Epidemiology (3)
What is causation?

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References

- The full text of Chapter 3 is freely available online
  https://global.oup.com/us/companion.websites/9780199754557/pdf/2e-Chap3.pdf
- Other references available online
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  - Pearl, J. Causal inference in statistics:An overview. *Statistics Surveys*, 3: 96–146 (2009). http://dx.doi.org/10.1214/09-SS057
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Development of human causation

- An infant experiences a jumble of sensations (hungry, thirsty, …)
  - Gradually the infant perceives the patterns of the one's action and results (eg. Crying leads to begin fed)
  - Eventually the infant assembles an inventory of associated perceptions
  - It reaches **the general idea** that some events or conditions can be considered **causes** of other events or conditions
- Causation is first based on our own observation
  - Turning light switch on and off makes a child to see the light on and off. The child learns the causal relation between switch and light.
  - However, when the electric line to the building is down due to storm (or when the bulb is not working), turning the switch on makes no effect on the light (New observation to refuse the previous causation will be added at any time).
  - **Our perception will be revised**. The role of switch is not the single cause, but the final factor in causal mechanism.

THE CAUSAL PIE MODEL

- Figure 3-1 shows the three (existing maybe more) possible sets of sufficient causes for a same disease. The pies are called as "causal pies". It's also referred as "sufficient component cause model".
  - One health event (including disease occurrence) can be caused by several different sets of sufficient causes.
    - A disease may occur as the result of one of the following sets of component causes [ABCDE], [ABFGH], and [ACFIJ].
  - Each set of sufficient causes include the component causes which can cause the event when all sufficient causes were met.
- Implications of the causal pie model
  - MULTICAUSALITY
  - STRENGTH OF CAUSES
  - INTERACTION BETWEEN CAUSES
  - SUM OF ATTRIBUTABLE FRACTIONS
  - INDUCTION TIME

MULTICAUSALITY

- Every causal mechanism involves the joint action of multitude of component causes.
  - (eg.) Broken hip
    - A traumatic injury to the head
    - Permanent disturbance of equilibrium
    - (many years)
    - Faulty equilibrium leads to a fall while walking on an icy path
    - The fall results in a broken hip
  - Other factors (type of shoe, lack of handrail, sudden gust of wind, body weight) may play roles
- Some causes (body weight, gait, behavior, recovery from the earlier trauma) are genetic, the other causes (wind, lack of handrail, …) are environmental (non-genetic).

(Column)
Genetic versus environmental causes

- **<u>Every case of every disease has both genetic and environmental causes</u>**.
  - Nearly all diseases can be said to be inherited.
    - Drunk driving caused by alcoholism which has genetic component causes (polymorphism of enzymes of ADH and ALDH having low activity to metabolize ethyl-alcohol and aceto-aldehyde) may lead to fatal traffic accident
  - Similarly, nearly all diseases can be said to be environmentally caused
    - Phenylketonuria and subsequent mental retardation is purely genetic, but can be prevented by appropriate dietary intervention (use of artificial milk without phenylalanine instead of breast milk), which means environmental cause in that disease

STRENGTH OF CAUSES

- Some component causes play more important roles than others?
- Consider the strength of causal effect
  - "Smoking has a strong effect on lung cancer risk, because smokers have about 10 times the risk of lung cancer as nonsmokers" or "Smoking has a weaker effect on myocardial infarction, because the risk of heart attack is only about twice as great in smokers as in nonsmokers" may be said.
  - However, for each case, all component causes in a sufficient cause are needed. No strong cause, no weak cause.
- Considering total burden of cases occurring in a population, we can define a **strong cause** to be a component cause that plays a causal role in a large proportion of cases and a **weak cause** to be a causal component in a small proportion of cases.
  - Strength of a cause depends on the prevalence of other causes
  - (eg.) For lung cancer, smoking is stronger causes and exposure to radon gas is weaker causes
- In this sense, the strength of a cause does not portray the biology of causation

INTERACTION BETWEEN CAUSES

- Several causal components act in concert to produce an effect
  - "Acting in concert" ≠ Factors act at the same time
    - Consider the hip fracture example
    - Component causes in a sufficient set of causes (a causal pie) interact each other
  - The model provides a **<u>biologic basis for the concept of interaction</u>** that differs from the more traditional statistical view of interaction
- The implication is further discussed in Chapter 11.

SUM OF ATTRIBUTABLE FRACTIONS

- The rate of head and neck cancer according to smoking status and alcohol exposure (Table 3-1)
- Suppose the difference in the rates reflect causal effect
  - Confounding can be ignored
- Among those who both smoking and drinking (12/10000), how much is attributable to smoking?
  - In nonsmoker, 3/10000
  - The difference (12/10000 – 3/10000 = 9/10000) reflects the causal role of smoking
  - (9/10000)/(12/10000) = 75% are attributable to smoking
- Similarly, (12-4)/12 = 67% are attributable to drinking

Table 3-1. Hypothetical rates of head and neck cancer (cases per 10000 person-years) according to smoking status and alcohol drinking

Smoking status	Alcohol drinking	
	No	Yes
Nonsmoker	1	3
Smoker	4	12

- Some cases are counted more than once as a result of the interaction between smoking and drinking (One of the result of interaction is that the proportions of disease attributable to various component causes do not sum to 100%)
- "40% of cancer is attributable to occupational exposure" was considered overestimate since the sum of percentages exceed 100% if so. But actually no upper limit in the sum

INDUCTION TIME

- Component causes act at different time
- The last component cause completes the causal mechanism to cause disease occurrence concurrently
- For earlier-acting component causes, **induction period** can be defined as the time interval from the action of each component cause to the last action (at the same time with disease occurrence)
  - (eg.) The induction time of head trauma to hip fracture was many years
  - Difficult to know until complete causal mechanism is clarified
  - With research data, it's possible to learn the causal mechanism
    - (eg.) Lengthy induction time: Exposure of a female fetus to DES (her mother took to prevent spontaneous abortion), more than 15 years later to develop adenocarcinoma of the vagina. Some hormonal action during adolescence may be part of carcinogenesis. But it's impossible to say that 15 years is the minimum induction time for clear cell carcinoma in general (because different causal pies without DES for carcinoma may exist).
  - In carcinogenesis, initiator and promoter are used to refer to component causes of cancer that act early and late, respectively.
- To note, the **time interval** between disease occurrence and its subsequent detection, whether by testing or by emergence of symptoms, is called as the **latent period**.
- Practically distinguishing the induction period from latent period may be difficult, but it's different. Improvement of detection technique may reduce latent period, but has no effect on induction period, though detecting intermediate stage of a causal mechanism may be possible by detecting biomarkers such as DNA adducts.

(Column) Is a catalyst a cause?

- Catalyst (substance to make a chemical reaction happen faster without being changed itself) may shorten the induction time of other agents.
  - Exposure to A without B → 10 years → epilepsy
  - Exposure to A and B → 2 years → epilepsy
  - Is B a catalyst or a cause?
    - Both. In the causal pie including B, it compose a part of sufficient causes
    - Without B, epilepsy will occur later only if the person survives an additional 8 years, which is uncertain.
- Any agent that postpones the onset of an event, drawing out the induction period for another agent, we consider to be a preventive.
  - In this sense, postponement is equivalent to prevention

THE PROCESS OF SCIENTIFIC INFERENCE

- How do we determine whether a given relation is causal?
  - By checklists for causal inference?
  - By complicated statistical approaches?
  - No.
- (In other words) How do we apply the scientific method to epidemiologic research?
  - It's the issue of scientific philosophy (far beyond the issue of epidemiology)
  - Here let's see 2 major philosophic doctrines influenced modern science: Induction and Refutationism

Induction (Note: Completely different from induction period)

- How to determine the truth about assertions to deal with empirical world? It's major concern in 17th C.
- Deductive method has been used to prove the validity of mathematic propositions. It's self-contained. Cumulative combination of logic leads to the next propositions
- Empirical science deals with real world. Empirical observation on nature is fallible and incomplete.
- Modern empiricists like **Francis Bacon** considered a new type of logic "induction". Indirect method to gain insight into what has been metaphorically described as the fabric of nature.
  - Starts with observations on nature.
  - The observations fall into a pattern → Induce the observer's mind a suggestion of a more <u>general statement</u> (hypothesis, natural law, natural relation) about the nature → The statement is reinforced with further observations or refuted by contradictory observations
    - (eg.) Repeated observation that water boils at 100 degree Celsius → (induction) → "The boiling point of water is 100 degree Celsius"
  - Critics by **David Hume**, "induction has no logical force" "It assumes that what had been observed in the past would continue to occur in the future" "A kind of circular reasoning"

Refutationism

- **Karl Popper** refined induction as **refutationism**.
  - Induction cannot validate a statement about nature.
  - Statements about nature can be "corroborated" by evidence but corroboration does not amount to a logical proof.
  - Statements about nature can be refuted by deductive logic.
- (eg.) **Repeated experiments** showing that water boils at 100 degree Celsius *corroborate* the **hypothesis** that water boils at 100 degree Celsius, but don't *prove* it. An experiment in Denver (1.6 km a.s.l.) may show that water boils at 94 degree Celsius. → The hypothesis is refuted by this single observation.
- Implications by refuting observation and by supporting observation are asymmetric. Hypothesis should be evaluated by subjecting them to crucial tests.
  - If a test refutes the hypothesis, a new hypothesis needs to be formulated such as "Boiling point of water is 100 degree Celsius under 1 atom and decrease in lower atomospheric pressure"
  - An endless cycle of "**Conjecture** and **Refutation**": It's the title of a book written by Karl Popper.
- (In epidemiology) If causal mechanisms are stated specifically, an epidemiologist can construct crucial tests of competing hypothesis.
  - (eg.) The cause of toxic shock syndrome was from a chemical in the tampon? Or the toxin produced by bacteria (staphylococci) which used a tampon as culture medium? By the experiment to observe various frequencies of changing tampon increases or decreases the risk of toxic shock may support (corroborate) one of the suggested causes (If chemical in tampon, frequent changing increases the risk, if staphyrococci-produced toxin, frequent changing reduces the risk).
- Critics: Refutation is not logically certain. By **Thomas Kuhn**, the collective beliefs of the community of scientists determine what is accepted as truth about nature. Feyerabend "Science proceeds through intellectual anarchy". Haack "Science as an extension of everyday inquiry"

Causal Criteria

- No simple checklist that can determine whether an observed relation is causal
- But several checklists were suggested.
- Most widely cited one is Hill's checklist (Table 3-2). Sometimes referred as Hill's criteria.
- Except temporality (Cause comes before the effect), all other items in the checklist have exceptions, but sometimes convenient.
  - (eg.) Some causal relation may have weaker relations than noncausal relations (Birth order in Down syndrome is noncausal but strong relation)
  - (eg.) The effects of smoking are causal but sometimes nonspecific
- Weiss observed that the **specificity** of effects might be important in inferring the beneficial effect of sigmoidoscopy in screening for colorectal cancer if the association between sigmoidoscopy and reduced death from colorectal cancer is stronger for cancer occuring at sites within reach of a sigmoidoscope. https://doi.org/10.1097/00001648-200201000-00003

- (Table 3-2) Causal criteria of Hill (For each criterion, problems are given)
  - 1. Strength: Strength depends on the prevalence of other causes; it is not a biologic characteristic and can be confounded
  - 2. Consistency: Causal relations have exceptions that are understood best with hindsight
  - 3. Specificity: A cause can have many effects
  - 4. Temporality: It may be difficult to establish the temporal sequence between cause and effect
  - 5. Biologic gradient: It can be confounded; threshold phenomena would not show a progressive reation
  - 6. Plausibility: Too subjective
  - 7. Coherence: How does it differ from consistency or plausibility?
  - 8. Experimental evidence: Not always available
  - 9. Analogy: Analogies abound

Generalization in Epidemiology

- Many people believe that generalizing from an epidemiologic study involves a mechanical process of making an inference about a target population of which the study population is considered a sample.
  - In survey sampling, statistical representativeness of a sample may give applicability of the result from the sample to the whole population.
- The goal of science is not always same as this mechanical process
  - Survey results may be quickly outdated, do not apply outside the populations from which the surveys were conducted.
  - Scientific results from epidemiologic studies seldom need to be repeated weekly to see if they still apply. If the exposure to ionizing radiation at Chicago caused cancer, it also causes cancer at Houston. No repeated observation is needed. Generalization about ionizing radiation and cancer is based on understanding of the underlying biology rather than on statistical sampling.
  - When we generalize the results in animal experiment, the biology of animal population is similar to (an representative of) that of humans.
- Generalization process is based more on scientific knowledge, insight, and conjecture about nature than it is on the statistical representativeness of the actual study participants. It's important in the design and interpretation (Chapter 7).