Epidemiology: the big picture

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McGill

Objective of the introductory lectures

- To completely put you off epidemiology
- To encourage you to seriously consider switching to another program

Why epidemiology?

- We are engaged in healthcare and health research
- To effectively practice medicine and public health, we need evidence/knowledge on 3 fundamental types of professional knowing “gnosis”:

Dia-gnosis	Etio-gnosis	Pro-gnosis	For individual (Clinical Medicine)
Dia-gnosis	Etio-gnosis	Pro-gnosis	For community (Public and community health)

Are these legitimate concerns for clinical medicine?

- Is ultrasonography accurate in detecting acute appendicitis?
- Do anti-depressants reduce the risk of suicides in people with depression?
- Will daily low dose aspirin reduce the risk of acute myocardial infarction?

Are these legitimate concerns for public health?

- Is mammography a good screening test for breast cancer?
- Does passive smoking increase the risk of spontaneous abortions?
- Are probiotics effective in preventing colon cancer?

If yes, how do we answer such questions?

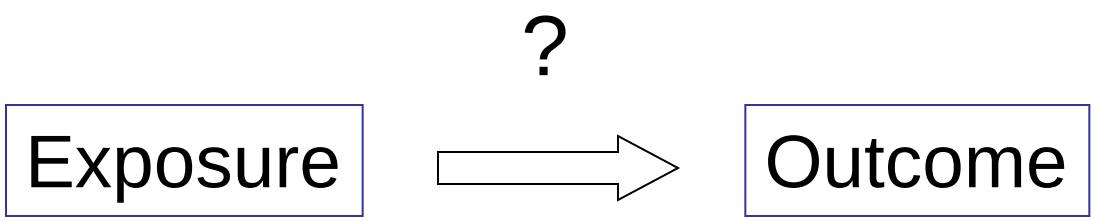
- Q: What is the strategy for answering salient questions for medical and public health practice?

- A: Epidemiologic research

- Without epidemiology, we would be hopelessly lost
- Even with epidemiology, we seem hopelessly lost!!

Of the 3 types of knowing ("gnosis") etio-gnosis (causality) is the central concern of epidemiology

- Most fundamental application of epidemiology: to identify etiologic (causal) associations between exposure(s) and outcome(s)



Causal claims and associations are frequent in the literature and often picked up by the media

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HEALTHY MEN

updated 3:14 p.m. EDT, Thu July 12, 2007

Men's Health: Truth or Myth?

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Laptops and sperm count

Truth or Myth:
Laptop computers may lower sperm count.

This actually is true. A recent study indicates that men who use a laptop computer on their lap may cause their scrotal temperatures to increase significantly. Increased testicular temperature has a well-documented link to reduced sperm count. The study concluded that long-term use of a laptop by teenage boys and young men could be damaging. The study said further testing was warranted.

Source: Oxford Journal Human Reproduction

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Last Updated: Wednesday, 1 August 2007, 11:51 GMT 12:51 UK

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Suicide rate rises in hot weather

The damp summer may have made us all miserable, but research suggests it is hot weather that poses a far more serious problem for vulnerable people.

Sunny weather: Not good news for all

A team from London's Institute of Psychiatry found that suicide rates go up during hot weather.

Analysis of more than 50,000 suicides in England and Wales between 1993 and 2003 showed the suicide rate rose when average daily temperatures topped 18C.

The study appears in the British Journal of Psychiatry.

The researchers found that once the daily average temperature rose above 18C each further degree increase was associated with a rise in suicides of almost 4%.

The rate in the rise of violent suicides was even higher, at 5% per degree rise in temperature.

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HEALTH NEWS

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A few cups of coffee may lower colon cancer risk

Posted: 01 August 2007 1708 hrs

TOKYO : Drinking a few cups of coffee a day may lower the risk of advanced colon cancer, at least for women, Japanese researchers said Wednesday.

The study, supported by Japan's health ministry, showed women who drink more than three cups of coffee a day were 56 percent less likely to develop advanced colon cancer than those who drink no coffee at all.

"Drinking coffee sustains the secretion of bile acid and keeps down cholesterol levels, the mechanisms thought to prevent colon cancer," the report said.

But unfortunately the effect was not seen in men, the medical research team said.

Many men smoke and drink alcohol more than women, and those habits probably offset the effect of coffee, the study said.

The research team tracked down about 96,000 people in Japan aged from 40 to 69 between the early 1990s and 2002, of whom 726 men and 437 wom
suffered colon cancer.

Causal claims are often inconsistent and contradictory!

Cancer News: Rectal Cancer: Article Printable Version

Rectal Cancer News

Coffee Does Not Decrease Risk of Colorectal Cancer

Researchers from the Harvard School of Public Health have reported that, contrary to the results of several previous studies, coffee consumption does not appear to reduce the risk of colorectal cancer. The details of this study were reported in the April 1, 2009 issue of the *International Journal of Cancer*.[1]

Habitual coffee drinking has been associated with a reduced risk of mortality and chronic diseases, including cancer. Current evidence suggests that coffee consumption is associated with a reduced risk of liver, kidney, and to a lesser extent, premenopausal breast cancer and colorectal cancer; coffee consumption has no association with prostate, pancreas, and ovarian cancers.

Some studies have indicated that coffee may have a protective effect against colon cancer; however, researchers continue to evaluate this link in an effort to establish more direct evidence. In order to examine the relationship between coffee consumption and colorectal cancer, researchers from Harvard conducted a review of 12 studies that included 646,848 participants and 5,403 cases of colorectal cancer.

They evaluated high versus low coffee consumption and found no significant effect of coffee consumption on colorectal cancer risk. The review included four studies in the United States, five in Europe, and three in Japan. The data from each country was very similar. There were no significant differences by gender or site of cancer; however, there was a slight inverse relationship between coffee consumption and colon cancer for women, which was even more pronounced among Japanese women (21% for total study, 38% for Japanese women).

The researchers observed that inverse associations between coffee consumption and colorectal cancer "were slightly stronger in studies that controlled for smoking and alcohol and in studies with shorter follow-up times."

They concluded that coffee is "unlikely to have a strong protective effect on colorectal cancer risk"; however, they also note that it does not appear to increase the risk of colorectal cancer either.

BBC NEWS

WATCH One-Minute World News

Last Updated: Friday, 8 August, 2003, 11:21 GMT 12:21 UK

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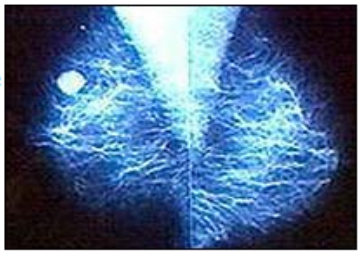
HRT 'doubles breast cancer risk'

Taking certain types of hormone replacement therapy (HRT) can double the risk of developing breast cancer, says a study of more than a million women.



Breast cancer could be more deadly after HRT

The largest ever study into the link between HRT and breast cancer was conducted by scientists at Cancer Research UK's Epidemiology Unit in Oxford.

The research suggests the single pill moderately increases the risk of breast cancer, but the combined pill doubles the risk.

It estimates HRT, taken by women to relieve the unpleasant symptoms of menopause, may have been responsible for an extra 20,000 cases of the disease i Britain in the last decade.

msnbc
A Fuller Spectrum of News

Combo HRT linked to lower-risk breast cancers

Tumors tend have better prognosis than after estrogen-only therapy

REUTERS
Updated: 8:42 p.m. ET June 5, 2007

The types of breast tumors that occur after combination hormone replacement therapy in women going through menopause and in post-menopausal women tend to have a better prognosis than those that occur after estrogen-only replacement therapy, Swedish researchers report.

A team at Malmo University Hospital conducted a study involving 12,583 peri- or post-menopausal women whose medical records were linked to national cancer registries. Of the group, 513 had a history of breast cancer prior to

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Health News

Drinking and Dementia: Is There a Link?

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Study Shows Drinkers With Genetic Predisposition to Alzheimer's Disease at Higher Risk

By Salynn Boyles
WebMD Medical News

Sept. 2, 2004 -- Drinking alcohol in middle age may increase the risk of late-life dementia in people who are genetically predisposed to develop Alzheimer's disease, according to findings from a Scandinavian study.

Researchers from Stockholm's Karolinska Institute reported that infrequent drinkers have a twofold increase in the risk of dementia in old age among carriers of a gene that has been linked to Alzheimer's. Gene carriers who frequently drink had a threefold increase in risk.

But the findings also show a protective effect for infrequent drinkers who did not have the genetic risk factor. Low-risk teetotalers and frequent drinkers in the study were twice as likely to experience mild cognitive declines later in life as infrequent drinkers.

The findings are reported in the Sept. 4 issue of the *BMJ* (formerly the *British Medical Journal*).

BBC NEWS

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Friday, 25 January, 2002, 12:13 GMT

Alcohol 'could reduce dementia risk'

Moderate alcohol consumption could be beneficial

Small amounts of alcohol could reduce the risk of dementia in older people regardless of the type of alcoholic drink consumed, research suggests.

It is known that light-to-moderate consumption lessens the risk of coronary heart disease and stroke, but Dutch scientists think it could be good for mental health.

See also:

- 17 Apr 01 | Health
  Alcohol 'protects old against heart failure'
- 01 Feb 01 | Health
  £6bn bill for alcohol abuse
- 06 Dec 00 | Health
  Alcohol 'improves IQ'
- 15 Apr 01 | Health
  Why alcohol affects women more
- 06 Jan 01 | Health
  Alcohol 'cuts strokes in women'
- 18 Dec 00 | Health
  Beer 'keeps cataracts away'
- 30 Oct 00 | Health
  Alcoholic liver disease linked to genes

Internet links:

- British Heart Foundation
- The Lancet
- Alzheimer's Society

From The Times
July 24, 2007

Taking statins may increase cancer risk

Nigel Hawkes, Health Editor

Lowering cholesterol with statins may slightly increase the risk of cancer, a study suggests.

It is not clear whether the cancer cases are caused by the drugs, or are a consequence of the low levels of "bad" LDL cholesterol produced by taking them.

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ASK THE TIMES DOCTOR

Heart problems?

Medscape Medical News

Statins Lower Cancer Risk

June 5, 2003 (Chicago) — Cholesterol-lowering statin drugs are associated with a statistically significant 20% reduction in cancer risk, a case-control shows. But researchers at the presentation here at the 39th annual meeting of the American Society of Clinical Oncology were quick to add that it's too soon to recommend that patients take the agents for cancer prevention.

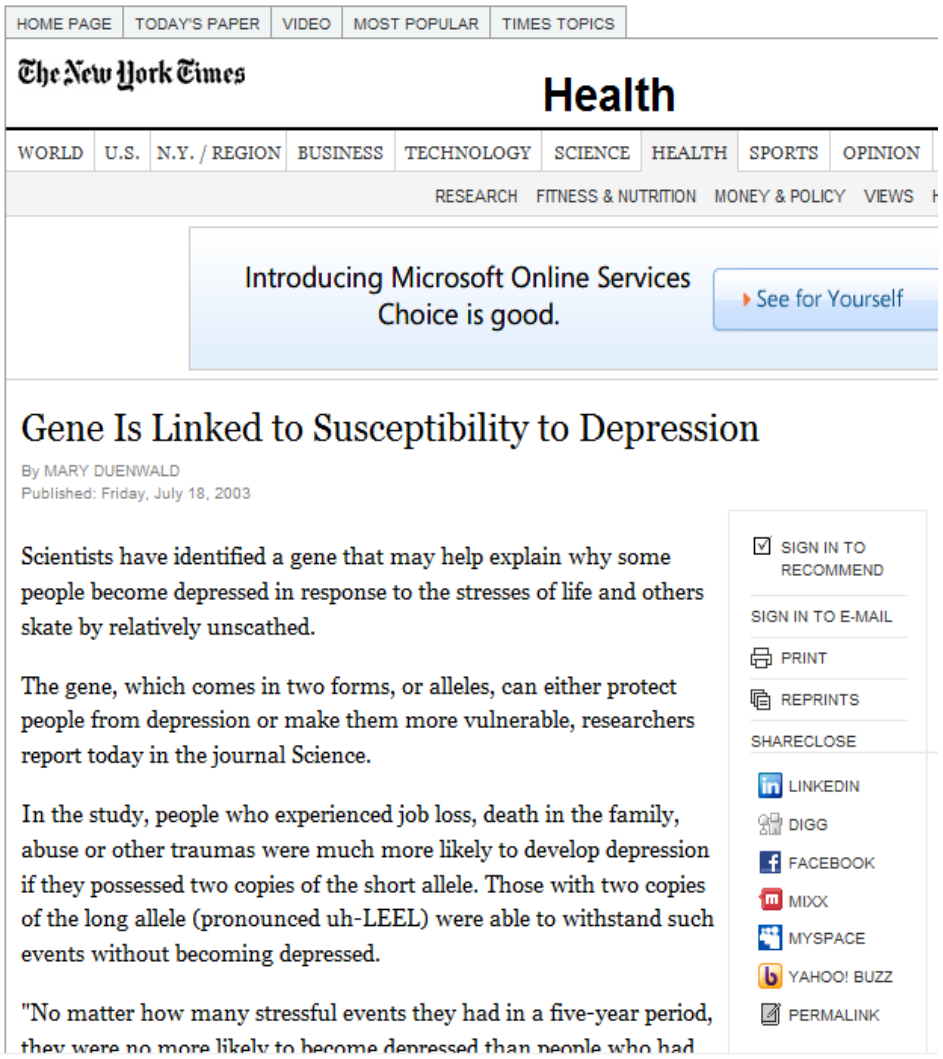
"Given the high number of people already on statins, the impact on public health could be quite considerable," said chief investigator Matthijs Graaf, PharmD, from the University of Amsterdam. "But since this is a case-control study, we need confirmation in a prospective randomized trial before we can suggest people take these agents to lower cancer risk."

William Gradishar, MD, from Northwestern University Feinberg School of Medicine in Chicago, Illinois, and moderator of a press conference at which the findings were discussed, agreed.

"This is provocative data," he said. "But the problem with interpreting it is that it's a population-based study. To make a blanket statement that statins should be used for cancer prevention would be premature."

Gene for Depression

2003



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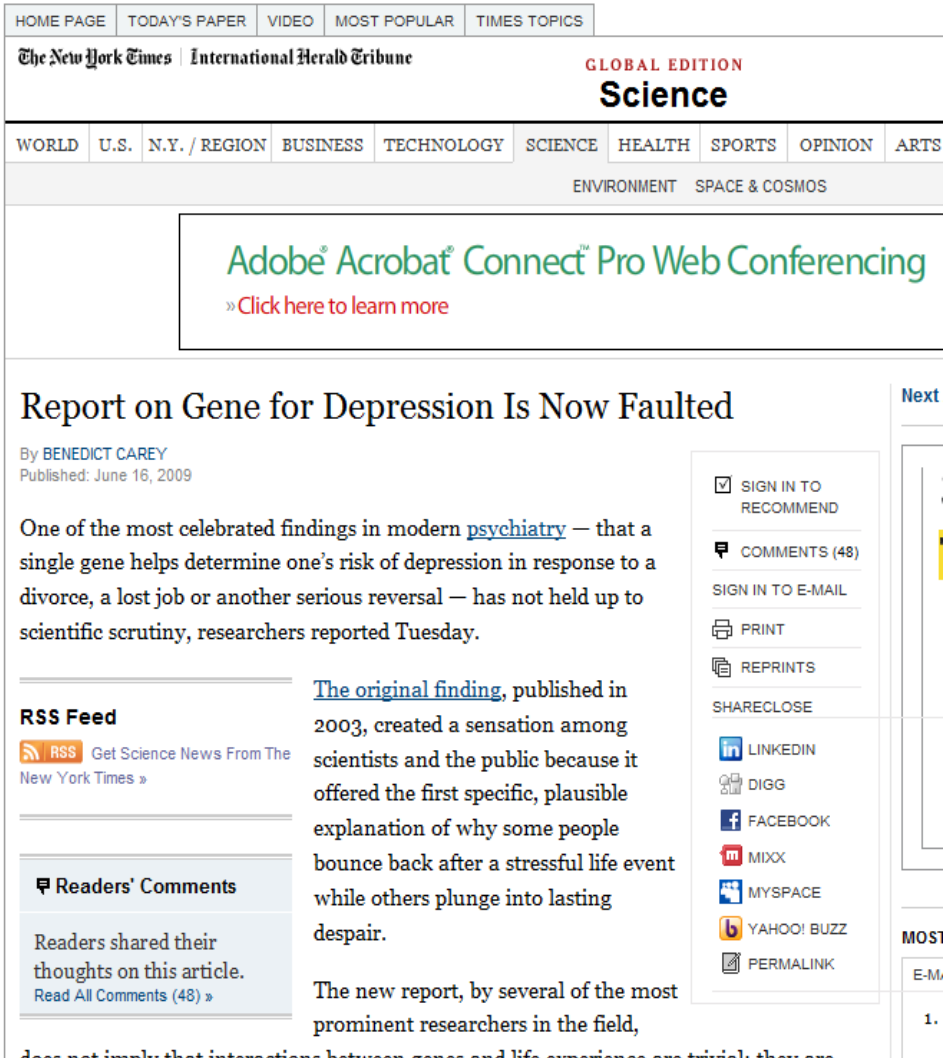


Studies clash on vitamin benefits

By **Elizabeth Landau**, CNN
April 19, 2010 8:56 a.m. EDT

Doctors recommend against taking multivitamin supplements if you can get the same nutrients in foods.

STORY HIGHLIGHTS

- Vitamins and calcium show protective effects against breast cancer in a Puerto Rican study
- A large Swedish study finds that vitamins may increase risk of breast cancer
- A diet high in B-vitamins is found to lower heart risks in Japanese study

(CNN) -- To take the multivitamin or to not take the multivitamin: That is the question researchers are still trying to answer.

New research on vitamins has offered conclusions that weren't crystal clear. But researchers generally recommend getting vitamins from foods, not supplements, to boost your health.

Vitamin supplements and cancer

CATEGORIES: HEALTH

Right out of the mouths of snakes

The magic ingredient in the $525-a-jar cream sold at Saks and Harrods: viper venom

by Alexandra Shimo on Thursday, April 15, 2010 9:30am - 1 Comment

Getty; iStock; Photo Illustration by Adam Cholewa

The venom of the temple viper, or *Tropidolaemus wagleri*, causes a mouse to stop breathing, its muscles paralyzed. It dies within minutes, and it is this phenomenon, or at least the paralytic quality, that made scientists realize its potential as a skin cream.

Forty-five female volunteers, aged between 40 to 60, were told to use the cream twice daily for 28 days. Some were given the snake venom cream, others another anti-aging cream, and some a placebo. The product seemed to work well—using a highly sensitive camera, the scientists measured a 73 per cent improvement of forehead wrinkles. But then again, the placebo had almost the same success rate (71 per cent) as did the other anti-aging cream (73 per cent). Even in a lab report, it seems, beauty can be in the eye of the beholder.

Costing $525, it works out to $17.50 per millilitre. But that doesn't seem to have deterred the excitement over the cream. Described on fashion blogs and in the media as "Botox in a bottle," a "miracle drug" or "better than Botox," the cream produces serious results, says Daniella Durov, a sales representative at the Toronto upscale retailer Andrews, which carries the cream. "Our clients all come back and they love it. They can't be without it, not even for a week."

http://www2.macleans.ca/2010/04/15/right-out-of-the-mouths-of-snakes/#more-119200

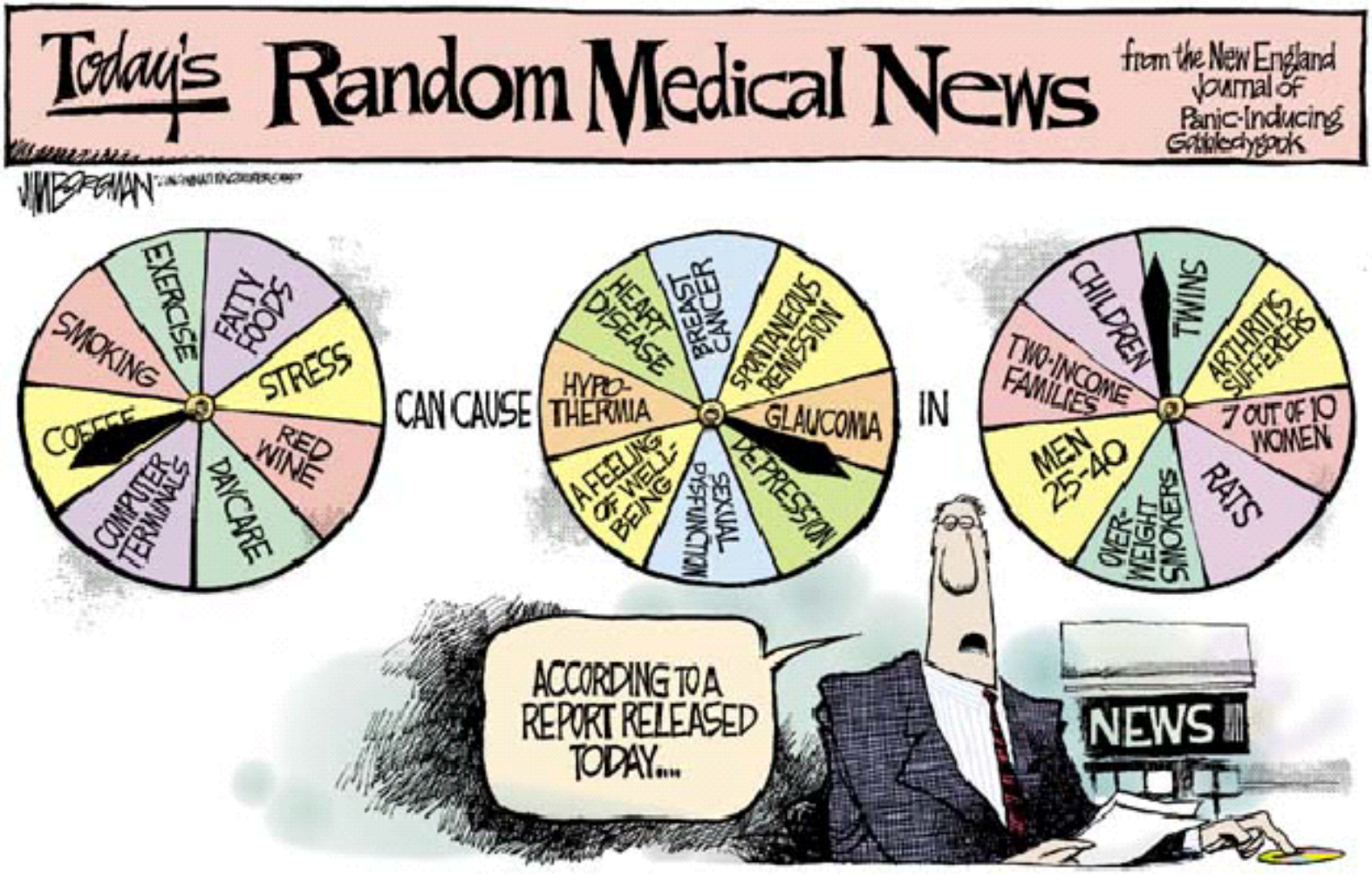


Figure 3: New England Journal of Panic-Inducing Gobbledygook.
Source: Jim Borgman, The Cincinnati Enquirer (27 April 1997, E4).

JNCI Journal of the National Cancer Institute Advance Access published November 20, 2009

EDITORIALS

Promoting Healthy Skepticism in the News: Helping Journalists Get It Right

Steven Woloshin, Lisa M. Schwartz, Barnett S. Kramer

Table 1. A recent medical journal article and excerpts of subsequent media coverage

The Study Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers (1)
Phase I study of olaparib in which 60 patients were enrolled with a variety of treatment refractory solid tumors. All were given the drug at various doses (to establish dosing and safety).
Response (improvement or no progression according to radiologic or tumor markers) was only seen in 12 of the 19 patients with BRCA1 or 2 mutations and ovarian, breast or prostate cancer.
Olaparib had fewer of the adverse effects typically seen with conventional chemotherapy.
Television Covered by three national television news programs: ABC, CBS, NBC
New cancer medicine might provide new era in treatment (NBC Nightly News) (2)
. . . [NBC's anchor]: "Now we turn to what some are calling the most important cancer treatment breakthrough in a decade. While we caution this is a small study, the New England Journal of Medicine tonight is saying it shows so much promise this could mean a whole new direction for cancer drugs, especially for those patients vulnerable to breast, ovarian and prostate cancer.
. . . [NBC's chief medical correspondent]: Patricia Buckles is a 29-year veteran of the battle with breast cancer, with all the suffering that surgeries and chemotherapy can bring. Almost out of options, she joined a trial of a new class of drugs, pills called PARP inhibitors.
Ms. PATRICIA BUCKLES: I went up there with growing cancer, measurable cancer, and I'm to the point now where the CAT scans show no evidence of disease.
. . . [NBC's chief medical correspondent]: Julian Lewis had prostate cancer that had resisted all treatments and spread throughout his body, until he got into a PARP inhibitor trial.
Mr. JULIAN LEWIS: My PSA level, which is a marker of the tumor, went right down to a very low level and it stayed low. And my bone metastases also seemed to have almost disappeared, judged from MRI scans.
. . . [NBC's chief medical correspondent]: As I said, many scientists believe these drugs could treat some people who don't have the genetic mutations, especially for ovarian cancer. Those studies are under way. But whatever else happens, these drugs look like they will eventually save thousand of lives."

A 1995 report in *Science* flayed epidemiology and this led to a lot of soul searching

SPECIAL NEWS REPORT

Epidemiology Faces Its Limits

The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty

The news about health risks comes thick and fast these days, and it seems almost constitutionally contradictory. In January of last year, for instance, a Swedish study found a significant association between residential radon exposure and lung cancer. A Canadian study did not. Three months later, it was pesticide residues. The *Journal of the National Cancer Institute* published a study in April reporting—contrary to previous, less powerful studies—that the presence of DDT metabolites in the bloodstream seemed to have no effect on the risk of breast cancer. In October, it was abortions and breast cancer. Maybe yes. Maybe no. In January of this year it was electromagnetic fields (EMF) from power lines. This time a study of electric utility

ROBERT VISSER/GREENPEACE

Anxiety epidemic. Protesting risks that may—or may not—be real.

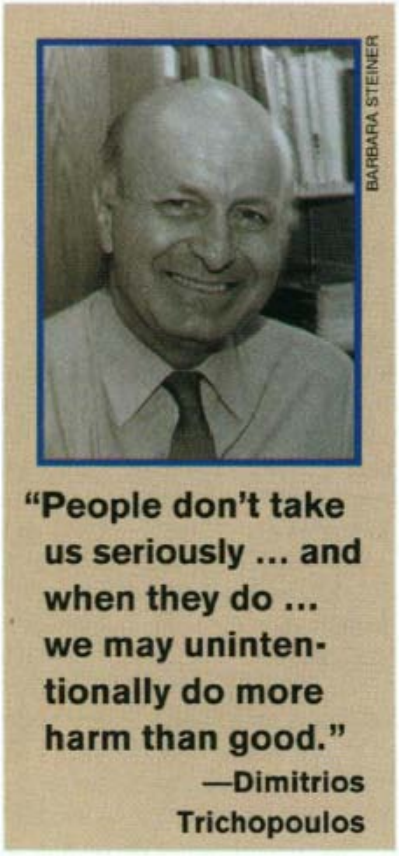
on the press for its reporting of epidemiology, and even on the public "for its unrealistic expectations" of what modern medical research can do for their health. But many epidemiologists interviewed by *Science* say the problem also lies with the very nature of epidemiologic studies—in particular those that try to isolate causes of noninfectious disease, known variously as "observational" or "risk-factor" or "environmental" epidemiology.

The predicament of these studies is a simple one: Over the past 50 years, epidemiologists have succeeded in identifying the more conspicuous determinants of noninfectious diseases—smoking, for instance, which can increase the risk of developing lung cancer by as much as 3000%. Now they are left to search for subtler links be-

Rothman, editor of the journal *Epidemiology*: "We're pushing the edge of what can be done with epidemiology."

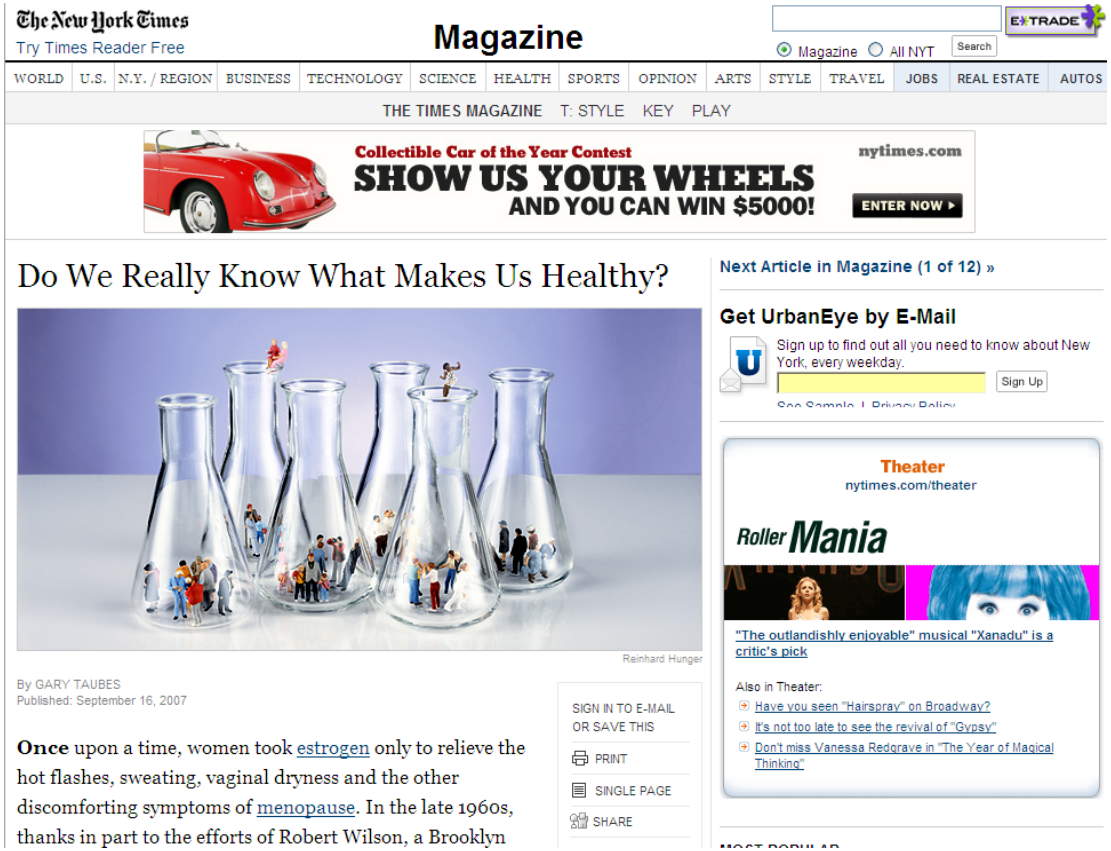
With epidemiology stretched to its limits or beyond, says Dimitrios Trichopoulos, head of the epidemiology department at the Harvard School of Public Health, studies will inevitably generate false positive and false negative results "with disturbing frequency." Most epidemiologists are aware of the problem, he adds, "and tend to avoid causal inferences on the basis of isolated studies or even groups of studies in the absence of compelling biomedical evidence. However, exceptions do occur, and their frequency appears to be increasing." As Trichopoulos explains, "Objectively the problems are not more than they used to be, but the pressure is greater on the profession, and the number who practice it is greater."

As a result, journals today are full of studies suggesting that a little risk is not nothing at all. The findings are often touted in press releases by the journals that publish them or by the researchers' institutions, and newspapers and other media often report the claims uncritically (see box on p. 166). And



Taubes G. Science 1995

Taubes returned in 2007, to take another swing at epidemiology!



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Do We Really Know What Makes Us Healthy?

Reinhard Hunger

By GARY TAUBES
Published: September 16, 2007

Once upon a time, women took estrogen only to relieve the hot flashes, sweating, vaginal dryness and the other discomforting symptoms of menopause. In the late 1960s, thanks in part to the efforts of Robert Wilson, a Brooklyn

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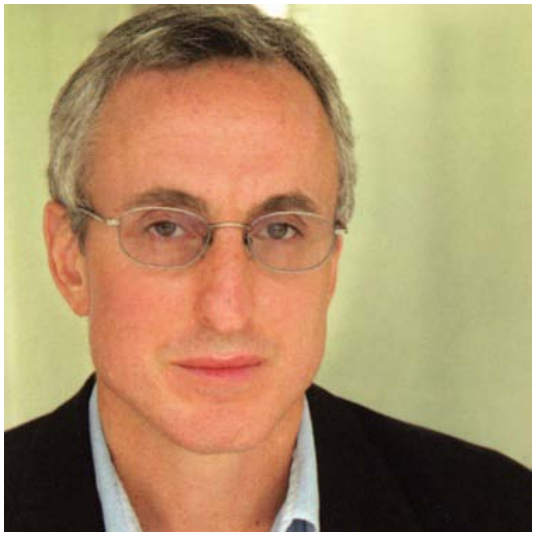


"Much of what we're told about diet, lifestyle and disease is based on epidemiologic studies.

What if it is just bad science?"

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

factors that influence this problem and some corollaries thereof.

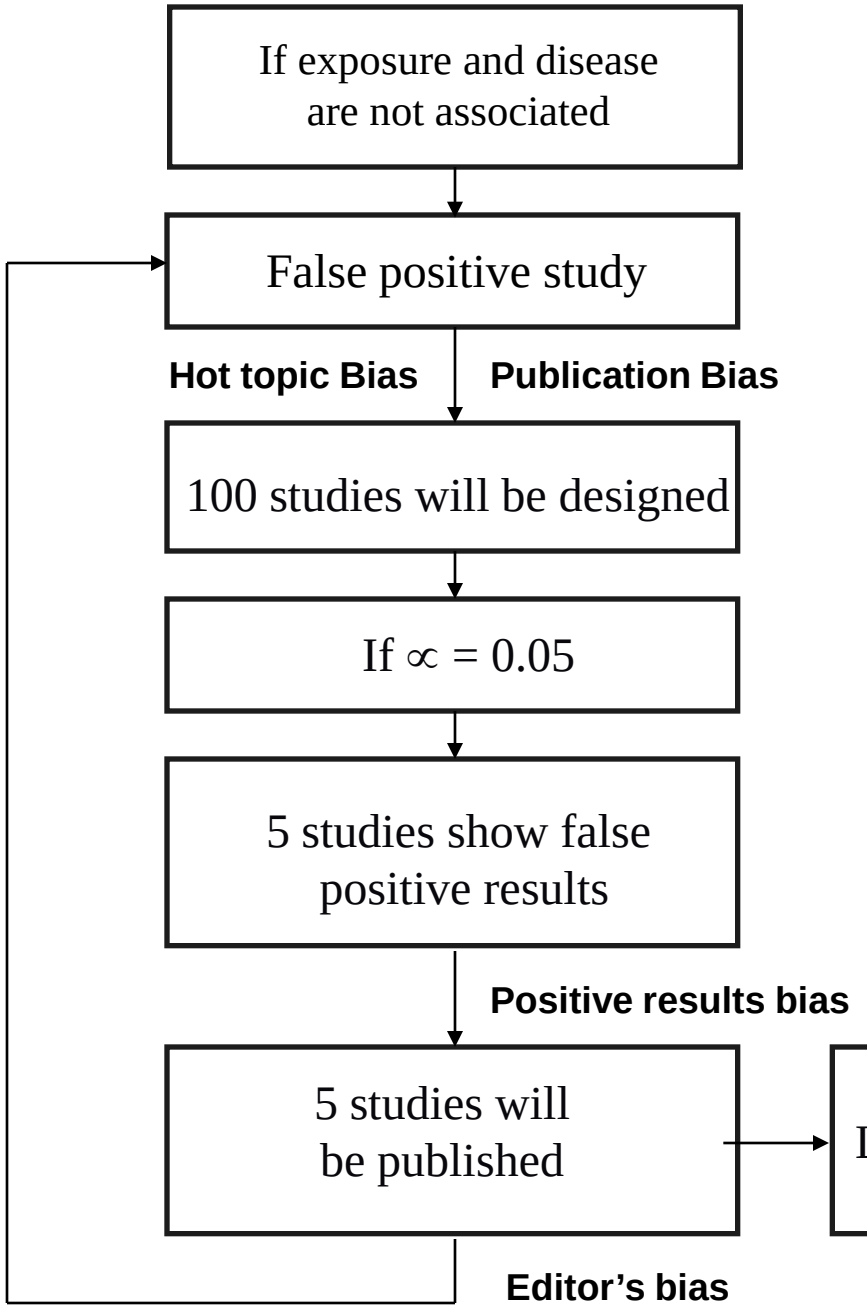
Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2



THE FALSE POSITIVE RESEARCH CYCLE

(Choi, 1998)

Courtesy: Bernard Choi, PHAC

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most prominent when high-impact research is involved.

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

JAMA. 2005;294:218-228 www.jama.com

CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.[1,2]

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.[3-5] Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives

Persistence of Contradicted Claims in the Literature

Athina Tatsioni, MD
Nikolaos G. Bonitsis, MD
John P. A. Ioannidis, MD

Context Some research findings based on observational epidemiology are contradicted by randomized trials, but may nevertheless still be supported in some scientific circles.

Objectives To evaluate the change over time in the content of citations for 2 highly cited epidemiological studies that proposed major cardiovascular benefits associated with vitamin E in 1993; and to understand how these benefits continued being defended in the literature, despite strong contradicting evidence from large randomized clinical trials (RCTs). To examine the generalizability of these findings, we also examined the extent of persistence of supporting citations for the highly cited and contradicted protective effects of beta-carotene on cancer and of estrogen on Alzheimer disease.

Data Sources For vitamin E, we sampled articles published in 1997, 2001, and 2005 (before, early, and late after publication of refuting evidence) that referenced the highly cited epidemiological studies and separately sampled articles published in 2005 and referencing the major contradicting RCT (HOPE trial). We also sampled articles published in 2006 that referenced highly cited articles proposing benefits associated with beta-carotene for cancer (published in 1981 and contradicted long ago by RCTs in 1994-1996) and estrogen for Alzheimer disease (published in 1996 and contradicted recently by RCTs in 2004).

Data Extraction The stance of the citing articles was rated as favorable, equivocal, and unfavorable to the intervention. We also recorded the range of counterarguments raised to defend effectiveness against contradicting evidence.

Results For the 2 vitamin E epidemiological studies, even in 2005, 50% of citing articles remained favorable. A favorable stance was independently less likely in more recent articles, specifically in articles that also cited the HOPE trial (odds ratio for 2001, 0.05 [95% confidence interval, 0.01-0.19; $P < .001$] and the odds ratio for 2005, 0.06 [95% confidence interval, 0.02-0.24; $P < .001$], as compared with 1997), and in general/internal medicine vs specialty journals. Among articles citing the HOPE trial in 2005, 41.4% were unfavorable. In 2006, 62.5% of articles referencing the highly cited article that had proposed beta-carotene and 61.7% of those referencing the highly cited article on estrogen effectiveness were still favorable; 100% and 96%, respectively, of the citations appeared in specialty journals; and citations were significantly less favorable ($P = .001$ and $P = .009$, respectively) when the major contradicting trials were also mentioned. Counterarguments defending vitamin E or estrogen included diverse selection and information biases and genuine differences across studies in participants, interventions, cointerventions, and outcomes. Favorable citations to beta-carotene, long after evidence contradicted its effectiveness, did not consider the contradicting evidence.

Conclusion Claims from highly cited observational studies persist and continue to be supported in the medical literature despite strong contradictory evidence from randomized trials.

SOME RESEARCH FINDINGS THAT have received wide attention in the scientific community, as proven by the high citation counts of the respective articles, are eventually contradicted by subsequent evidence.[1] A number of such high-profile contradictions pertain to differences between nonrandomized and randomized studies. For example, the effect of vitamin E on cardiovascular disease prevention has been in the center of a major debate in clinical research over the last 2 decades. Vitamin E is known to have antioxidant activity, and a long list of citations in the preclinical literature on antioxidants[2-4] suggested that these agents may be beneficial for cancer and cardiovascular disease. Two highly cited publications suggested in the 1990s that vitamin E could decrease cardiovascular disease risk by almost half in men and in women.[5,6] However, subsequent randomized trials showed no benefit or even suggested increased harm.[7,8] Several other highly prominent contradictions have also been recorded pertaining to the effects of other dietary components and hormones.[9-15] The prominent refutation of the epidemiological studies has spurred considerable controversy for observational epidemiology in general.[16-21]

Such debate offers opportunities to

JAMA. 2007;298(21):2517-2526

Why Most Discovered True Associations Are Inflated

John P. A. Ioannidis

Abstract: Newly discovered true (non-null) associations often have inflated effects compared with the true effect sizes. I discuss here the main reasons for this inflation. First, theoretical considerations prove that when true discovery is claimed based on crossing a threshold of statistical significance and the discovery study is underpowered, the observed effects are expected to be inflated. This has been demonstrated in various fields ranging from early stopped clinical trials to genome-wide associations. Second, flexible analyses coupled with selective reporting may inflate the published discovered effects. The vibration ratio (the ratio of the largest vs. smallest effect on the same association approached with different analytic choices) can be very large. Third, effects may be inflated at the stage of interpretation due to diverse conflicts of interest. Discovered effects are not always inflated, and under some circumstances may be deflated—for example, in the setting of late discovery of associations in sequentially accumulated overpowered evidence, in some types of misclassification from measurement error, and in conflicts causing reverse biases. Finally, I discuss potential approaches to this problem. These include being cautious about newly discovered effect sizes, considering some rational down-adjustment, using analytical methods that correct for the anticipated inflation, ignoring the magnitude of the effect (if not necessary), conducting large studies in the discovery phase, using strict protocols for analyses, pursuing complete and transparent reporting of all results, placing emphasis on replication, and being fair with interpretation of results.

(*Epidemiology* 2008;19: 640–648)

prognostic studies, and so forth. I start here with the assumption that a research finding is indeed true (non-null), ie, it reflects a genuine association that is not entirely due to chance or biases (confounding, misclassification, selection biases, selective reporting, or other). The question is: do the effect sizes for such associations, at the time they are first discovered and published in the scientific literature, accurately reflect the true effect sizes?

The article has the following sections: a brief literature review on inflated early-effect sizes based on theoretical and empirical considerations; a description of the major reasons why early discovered effects are inflated and the major countering forces that may occasionally lead to deflated effects (underestimates); and suggestions on how to deal with these problems.

Evidence About Inflated Early-Effect Sizes

Table 1 cites articles suggesting that early studies give (on average) inflated estimates of effect.[2–34] I list here only selected evaluations that cover either many different articles/effects or a whole research domain or method. This list is nowhere close to exhaustive. For some topics, such as the inflation of regression coefficients for variables selected through stepwise statistical-significance-based processes, the literature is

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

ABSTRACT

BACKGROUND

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

RESULTS

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

While almost all trials with “positive” results on antidepressants had been published, trials with “negative” results submitted to the US Food and Drug Administration, with few exceptions, remained either unpublished or were published with the results presented so that they would appear “positive”

Non-replicated studies and publication bias

Human Heredity

Hum Hered 2007;64:203–213
DOI: 10.1159/000103512

Received
Accepted
Published

Non-Replication and Inconsistency in the Genome-Wide Association Setting

John P.A. Ioannidis

Clinical and Molecular Epidemiology Unit and Evidence-Based Medicine and Clinical Trials Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Biomedical Research Institute-Foundation for Research and Technology-Hellas, Ioannina, Greece; Department of Medicine, Tufts University School of Medicine, Boston, Mass.., USA

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EJC

Almost all articles on cancer prognostic markers report statistically significant results

Panayiotis A. Kyzas[a], *Despina Denaxa-Kyza*[a], *John P.A. Ioannidis*[a,b,c,*]

Is epidemiology inherently prone to "optimism bias"?

What are the implications of optimism bias in clinical research?

Two decades ago, Peter Gøtzsche drew attention to the issue of citation bias: studies of new treatments are more likely to cite previous studies reporting positive results than equally valid studies with disappointing results.[1] John Ioannidis[2] has recently provided compelling evidence for the persistence of this phenomenon in a study of 49 reports of frequently-cited original clinical research. While almost all of the reports (n=45) claimed to show intervention effectiveness, in almost a third of cases (n=14), subsequent studies yielded estimates of effects that were either weaker than (n=7), or actually contradicted (n=7) the original studies.

Citation bias is, however, just one manifestation of what might be called optimism bias—unwarranted belief in the efficacy of new therapies. It has been shown that optimism bias is more likely to be promoted by research sponsored by industry than it is by publicly-funded research.[3] This difference reflects either biased under-reporting of less favourable studies, or

Peter Gøtzsche (left), John Ioannidis (middle), David Spiegelhalter (right)

randomised trials. Despite its ethical and scientific benefits, this practice is not yet done routinely. One result of this indefensible situation is that some trials are less well designed than they should be, and others are frankly unnecessary.[10] Optimism bias could also be countered by using quantitative methods to assess the inherent credibility of new findings.[11]

Optimism bias raises a crucial empirical question: what is the prior probability, on average, of a proposed

"Optimism bias—unwarranted belief in the efficacy of new therapies. It has been shown that optimism bias is more likely to be promoted by research sponsored by industry than it is by publicly-funded research. This difference reflects either biased under-reporting of less favourable studies, or inappropriately selected comparators. More recently, it has been suggested that optimism bias is likely to be encouraged not only by selective reporting of complete studies, but also by selective reporting of outcomes within studies, and by early stopping of studies."

Chalmers I et al. Lancet 2006;Vol 367 February 11, 2006

State-of-the-art: epidemiology is a mess!

- Too many causal claims; optimism bias is pervasive
- Inconsistency in study findings and too many apparent contradictions
- Causal inferences made on the basis of isolated studies
- Most studies biased or inconclusive or false
- Most discovered true associations are inflated
- Fear and panic inducing rather than helpful; media-induced hype
- Cannot detect small effects; big effects are not to be found anymore
- Lack of consistency in concepts and terminology
- No consensus on the “theory of epidemiology”
- Accused of being too “fuzzy” and not rigorous

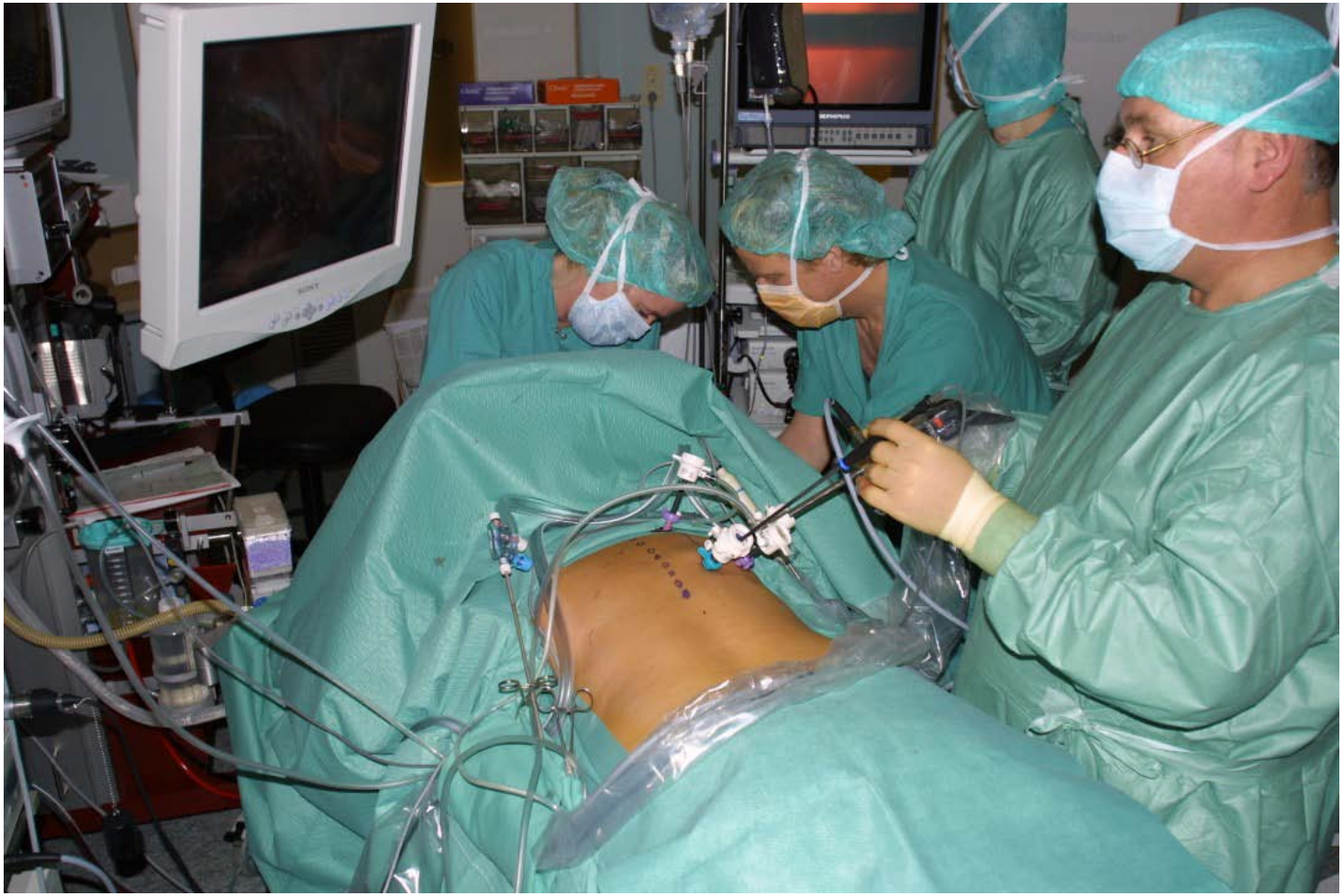
Given this mess, here are some key questions:

- Where is the guarantee that causal claims are true?
- Can epidemiological studies be wrong?
- Can they make misleading conclusions?
- How can we know when a study result is incorrect?
- Is common sense adequate to judge and interpret epidemiologic literature?

Causality: is it intuitive?

- Most of us intuitively understand causality, even if we have never formally studied it!
- Even as children, we grow up making associations and causal connections
- However, is epidemiology merely applying common sense?

Are senior surgeons incompetent?



Does anti-snake venom help or kill?

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2005.01535.x

VOLUME 11 NO 1 PP 22–30 JANUARY 2006

Clinical predictors of in-hospital mortality in patients with snake bite: a retrospective study from a rural hospital in central India

Shriprakash Kalantri[1,2], Amandeep Singh[1], Rajnish Joshi[1,2], Samuel Malamba[2], Christine Ho[2], Joseph Ezoua[2] and Maureen Morgan[2]

1 *Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram, India*
2 *Division of Epidemiology, University of California at Berkeley, Berkeley CA, USA*

Summary

OBJECTIVE To determine the association between selected admission risk factors and in-hospital mortality in patients admitted with venomous snake bite to a rural tertiary care hospital in central India.

METHODS Retrospective cohort study of patients aged 12 years or older admitted to a rural hospital in central India between January 2000 and December 2003 with venomous snake bites. The primary endpoint was in-hospital mortality. We used Cox proportional-hazards regression analysis to evaluate the association between risk factors (home-to-hospital distance, bite-to-hospital time, vomiting, neurotoxicity, urine albumin, serum creatinine concentration and whole-blood clotting time) and in-hospital mortality.

RESULTS Two hundred and seventy-seven patients [mean age 32 (SD 12) years; 188 men (68%)] were admitted with venomous snake bite, 29 patients (11%) died. The probability of survival at day 7 was 83%. Vomiting [hazard ratio 6.51 (95% CI 1.94–21.77), $P \leq 0.002$], neurotoxicity [hazard ratio 3.15 (95% CI 1.45–6.83), $P = 0.004$] and admission serum creatinine concentration [hazard ratio 1.35 (95% CI 1.17–1.56), $P \leq 0.001$] were associated with higher risk of death in the adjusted analysis.

CONCLUSIONS In our rural hospital setting, the overall mortality rate was 11 per 100 cases of snake bite. Vomiting, neurotoxicity and serum creatinine are significant predictors of mortality among inpatients with snake bite. These predictors can help clinicians assess prognosis of their patients more accurately and parsimoniously and also serve as useful signposts for clinical decision-making.

Does pet ownership reduce risk of cardiovascular disease?

Does HRT lower CHD risk?

- HRT was shown to reduce coronary heart disease (CHD) in women in several observational studies
- Subsequently, RCTs showed that HRT might actually increase the risk of heart disease in women
- What can possibly explain the discrepancy between observational and interventional studies?
  - Women on HRT in observational studies were more health conscious, thinner, and more physically active, and they had a higher socioeconomic status and better access to health care than women who are not on HRT
  - Self-selection of women into the HRT user group could have generated uncontrollable confounding and lead to "healthy-user bias" in observational studies.
  - Also, individuals who adhere to medication have been found to be healthier than those who do not, which could produce a "compliance bias"
  - Furthermore, there is the issue of "prescriber effect" and "eager patient effect"

- Full story in Gary Taubes' NYT article!
- Also see a B-File on the HRT story

Observational studies should carry a health warning

Observational studies have their place, although the results often depend crucially on the type of analysis used to generate them. A good illustration of this principle comes from a study comparing four different ways of looking at the effects of invasive revascularisation after heart attack. Essentially, all four methods adjusted for the many baseline differences between people who have invasive treatments and people who don't, differences that would normally be eliminated by randomisation in a randomised trial.

Using data from 73238 Medicare patients, the authors showed that standard analytical methods—multivariate risk adjustment and two methods based on propensity scoring—came up with a survival benefit of around 50% (adjusted relative risks 0.51, 0.54, and 0.54). A newer method called instrumental variable analysis indicated a more modest survival benefit of 16% (adjusted relative risk 0.84), closer to the results from randomised trials. Does the new analysis get nearer "the truth" than other methods?

Not necessarily, says a linked editorial (pp 314-6). Estimating treatment effects from observational studies will never be an exact science. The best researchers can do is make sure their analysis includes all the important baseline variables and balances them between treated and untreated groups. The best we can do is to interpret any results with caution.

JAMA 2007;297:278-85

BMJ 2007

HRT: It's the way you take it

Treatment for menopause symptoms does not raise heart-attack risk, study says

Reuters
Published: 12 hours ago

Women who take hormone replacement therapy to treat menopause symptoms do not have a higher than usual risk of heart attack, especially if they use a cream or skin patch or take "cyclic" hormone combinations, Danish researchers reported yesterday.

Their study, published in the European Heart Journal, suggests it is not hormone replacement therapy that raises the risk of heart attacks in women, but the way it is taken.

It also shows that a large study called the Women's Health Initiative, which frightened many women away from HRT after it was stopped in 2002, may not be the last word on treatment.

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BOOKMARK

"This study is the first, big observational study that addresses the influence of various regimens, doses and routes of administration," said Ellen Lokkegaard of the Rigshospitalet in Copenhagen, who led the study.

The Women's Health Initiative was stopped in early 2002 because HRT combining estrogen and progestin appeared to cause a 24-per-cent higher risk of breast cancer. Women taking the combination of hormones had twice the normal rate of blood clots, and higher risks of stroke and heart attack.

Most of the women took Premarin or Prempro, made by Wyeth. Sales of all HRT drugs plummeted.

But some experts suggested the study gave a very limited picture of HRT and said perhaps different drugs, taken by women at younger ages, might have other effects.

Lokkegaard's team studied 698,000 women aged 51 to 69 in Denmark, who take part in a national health database.

"Overall, we found no increased risk of MI (heart attack) with the current hormone therapy compared with women who never used hormone therapy," they wrote .

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Today's Gazette

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Robert Shiller predicted both the 1990s stock market boom and bust and the U.S. ...

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Medical Papers by Ghostwriters Pushed Therapy

By NATASHA SINGER
Published: August 4, 2009

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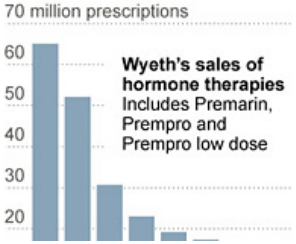
Newly unveiled court documents show that ghostwriters paid by a pharmaceutical company played a major role in producing 26 scientific papers backing the use of hormone replacement therapy in women, suggesting that the level of hidden industry influence on medical literature is broader than previously known.

Steep Drop

Wyeth's sales of hormone therapies have dropped sharply since a federal study in 2002 found that drugs like Prempro could increase the risk of certain diseases.



The articles, published in medical journals between 1998 and 2005, emphasized the benefits and de-emphasized the risks of taking hormones to protect against maladies like aging skin, heart disease and dementia. That supposed medical consensus benefited Wyeth, the pharmaceutical company that paid a medical communications firm to draft the papers, as sales of its hormone drugs, called Premarin and Prempro, soared to nearly $2 billion in 2001.

But the seeming consensus fell apart in 2002 when a huge federal study on hormone therapy was stopped after

Well
Tara Parker-Pope on Health

Protecting Young Athletes From Concussions
August 25, 2009, 11:29 AM

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August 25, 2009, 10:17 AM

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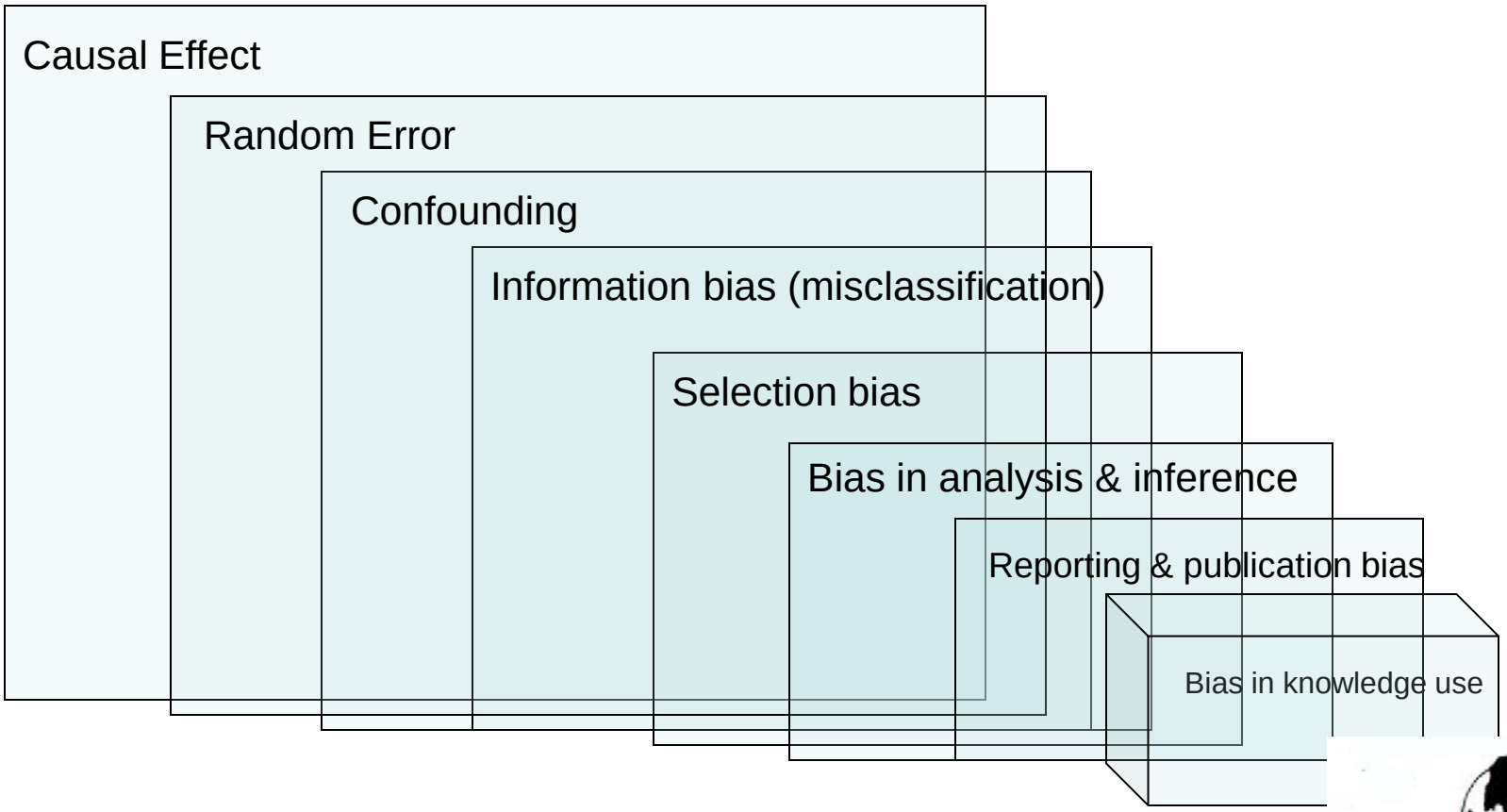
August 24, 2009

Losing Dental Insurance
August 24, 2009

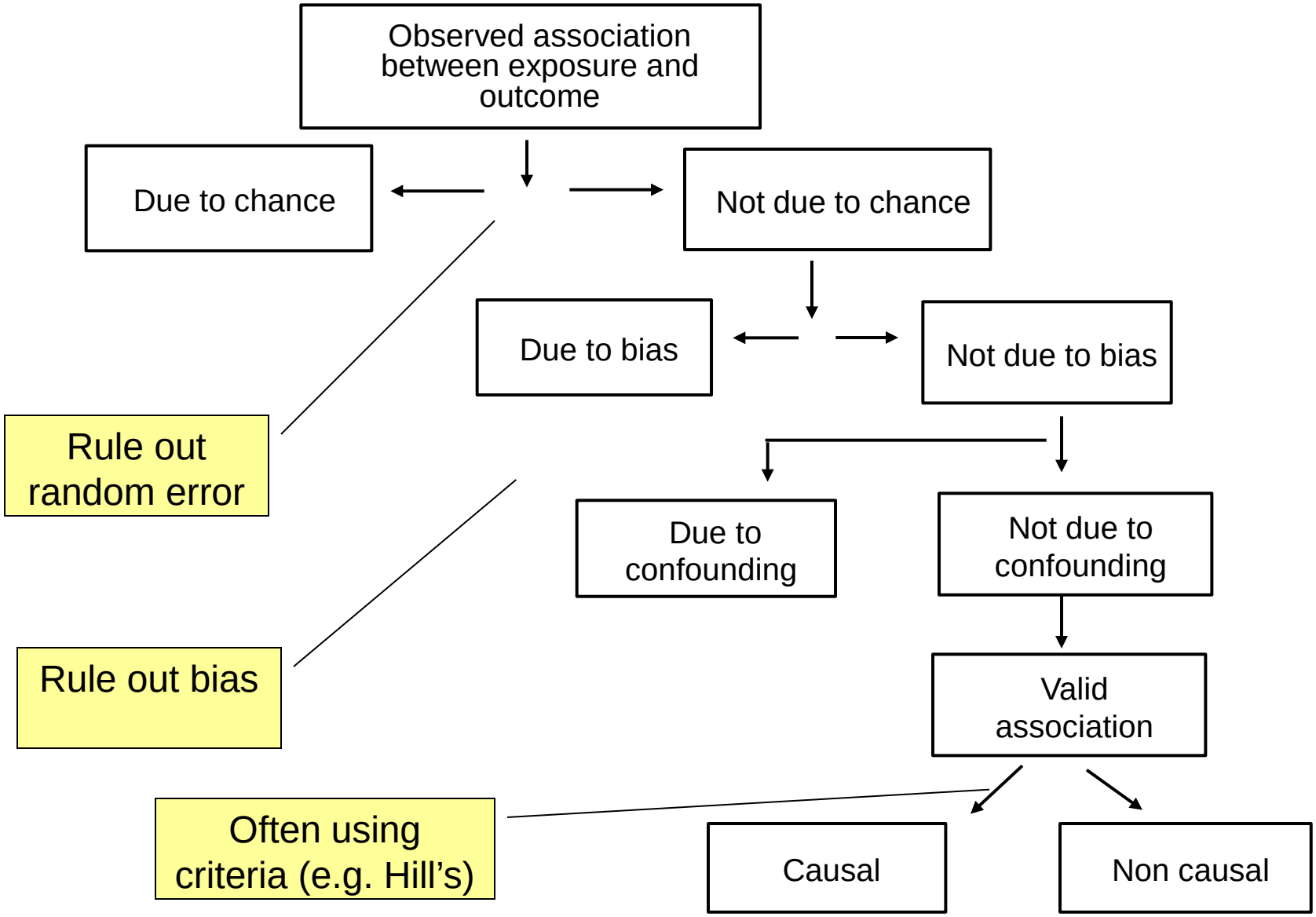
The long road to causal inference (the “big picture”)

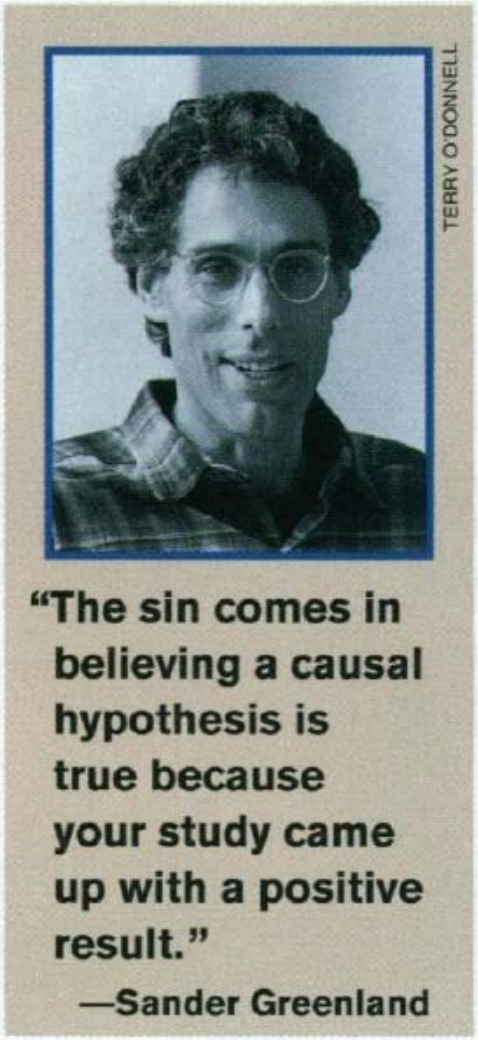


RR_{causal} “truth” → the long road to causal inference… → $RR_{association}$

Adapted from: Maclure, M, Schneeweis S. Epidemiology 2001;12:114-122.

A Skeptic's Algorithm for Associations



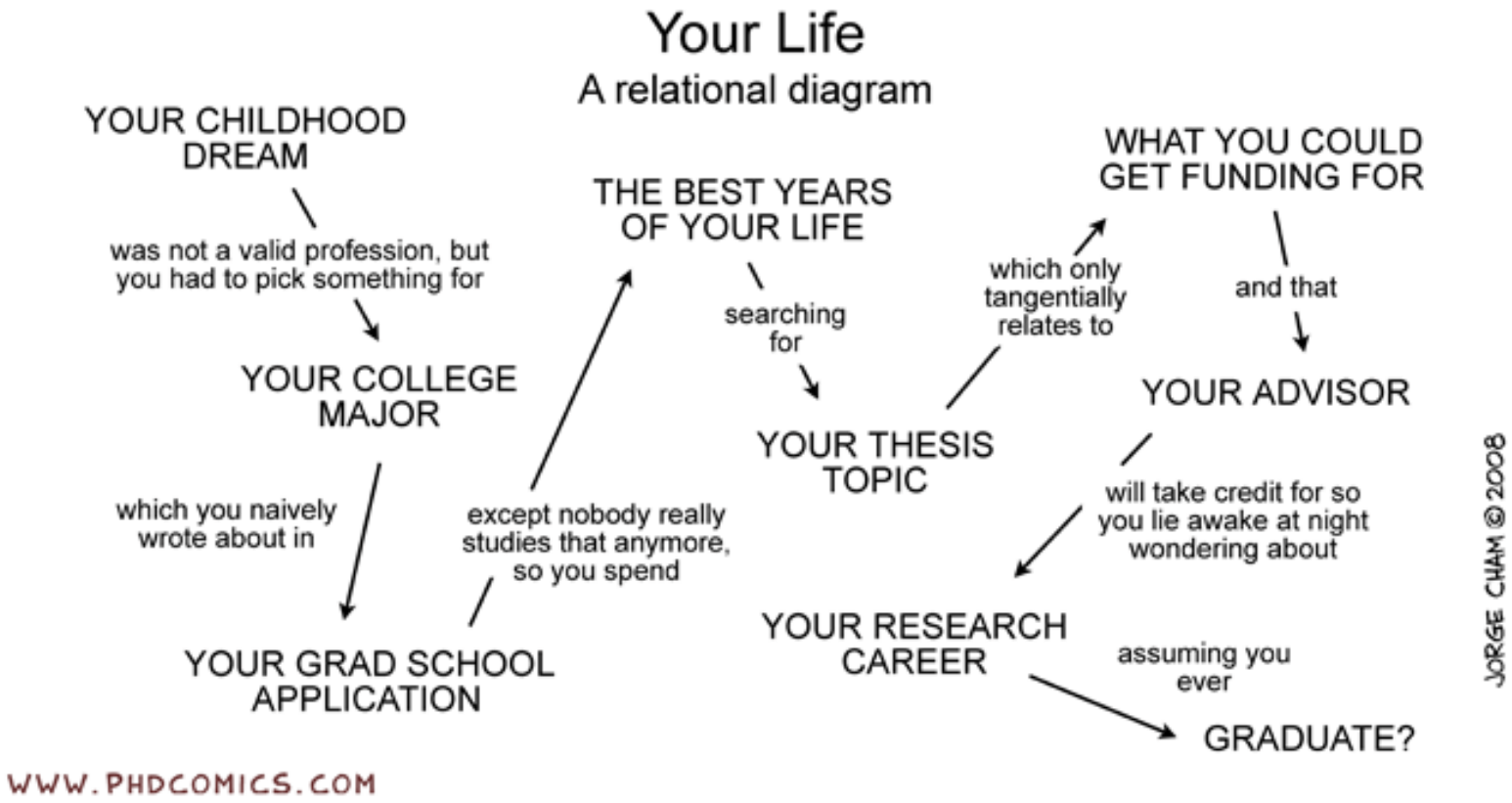


"there is nothing sinful about going out and getting evidence, like asking people how much do you drink and checking breast cancer records. There's nothing sinful about seeing if that evidence correlates. There's nothing sinful about checking for confounding variables. The sin comes in believing a causal hypothesis is true because your study came up with a positive result, or believing the opposite be- cause your study was negative."

Taubes G. Science 1995

Readings for next class

- Article:
  - Taubes G. Epidemiology faces its limits. *Science* 1995
  - Taubes G. Unhealthy Science. NY Times Magazine, 2007
- Rothman text:
  - Chapter 1: Intro to epidemiologic thinking
- Gordis text:
  - Chapter 1: Introduction


Your Life
A relational diagram
YOUR CHILDHOOD DREAM
was not a valid profession, but you had to pick something for
YOUR COLLEGE MAJOR
which you naively wrote about in
YOUR GRAD SCHOOL APPLICATION
except nobody really studies that anymore, so you spend
THE BEST YEARS OF YOUR LIFE
searching for
YOUR THESIS TOPIC
which only tangentially relates to
WHAT YOU COULD GET FUNDING FOR
and that
YOUR ADVISOR
will take credit for so you lie awake at night wondering about
YOUR RESEARCH CAREER
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