The Perfect Doctor: An Introduction to Causal Inference

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TN-CTSI seminar on statistical reasoning in biomedical research
https://tnctsi.uthsc.edu/

“Correlation is not Causation”
“Association is not Causality”

We will understand more of these statements shortly, but there will be some notation along its way...

- Individual, average, and causal treatment effects
- Potential outcomes; factual and counterfactual outcomes
- Random assignment of treatments;
- Expected vs. observed outcomes
Causation vs. Correlation

Middle Ages:
Europeans believed that lice were good for one's health. As an observation, lice were less often found on diseased individuals. (This was before the medical thermometer was invented. Lice seem to be sensitive to even slight rises in body temperature and look for a new host when body temperature rises.)

Seriously:
A city's ice cream sales are positively correlated with the number of drownings in its swimming pools. An increase in ice cream sales is typically observed first with drownings following in time (Granger causality in time-series analysis holds).

Examples from the wild...

Tyler Vigen: “Now a ridiculous book” – Spurious Correlations
http://www.tylervigen.com/spurious-correlations

Koch’s postulates
How can we detect whether a microbe causes a disease?
(Robert Koch, 1843 – 1910, German physician, founder of modern bacteriology)

Known for his work with Anthrax, Tuberculosis, Cholera, among others: diseases can be caused by microorganisms (germ theory of disease).

Koch himself realized that especially 1) is not universally true: asymptomatic carriers can exist.
The idea that surgeons should wash their hands before surgery is only 151 years old!


Hill’s “criteria”

When is an association causal?

(Bradford Hill, 1897 – 1991, English epidemiologist and statistician)

Linked cigarette smoking to lung cancer (together with Richard Doll).

Aspects for establishing a causal relationship:
1. Strength: large associations are more likely to be causal
2. Consistency (reproducibility): different persons, places, samples,...
3. Specificity: More specific associations are more likely to be causal
4. Temporality: Effect must occur after the cause.
5. Biologic gradient: dose-response relationship
6. Plausibility: a plausible mechanism is evidence for a causal relationship
7. Coherence: epidemiological and laboratory findings should agree and should not be in disagreement with the known natural history and biology
8. Experimental evidence: “Occasionally it is possible to appeal to experimental evidence”
9. Analogy: What is known about similar factors/situations?

Noteworthy:

Hill himself:
• called these guidelines to separate causal from noncausal explanations.
• Rejected the idea that causality could be inferred based on a checklist.
• Rejected the emphasis on statistical significance testing to infer on causality.

Rothman et al. (2008) call the idea that Hill’s viewpoints should be considered a criteria list for causality a “misguided but popular view” (ibid., p. 26) and provide a critical elaboration on each of the aspects.

They emphasize:
• “that epidemiologists have not agreed on a set of causal criteria or on how to apply them” (p. 31)
• That “causal inference cannot attain the certainty of logical deductions” (p. 30) — David Hume’s view on the problem of induction.

A different approach to causality

A. Forget about all fuzzy thought about “causality”
B. Define what causality means in the scientific/medical field
C. Use that definition in its strict meaning
D. If the framework is not satisfied, don’t call it causal.

This has been a fruitful approach before!

Kolmogorov axioms of probability:
1. P(event) is a non-negative real number.
2. P(whole sample space) = 1
3. Countable additivity: P(union of any countable sequence of disjoint sets) = sum (P(individual sets))

The Perfect Doctor: A small world example
Potential outcomes and counterfactuals

Patient ID | Outcome under treatment A | Outcome under treatment B | True treatment effect (treat. B - treat. A)
--- | --- | --- | ---
ID1 | 13 | 14 | 1
ID2 | 6 | 0 | -6
ID3 | 4 | 4 | 0
ID4 | 5 | 2 | -3
ID5 | 6 | 3 | -3
ID6 | 6 | 1 | -5
ID7 | 8 | 10 | 2
ID8 | 8 | 9 | 1

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Average (true) treatment effect = -1.625

\[
\frac{1}{N} \sum_{i=1}^{N} (a_i - b_i) = \frac{1}{N} \sum_{i=1}^{N} a_i - \frac{1}{N} \sum_{i=1}^{N} b_i
\]

The Perfect Doctor picks the treatment

The doctor is perfect, because she has the ability to pick for each patient the treatment that is better for that patient!

Patient ID | Outcome under treatment A | Outcome under treatment B | Applied treatment and observed outcome
--- | --- | --- | ---
ID1 | 13 | 14 | B: 14
ID2 | 6 | 0 | A: 6
ID3 | 4 | 4 (draw) | B: 4
ID4 | 5 | 2 | A: 5
ID5 | 6 | 3 | A: 6
ID6 | 6 | 1 | A: 6
ID7 | 8 | 10 | B: 10
ID8 | 8 | 9 | B: 9

Estimated treatment effect (B – A): 

\[
\frac{(14 + 4 + 10 + 9)}{4} - \frac{(6 + 5 + 6 + 6)}{4} = 9.25 - 5.75 = 3.5
\]

B appears much better!

(Average (true) treatment effect = -1.625)
The Perfect Doctor picks the treatment

Two observations:
1. If that doctor would exist, I would like to be her patient!
2. Observing the perfect doctor suggests a treatment effect of 3.5 in favor of treatment B, but we know that B is actually inferior (average (true) treatment effect = -1.625)

How can we get it THAT WRONG??

How can we get it right?

We get it wrong, because the doctor’s selection introduces a bias!
- Patients for which B is the better treatment, have a tendency to have better outcomes under both treatments.
- That creates the impression that B is better than A when the perfect doctor picks the treatment!

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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<td>14</td>
<td>B: 14</td>
</tr>
<tr>
<td>ID2</td>
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<td>B: 10</td>
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<td>ID8</td>
<td>8</td>
<td>9</td>
<td>B: 9</td>
</tr>
</tbody>
</table>

Possible allocation # Allocation sequence for all enrolled participants Observed trial outcome (mean B - mean A)
1 A, A, A, A, B, B, B, B -1.250
2 A, A, A, B, B, B, B, B -1.750
3 A, A, A, A, B, B, B, B -1.500
4 A, B, A, A, B, B, B, B -2.000
5 B, A, A, A, B, B, B, B 3.250
6 B, A, A, B, A, B, B, B 3.750
7 B, A, B, A, B, A, B, B -1.500
-- -- -- --
69 A, B, B, B, B, A, A, A --
70 B, B, B, B, B, A, A, A --
Averaged treatment effect -1.625

The Perfect Doctor: Conclusion

In order to make correct conclusions “on average” we have to have control over who is receiving which treatment.

Only a random mechanism is blind towards what we know and what we are unaware of: (One can “direct” the random mechanism by, e.g., applying stratification or unequal assignment probabilities depending on known covariates, but that mechanism must be known exactly and has to be accounted for in the subsequent analysis.)

All observational studies are plagued with the problem that we can only correct for known and measured covariates but not for the unknown or unmeasured covariates. Randomized studies do not have that problem and any imbalance in unobserved covariates is only coincidental and not systematic! (Unless something “went wrong” in the random assignments or biases are introduces by selective follow-up/informative attrition, evaluation bias by not properly blinding those who take measurements etc.)
Association vs. causation


Some are exposed (X = 1) and some are unexposed (X = 0). The population causal effect is the averaged outcome when all are exposed vs. when none is exposed (left part).

A valid estimate of that population causal effect requires that the expected value of the observed effect coincides with the true effect (is unbiased or with little bias).

Terminology/Summary

- Individual, average, and causal treatment effects
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Note: These slides elaborated on Rubin’s causal model. Other approaches exist as well: Causal structural equation models, Pearl’s artificial intelligence perspective (do-calculus), Dawid’s decision theoretic formulation

Structural Equation Models are not generally “causal”!


Causal inference reading list


More about causality:

Statistical Methods for Observational Studies (BIOE 864)
- offered this Fall (T2) Oct. 09 to Dec. 11 – 1 credit hour
- CRN 43734 (Banner identifier for fall 2019)

Department of Preventive Medicine
Division of Biostatistics

Additional Seminars in the Series:

- April 30 P-values: What They Are and What They Are Not (Fridtjof Thomas, PhD)
- May 7th Should We eliminate P-Values or Use More of Them: A Discussion on the P-Value Controversy (Saunak Sen, PhD)
- May 14th The Bayesian Approach to Data Analysis (Fridtjof Thomas, PhD)
- May 21st Multiple Testing and the False Discovery Rate (Saunak Sen, PhD)
- May 28th The Perfect Doctor: An introduction to Causal Inference (Fridtjof Thomas, PhD)
- June 4th Enhancing Statistical Methods in Grants and Papers (Saunak Sen, PhD)