
بسم الله الرحمن الرحيم
In the name of ALLAH
the most Beneficent and the most merciful

ASSOCIATION AND CAUSATION

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The terms "association" and "relationship" are often used interchangeably.

- Association may be defined as the concurrence of two variables more often than would be expected by chance.
- In other words, events are said to be associated when they occur more frequently together than one would expect by chance . Association does not necessarily imply a causal relationship.

Association can be broadly grouped under three headings

a. Spurious association

b. Indirect association

c. Direct (causal) association

(i) one-to-one causal association

(ii) multifactorial causation.

a. Spurious association

- Sometimes an observed association between a disease and suspected factor may not be real.
- For example, a study in UK of 5174 births at home and 11,156 births in hospitals showed perinatal mortality rates of 5.4 per 1000 in the home births, and 27.8 per 1000 in the hospital births

a. Spurious association

- Apparently, the perinatal mortality was higher in hospital births than in the home births.
- It might be concluded that homes are a safer place for delivery of births than hospitals.

a. Spurious association

- Such a conclusion is spurious or artifactual, because in general, hospitals attract women at high risk for delivery because of their special equipment and expertise, whereas this is not the case with home deliveries.
- The high perinatal mortality rate in hospitals might be due to this fact alone, and not because the quality of care was inferior.

a. Spurious association

- There might be other factors also such as differences in
- age,
- parity,
- prenatal care,
- home circumstances,
- general health and disease state between the study and control groups.

a. Spurious association

- This type of bias where "like" is not compared with "like" (selection bias) is very important in epidemiological studies.
- It may lead to a spurious association or an association when none actually existed.

b. Indirect association

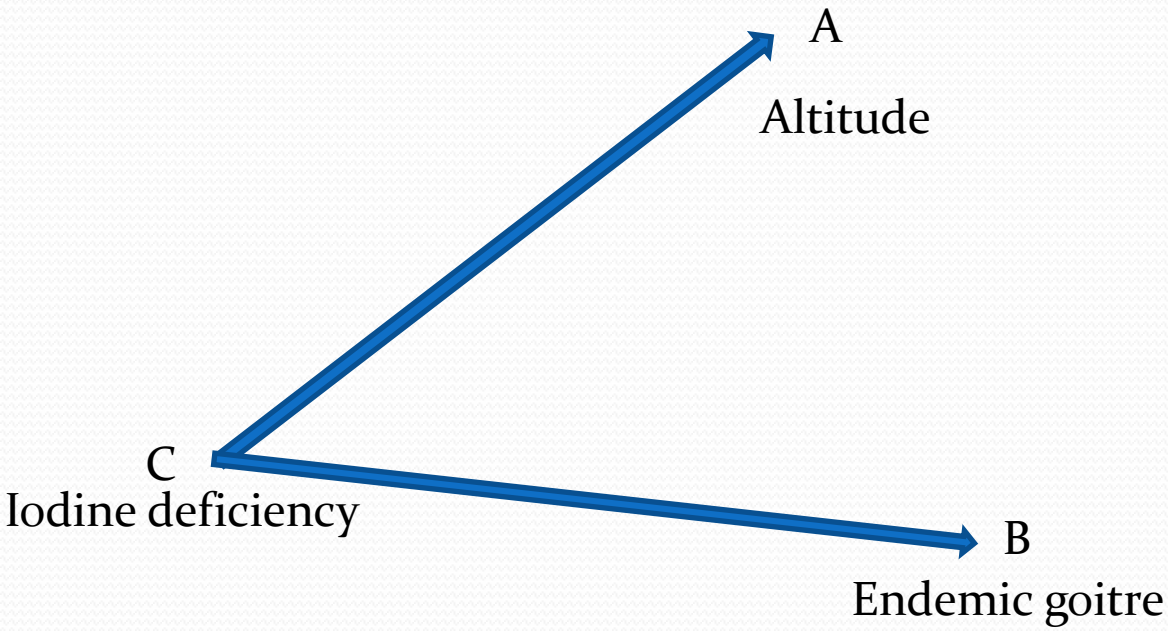
- Many associations which at first appeared to be causal have been found on further study to be due to indirect association.
- The indirect association is a statistical association between a characteristic (or variable) of interest and a disease due to the presence of another factor, known or unknown, that is common to both the characteristic and the disease.

b. Indirect association

- This third factor (i.e., the common factor) is also known as the "confounding" variable. Since it is related both to the disease and to the variable, it might explain the statistical association between disease and a characteristic wholly or in part.

Two examples of an indirect association are

- (a) Altitude and endemic goitre



b. Indirect association

- Endemic goitre is generally found in high altitudes, showing thereby an association between altitude and endemic goitre. We know, that endemic goitre is not due to altitude but due to environmental deficiency of iodine. Fig. illustrates how a common factor (i.e., iodine deficiency) can result in an apparent association between two variables, when no association exists.

(b) Sucrose and CHD

- Yudkin and Roddy found a higher intake of sugar by patients with myocardial infarction. Their study was based on an enquiry by questionnaire method into dietary habits of cases and controls. They put forward an attractive hypothesis that people who consume lot of sugar are far more likely to have a heart attack than those who take little.

b. Indirect association

- Further studies were undertaken to test whether sugar intake was associated with other variables such as cigarette smoking, which might be causally related to CHD.

b. Indirect association

- Bennet and others found that heavy cigarette smoking was positively associated with an increase in the number of cups of hot drinks consumed daily and the amount of sugar consumed. They concluded that it was cigarette smoking and not sugar consumption which was implicated in the aetiology of CHD.

b. Indirect association

- In their study, they did not find any evidence of increasing trend of CHD with increasing consumption of sugar. Finally, proof came from experimental studies that high sucrose feeding did not induce arteriosclerotic disease in animals.

Direct(causal) association

- (i) One-to-one causal relationship
- Two variables are stated to be causally related (AB) if a change in A is followed by a change in B. If it does not, then their relationship cannot be causal. This is known as "one to-one" causal relationship.

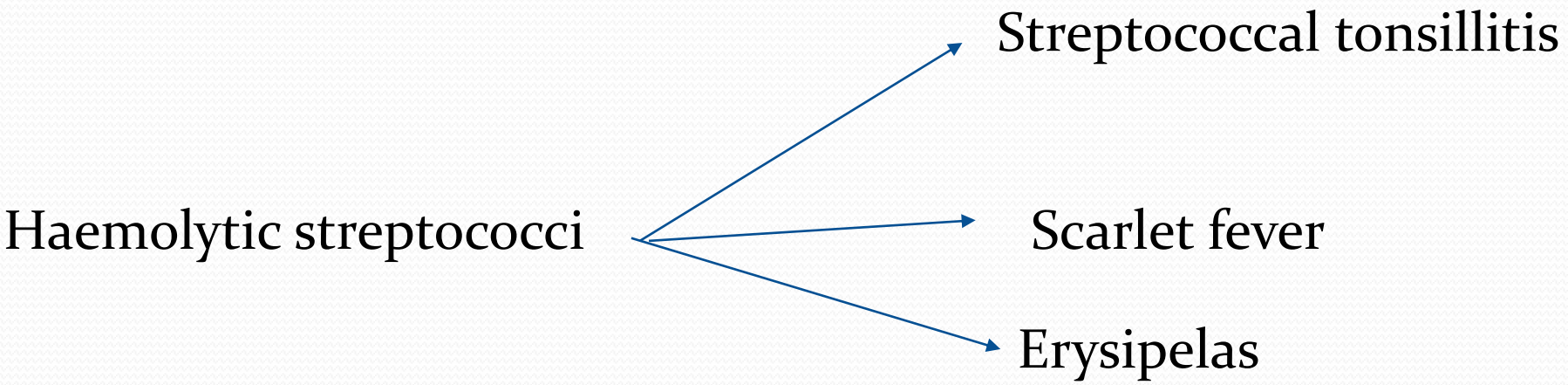
Direct(causal) association

- This model suggests that when the factor A is present, the disease B must result. Conversely, when the disease is present, the factor must also be present.

Direct(causal) association

- The concept of one-to-one causal relationship is further complicated by the fact that sometimes, a single cause or factor may lead to more than one outcome. In short, one-to-one causal relationship, although ideal in disease aetiology, does not explain every situation.

Direct(causal) association

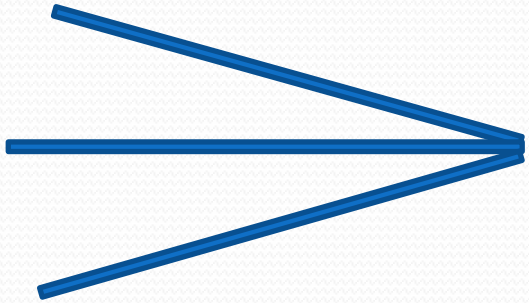


(ii) Multifactorial causation

- The causal thinking is different when we consider a non communicable disease or condition (e.g., CHD) where the aetiology is multifactorial. Two models are presented to explain the complex situation. In one model there are alternative causal factors (Factors 1, 2 and 3) each acting independently.

(ii) Multifactorial causation

- Factor 1
- Factor 2
- Factor 3



Reaction at cellular level-------Disease

(ii) Multifactorial causation

- In the second model the causal factors act cumulatively to produce disease. This is probably the correct model for many diseases. It is possible that each of the several factors act independently, but when an individual is exposed to 2 or more factors, there may be a synergistic effect.

(ii) Multifactorial causation

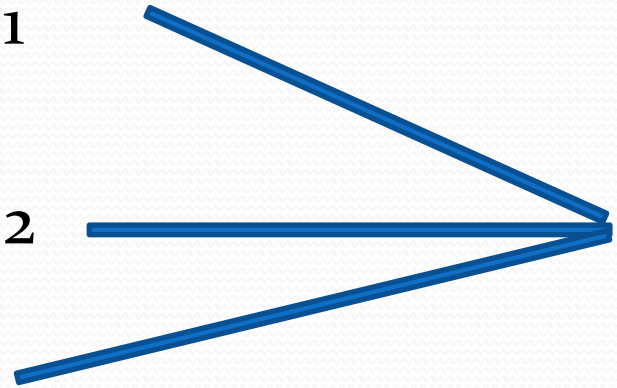
- Factor 1

  +

- Factor 2

  +

- Factor 3



Reaction at cellular level-------Disease

ADDITIONAL CRITERIA FOR JUDGING CAUSALITY

- In the absence of controlled experimental evidence to incriminate the "cause", certain additional criteria have been evolved for deciding when an association may be considered a causal association.

ADDITIONAL CRITERIA FOR JUDGING CAUSALITY

- Bradford Hill and others have pointed out that the likelihood of a causal relationship is increased by the presence of the following criteria.
- 1. Temporal association
- 2. Strength of association
- 3. Specificity of the association
- 4. Consistency of the association
- 5. Biological plausibility
- 6. Coherence of the association

ASSOCIATION BETWEEN CIGARETTE SMOKING AND LUNG CANCER

1. Temporal association

- This criterion centers round the question:
- Does the suspected cause precede the observed effect ?
- A causal association requires that exposure to a cause must precede temporarily the onset of a disease. This requirement is basic to the causal concept.

1. Temporal association

- Lung cancer occurs in smokers of long-standing; this satisfies the temporal requirement.
- Further, the increase in consumption of cigarettes preceded by about 30 years the increase in death rates from lung cancer. These observations are compatible with the long latent period characteristic of carcinogenesis.

2. Strength of association

- The strength of association is based on answers to two questions:
- a. Relative risk is it large ?
- b. Is there a dose-response, duration-response relationship ?
- In general, the larger the relative risk, the greater the likelihood of a causal association.

2. Strength of association

- Furthermore, the likelihood of a causal relationship is strengthened if there is a biological gradient or dose-response relationship - i.e., with increasing levels of exposure to the risk factor, an increasing rise in incidence of the disease is found. If there is no dose response or duration-response relationship, that would be an argument against the relationship being causal.

2. Strength of association

- In the absence of experimental data on humans, the causal relationship of cigarette smoking and lung cancer has been based on three points :
- (a) relative risk
- (b) dose response relationship, and
- (c) the decrease in risk on cessation of smoking.

Table presents data showing relative risk and dose-response relationship.

Death rate and relative risk for smokers and non-smokers			
Daily average cigarettes smoked	Death rate per 1000		Relative risk
	Smokers	Non-smokers	
1-14	0.47	.07	6.7
15-24	0.86	.07	12.3
25+	1.66	.07	23.7

2. Strength of association

- Such high relative risks are rarely seen in epidemiological studies.
- The dose-response relationship has, in fact, played a major role in acceptance of relationship as causal. If there has been no dose-response relationship, that would have been a strong argument against the causal hypothesis.

2. Strength of association

- Another factor that has added to the weight of evidence is the fact that lung cancer death rates among moderate smokers were intermediate between those among light smokers and heavy smokers

2. Strength of association

- Cessation experiment
- Another piece of evidence is provided by the cessation experiment. Table shows the mortality ratios in ex cigarette smokers by number of years stopped smoking among British doctors. The results confirmed that the mortality ratios were reduced in a way that would be expected if smoking were the cause of the disease. This is a strong point in the evidence favouring the hypothesis.

Lung cancer mortality ratios in ex-cigarette-smokers, by number of years stopped smoking, British physicians

Years stopped smoking	Mortality ratio
Still smoking	15.8
1-4	16.0
5-9	5.9
10-14	5.3
15+	2.0
Non smokers	1.0

3. Specificity of the association

- The concept of specificity implies a "one-to-one" relationship between the cause and effect. In the past, much of the controversy over cigarette smoking and lung cancer centered round lack of specificity of the association.

3. Specificity of the association

- That is, cigarette smoking is linked with not only lung cancer but several others such as coronary heart disease, bronchitis, emphysema, cancer cervix, etc.
- This was used, for several years, as an argument against the acceptance of the association as causal.

3. Specificity of the association

- It is true that cigarette smoking is associated with so many diseases reflecting an apparent lack of specificity, but that cannot be a strong argument, so as to dismiss the causal hypothesis. This is because the requirement of specificity is a most difficult criterion to establish not only in chronic disease but also in acute diseases and conditions.

3. Specificity of the association

- The reasons are :
- first, a single cause or factor can give rise to more than one disease.
- Secondly, most diseases are due to multiple factors with no possibility of demonstrating one-to-one relationship.

3. Specificity of the association

- The lack of specificity can be further explained by the fact that tobacco smoke is a complex of substances containing several harmful ingredients or factors such as nicotine, carbon monoxide, benzpyrene, particulate matter and many other ingredients with possible additive and synergistic action.

3. Specificity of the association

- The different components of tobacco smoke could as well be responsible for different states. In spite of this, it can be seen from Table that the association of lung cancer with cigarette smoking is far more striking than any other association reflecting a definite causal association. In short, specificity supports causal interpretation but lack of specificity does not negate it

Expected and observed deaths for smokers of cigarettes compared to non-smokers: Seven prospective studies combined for selected causes of death

Underlying cause of death	Expected deaths (E)	Observed deaths (o)	Mortality ratio (o/E)
Cancer of lung,	170.3	1.833	10.8
Bronchitis and emphysema	89.5	546	6.1
Cancer of larynx	14.0	75	5.4
Cancer oesophagus	37.0	152	4.1
Peptic ulcer	105.1	294	2.8
Cancer bladder	111.6	216	1.9
CHD	6,430.7	11,177	1.7
Cancer rectum	207.8	213	1.0
All causes of death	15,653.9	23,223	1.7

3. Specificity of the association

- The concept of specificity cannot be entirely dissociated from the concept of association. It has been estimated that about 80-90 per cent of lung cancer can be attributed to cigarette smoking. To say this, it is assumed that the association between smoking and lung cancer is causal.

3. Specificity of the association

- Under the heading of specificity, two more observations require comment :
- (a) not everyone who smokes develops cancer, and
- (b) not everyone who develops lung cancer has smoked. It may well be that there are other factors as yet unidentified which must be present in conjunction with smoking for lung cancer to develop.

3. Specificity of the association

- As for lung cancer in non-smokers, it is known that there are factors other than smoking which increase the risk of lung cancer such as *occupational exposure* to chromates, asbestos, nickel, uranium and exposure to air pollution. Deviations from one-to-one relationship between cigarette smoking and lung cancer therefore, cannot be said to rule out a causal relationship

4. Consistency of the association

- The association is consistent if the results are replicated when studied in different settings and by different methods. That is, evidence from a single study is seldom sufficient to establish "causal" association. If there is no consistency, it will weaken a causal interpretation.

4. Consistency of the association

- A consistent association has been found between cigarette smoking and lung cancer. More than 50 retrospective studies and at least nine prospective studies in different countries had shown a consistent association between cigarette smoking and subsequent development of lung cancer, lending support to a causal association.

5. Biological plausibility

- Causal association is supported if there is biological credibility to the association, that is, the association agrees with current understanding of the response of cells, tissues, organs, and systems to stimuli. For example, the notion that food intake and cancer are interrelated is an old one.

5. Biological plausibility

- The positive association of intestine, rectum and breast cancers is biologically logical, whereas the positive association of food and skin cancer makes no biological sense suggesting that strength of association by itself does not imply causality.

5. Biological plausibility

- The cigarette smoking and lung cancer hypothesis is biologically plausible. It is not hard to visualize the inhalation of hot smoke into the lungs and deposition of a chemical carcinogen over a period of time probably building itself up to a threshold level and initiating neoplastic changes in the lungs.

6. Coherence of the association

- A final criterion for the appraisal of causal significance of an association is its coherence with known facts that are thought to be relevant. For example, the historical evidence of the rising consumption of tobacco in the form of cigarettes and the rising incidence of lung cancer are coherent.

6. Coherence of the association

- Male and female differences in trends of lung cancer death rates are also coherent with the more recent adoption of cigarette smoking by women. Death rates rose first in males and are now increasing relatively more rapidly in females.

6. Coherence of the association

- The fall in the relative risk of lung cancer when cigarette smoking is stopped, and the occurrence of lung cancer from occupational exposure to other carcinogens such as asbestos and uranium and the demonstrated increase in lung cancer risk when workers exposed to these substances also smoked, enhance the significance of a causal association.

6. Coherence of the association

- In conclusion, it may be stated that the association between cigarette smoking and lung cancer can never be proved by a direct experiment on humans. It is an illusory and virtually unattainable goal. It is well known that epidemiology depends heavily on inferences drawn from observations rather than on the ultimate experiment.


Thanks