like to be added to the distribution list, please fill out the form below:**

Name: \_\_\_\_\_

Degree(s): \_\_\_\_\_

Address: \_\_\_\_\_

City, State, Zip: \_\_\_\_\_

Telephone Number: \_\_\_\_\_

Fax Number: \_\_\_\_\_

E-mail Address: \_\_\_\_\_

Affiliation: VA \_\_\_\_\_ Other Gov't \_\_\_\_\_  
Academic \_\_\_\_\_ Other/Private \_\_\_\_\_

**Please fax to:** 919-416-5839 – Attn: Beth Armstrong or

**Email to:** beth.armstrong@duke.edu

**Mail to:** Beth Armstrong, ERIC Program Manager, VA Medical Center (152), 508 Fulton Street, Durham, NC 27705

### Upcoming Topics

- Health Care Epidemiology
  - Population Perspectives
  - Health Outcomes
  - Evidence Based Medicine

Please let Beth Armstrong know which topics are of special interest to you so that we can include them in a future issue.

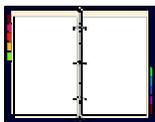
**beth.armstrong@duke.edu**

#### **Reminder:**

ERIC Notebook can be viewed online at

<http://sph.unc.edu/courses/eric> or

<http://hsrd.durham.med.va.gov/ERIC/Education/Education.html>.



# ERIC Notebook

BETH ARMSTRONG, ERIC PROGRAM MANAGER  
VA MEDICAL CENTER (152)  
508 FULTON STREET  
DURHAM, NC 27705