Causality and Epidemiologic Studies

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- Associate Professor of Epidemiology, 2008-
  - Gillings School of Global Public Health at UNC Chapel Hill
- Assistant/Associate Professor of Epidemiology, 2000-08
  - Johns Hopkins Bloomberg School of Public Health
- Postdoctoral Fellow, 1998-00
  - Harvard Medical School
- Continuous NIH funding throughout career
  - PI NIAID R03, PI NIAAA R01, Co-PI NCI R01, Core-director NIAID R24
- >125 peer-reviewed papers; >1985 citations
- Editorial boards: Am J Epidemiology and Epidemiology
- Interest area is quantitative epidemiologic methods

All study designs are cohorts and all error is due to missing information

Outline

1. Existing framework and shortcomings
2. Novel approaches to causality in epidemiology
3. Steps forward

1. Existing Framework

Hill AB.

The Environment and disease: association or causation?

J Roy Soc Med 1965:58: 295-3000

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Hill's Criteria

1. Strength (of association)
2. Consistency (in different settings)
3. Specificity (in action/outcome)
4. Temporality (4th?)
5. Biological gradient (or dose-response)
6. Plausibility (e.g., a biological or other model)
7. Coherence (i.e., doesn't conflict with existing knowledge)
8. Experiment (8th? Likely because rare)
9. Analogy

I sometimes group as: 4+8, 1+5, 2+3, 6+7+9

Shortcomings of Hill's Criteria

- Not transparent
- Overlap (e.g., coherence and plausibility)
- Qualitative
- Assumptions* not explicit
  - *Consistency, positivity, and exchangeability
- Bias (or systematic errors) not mentioned
- Impermanent:
  - Displaced Koch's postulates for chronic diseases
  - Are to be displaced themselves

There are likely other shortcomings

Impact of Shortcomings on Risk Assessment

- Hill's criteria selectively applied
- Attention should be paid to all criteria, but not all criteria are necessary (or even sufficient) for causation
- A precautionary principle is implied by the criteria
  - Focuses risk assessment on studies demonstrating elevated risk due to exposures
  - Undue emphasis on positive studies
- Single positive results can (inappropriately) make the case for causation

There are likely other impacts of shortcomings

Cochran Collaboration, founded 1993

Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults (Review)

Siegfried N, Uthman OA, Rutherford GW

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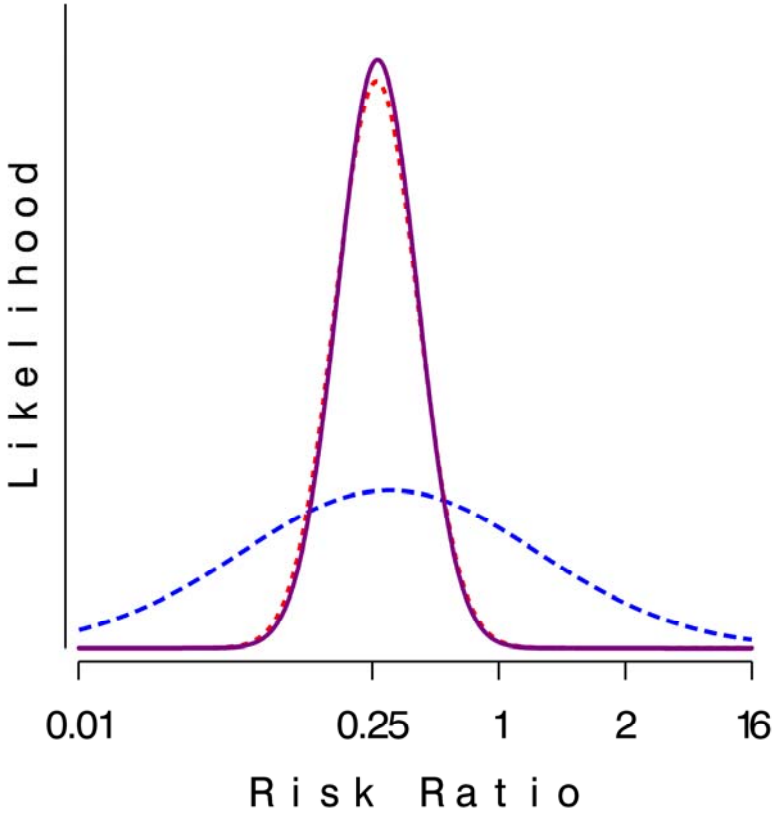
"Review" is 1 study!



SMART study
RR = 0.30
95% CL: 0.01, 7.31

CIPRAHT001 study
RR = 0.26
95% CL: 0.11, 0.63

Summary
RR = 0.26
95% CL: 0.11, 0.62

* SMART estimate based on a continuity-correction because there were 0 deaths in early TX and 1 in deferred TX.

Data: Deaths/N for CIPRAHT001 and SMART were: 6/408 and 0/131 in early and 23/408 and 1/118 in deferred, respectively.

2. Novel Approaches

Novel Approaches to Causality in Epidemiology

Three important approaches are emerging in epidemiology:

A. Bayesian methods for inference
B. Causal diagrams
C. Potential outcomes (or counterfactuals)

Novelty is present in the convolution of these three approaches

A. Bayesian Methods for Inference

- We want to learn about a parameter B, say the 20 year risk of lung cancer in a given setting, which must between 0 and 1
- Current standard epidemiologic practice is a convolution of frequentist methods, which cannot speak directly about the uncertainty of this parameter B and treats it as a fixed unknown
- Bayesian methods meld existing knowledge (the “prior”) with a summary of the current data (the “likelihood”) to yield our updated knowledge (the “posterior”) about the parameter B
- Priors exist, but are hidden, in many current approaches!

Debates about whether the Bayesian approach is right, or feasible, are over.

B. Causal Diagrams

- For decades epidemiologists have informally used diagrams to convey relations in complex systems
- In a ground-breaking 1995 paper, Pearl codified these diagrams as directed acyclic graphs which provide powerful tools for bias assessment

C. Potential Outcomes

- Potential outcomes have underpinned the experimental method for nearly a century,
- Their application to simple observational research settings was described by Rubin in a ground-breaking 1974 paper
- For complex observational research settings by Robins in a series of ground-breaking papers beginning in 1986

Debates about whether counterfactuals are right, or useful, are largely over.

An Example: The Healthy Worker Effect

- Bayesian methods allow us to learn from prior evidence
  - Say in a similar research setting a risk ratio of 1.35 with a 95% confidence/credible interval of 0.7, 2.10 was reported
  - Should we place equal probability on seeing a 1 as a 10^6?
- Causal diagrams succinctly state the problem:

- Methods based on potential outcomes allow proper analyses
  - Structural nested models were developed using potential outcomes, and properly account for time varying variables like Work status that are both confounders for future exposure and mediators for past exposure

Panacea?

No!

- Bayesian inference are only as good as the prior and data
- Causal diagrams have major shortcomings with respect to effect measure modification and describing dose-response
- Methods for potential outcomes are sometimes inefficient because they sacrifice precision for validity

We do not expect that one (or all three) approach will provide a “solution”

Conclusions

- A combination of the approaches introduced here provides a stronger foundation for making causal inferences from epidemiologic data than the existing (nearly 50 year old) criteria

- These approaches dove-tail well to provide inputs for quantitative risk assessments

- We stand at the precipice of a new era in epidemiology, and features of this new era have direct, important consequences for risk assessment

3. Steps Forward

Steps Forward

1. Identify a work group
   - 10 leaders in epidemiology
   - Teleconferences to structure symposium
2. Conduct a symposium
   - Broader, larger symposium group
   - 2-day meeting
   - Open debate
3. Publish proceedings
   - Consensus statement
   - Peer-reviewed journal

A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.

-Max Planck

Thank you

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