CME

Criteria for Causality

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Abstract:

Epidemiology is the study of the distribution, determinants and deterrents of morbidity and mortality in human populations. Therefore, one of primary goals of epidemiology is to discover "causes". Better understanding of "causes" frequently leads to more effective prevention and control measures, and consequently to a reduction of incidence, prevalence or severity of disease. Testing an epidemiologic hypothesis however, involves consideration of the concept of association between a particular exposure and disease. Multiple philosophies exist for evaluating causality. But, none are definite. A final decision regarding causation should be based on all relevant information and not on the basis of one or two studies. The set of causal criteria offered by Hill are discussed in this paper. They are useful to determine whether an association is likely to be causal. Of the six criteria, only correct temporal sequence is an absolute must, and the others are highly suggestive of causation.

Key Words: Association, Causation, Hill's Postulates.

Introduction:

Epidemiology is the study of the distribution, determinants and deterrents of morbidity and mortality in human populations. [(1)] Therefore, one of primary goals of epidemiology is to discover "causes". Better understanding of "causes" frequently leads to more effective prevention and control measures, and consequently to a reduction of incidence, prevalence or severity of disease. The formulation of etiologic hypotheses most often occurs through the use of descriptive studies. While testing them is the primary function of the analytic study designs.

Testing an epidemiologic hypothesis however, involves consideration of the concept of association between a particular exposure and disease. **Association** refers to the **statistical dependence** between two variables, the degree to which the rate of disease in those with specific exposure is either higher or lower than the rate of disease among those without the exposure. A Hypothesis is defined as a "tentative explanation for an observation, phenomenon, or scientific problem that can be tested by further investigation". [(2)]

An association does not necessarily imply that the observed relationship is one of cause and effect. In order to be considered a cause a change in the exposure must produce a corresponding change in the outcome.[(3)] A whimsical example is provided by Max Michael III, W. Thomas Boyce, and Allen J. Wilcox[(4)], they conducted a prospective cohort study to test a hypothesis that gambling causes cancer. They chose two states; in one gambling was legal and in the other it was not and they noted a significantly positive association. This association although real was not one of cause and effect. In one state actually tobacco and alcohol use was banned and this also showed lower cancer rate. The relationship shown was secondary association due to confounding by alcohol and tobacco use. These are non-causal associations or spurious and can lead to erroneous conclusion.

One of the most important aspects in clinical research is the inference; that an association represents a cause and effect relationship. Making judgments about causality involves a chain of logic that addresses two major areas: whether the association is valid and whether the totality of evidence (taken from a number of sources) supports a judgment of causality. Assessing validity (true relationships between exposure and disease) is a matter of determining the likelihood that alternative explanations (chance, bias and confounding) could account for the findings. Judging if the association is causal extends beyond validity of the results of any single study and includes consideration of other epidemiologic data as well as the biologic credibility of the hypothesis.

Statistically significant associations between exposures and outcomes may be categorized into 3 types. **Spurious;** are false associations usually resulting from sampling error or bias (Random error: alpha=0.05; 5 out of 100 even in well designed studies. And systematic error: bias). **Noncasual;** real but not causal. Usually represent secondary associations due to confounding factors. **Causal;** changes in the exposure produce changes in the outcome. However, this is a relative statement as in epidemiology we cannot 'prove' hypothesis; we can only make judgments using accumulated knowledge.

Causal Associations: A valid association in not due to chance, bias or confounding and is evaluated for effect-modification. Now the other area to understand is that "Is the 'valid' association causal? That is, "Is there sufficient evidence to infer that a causal association exists between the exposure and the disease? So, it is important to note that the process of causal inference/judgment of causality requires: valid statistical association and assessing whether exposure has actually caused the outcome where chance or uncontrollable force seems to have no assignable cause; is unforeseeable & unpredictable process.

Evaluating Causal Associations: Causality is a philosophical concept merged with practical guidelines. Epidemiology can never "prove" causality but can only infer it. The presence of a valid statistical association does not imply that it is a causal one. Therefore, a judgment of causality must be made in the presence of all available data, and reevaluated with each new finding. Remember, "Never to marry a hypothesis. Change your mind as the data change. A good scientist has an open mind and maintains objectivity".

Disease Etiology; Causation: Different criteria and philosophical views have been proposed to assess causality that is, there are several models of disease causation. All of them require the precise interaction of factors and conditions before a disease will occur. Models are guidelines that provide a framework for considering causation at a practical level. 'Cause' is a concept that is still debated and that is why there are several models to try to explain it.

Cause of disease is defined as a factor (characteristic, behavior, event, etc.) that precedes and influences the occurrence of disease (not the opposite) and has a statistical dependence *(*here; time order, direction & association are important*)*. In order to be considered a cause a change in the exposure must produce a corresponding change in the outcome [(3)]. Increase in the factor leads to an increase in disease, reduction in the factor leads to a reduction in disease. There are also inverse relationships.

Models of causation: We very well know about "Germ theory: Pasteur, Henle-Kock postulates" in the history of causation of disease, but all diseases are not infectious. Then came the "Epidemiologic triad (triangle) also known as Ecological model, a relatively simple paradigm for explaining infectious disease causation in terms of agent, host and environmental (brings the other two together; influences the route of transmission of the agent from a source to the host) factors. While useful in explaining infectious diseases, the model seems less applicable to many contemporary health issues and therefore has often been replaced by more complex models, including Holistic Models of health such as the Health Field Concept and the model of Evans and Stoddart [(5)]. Health is usually conceived as a state of well-being and positive functioning and not just the absence of disease.

It is important to note that multiple philosophies exist for evaluating causality but none are so far definitive. Having said this, let us come back to our focus on discussion of evaluating causal associations. A given association may not be clearly spurious, non-causal or causal. This is because sampling error can never be completely eliminated as a possible reason of an association in epidemiologic studies which are based on samples although it can be greatly minimized. The same stands true for bias and confounding. Thus, it is not an easy task for epidemiologist to determine which type of association is more likely. Also our main concern is to identify causal associations. So, some guidance is needed to determine whether an association is likely to be a causal one. In

practice, the determination of a cause-effect relationship is based on a review and judgment of all relevant information available, and never on the basis of one or two studies alone.

In 1965, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics with the University of London, delivered a landmark address where he outlined nine criteria that could be used to determine if statistical associations were likely to represent causal associations [(6)]. They are: Temporality, Strength of the association, Consistency with other research, Dose-response relationship, Biologic credibility/plausibility, and Experimental evidence (not always available or applicable in all settings). These are the six main ones; however process of determining causation is largely subjective except for temporality which is a must. The other three are: Specificity that implies; the more the diseases an exposure is related to (e.g., smoking), the less likely it is to be causal (faulty), Coherence (similar to consistency and plausibility), and Analogy.

These six criteria as postulated by Hill are discussed comprehensively in the following text.

1. Temporality/ Correct Temporal Sequence:

By definition, a cause of disease must precede onset of the disease. So, of all the criteria used to judge whether an association is causal or not, this is the only one that is an absolutely essential. This is reliable for prospective studies. But the problem is with cross-sectional studies (exposure and outcome occurring concurrently) and sometimes with case-control studies if not well designed wherein the existence of an appropriate time sequence can be difficult to establish. For example, in a cross-sectional study to determine if there is a relationship between prevalence of stress and overeating it may not be clear, that did stress lead to overeating or did overeating lead to stress?

2. Strength of the Association:

Generally speaking, the stronger the association, the less likely the relationship is due merely to an unsuspected or uncontrolled confounding variable/bias. This is not to say that those small associations cannot be causal in nature. Ratio measures for e.g. Relative Risk (RR) may be comparatively small for common exposures and diseases (e.g. smoking and cardiovascular disease), but are causal. The other con is that strong but non-causal associations are common. For example, non-causal relation between Down's syndrome and birth rank, which is confounded by maternal age. The other point to be noted is that when there are many component causes for a disease, each may not have a very strong association with the outcome. The RR/OR (Odds Ratio) is not always informative in and of itself. Take for example; Relative risk = 2 means incidence rate of Disease is twice as high in exposed v/s unexposed. RR = also 2 when p1/p2 =0.02/0.01 or =0.000002/0.000001, hence the term "relative" risk has been given. In the first case, incidence rate has increased from 1/100 to 2/100 at risk (difference in risk is 2-1 = 1/100) and in the other, incidence rate has increased from 1/100,000 to 2/100,000 at risk (difference in risk is 2-1 = 1/100,000). RR/OR is used to measure strength of association and used in judgment of validity and causal nature of an association. Whereas attributable risk (risk difference, absolute excess) are measures of difference that is the excess risk in the exposed group due to exposure and have significance from a public health perspective. Because of the cons as stated, several criteria are needed to judge causality.

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3. Consistency of findings with other research:

Due to the "inexact" nature of epidemiologic investigations, evidence of causality is persuasive when several studies conducted by different investigators at different times and in different populations yield similar results. Take for example, in concluding that cigarette smoking is a cause of lung cancer, the Advisory Committee to the Surgeon General of the United States cited diverse epidemiologic and other studies showing a strong relationship between smoking and lung cancer[(7)]. The con is that some effects are produced by their causes only under unusual circumstances. Also, studies of the same phenomena can be expected to yield different results simply because they differ in their methods and from random errors. The possibility of publication bias, which is

publication of positive studies most of the times, should also be kept in mind.

4. **Dose-response Relationship/Biologic Gradient:**

Logically, most harmful exposures could be expected to increase the risk of disease in a gradient fashion (e.g. if a little is bad, a lot should be worse). Heavy smokers, (number of cigarettes smoked per day) for example, have been shown to be at a higher risk of lung cancer than light smokers. It is important to note that some associations show a single jump (threshold) rather than a monotonic trend. Below the threshold, there are no observed effects, copper for instance may be found in small quantities in drinking water demonstrates a threshold; that is, it has no adverse effects until it reaches a certain level. In fact, in very small quantities it is an essential mineral for growth and development. We cannot rule out confounders as possible explanation on the other hand. Once again, several criteria should be considered in making a judgment about causality.

5. Biologic plausibility of the hypothesis:

A known or postulated biologic mechanism by which the exposure might reasonably alter the risk of developing the disease is intuitively appealing. But, plausibility is often based on prior beliefs rather than logic or actual data. Also, what is considered biologically plausible at any given time depends on the current state of knowledge. In other words, what does not make sense today may make sense sometime in the future. From a contemporary vantage point, it seems difficult to understand as to why the theory of contagion was considered controversial as an explanation for the spread of epidemics during the Middle Ages.

6. Experimental Evidence:

Having experimental evidence to support an association between an exposure and an outcome strengthens the case for a causal association. Well designed randomized controlled trials and randomized community trials can provide strong corroboration of a suspected causal association for the reason that they virtually eliminate selection bias and confounding. Hence, can be powerful tools when establishing causation.

To conclude, multiple philosophies exist for evaluating causality. But, none are definite. A final decision regarding causation should be based on all relevant information and not on the basis of one or two studies. The set of causal criteria offered by Hill are useful to determine whether an association is likely to be causal. Of the six criteria, only correct temporal sequence is an absolute must, and the others are highly suggestive of causation. But these are also saddled with reservations and exceptions. Always keep an open mind when evaluating evidence from epidemiologic studies. I would like to end by quoting an important advice given by Medewar in 1979, in his own words, "I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether or not it is true". [8]

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