

False Positives & False Negatives in Cancer Epidemiology

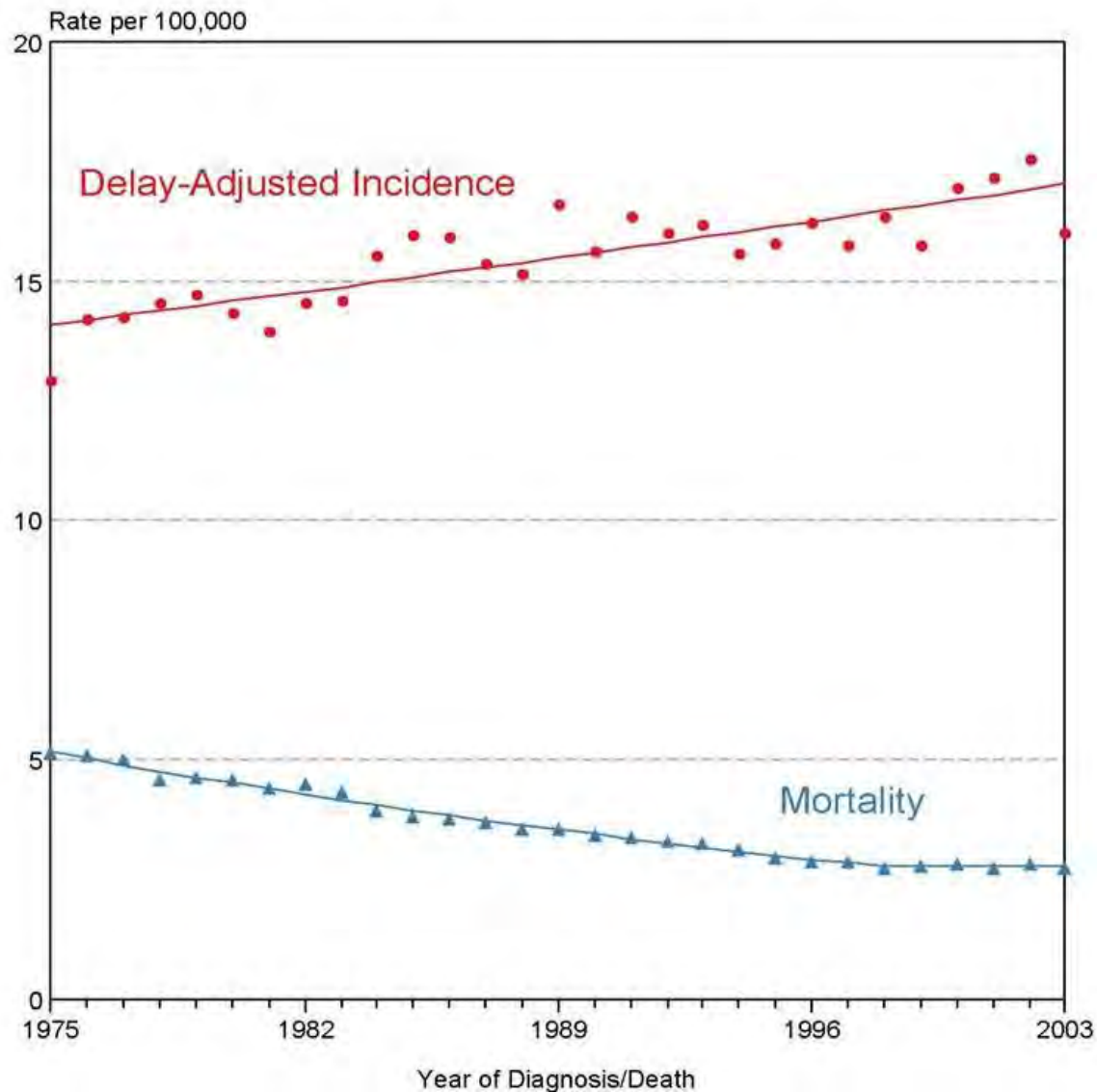
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Torino, 2 Ottobre 2008

First Context

- Most causes of most cancers are largely unknown.
- Do you agree?
 - Here are 2 ways to think about this:
 1. What fraction of the variability in outcome do cancer epi models explain?
 2. If we knew most of the risk factors, our models would have RRs > 10 , and useful for screening. Apart from smoking and asbestos, there are almost no other examples.

SEER Delay-Adjusted Incidence and US Mortality All Childhood Cancers, Under 20 Years of Age Both Sexes, All Races, 1975-2003



Good evidence for environmental causes of Childhood brain cancer and leukemias:

- Pesticides
- Solvents
- Radiation
- Enva'l Tobacco Smoke

Second Context

- Before 1900, the human body contained few chemicals that are not manufactured by cells.
 - Exceptions?
 - Combustion products (but not chlorinated)
 - Certain inorganics in particular locales: radon, asbestiform fibers, etc. But localized!
- After WW II, synthetic organic chemistry
 - Environmental epidemiology is to a large degree about identifying which industrial products are hazardous.

One-at-a-time risk assessment is not an adequate protection against carcinogens

- 82,000 chemicals in commerce
 - ~ 3,000 high volume
 - (> 1 million pounds/year or 450,000 kg/yr)
 - very few have been adequately screened for toxicity
- > 1,000 new chemicals every year
 - ~ half have basic human toxicity data

One-at-a-time risk assessment is not an adequate protection against carcinogens

- Only 2% of chemicals have been tested for carcinogenesis
 - And we could debate the adequacy of the evidence for almost every one!

Many hazards are probably being missed

- Single exposure approach to prevention contradicts known aspects of cancer mechanism
 - causal pathways include several stages, exposures can lead to cancer by “completing” a causal chain initiated by previous exposures
 - means “earlier” and “later” causes are not independent

While there are political pressures that make prevention difficult, this is not the main roadblock

- There are fundamental limits to how much we can accomplish with one chemical-at-a-time risk assessment and management

False positives & false negatives

- False compared to what?
 - If epidemiology is fundamentally a search for “truth”, then the only “gold standard” is a scientific consensus
 - If epidemiology is fundamentally in service to public health, then another gold standard is whether policy decisions or action is taken

This corresponds to 2 different models of getting to “causal”

1. Knowledge accumulates until a threshold is reached: risk is “real”

OR:

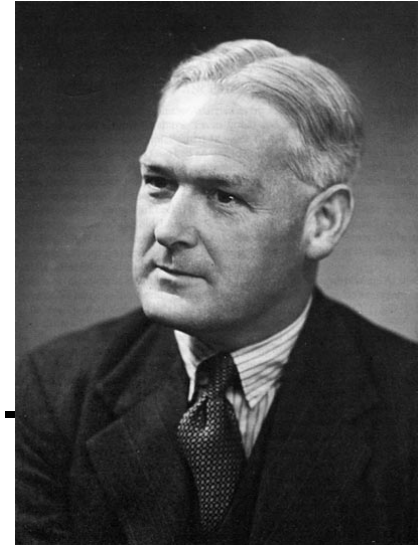
2. Knowledge accumulates, never reaching a threshold.

- different amounts of evidence justify different responses, e.g.:
 - “more study needed”
 - funding search for safer alternatives
 - eliminating unnecessary uses

Two models of getting to “causal”

- Under 2nd model, process cannot be entirely conducted within scientific community
- Regulators, courts, employers, employees necessarily have relevant roles
 - scientists need to speak to a broader audience: assumptions, choice of methods, etc. have implications for weight of evidence

Bradford Hill on action



- *“All scientific work is incomplete whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”*

Causal inference

- Debates over the scientific (epistemological) idea of cause can be used to distract attention from prudent public health action.
- Rather than debating cause, it may be better to ask:
 - *When do we know enough to act as if an association is causal?*

When do we know enough to act?

- Determination of “sufficient evidence” for preventive action depends on context:
 - availability of alternative ways of achieving the same social good
 - consequences of inaction or acting in error

What is “sufficient” evidence depends on context

- Why allow children to chew on plastics containing phthalate plasticizers when:
 - evidence for harmfulness of phthalates is equivocal, but...
 - it is economically feasible to make toys without phthalates?

Epidemiologic research and policy making are separate aspects of promoting public health. But...

- In practice, it is not easy to divide them.
 - Policy makers set agendas that determine the questions asked
 - Epidemiologists formulate hypotheses limited by our tools and imaginations; thus, information provided to policy makers is not independent of social forces.
 - There is a complicated feedback relation between the discoveries of science and the setting of policy.

I think false negatives are a much bigger problem than false positives

- Which error has greater public health impact?
- Epidemiology has inherent limitations which are more likely to lead to negative biases than positive biases

Common problems in epidemiology and their likely impacts

Sources of bias	Likely Impact on Findings	
Exposure misclassification	↓	False Negative
Outcome misclassification	↓	False Negative
Incomplete control of confounding	↓ ↑	Either
Low statistical power	↓	False Negative
Wrong statistical model	↓ ↑	Either
Manufactured uncertainty	↓	False Negative
“Classic” publication bias	↑	False Positive
Corporate suppression of findings	↓	False Negative

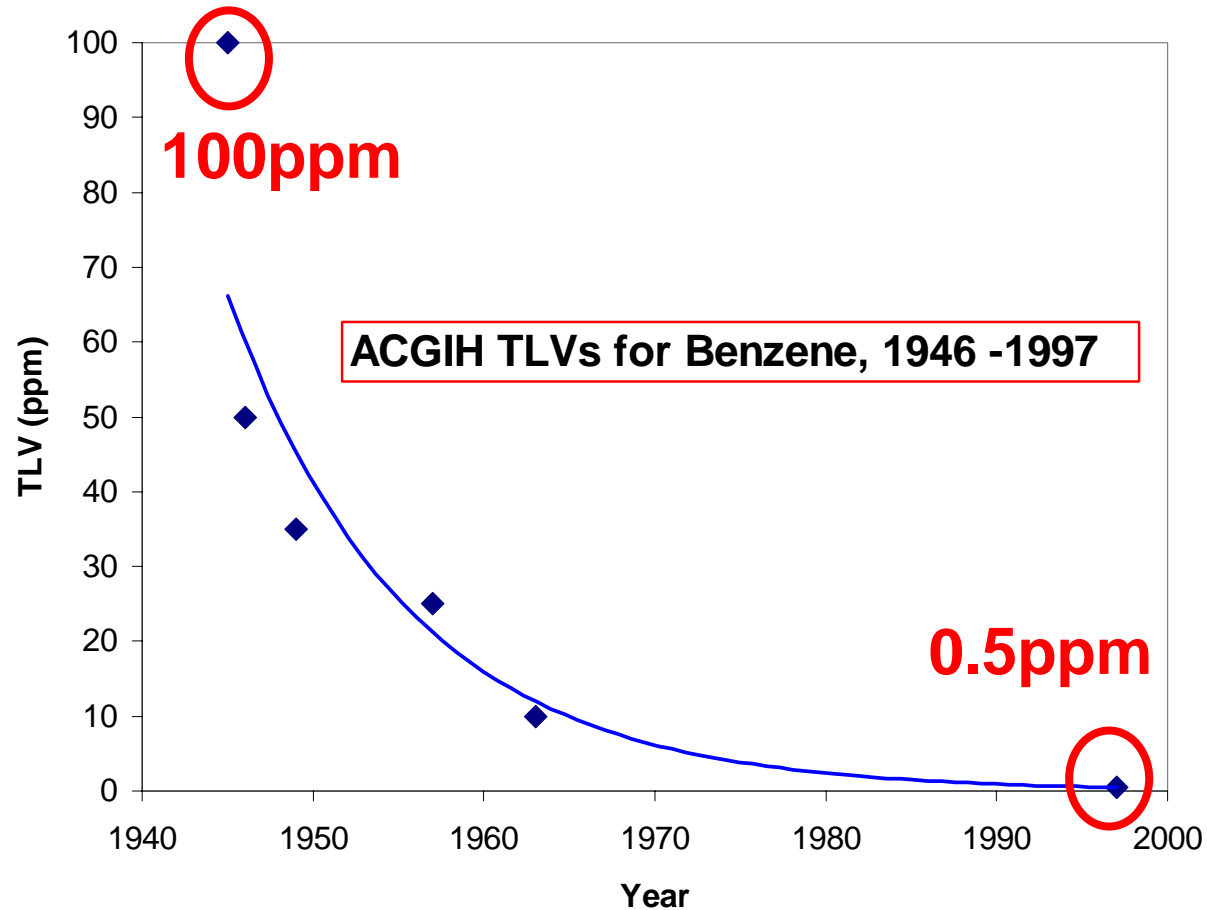
Late lessons from early warnings: the precautionary principle 1896–2000

- European Environment Agency, 2001
 - Poul Harremoës
 - David Gee
 - Malcolm MacGarvin
 - Andy Stirling
 - Jane Keys
 - Brian Wynne
 - Sofia Guedes Vaz

Late lessons from early warnings: the precautionary principle 1896–2000

- There were long delays in acting on evidence of risk for:
 - Asbestos
 - Benzene
 - PCBs
 - DDT
 - Many others

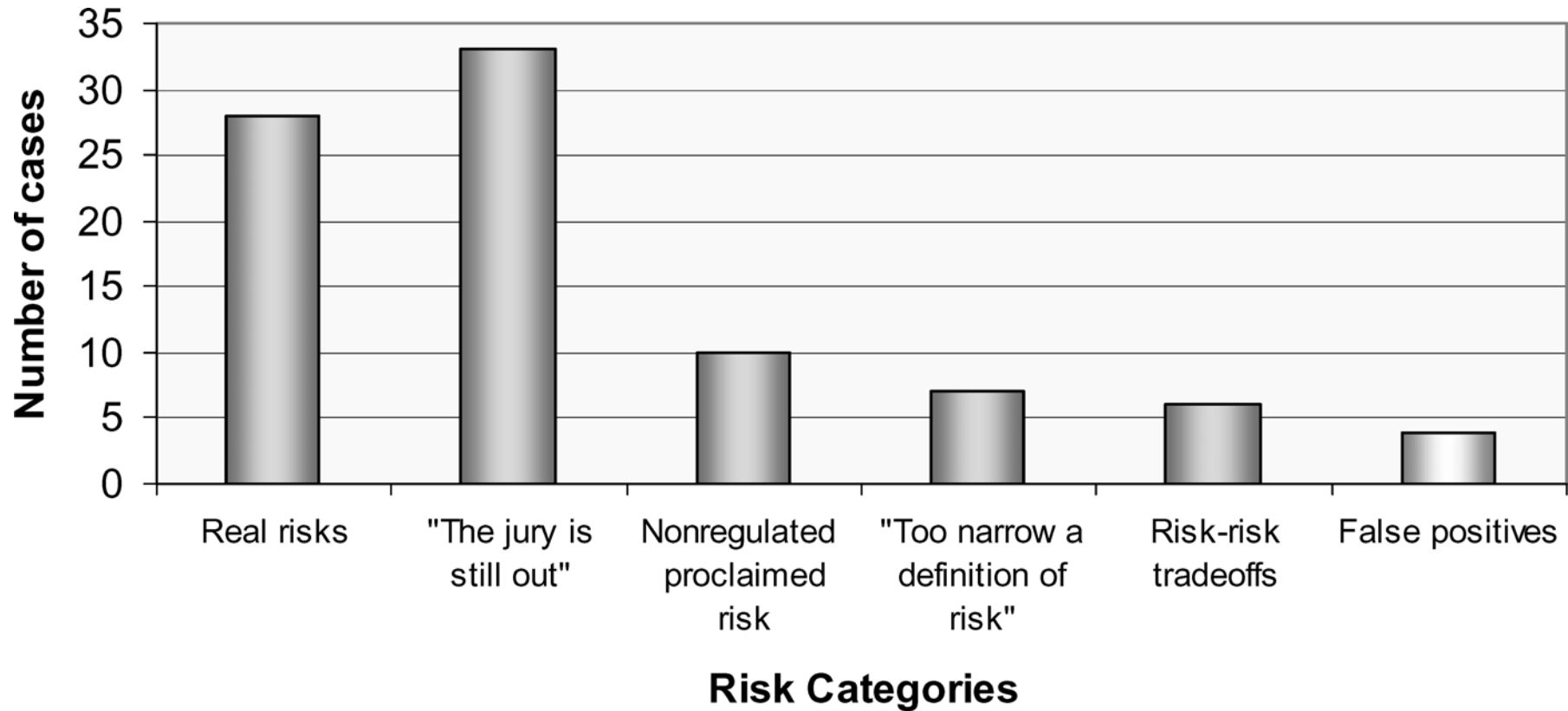
Benzene: action to control leukemia risk was delayed for decades by “scientific” debates



False positives are often something else

- Sometimes they are not false
- Sometimes they are not positive

Analysis of 88 cases of proclaimed “false positives” in the science policy literature



Hansen SF, Krayner von Krauss MP, Tickner JA. Risk Analysis 2007; 27: 255-269.

Two specific issues in epidemiology

- Publication bias
- “Subgroup analysis”

Publication Bias

- If not all studies are published, then summaries of study results may be biased
- The “file drawer problem”
 - Perhaps studies are done, but not published
 - But which ones?

Publication Bias

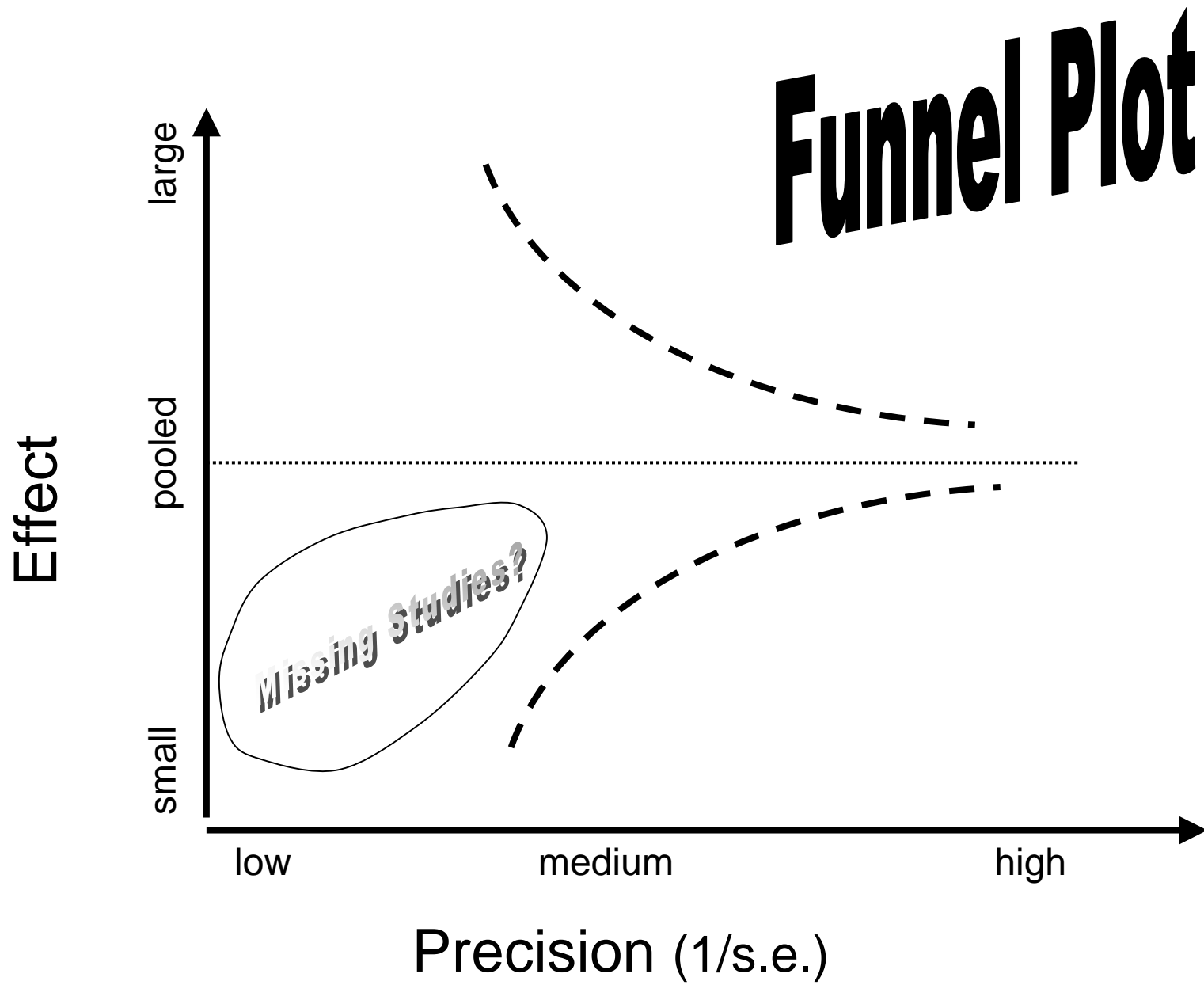
- It is typically assumed that small, negative studies are less likely to be published
- The argument:
 - big studies too expensive to not publish,
 - small positive studies published because they “found something”

Publication Bias

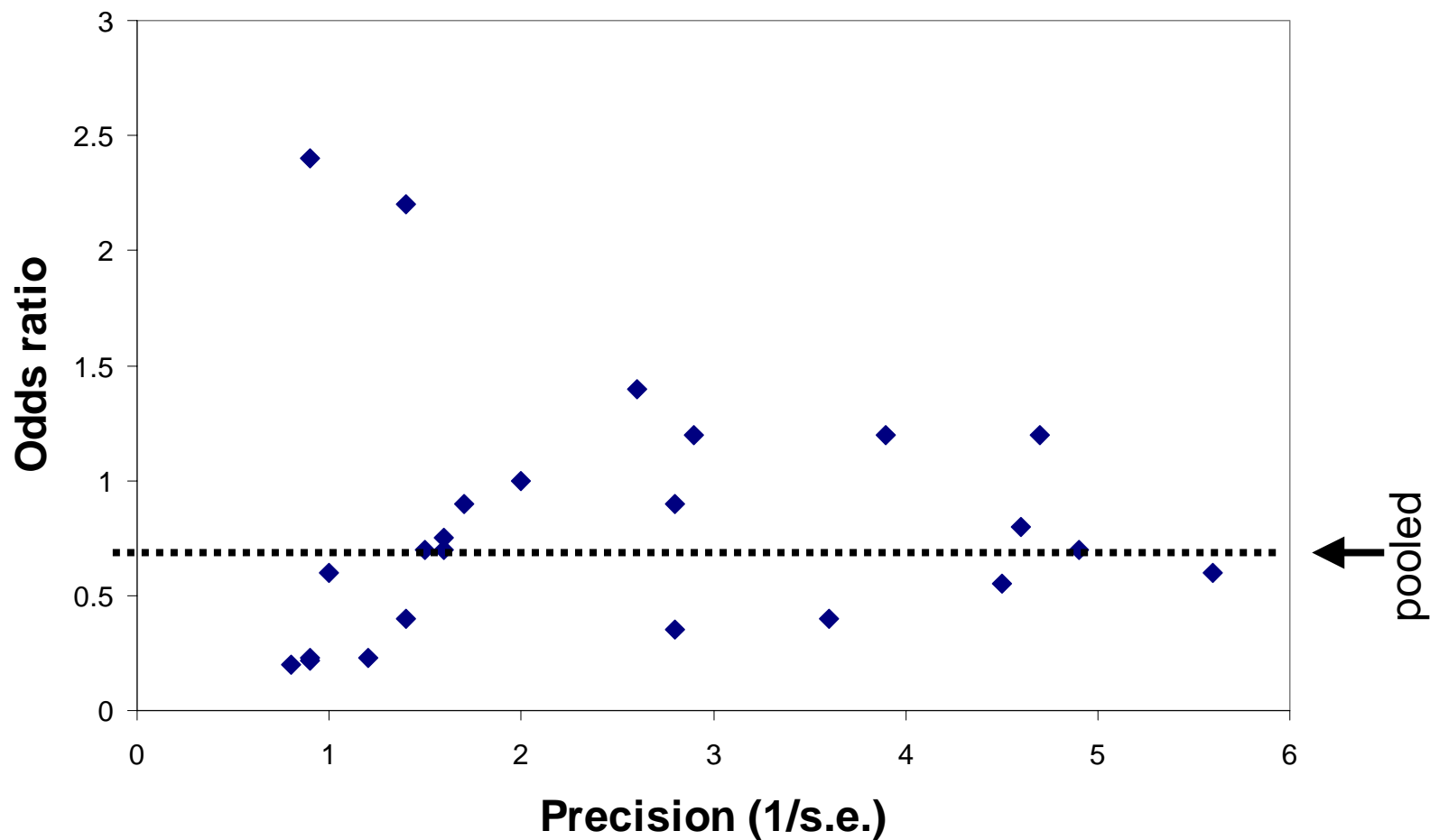
- But this logic is complicated by financial interests
 - which studies will remain unpublished depends on who paid for them, and what their biases are

Publication Bias

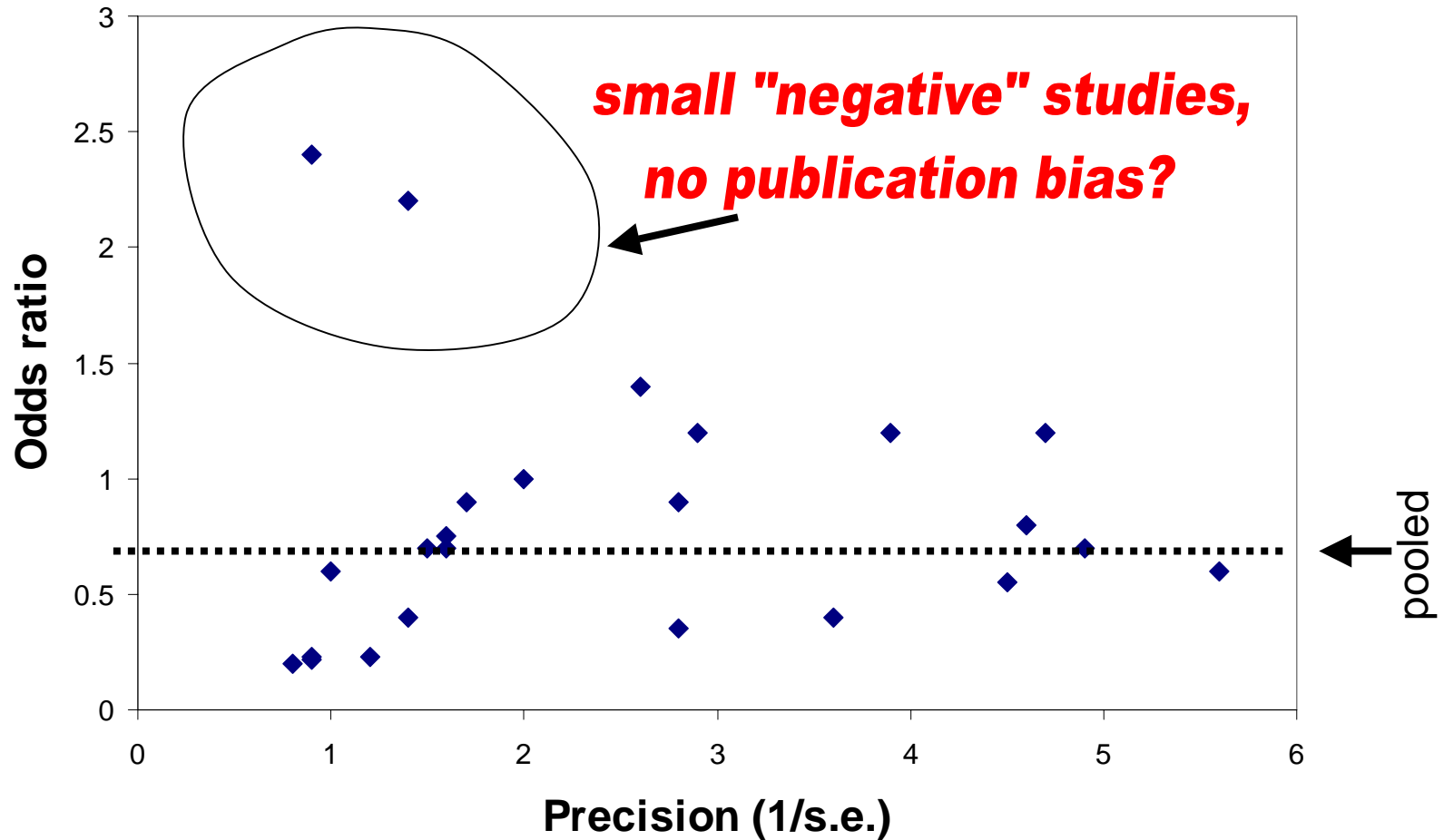
- Under ideal circumstances (clinical trials), publication bias may be quantified.
 - “Fail-safe N”:
 - how many negative studies would it take to cancel the observed effect?
 - is it plausible to believe this many studies remain unpublished?
 - Funnel plot



Meta-analysis of the protective effect of streptokinase in myocardial infarction



Meta-analysis of the protective effect of streptokinase in myocardial infarction



Publication Bias in Environmental Epidemiology

- Small negative studies may be *over-*represented in published literature
 - Chemical industry studies of dioxin and soft tissue sarcoma

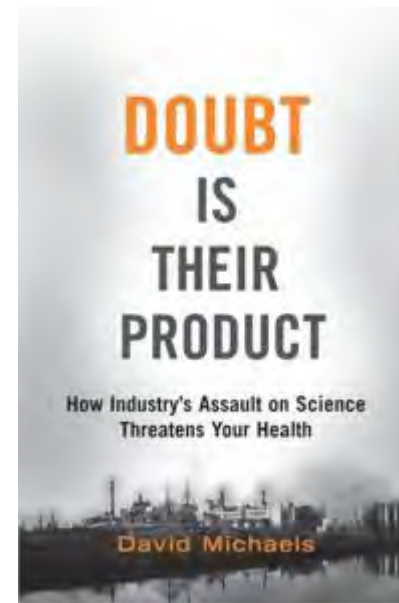
Publication Bias in Environmental Epidemiology

- Large positive studies may be suppressed
 - U.S. EPA requirement for industries to report data on toxicity was largely ignored
 - an “amnesty” on paying fines for not reporting yielded 11,000 never-published scientific studies from 120 companies

“LaMontagne AD, Christiani DC. Prevention of Work-related Cancers. Chapter 22 in: Colditz GA, Hunter D. Cancer Prevention: The Causes and Prevention of Cancer -- Volume I. Boston:Kluwer, 2000.

Economic Forces Create Biases

- Manufactured uncertainty
 - Several industries have learned that this is a cost-effective way to expand markets and impede regulation



The strongest predictor of the passive smoking -- health risk association was the affiliation of the authors

Passive Smoking Conclusion:	Author Affiliation	
	Tobacco	Non-Tobacco
Harmful	2	65
Not Harmful	29	10
RR = 7.0 (95% CI: 3.9 - 12.6)		

Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA 1998; 279:1566-1570

“Subgroup analysis”

- Epidemiologists are cautious about interactions
 - Tests for interaction terms are weak
 - Increase chances of finding “post-hoc” associations
- But...

Understanding the role of environment in human health means unraveling complex systems

- Despite decades of research, we are still largely ignorant about many critical components of these complex systems:
 - Human pathophysiology
 - Pollutant fate and transport
 - Human health behaviors

All share these characteristics:

- Tangled webs of causes & effects
- Dynamics are often synergistic, with indirect relationships, long delays between cause & effect

Complex time patterns are probably common (but hard to study!)

DDT and Breast Cancer in Young Women: New Data on the Significance of Age at Exposure

Barbara A. Cohn,¹ Mary S. Wolff,² Piera M. Cirillo,¹ and Robert I. Sholtz¹

Environ Health Perspectives 2007; 115:1406.

- California women who were < 14 years old in 1945 (year of DDT introduction), showed strong association between serum DDT and breast cancer risk
- Those born earlier showed to association

Conclusions

- FP & FN are real problems
 - But their definitions depend on what “gold standard” is used
- Adequate public health surveillance will lead to both FP & FN – they are inevitable!
- Efforts to reduce FPs MUST increase FNs
 - Which are more serious risks?