THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

The Perfect Doctor: An Introduction to Causal Inference

The Perfect Doctor: An Introduction to Causal Inference

Fridtjof Thomas, PhD

Associate Professor, Division of Biostatistics

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

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)

"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

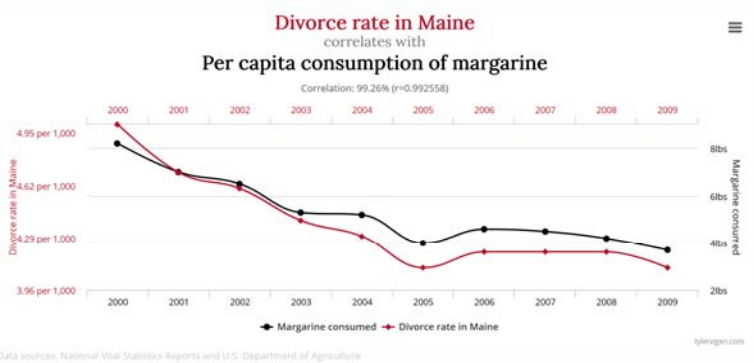
Causation vs. Correlation

Middle Ages:
Europeans believed that lice were good for ones 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).

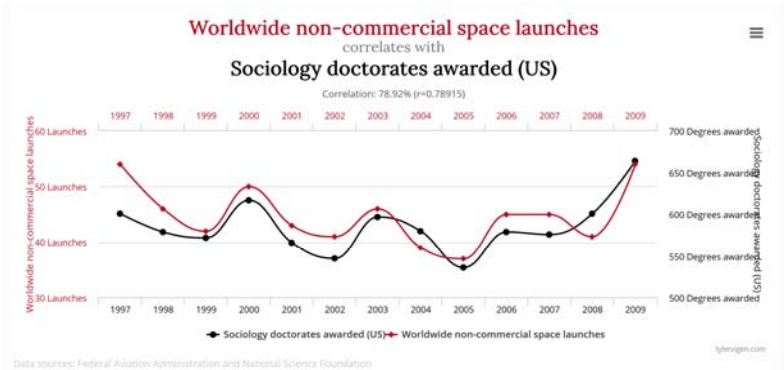
Examples from the wild…

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



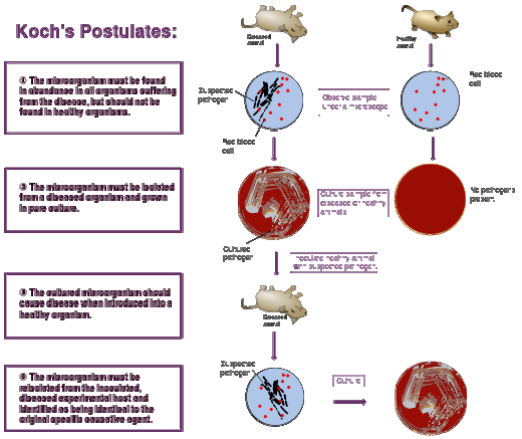
Examples from the wild…

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)



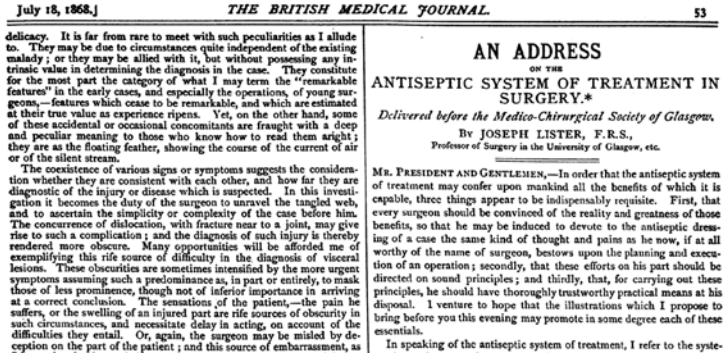
Known for his work with Anthrax, Tuberculosis, Cholera, among others: diseases can be caused by microorganisms (germ theory of disease).

Koch himself realized that especially 1) is not universally true: asymptomatic carriers can exist.

Source: https://commons.wikimedia.org/wiki/File:Koch%27s_Postulates.svg

The idea that surgeons should wash their hands before surgery is only 151 years old!

Lister J. An Address on the Antiseptic System of Treatment in Surgery. *British Medical Journal*. 1868;2(394):53-6. doi: 10.1136/bmj.2.394.53. PubMed PMID: 20745202.



July 18, 1868.] THE BRITISH MEDICAL JOURNAL. 53

delicacy. It is far from rare to meet with such peculiarities as I allude to. They may be due to circumstances quite independent of the existing malady; or they may be allied with it, but without possessing any intrinsic value in determining the diagnosis in the case. They constitute for the most part the category of what I may term the "remarkable features" in the early cases, and especially the operations, of young surgeons,—features which cease to be remarkable, and which are estimated at their true value as experience ripens. Yet, on the other hand, some of these accidental or occasional concomitants are fraught with a deep and peculiar meaning to those who know how to read them aright; they are as the floating feather, showing the course of the current of air or of the silent stream.

The coexistence of various signs or symptoms suggests the consideration whether they are consistent with each other, and how far they are diagnostic of the injury or disease which is suspected. In this investigation it becomes the duty of the surgeon to unravel the tangled web, and to ascertain the simplicity or complexity of the case before him. The concurrence of dislocation, with fracture near to a joint, may give rise to such a complication; and the diagnosis of such injury is thereby rendered more obscure. Many opportunities will be afforded me of exemplifying this rife source of difficulty in the diagnosis of visceral lesions. These obscurities are sometimes intensified by the more urgent symptoms assuming such a predominance as, in part or entirely, to mask those of less prominence, though not of inferior importance in arriving at a correct conclusion. The sensations of the patient,—the pain he suffers, or the swelling of an injured part are rife sources of obscurity in such circumstances, and necessitate delay in acting, on account of the difficulties they entail. Or, again, the surgeon may be misled by deception on the part of the patient; and this source of embarrassment, as

AN ADDRESS

ON THE

ANTISEPTIC SYSTEM OF TREATMENT IN SURGERY.*

Delivered before the Medico-Chirurgical Society of Glasgow.

By JOSEPH LISTER, F.R.S.,
Professor of Surgery in the University of Glasgow, etc.

MR. PRESIDENT AND GENTLEMEN,—In order that the antiseptic system of treatment may confer upon mankind all the benefits of which it is capable, three things appear to be indispensably requisite. First, that every surgeon should be convinced of the reality and greatness of those benefits, so that he may be induced to devote to the antiseptic dressing of a case the same kind of thought and pains as he now, if at all worthy of the name of surgeon, bestows upon the planning and execution of an operation; secondly, that these efforts on his part should be directed on sound principles; and thirdly, that, for carrying out these principles, he should have thoroughly trustworthy practical means at his disposal. I venture to hope that the illustrations which I propose to bring before you this evening may promote in some degree each of these essentials.

In speaking of the antiseptic system of treatment, I refer to the syste-

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?

Rothman, Greenland, Poole, and Lash: Causation and Causal Inference. In: Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* Third ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

Hill's "criteria"

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.

Rothman, Greenland, Poole, and Lash: Causation and Causal Inference. In: Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* Third ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

A different approach to causality

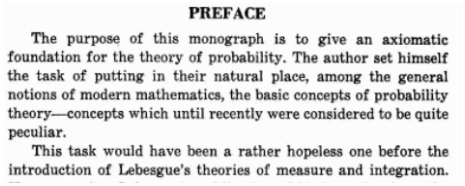
A. Forget about all fuzzy thought about "causality"
B. Define what causality means in the scientific/medical field
C. Use that definition in its strict meaning
D. If the framework is not satisfied, don't call it causal.

This has been a fruitful approach before!

Kolmogorov axioms of probability:

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

Andrey Kolmogorov (1933): Grundbegriffe der Wahrscheinlichkeitsrechnung. Berlin: Springer. English version: 1956 - Foundations of the Theory of Probability (2nd ed.), New York: Chelsea.



PREFACE

The purpose of this monograph is to give an axiomatic foundation for the theory of probability. The author set himself the task of putting in their natural place, among the general notions of modern mathematics, the basic concepts of probability theory—concepts which until recently were considered to be quite peculiar.

This task would have been a rather hopeless one before the introduction of Lebesgue's theories of measure and integration.

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

Small world example

Everything you need to know about causal inference with Donald B. Rubin, June 16-18, 2004, Karolinska Institutet, Stockholm, Sweden.
(Donald B. Rubin , Elizabeth Stuart, Samantha Cook)

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

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

Treatment comparison	**# patients**
Treatment A is better	4
Treatment B is better	3
No difference between treat. A and B	1

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

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):

(14 + 4 + 10 + 9)/4 - (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?

How can we get it THAT WRONG??

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!

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**

How can we get it right?

1. Use random assignments of patients to treatment!
2. Be aware of that a single trial can be "off"
3. Use "statistics" to compute how far off one likely can be
4. Use many trials or a large trial if you need to come close to the true average treatment effect.

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, A, B, B, B	-1.750
3	A, A, B, A, A, B, B, B	-1.500
4	A, B, A, A, A, B, B, B	-2.000
5	B, A, A, A, A, B, B, B	3.250
6	B, A, A, A, B, A, B, B	3.750
7	A, B, A, A, B, A, B, B	-1.500
…	…	…
69	A, B, B, B, B, A, A, A	-6.500
70	B, B, B, B, A, A, A, A	-2.000
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

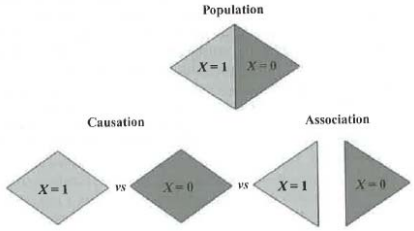


Figure 2.1 Association versus causation.

Source: Sjölander, Arvid (2012): The language of potential outcomes. In: Berzuini C, Dawid P, Bernardinelli L, eds. Causality: Statistical Perspectives and Applications. Chichester, West Sussex, U.K.: Wiley; 2012.

Hernán MA, Robins JM. Causal Inference. Boca Raton: Chapman & Hall/CRC; 2018 - forthcoming as of 05/28/19.

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
- Potential outcomes; factual and counterfactual outcomes
- Random assignment of treatments;
- Expected vs. observed outcomes

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"!
Bollen KA, Pearl J. Eight Myths about Causality and Structural Equation Models. In: Morgan SL, ed. *Handbook of Causal Analysis for Social Research, Chapter 15*: Springer; 2013:301-328.

Causal inference reading list

Maldonado G, Greenland S. Estimating causal effects. *International Journal of Epidemiology.* 2002;31(2):422-429.

Pearl J, Glymour M, Jewell NP. Causal Inference in Statistics - A Primer. Chichester, West Sussex, UK: Wiley; 2016.

Lindley DV. Seeing and doing: the concept of causation. *Int Stat Rev.* 2002;70(2):191-197.

Berzuini C, Dawid P, Bernardinelli L, eds. *Causality: Statistical Perspectives and Applications.* Chichester, West Sussex, U.K.: Wiley; 2012.

Imbens GW, Rubin DB. Causal Inference for Statistics, Social, and Biomedical Sciences. New York: Cambridge University Press; 2015.

VanderWeele TJ. Explanation in Causal Inference - Methods for Mediation and Interaction. New York: Oxford University Press; 2015.

Hernán MA, Robins JM. Causal Inference. Boca Raton: Chapman & Hall/CRC; 2018 - forthcoming as of 05/28/19. (https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/)

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)

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)**