Critical Reading of an Article about Causation and Harm

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Objectives

By reading this chapter, readers will be able to:

Describe the cause and effect relationship; and Understand and apply Bradford Hill’s criteria for establishing causality in the study of health problems.

Case Study

You are the Family Physician who is treating a 55 years old diabetic male nurse, for the last 5 years, who is on Metformin and Gliclazide full dose. His HbA1c is > 9.0 for the last 6 months. You added Pioglitazone as a third medication according to guidelines. After a few days, he called up and requested to see you urgently, as he read an article about Pioglitazone use and the risk of urinary bladder cancer. You advised him to visit you the next day.

You formulated a question in PICO format to guide your search:

P : T2 diabetic patient
I : Pioglitazone
C : No Pioglitazone
O : Incidence of bladder cancer

You searched PubMed and found a systematic review that addresses your question. The systematic review is of accepted quality and shows that the incidence of bladder cancer increases with increased dose and/or duration of Pioglitazone use.

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The stronger the design of a study, the more likely it is to prove a relationship between cause and effect. Not all study designs are capable of proving a cause-and-effect relationship. The cause is the independent variable and is set by the researcher (e.g., Rosiglitazone medication as treatment for diabetes) or the environment (e.g., asbestos).

However, the effect is the dependent variable. It can be an outcome, such as death or survival, or the degree of improvement on a clinical score.

It is not always easy to establish an association or link!

You may think that hyperlipidemia is a cause for cardiovascular disease; but, how can we be sure that this is a cause and not just a related factor (confounder)? Perhaps hyperlipidemia is caused by the lack of exercise, which actually causes both!
I. Strength of Association

There is a direct relationship between the magnitude of an effect and the causative factor, i.e. the higher the magnitude of an effect, the stronger the association between the proposed risk factor and the outcome.

Effect measures are expressed as Relative Risk (Risk ratio) (RR) and/or Odds ratio (OR), both RR & OR can be used in cohort studies; however RR can’t be used in case-control studies, because the number of cases and controls is pre-determined by the study authors. Hazard ratio is another effect measure, where it’s calculation and interpretation is similar to RR except that time intervals are taken into account.

The degree of “strong” association may be understood by the following “rule-of-thumb” as depicted in Table 1.

Table 1: “Rule of Thumb” Degree of Association

<table>
<thead>
<tr>
<th>Risk Ratio (RR)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 – 1.3</td>
<td>Weak</td>
</tr>
<tr>
<td>1.4 – 1.7</td>
<td>Modest</td>
</tr>
<tr>
<td>1.8 – 3.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>3.0 – 8.0</td>
<td>Strong</td>
</tr>
<tr>
<td>8.0 – 16.0</td>
<td>Very strong</td>
</tr>
<tr>
<td>16.0 – 40.0</td>
<td>Dramatic</td>
</tr>
<tr>
<td>40 +</td>
<td>Overwhelming</td>
</tr>
</tbody>
</table>

Why this criterion is important: When there is a high magnitude of the effect measure (e.g. RR > 3.0), it is less likely to be due to other etiologic factors (confounders).

Example 1:
RR for lung cancer and cigarette smoking from various studies are around 10.0 while RR for breast cancer and cigarette smoking from various studies are between 1-1.5; which suggests that the association between smoking and lung cancer is more likely to be causal than smoking and breast cancer.

Example 2:
Palomaki et al., (1991) studied the relationship between sleep apnea including snoring and stroke.

Risk of stroke is 1.22 times in patients who snore (i.e., a single symptom); while, it is 8.00 times in patients having the full picture of obstructive sleep apnea syndrome. There is a stronger association between obstructive sleep apnea and stroke compared to snoring alone and stroke.

Example 3:
Rosiglitazone (Avandia) is an oral medication for treatment of diabetes; the published systematic reviews show that it moderately increases cardiovascular risk (RR 1.43).

Relatively weak association is common but one can rely on proper study designs that minimize bias (selection, information, and confounding). One rule to remember is: Absence of a strong association does not rule out a causal effect.

II. Consistency

When a casual relationship is observed repeatedly across studies.

When there are similar results from different studies which were conducted in different populations, in different methods by different researchers in different centers, if this happened, it increases our confidence of the causal association.

Examples
Many RCTs were published with a consistent result of the relationship between Rosiglitazone and cardiovascular events (RR 1.38 - 1.44).

Another example; the three published studies show a relationship between sleep apnea and stroke with similar results.

Conversely, studies addressing the same question may have different results. This may be due to:

1. Different study designs and conduct (error-prone versus error-free methods);
2. Presence of a confounder, which is an independent, unintended to study variable that affects the outcome; and,
3. The role of chance. If inconsistency is present, look for reasons, e.g., different population, methods and exposure.

Consistency is not always necessary to explain the cause and effect relationship. Sometimes, inconsistency provides useful insights of the causal components of an outcome.

III. Specificity of the Association

A factor influences specifically a particular outcome or population

Specificity of the association suggests that one exposure is specific to one disease, i.e., Rubella virus causes rubella. This criterion is best evidenced among infectious diseases.

This criterion is not applicable to all exposure-disease associations because a disease can be caused by several exposures, and an exposure may cause several diseases.

Example:
Diabetes is associated with end stage renal disease (ESRD) and other micro and macro vascular complications. On the other hand, ESRD is caused by diabetes and other diseases.

An exposure is likely to have a harmful effect on a specific mechanism (i.e., at a cellular or molecular level) that may then lead to one or more diseases. For example, an exposure such as smoke from cigarette smoking is comprised of many smaller chemical components.
The value of this rule lies in its combination with the strength of an association. For instance, among smokers, the risk of death from lung cancer should be elevated to a higher degree as compared to the risk of other causes of death.

When present high specificity does provide evidence of causality, low specificity value does not exclude causation.

IV. Temporal Relationship
The cause must precede the effect in time. This is the only one among Hill’s criteria that everyone agrees upon.

Prospective studies clearly establish the correct temporal relationship between an exposure and a disease.

Temporal direction might be difficult to establish if a disease developed slowly and initial forms of a disease were difficult to measure (e.g., the egg first or chicken argument).

Example 1:
The reports of increased suicidal ideation associated with the use of anti-depressant fluoxetine illustrate the importance of this question. However, one must realize that the reason for using fluoxetine is depression, which is the actual cause of suicide.(9)

Depression ⇨ Fluoxetine ⇨ Suicidal ideation

Example 2:
Children given antibiotics have greater incidence of asthma. But this ignores the fact that they were given antibiotics because of previous chest infections.(10)

Chest infection ⇨ Antibiotics ⇨ Bronchial Asthma

V. Dose Response Gradient (Biological gradient)
As quantity or the duration of exposure to harmful exposure increases, the risk of the adverse effect also increases. If risk increases with increasing exposure, it supports the notion of a causal association. However, the absence of dose-response does not preclude causal association.

Example 1:
The risk of dying from lung cancer in male physician smokers is dose dependent. The risk increases by 50%, 132% and 220% for 1-14, 15-24 and 25 or more cigarettes smoked per day, respectively.

Example 2:
Effect of neuraminidase inhibitors (Oseltamivir) compared with placebo on prophylaxis against laboratory confirmed influenza. RR is 0.39 with Oseltamivir 75 mg reduced to 0.27 with 150 mg.(11)

Example 3:
A meta-analysis of the association of pioglitazone use and risk of bladder cancer among diabetics showed that those who used pioglitazone for more than two years or used a dose higher than 28,000 mg have higher risk of bladder cancer (RR 1.44 CI 95% 1.19 - 1.74) compared with those who used it for less than one year (RR 1.03) or less than 10,500 mg (RR 1.13).(1)

VI. Biological Plausibility and Coherence
Does the association make biological sense? If there is plausible biological or pathological mechanism that could explain the relationship, the possibility of causation is increased.

Example:
The association between cigarette smoking and lung cancer can be explained by presence of many carcinogens in cigarettes like polycyclic aromatic hydrocarbons (PAH).

At the same time, research that disagrees with established biological theory is not necessarily false; it may, in fact, force a reconsideration of accepted beliefs and principles.

Coherence:
The cause-and-effect interpretation for an association does not conflict with the current knowledge of the natural history and biology of the disease.

VII. Reversibility and Experimental Evidence
All or none rule: All subjects will be vulnerable to disease when exposure present, however, all subjects will not be affected when exposure is removed. Best example is vaccination.

Well-designed experiments may give strong reason to believe that causation is at work. RCTs reduce the likelihood that there may be a systematic difference between the treatment and control groups.

Are the comparison groups similar?
Only RCT design gives two balanced groups (intervention and control groups), while other designs (Cohort or Case control) don’t.

Example
Clinical trials have shown that diabetes can be prevented through lifestyle modification programs, with reduced cumulative incidence of 58% compared to placebo.(12)

VIII. Analogy
Judgment from analogy, observes what effects a similar drug has on a disease.

Example:
If one COX-2 inhibitor has a certain side effect, then it is more plausible that another one will cause the same side effects too.

Another example:
Glitazone group causes heart failure.
Were the exposures and outcomes measured in the same way as the groups being compared?

- In case-controlled ascertainment of exposure: Recall bias and interviewers bias
- Example: Patients with leukemia, when asked about prior exposure to solvents, may be more likely to recall exposure than would a control group; either because of increased patient motivation (recall bias) or greater probing by an interviewer (interviewer bias).
- In RCT and Cohort ascertainment of outcome: When intervention group is not blinded, investigators diligently search for outcome.

Results:
The association between exposure and outcome can be presented as follows: Ratios for RCT and RR for cohort and case control = OR for case control.

The RR is the risk (or incidence) of the adverse effect in the exposed group divided by the risk of the adverse effect in the unexposed group. Values >1 represent an increase in risk associated with the exposure; while values <1 represent a reduction in risk; and, values = 1 means both have similar effects.

Example:
In a cohort study assessing in-hospital mortality following non-cardiac surgery in males, 23/289 patients with a history of hypertension died, compared with 3/185 patients without.

Risk with HTN = 23/289 = 0.07958
Risk without HTN = 3/185 = 0.01622
RR = 4.9

Interpretation:
The relative risk tells us that death occurs almost 5 times more often in the hypertensive patients than in normotensive patients.

Very large values of RR or OR represent strong associations that are less likely to be due to confounding or bias.

References