Dilution of evidence-based medicine and strategies towards high quality research that makes a difference: Editor's perspective

Dr. Wim Weber

European editor

The BMJ

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Present medical research

has a credibility problem

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2008

	BMJ 181	Lancet 169	JAMA 164	NEJM 178
UK	81	35	3	17
USA		40	120	100
Rest Wor	58 +USA	44	16	24
EU	8	18	-	-
Netherl	9	6	11	4
Scandina	17	9	5	10
Germany	-	-	1	8
France	2	6	4	9
Total Europe	42	39	21	31

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Papers from Europe (ex UK) in BMJ 2012

31 %:

- EU 4
- Denmark 22
- Netherlands 17
- Sweden 13
- Norway 3
- Finland 2
- France 10
- Germany 4
- Spain 2
- Belgium, Poland, Switzerland, Portugal 1

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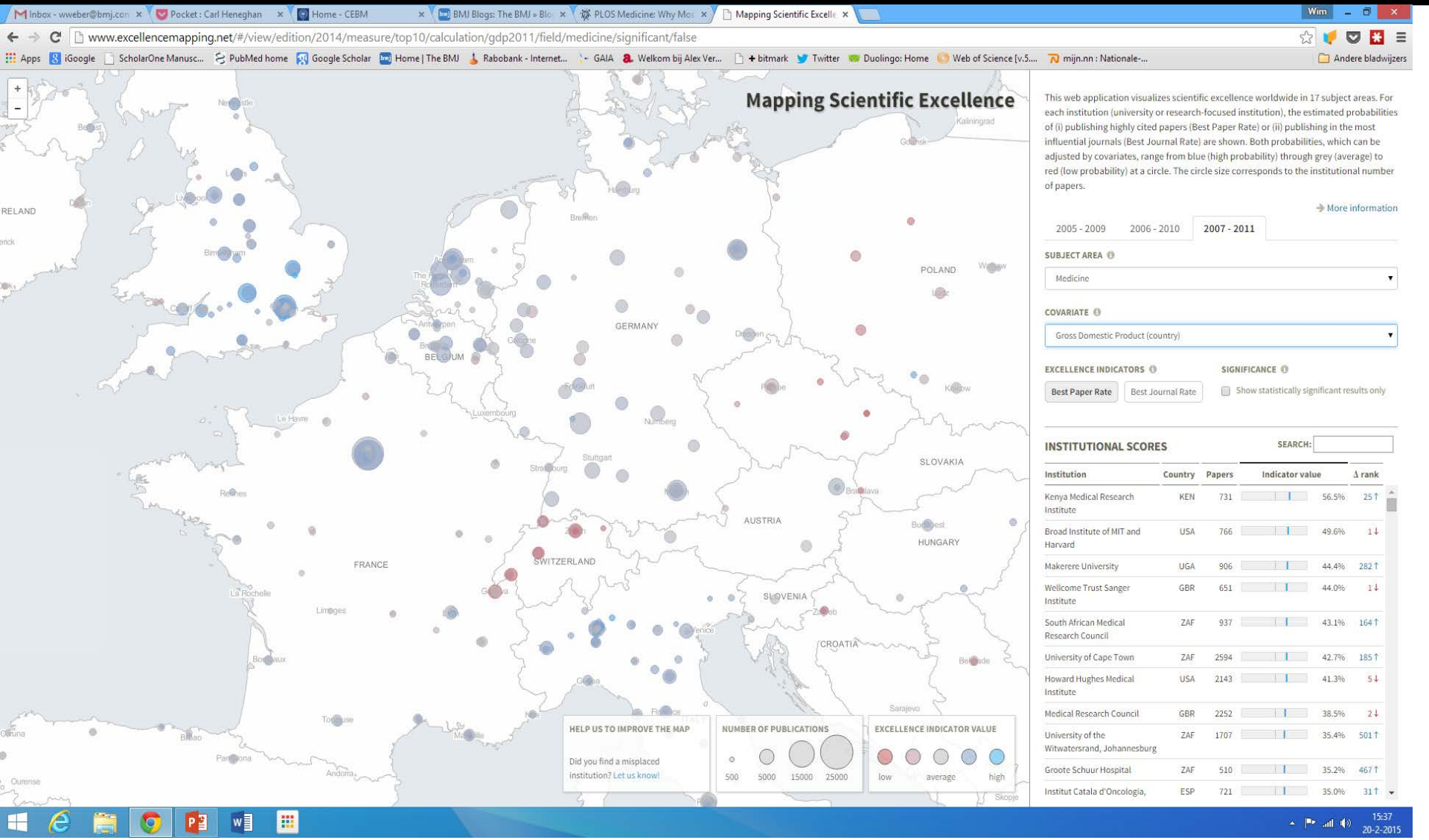
Mapping Scientific Excellence
This web application visualizes scientific excellence worldwide in 17 subject areas. For each institution (university or research-focused institution), the estimated probabilities of (i) publishing highly cited papers (Best Paper Rate) or (ii) publishing in the most influential journals (Best Journal Rate) are shown. Both probabilities, which can be adjusted by covariates, range from blue (high probability) through grey (average) to red (low probability) at a circle. The circle size corresponds to the institutional number of papers.
More information
2005 - 2009
2006 - 2010
2007 - 2011
SUBJECT AREA
Medicine
COVARIATE
Gross Domestic Product (country)
EXCELLENCE INDICATORS
Best Paper Rate
Best Journal Rate
SIGNIFICANCE
Show statistically significant results only
INSTITUTIONAL SCORES
SEARCH:
Institution
Country
Papers
Indicator value
Δ rank
Kenya Medical Research Institute KEN 731 56.5% 25↑
Broad Institute of MIT and Harvard USA 766 49.6% 1↓
Makerere University UGA 906 44.4% 282↑
Wellcome Trust Sanger Institute GBR 651 44.0% 1↓
South African Medical Research Council ZAF 937 43.1% 164↑
University of Cape Town ZAF 2594 42.7% 185↑
Howard Hughes Medical Institute USA 2143 41.3% 5↓
Medical Research Council GBR 2252 38.5% 2↓
University of the Witwatersrand, Johannesburg ZAF 1707 35.4% 501↑
Groote Schuur Hospital ZAF 510 35.2% 467↑
Institut Catala d'Oncologia, ESP 721 35.0% 31↑
HELP US TO IMPROVE THE MAP
Did you find a misplaced institution? Let us know!
NUMBER OF PUBLICATIONS
500
5000
15000
25000
EXCELLENCE INDICATOR VALUE
low
average
high
GERMANY
FRANCE
SWITZERLAND
AUSTRIA
POLAND
SLOVAKIA
HUNGARY
SLOVENIA
CROATIA
BELGIUM

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Registered trials

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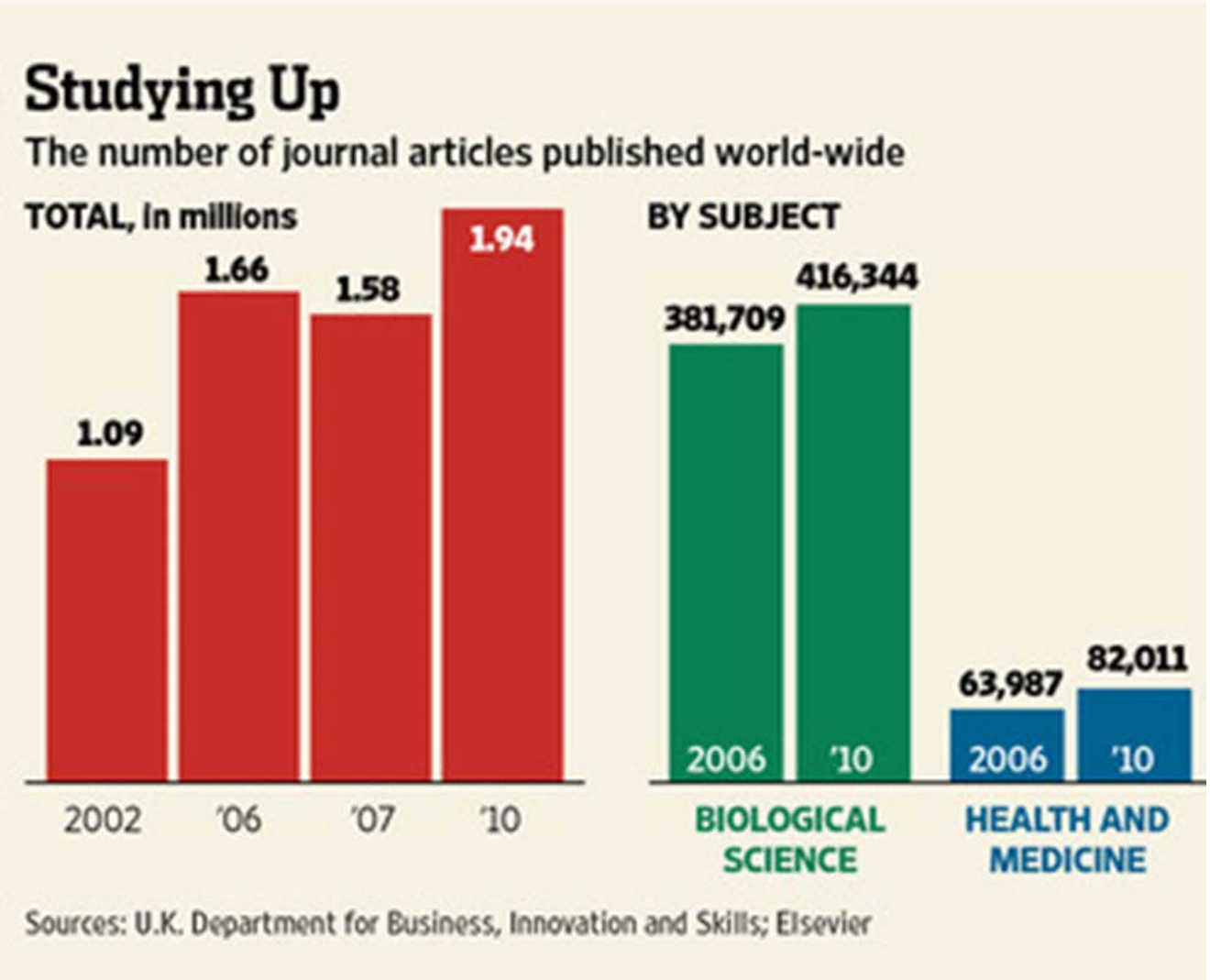
The problem ?



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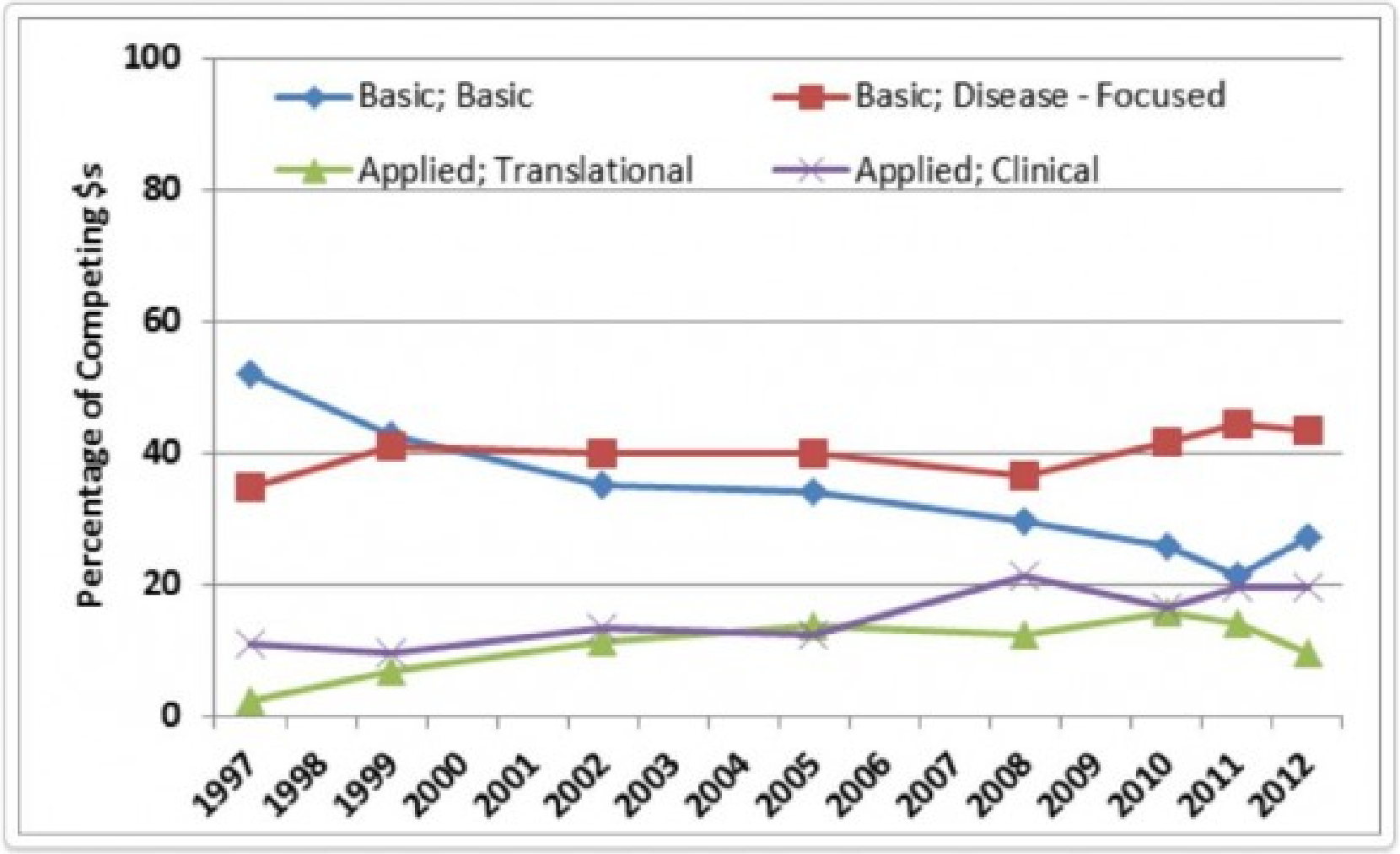
Money allocated to basic research



Too much basic research,

is that bad ?

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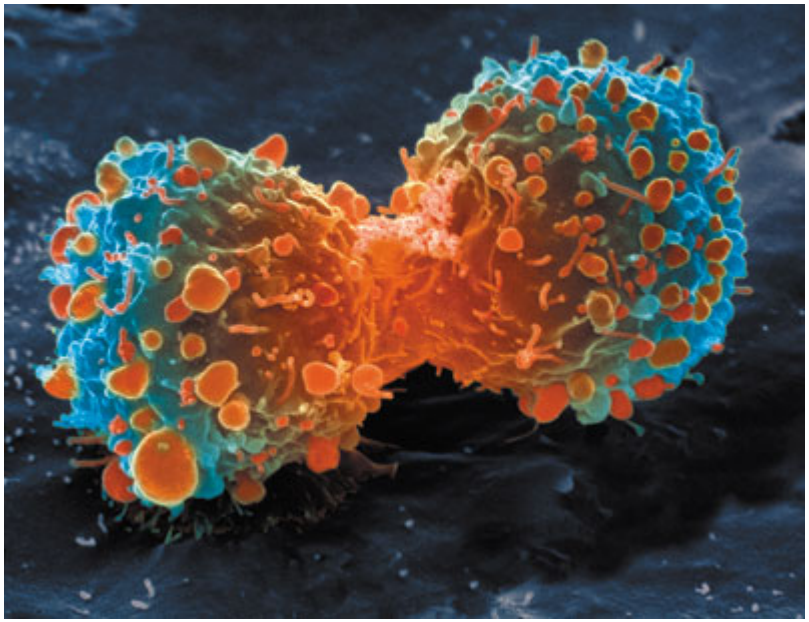
Most studies are not reproducable

Amgen researchers were able to replicate

only 6 of 53 landmark cancer studies



Nature *2012 Mar 28;483:531-3.*

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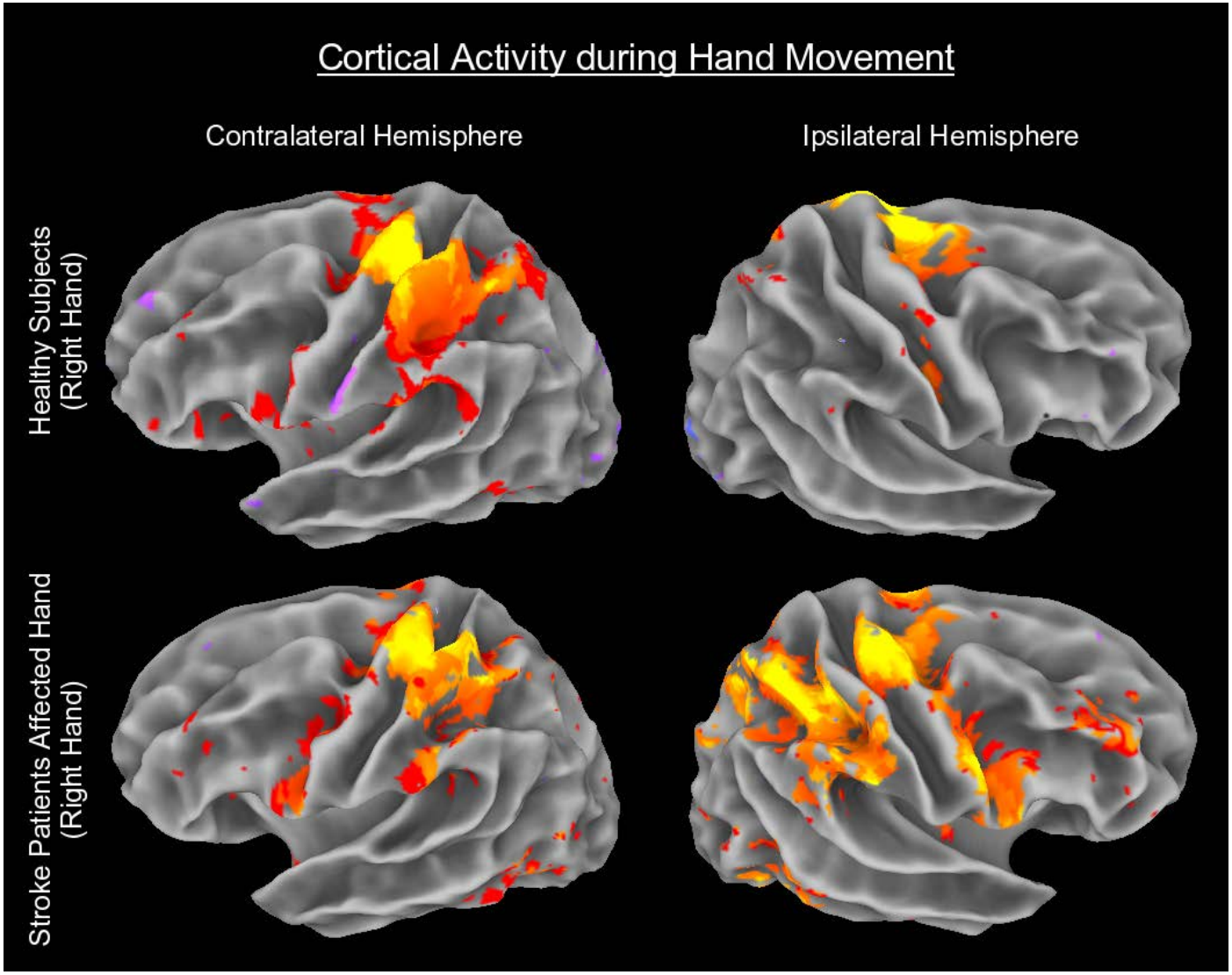
Functional MRI in neuroscience



What happens when you scan a dead fish ?

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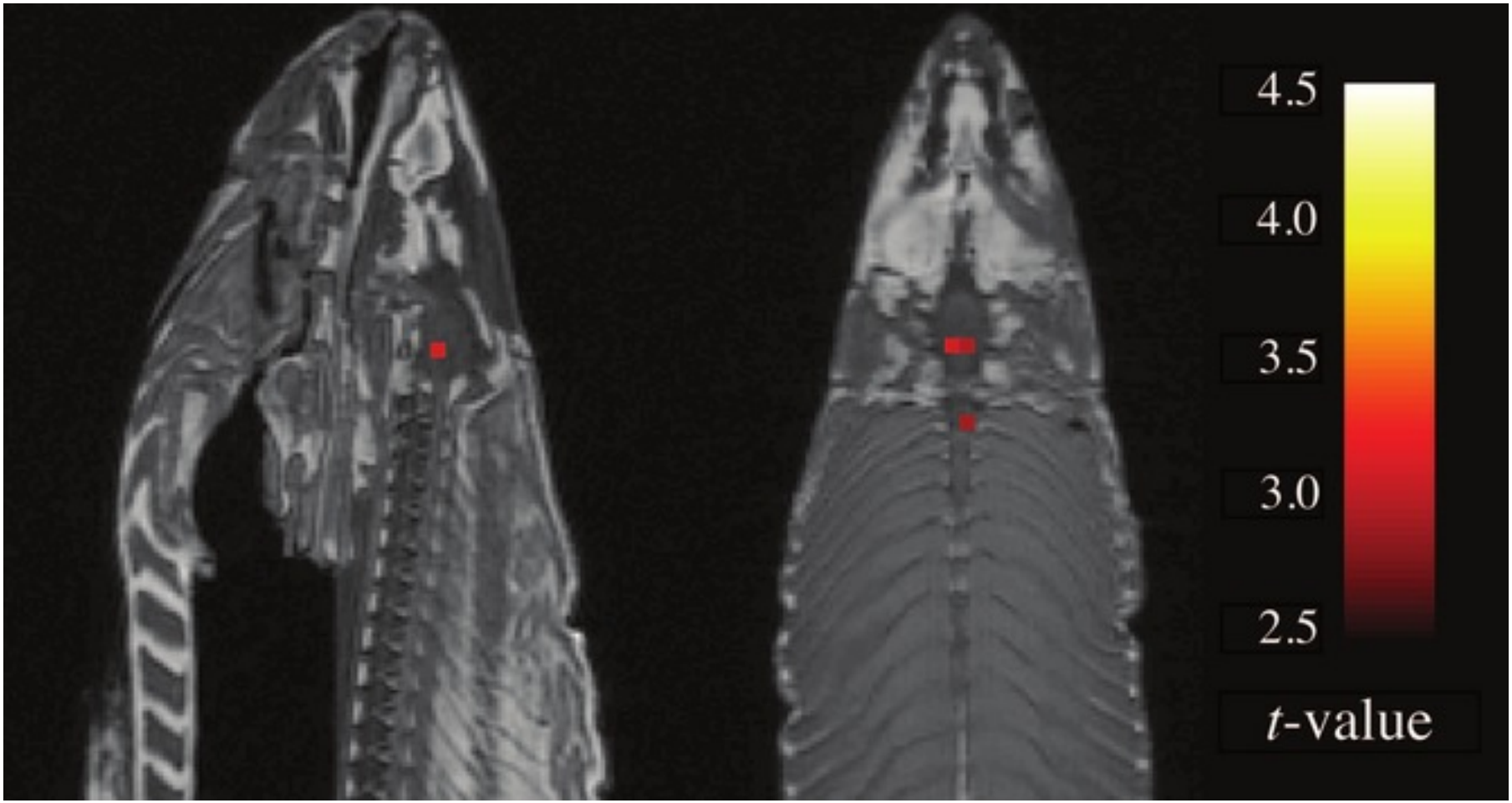
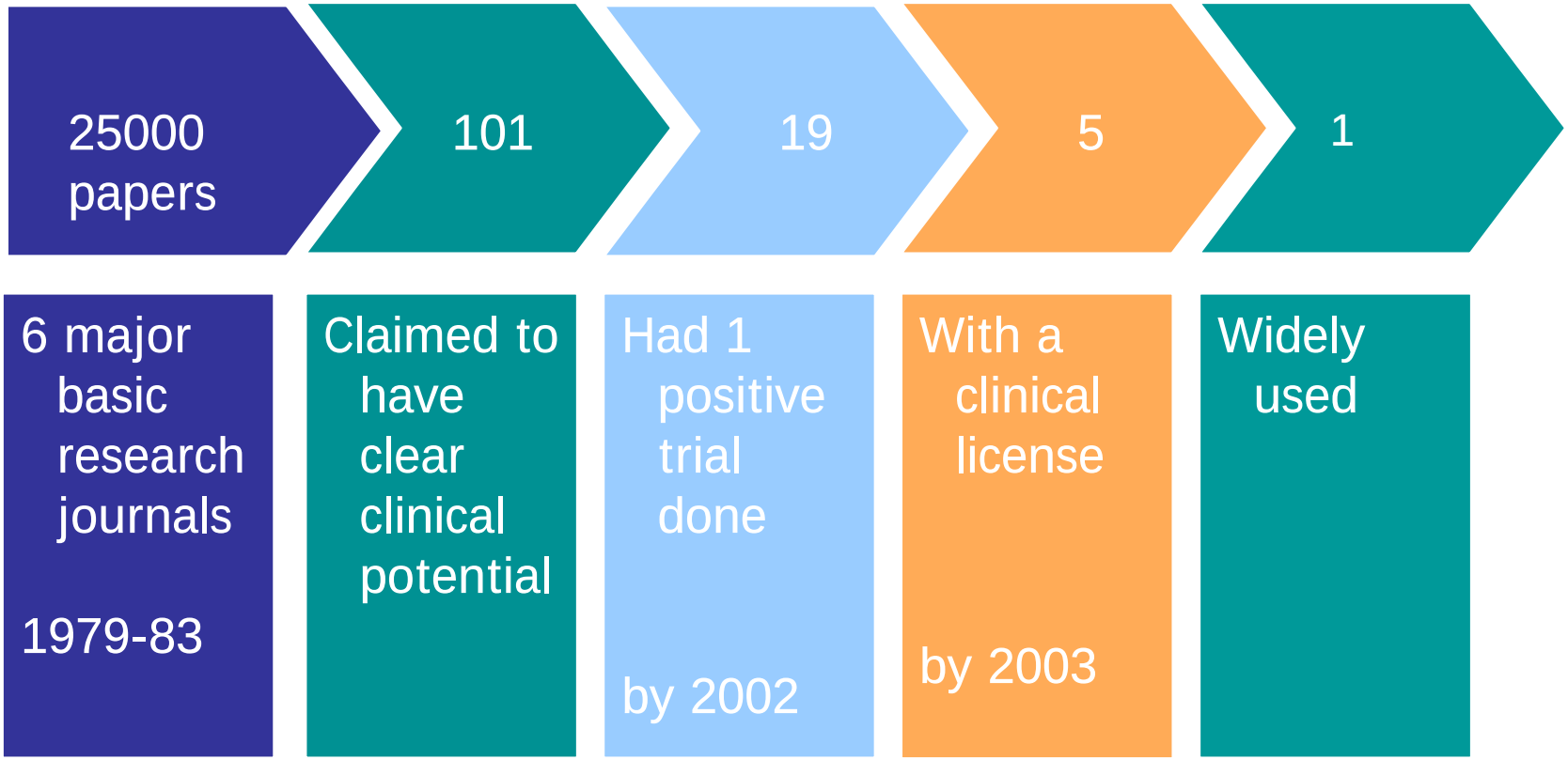


Translation of medical research



Am. J. Med. 114, 477 (2003).

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What causes this bias ?

In 4455 animal studies

3x positive studies

Overestimates of effect size

PLoS Biology 2013: 1001609

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Increase in proportion of meta-analyses in PubMed, 1999-2011

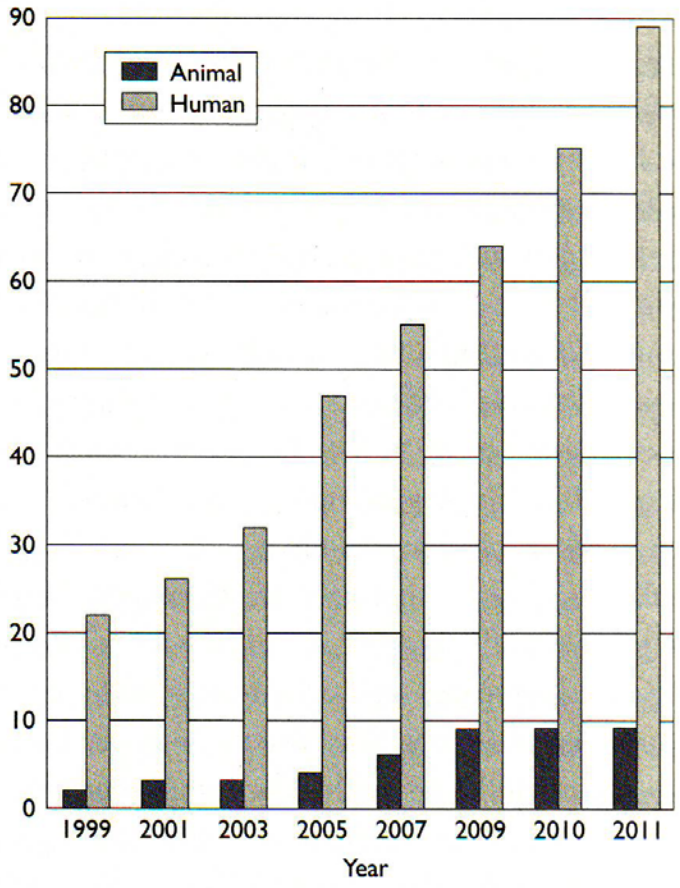

Figure 13.3. Number of meta-analyses for every 10,000 publications in PubMed, 1999–2011.

Bracken 2012

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512 meta-analyses of animal studies

Of low quality:

- did not assess methodological quality of the included studies (71%)
- nor did they assess heterogeneity (81%)
- or dissemination bias (87%)

K. Müller et al PLoS ONE 2014

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ESSAY

Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005 • DOI: 10.1371/journal.pmed.0020124

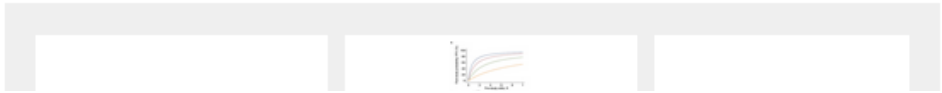
- for many current scientific fields,

claimed research findings may often be simply

accurate measures of the prevailing bias

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.

Figures



Subject Areas

Clinical research de...

Gene prediction

Genetic epidemiology

Genetics of disease

Randomized controll...

Unfortunately,

clinical research is no less biased

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HEALTH INDUSTRY | SEPTEMBER 24, 2010

Regulators Scuttle Drug for Diabetes

Article | Comments (33)

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By ALICIA MUNDY, JENNIFER CORBETT DOOREN And JEANNE WHALEN

WASHINGTON—U.S. regulators put tight curbs on the diabetes drug Avandia and European authorities said they were stopping its sales, effectively ending widespread use of a medicine that was once a multibillion-dollar-a-year seller.

View Full Image

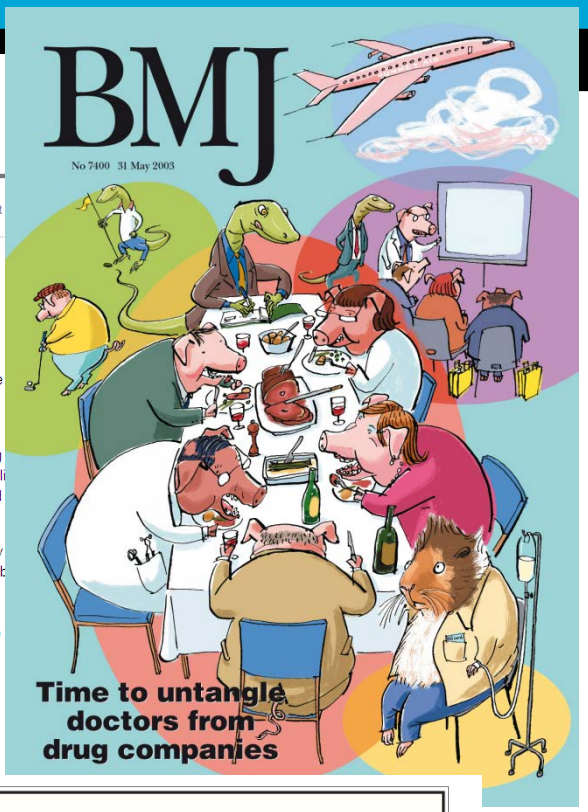
Bloomberg News

Avandia

The Food and Drug Administration and European regulators said they were taking action on Avandia, made by GlaxoSmithKl PLC, because of data tying it to increased risk of heart attacks.

The FDA move marks a tougher stance by the agency's leadership, named last year b President Barack Obama, and signals to pharmaceutical makers and patients that mass-market drugs with troublesome side effects are getting closer scrutiny.

for real business.



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Saturday, October 30, 2010

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EARNINGS | OCTOBER 30, 2010

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SAMPLE OF SUBSCRIBER CONTENT

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By PETER LOFTUS

Merck & Co.'s profit plunged 90% as the drug maker set aside $950 million to pay for an anticipated resolution of a government probe of its former pain drug Vioxx.

The company's earnings excluding the Vioxx charge and other items exceeded expectations, though revenue fell short. Many drug makers have reported weake third-quarter revenue due to European pricing pressure and other challenges, bu able to offset the sluggishness with layoffs and other cost cuts.

Merck also raised the lower end of its 2010 forecast range of earnings excluding

The New York Times **Business**

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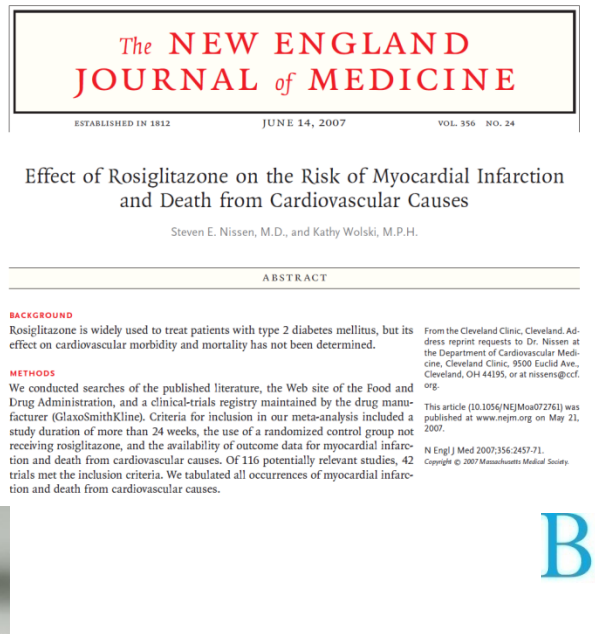
Evidence in Vioxx Suits Shows Intervention by Merck Officials

By ALEX BERENSON

Published: April 24, 2005

In 2000, amid rising concerns that its painkiller Vioxx posed heart risks, Merck overruled one of its own scientists after he suggested that a patient in a clinical trial had probably died of a heart attack.

In an e-mail exchange about Vioxx, the company's most important new drug at the time, a senior Merck scientist repeatedly urged the researcher to change his views about the death "so that we don't raise concerns." In later reports to the Food and Drug Administration and in a paper published in 2003, Merck listed the cause of death as "unknown" for the patient, a 73-year-old woman.



Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

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Some of the problems

- Trials measure outcomes not relevant to patients
- Failure to acknowledge earlier research
- Non-publication of negative results

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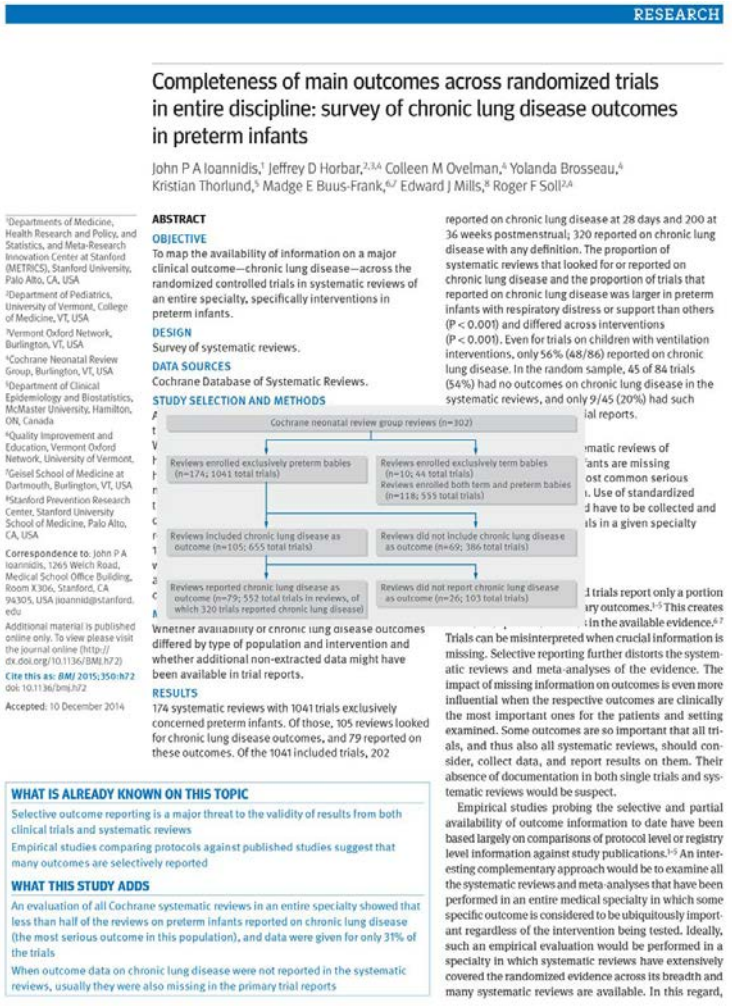
Systematic reviews that evaluated interventions in preterm infants.



RESEARCH

Completeness of main outcomes across randomized trials in entire discipline: survey of chronic lung disease outcomes in preterm infants

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[6]Quality Improvement and Education, Vermont Oxford Network, University of Vermont
[7]Geisel School of Medicine at Dartmouth, Burlington, VT, USA
[8]Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, CA, USA

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/BMJ.h72)

Cite this as: *BMJ* 2015;350:h72
doi: 10.1136/bmj.h72

Accepted: 10 December 2014

ABSTRACT

OBJECTIVE
To map the availability of information on a major clinical outcome—chronic lung disease—across the randomized controlled trials in systematic reviews of an entire specialty, specifically interventions in preterm infants.

DESIGN
Survey of systematic reviews.

DATA SOURCES
Cochrane Database of Systematic Reviews.

STUDY SELECTION AND METHODS

Cochrane neonatal review group reviews (n=302)

Reviews enrolled exclusively preterm babies (n=174; 1041 total trials)

Reviews enrolled exclusively term babies (n=10; 44 total trials)

Reviews enrolled both term and preterm babies (n=118; 555 total trials)

Reviews included chronic lung disease as outcome (n=105; 655 total trials)

Reviews did not include chronic lung disease as outcome (n=69; 386 total trials)

Reviews reported chronic lung disease as outcome (n=79; 552 total trials in reviews, of which 320 trials reported chronic lung disease)

Reviews did not report chronic lung disease as outcome (n=26; 103 total trials)

whether availability of chronic lung disease outcomes differed by type of population and intervention and whether additional non-extracted data might have been available in trial reports.

RESULTS
174 systematic reviews with 1041 trials exclusively concerned preterm infants. Of those, 105 reviews looked for chronic lung disease outcomes, and 79 reported on these outcomes. Of the 1041 included trials, 202 reported on chronic lung disease at 28 days and 200 at 36 weeks postmenstrual; 320 reported on chronic lung disease with any definition. The proportion of systematic reviews that looked for or reported on chronic lung disease and the proportion of trials that reported on chronic lung disease was larger in preterm infants with respiratory distress or support than others ($P < 0.001$) and differed across interventions ($P < 0.001$). Even for trials on children with ventilation interventions, only 56% (48/86) reported on chronic lung disease. In the random sample, 45 of 84 trials (54%) had no outcomes on chronic lung disease in the systematic reviews, and only 9/45 (20%) had such

WHAT IS ALREADY KNOWN ON THIS TOPIC

Selective outcome reporting is a major threat to the validity of results from both clinical trials and systematic reviews

Empirical studies comparing protocols against published studies suggest that many outcomes are selectively reported

WHAT THIS STUDY ADDS

An evaluation of all Cochrane systematic reviews in an entire specialty showed that less than half of the reviews on preterm infants reported on chronic lung disease (the most serious outcome in this population), and data were given for only 31% of the trials

When outcome data on chronic lung disease were not reported in the systematic reviews, usually they were also missing in the primary trial reports

Trials can be misinterpreted when crucial information is missing. Selective reporting further distorts the systematic reviews and meta-analyses of the evidence. The impact of missing information on outcomes is even more influential when the respective outcomes are clinically the most important ones for the patients and setting examined. Some outcomes are so important that all trials, and thus also all systematic reviews, should consider, collect data, and report results on them. Their absence of documentation in both single trials and systematic reviews would be suspect.

Empirical studies probing the selective and partial availability of outcome information to date have been based largely on comparisons of protocol level or registry level information against study publications.[1-5] An interesting complementary approach would be to examine all the systematic reviews and meta-analyses that have been performed in an entire medical specialty in which some specific outcome is considered to be ubiquitously important regardless of the intervention being tested. Ideally, such an empirical evaluation would be performed in a specialty in which systematic reviews have extensively covered the randomized evidence across its breadth and many systematic reviews are available. In this regard,

Outcome of serious lung disease in less than 50% of trials

John P A Ioannidis et al. BMJ 2015;350:bmj.h72

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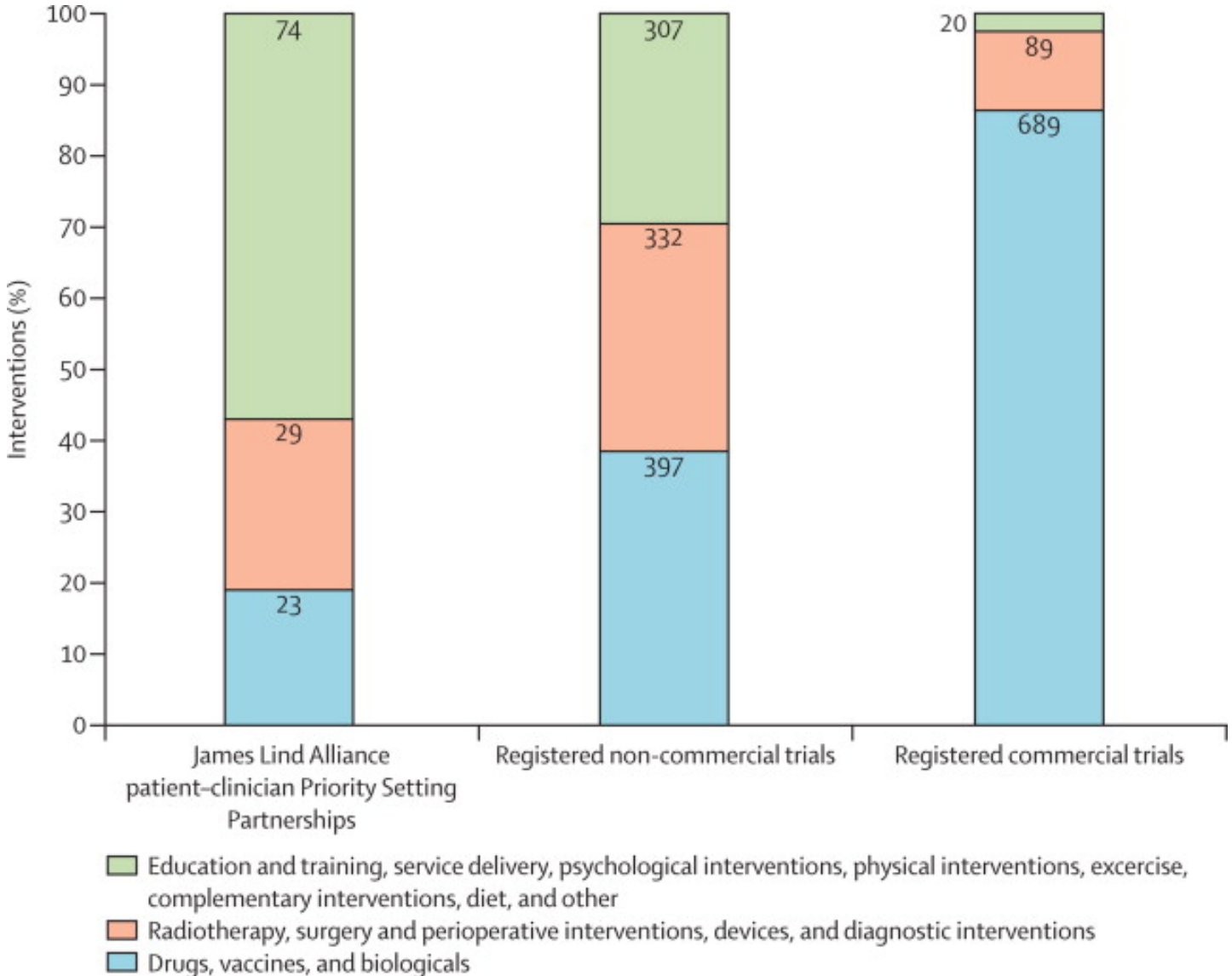
Do trials study what patients want ?



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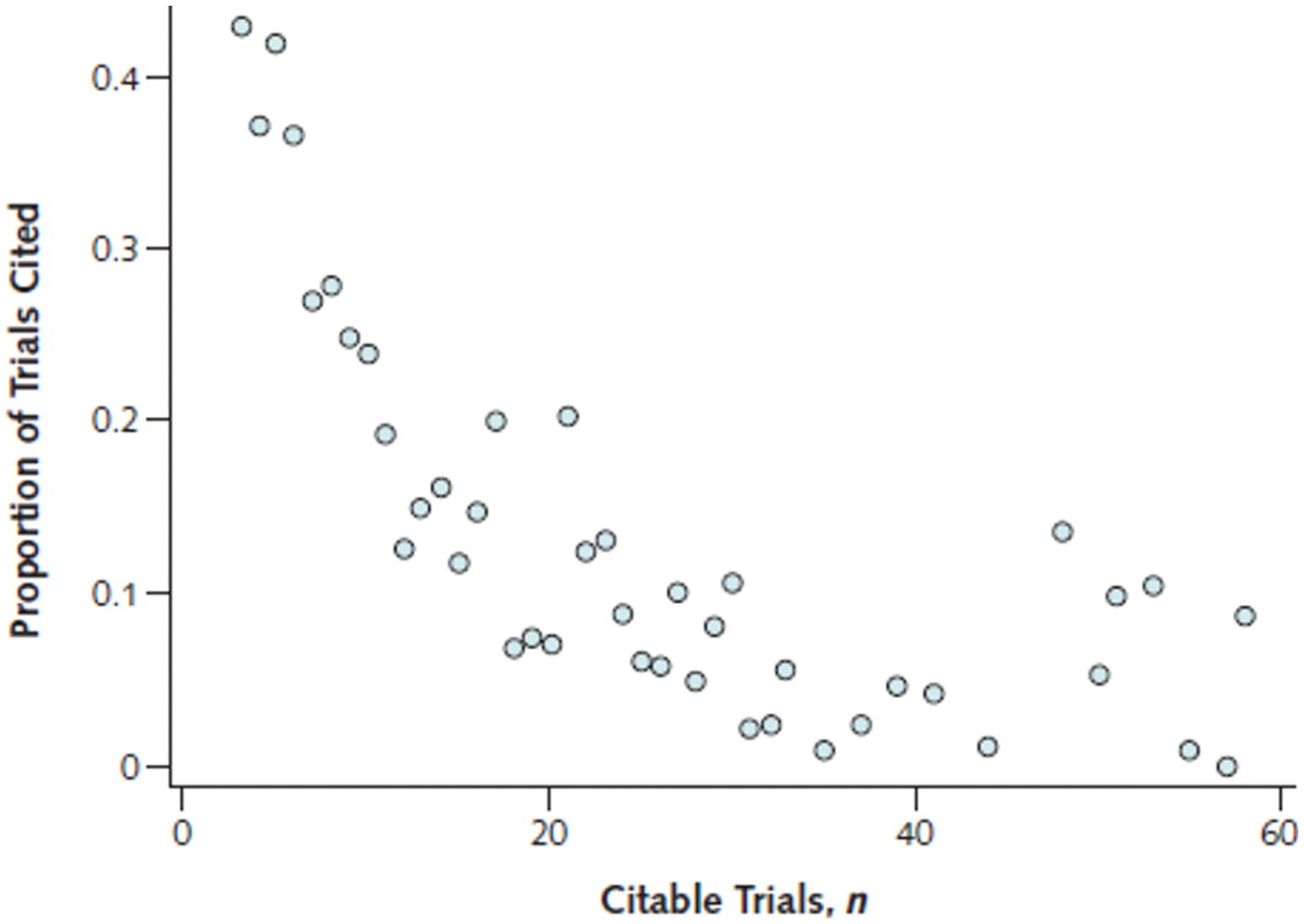
Trials acknowledging prior research



Ann Intern Med. 2011;154(1):50-55

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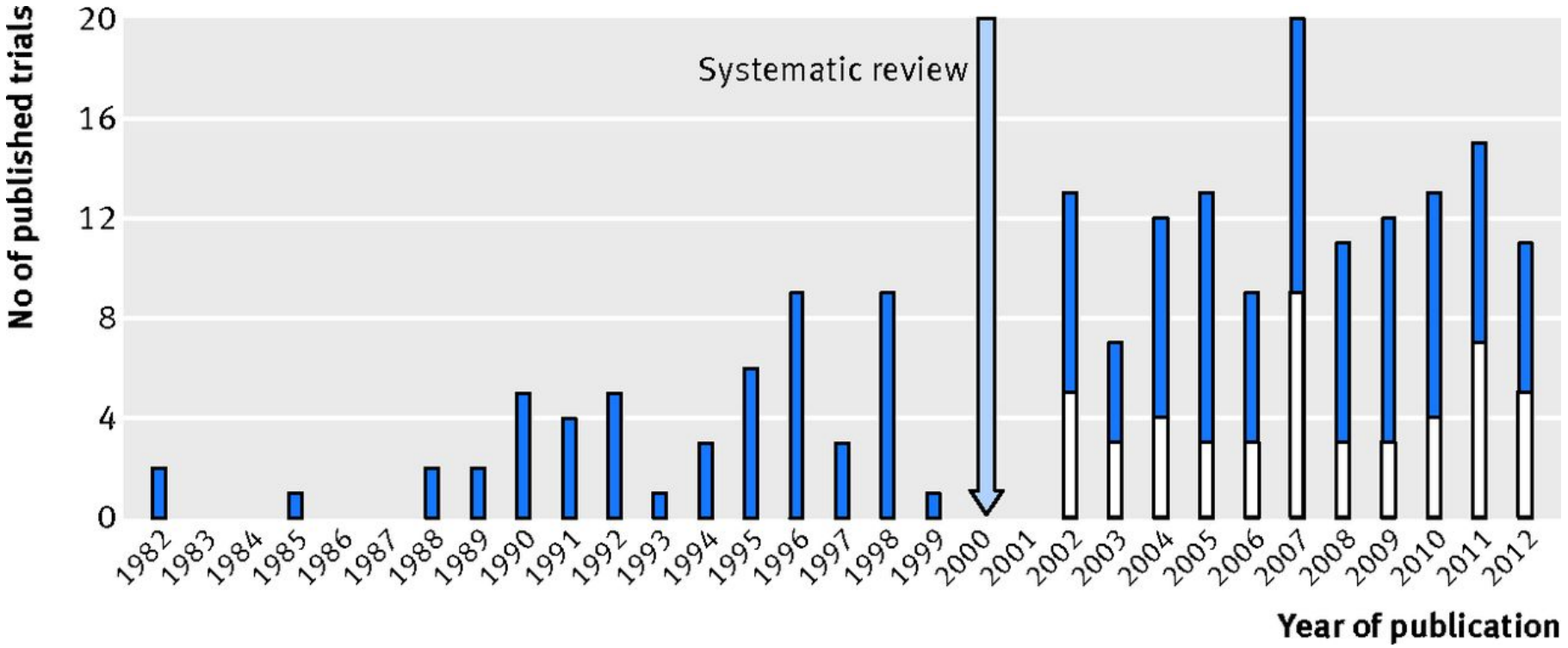
Number of published randomised controlled trials studying efficacy of interventions for prevention of pain from propofol injection.



Céline Habre et al. BMJ 2014;349:bmj.g5219

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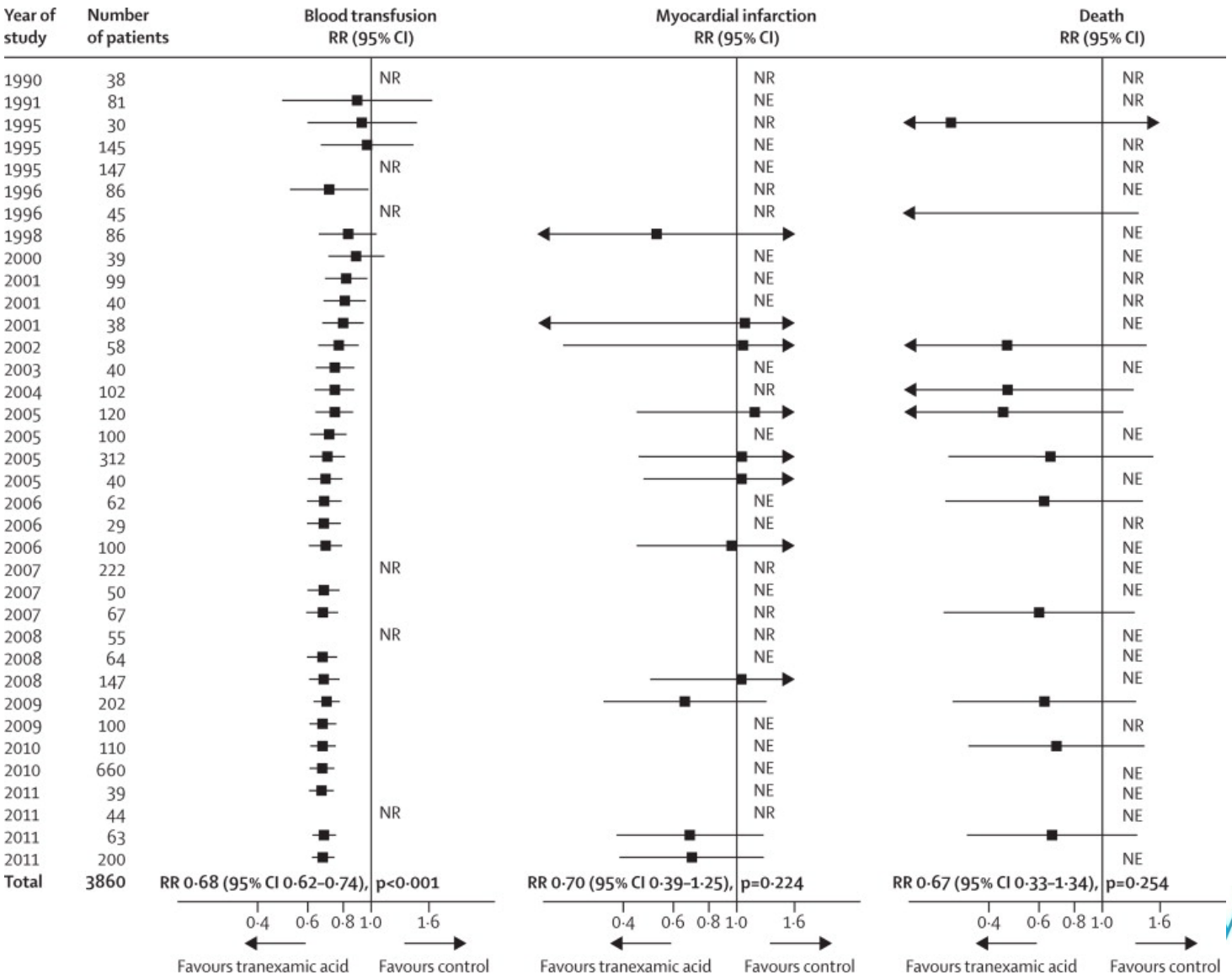
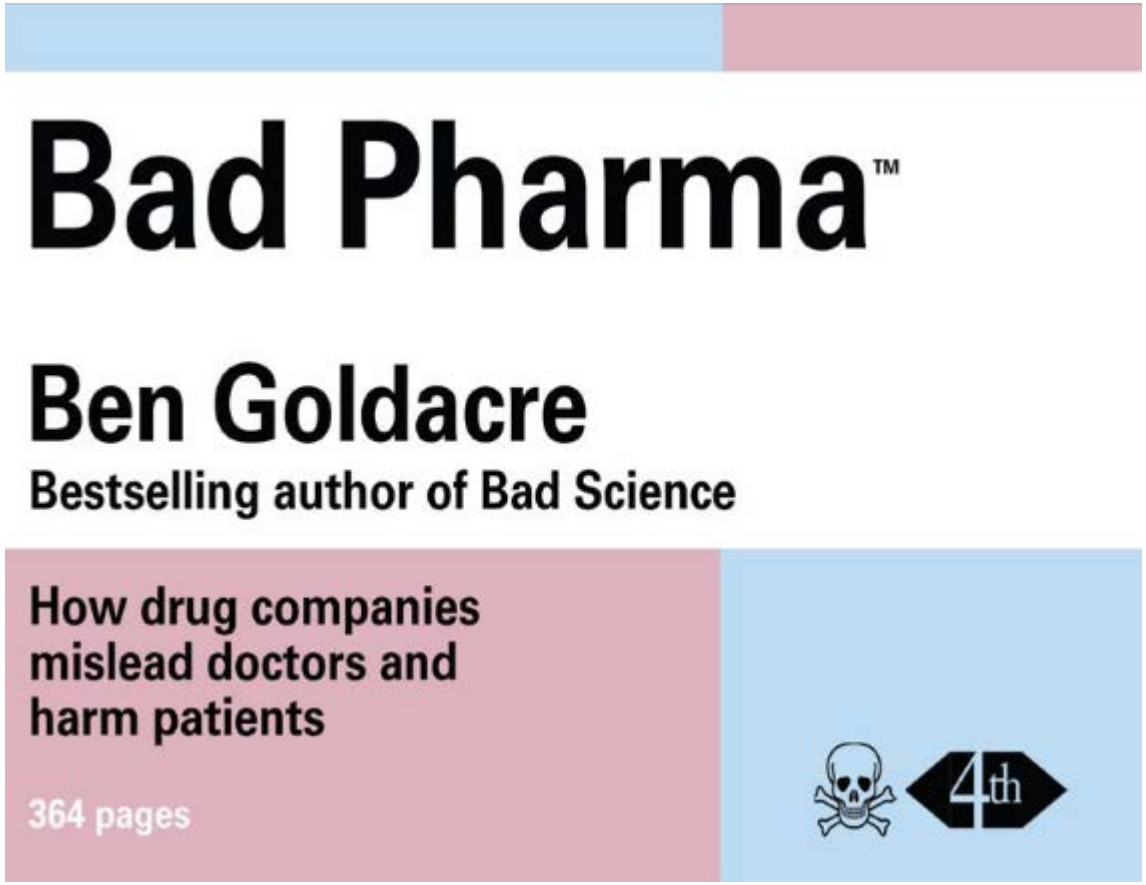
Tranexamic acid



Non-publication



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Cochrane review 2006:

Oseltamivir 150 mg daily prevented lower respiratory tract complications

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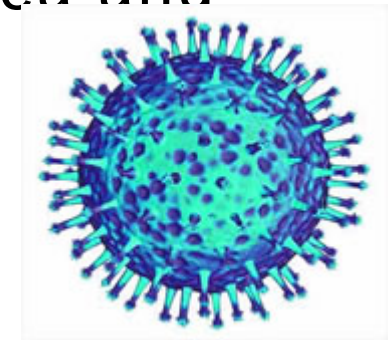
2009: Cochrane review updated, but:

- Only 2 / 10 RCTs published
- The pooled analysis was done by Roche
- Obtaining the original data has been very difficult

After 5 years Roche made all data available: and a new meta-analysis shows:

- There were **83** RCTs
- There is no evidence for effect on complications
- There are substantial side effects: nausea and psychiatric symptoms



BMJ. 2014 Apr 9;348:g2545

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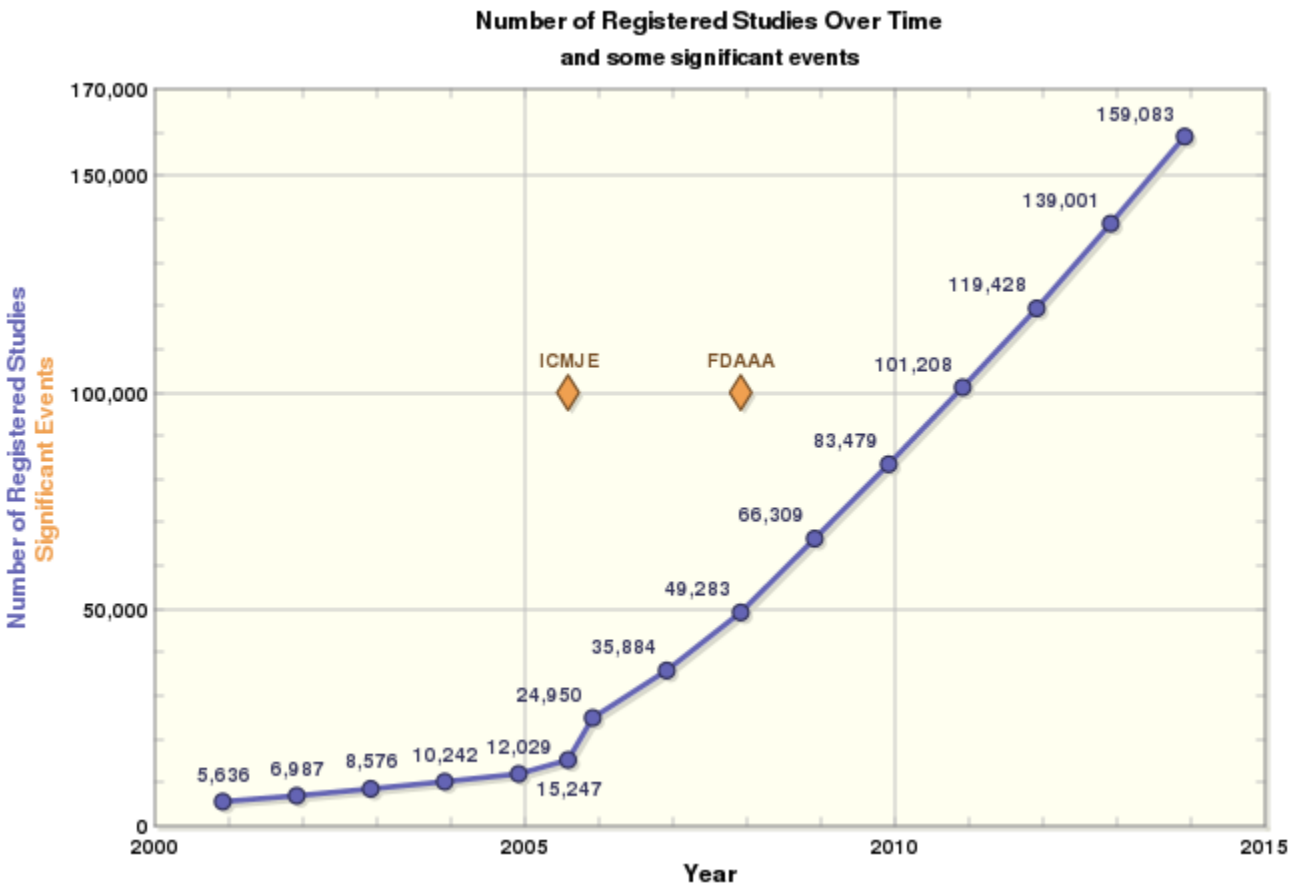
New EU legislation

Trials must be registered

Results must be published



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Sample of 757 ICMJE journals

- More than ½ do not adhere to ICMJE guidelines for registration

Neth J Med. 2014 Sep;72(7):349-55

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Survey of 400 surgical trials

- One in five surgical randomised controlled trials are discontinued early
- One in three completed trials remain unpublished
- Investigators of unpublished studies are frequently not contactable

BMJ 2014;349:g6870

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Are journals to blame ?

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Citation-based incentives are problematic

- Biased towards positive studies
- Negative studies are not cited

- Reproducibility is not honored

- Many high-impact journals have strong commercial CoIs

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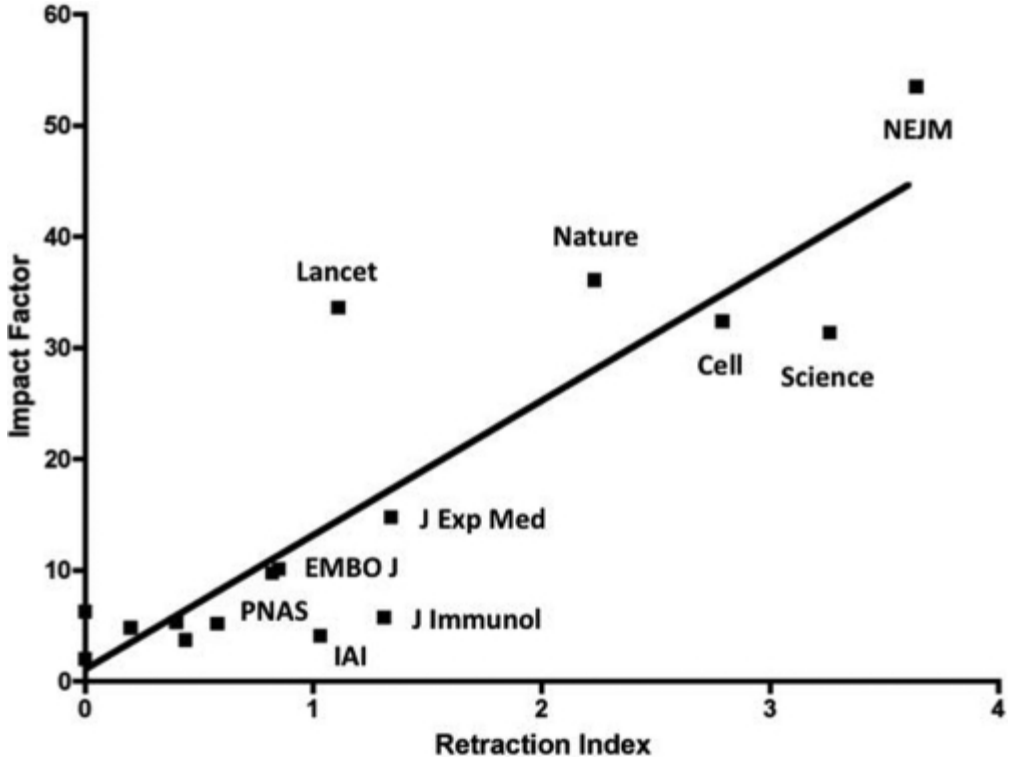
Impact factor and retractions



Infect Immun. 2011 Oct; 79(10): 3855–3859

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PQRST Index for appraising research

Table. PQRST Index for Appraising and Rewarding Research

Item in PQRST Index	Operationalization	
	Example	Data Source
P (productivity)	Number of publications in the top tier % of citations for the scientific field and year	ISI Essential Science Indicators (automated)
	Proportion of funded proposals that have resulted in ≥1 published reports of the main results	Funding agency records and automated recording of acknowledged grants (eg, PubMed)
	Proportion of registered protocols that have been published 2 y after the completion of the studies	Study registries such as ClinicalTrials.gov for trials
Q (quality of scientific work)	Proportion of publications that fulfill ≥1 quality standards	Need to select standards (different per field/design) and may then automate to some extent; may limit to top-cited articles, if cumbersome
R (reproducibility of scientific work)	Proportion of publications that are reproducible	No wide-coverage automated database currently, but may be easy to build, especially if limited to the top-cited pivotal papers in each field
S (sharing of data and other resources)	Proportion of publications that share their data, materials, and/or protocols (whichever items are relevant)	No wide-coverage automated database currently, but may be easy to build, eg, embed in PubMed at the time of creation of PubMed record and update if more is shared later
T (translational influence of research)	Proportion of publications that have resulted in successful accomplishment of a distal translational milestone, eg, getting promising results in human trials for intervention tested in animals or cell cultures, or licensing of intervention for clinical trials	No wide-coverage automated database currently, would need to be curated by appraiser (eg, funding agency) and may need to be limited to top-cited papers, if cumbersome

JAMA. 2014;312(5):483-484

We need less basic research, but

more epidemiologic research

We need another system to evaluate

output of medical researchers

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Thanks

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