Open Data & Closed Minds?

The pharmaceutical industry and its critics in the coming era of data-sharing

Stephen Senn

CRP SANTÉ
CENTRE DE RECHERCHE PUBLIC
MÉTHODOLOGY AND STATISTICS

Acknowledgements

Thank you for the invitation!

And in particular Per Larsson for organising things.

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Declaration of Interest

- I consult regularly for the pharmaceutical industry
- I used to work for the pharmaceutical industry
- My career is furthered by publishing
- I take malicious pleasure in exposing woolly arguments
- In short, I am a very bad person
- See http://www.senns.demon.co.uk/Declaration_Interest.htm to find out exactly how bad

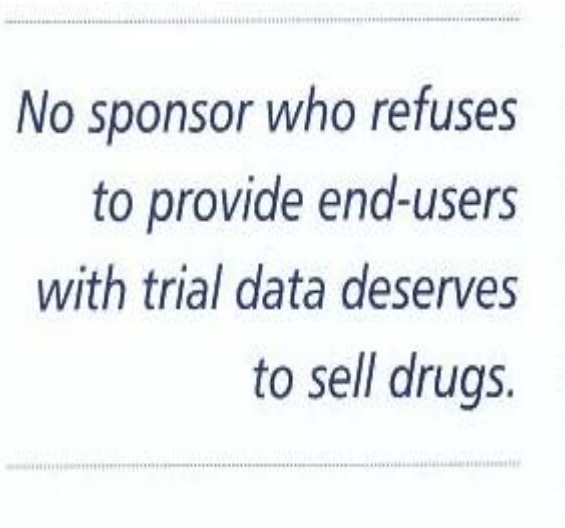
Outline

- The background to the AllTrials campaign
- Why are negative studies less likely to be published?
- How should we publish studies?
- What are the implications for the future?

The Problem

- Many clinical trials are unpublished
  - Negative trials less likely to be published
- Such trials may be of no further use to the sponsor but could still be useful for others
- Thus there is a waste to society
- And perhaps a betrayal of patient trust
- There is a growing acceptance that all trials should be published

The opinion of one ‘expert’



Senn, S. J. (2000). "Statistical quality in analysing clinical trials." Good Clinical Practice Journal **7(6): 22-26.**

Against a background of shifting paradigms of statistical inference but increasing statistical regulation, Stephen Senn, Professor of Pharmaceutical and Health Statistics at UCL (University College London), considers what makes for statistical quality in pharmaceutical clinical trials.

My own interest in this – for the record

- I have been calling for information to be made available to end users since 2000
  - And possibly even before
- In a presentation to pharma industry I said the same
- Nevertheless, and despite the fact that progress was slow, I think that there are some rather misleading reports around as to how the pharma industry has been doing
- BUT…the era in which this was a discussion between regulator and sponsor only is gone
- There is now a third party whose opinion needs to be taken account of and (rightly or wrongly) it is representing itself as acting on behalf of the general public

What is AllTrials?

- Organisation campaigning for all clinical trial results to be published
- An initiative of
  - Bad science
  - Centre for Evidence-based Medicine
  - Cochrane Collaboration
  - James Lind Library
  - PLOS
  - Sense about science
- Launched January 2013

All trial objectives

- The following should be observed
  - Registration of trials
  - Summaries should be made available
  - Full reports should be made available
- It is not necessary, however, that individual data be made available

Bad PHARMA

- Written by medical journalist Ben Goldacre
  - Published autumn 2012
- Hard hitting exposé of the pharmaceutical industry
- Also very critical of drug regulators
- Looks at the problem of missing studies in detail

What I Shall Assume

- Journal editors base their decision as to what to accept (at least in part) on quality
  - Other things being equal, higher quality papers are more likely to be accepted
  - Editors may or may not take study *outcome* into account
- Authors base their decision as to what to submit (at least in part) on quality
  - Other things being equal, higher quality papers are more likely to be submitted
  - Authors may or may not take study *outcome* into account

Goldacre's Thesis

'But to be kind, for the sake of completeness, and because industry and researchers are so keen to pass the blame on to academic journals, we can see if the claim is true….Here again the journals seem blameless: 74 manuscripts submitted to the *Journal of the American Association (JAMA*) were followed up, and there was no difference in acceptance for significant and non-significant findings.' Bad PHARMA

- Negative studies are less likely to be published
- This is not because editors are less likely to accept them
  - The evidence shows otherwise
- Authors are less likely to submit them
- The pharmaceutical industry is particularly bad at submitting negative studies to journals

That *JAMA* study

Olson et al, 2002

- Nine authors
  - Four were JAMA editors
- Prospective study of manuscripts submitted to *JAMA*
- Covered February 1996 to August 1999 inclusive
- Concluded there is no bias against negative studies

JAMA 2x2

	Accepted	Rejected	Total
Positive	78	305	383
Negative	55	307	362
Overall	133	612	745

Statistic based on the observed 2 by 2 table :

Binomial proportion for column <Negative > : pi_1 = 0.1519
Binomial proportion for column <Positive > : pi_2 = 0.2037

$$\text{Odds Ratio} = \frac{(\pi_2)/(1-\pi_2)}{(\pi_1)/(1-\pi_1)} = 1.427$$

My analysis using StatXact. The authors quote relative risk.

Results:

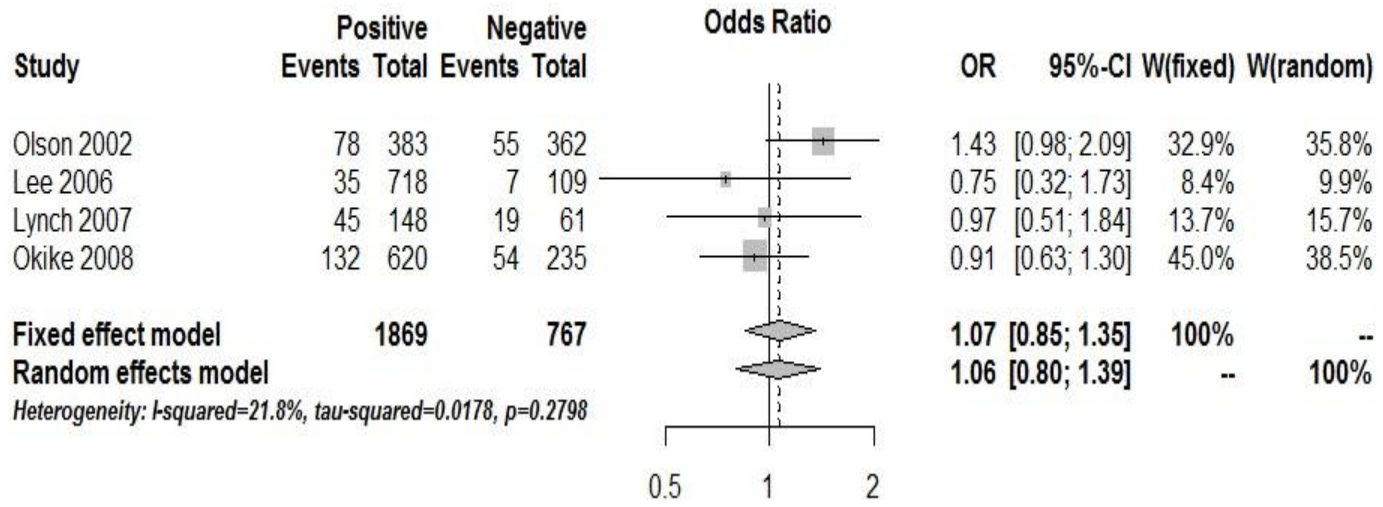
Method	P-value(2-sided)	95.00% Confidence Interval
Asymp (Mantel-Haenszel)	0.0662	(0.9765 , 2.087)
Exact	0.08020	(0.9605 , 2.130)

JAMA Logistic

Variables	Odds ratio(confidence limits)	P-value
Positive results vs negative	1.30 (0.87 - 1.96)	.21
Multi-centre vs single	1.60 (1.02 - 2.52)	.04
United States enrollment versus not	2.06 (1.20 - 3.52)	.008
Any funding versus no reported	1.42 (0.69 - 2.90)	.34
No. of participants >100 vs <100	1.38 (0.83 - 2.30)	.22
Sample size calculation vs none	1.90 (1.23 - 2.95)	.004
Randomisation described vs not	0.99 (0.65 - 1.52)	.98
Blinding vs not	1.51(0.98 - 2.34)	.06
Withdrawal reported vs not	1.35 (0.66 - 2.78)	.41
Analysis by treatment assignment vs not	1.22 (0.80 - 1.84)	.36

Taken from Table 2 of Olson et al,2002

Journals are *not* biased in favour of positive studies

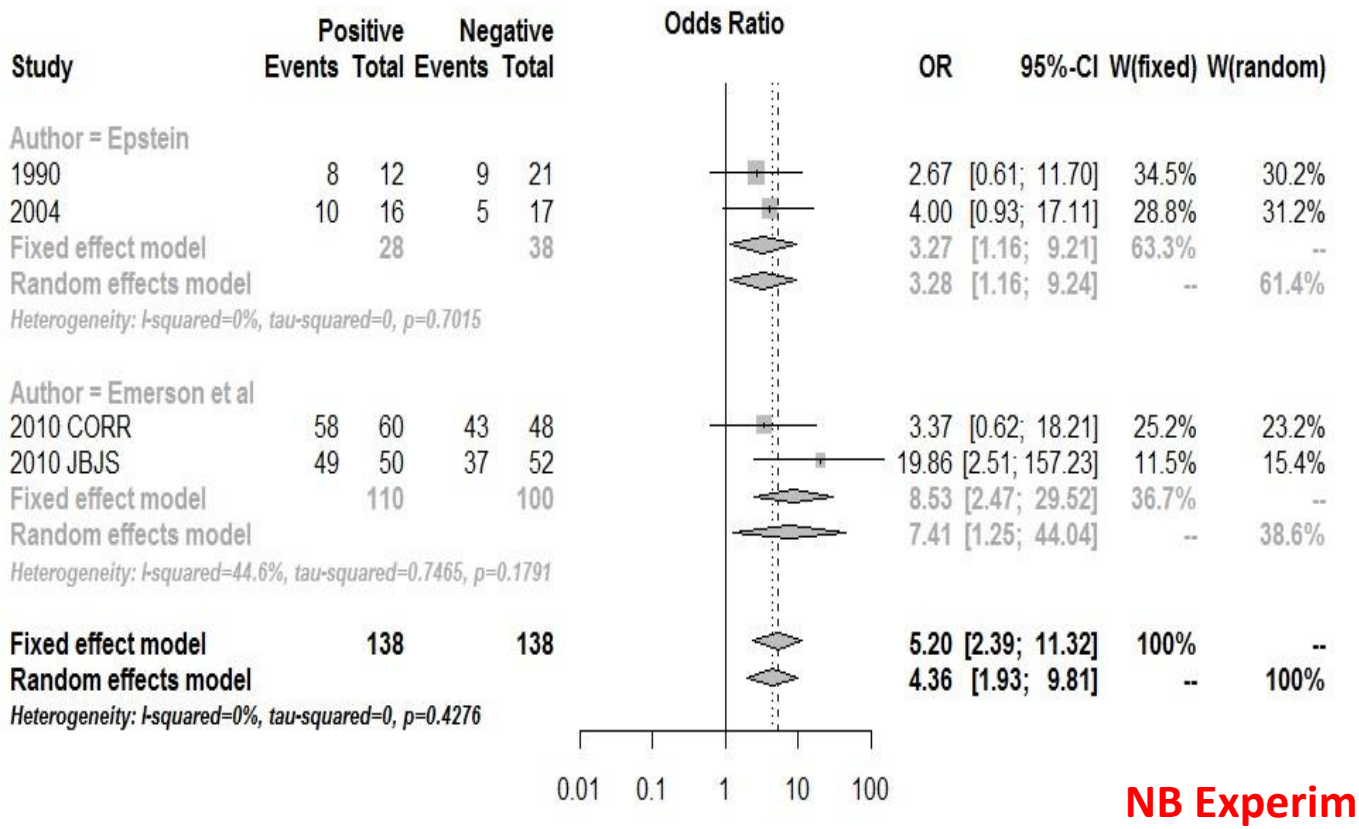


Data from Song et al, *BMC Medical Research Methodology* 2009, **9**:79

Analysis in R using Guido Schwarzer's meta package

NB Observational studies

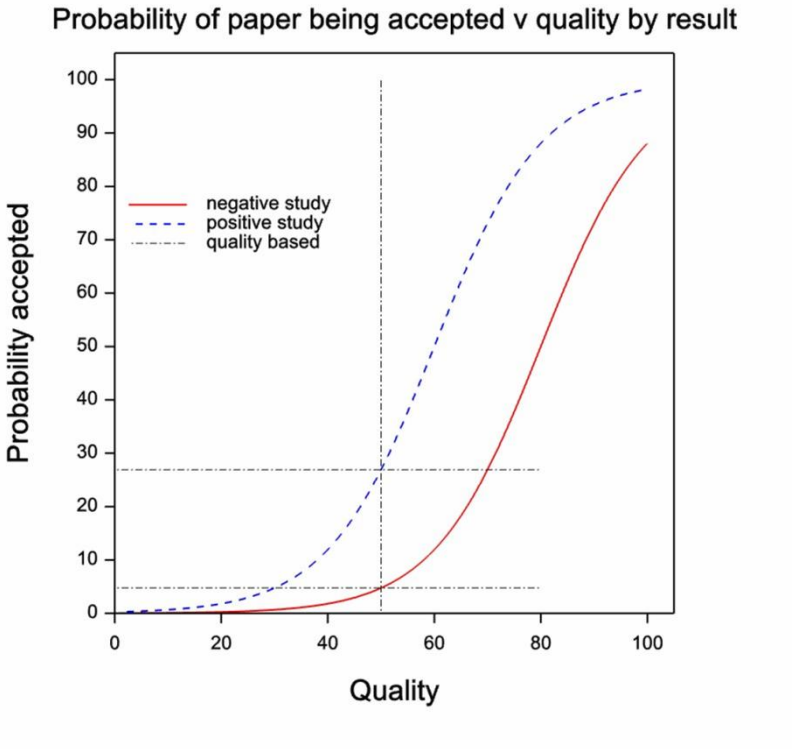
Journals *are* biased in favour of positive studies



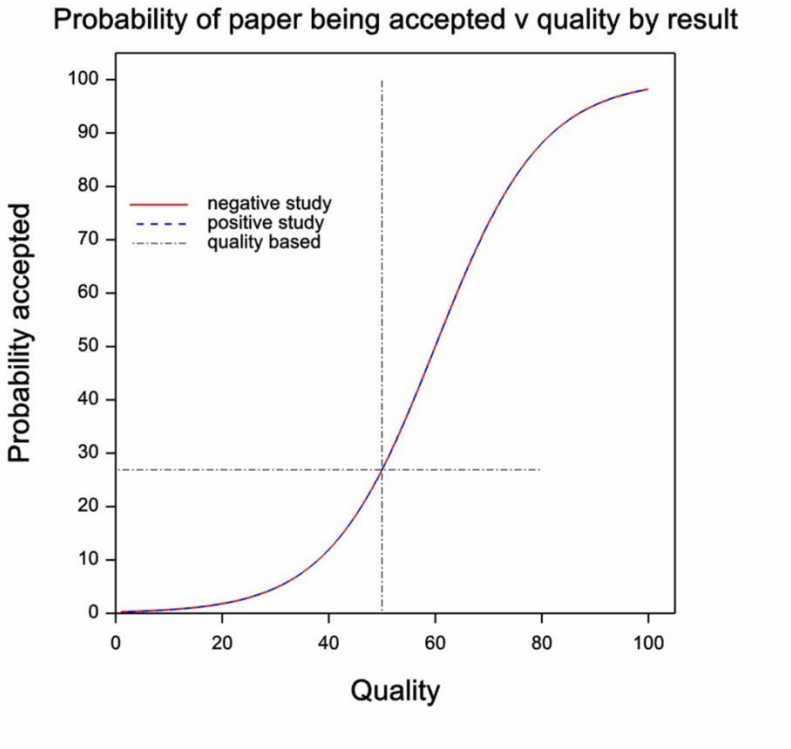
NB Experimental studies

Biased and unbiased acceptance curves

Bias



No bias



We have a puzzle

- The observational studies seem to suggest that editors are not biased against negative papers
- The experimental studies suggest that they are biased

Data Filter?

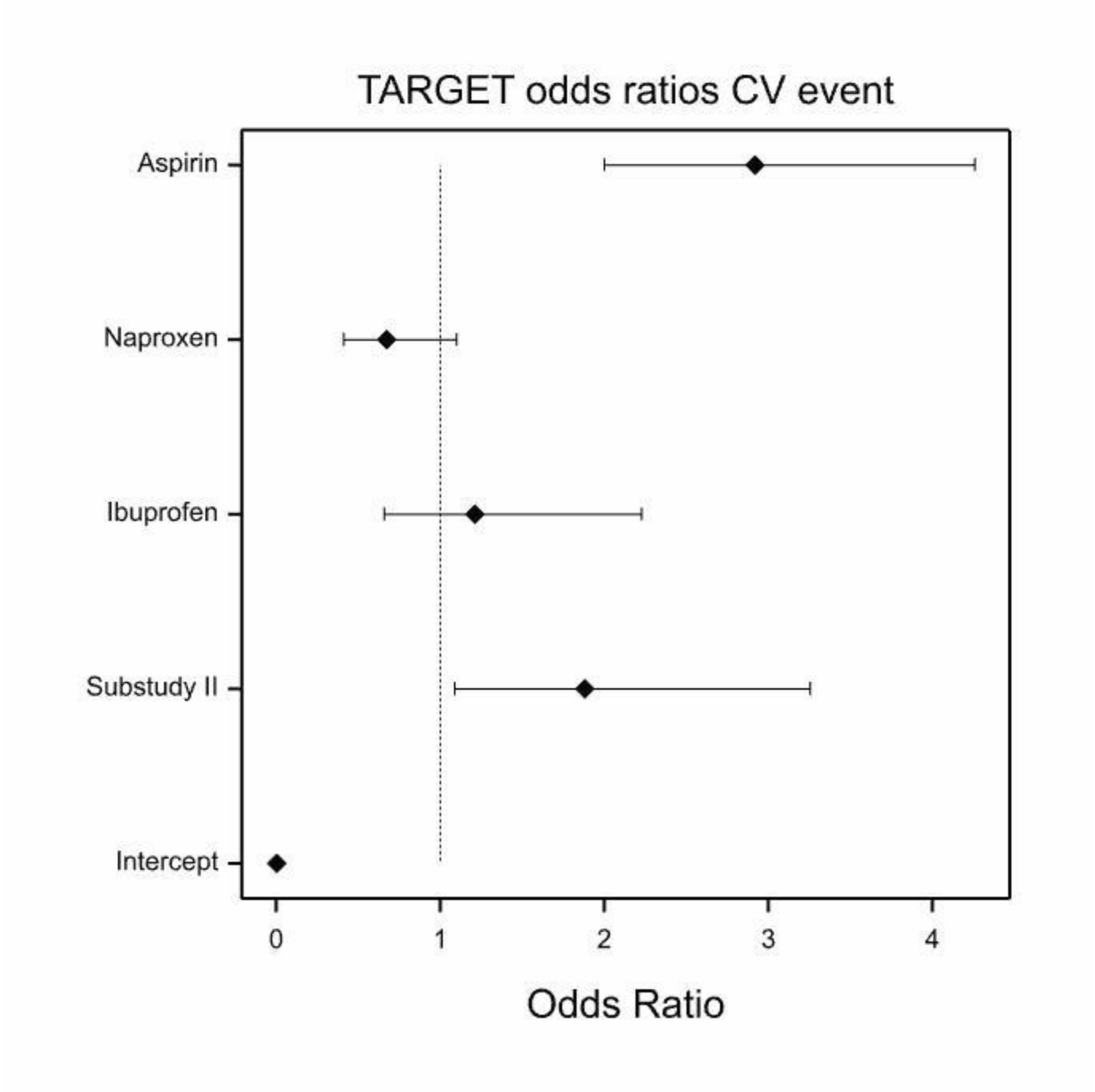
- However there may be the problem of data filtering
- Can the way that the data arrive be ignored?
- Is it safe to condition on what is seen and argue from that point onwards as if like were being compared with like?
- Or is there an inherent problem?
- Consider the following examples…

Data Filtering Some Examples

- Oscar winners lived longer than actors who didn't win an Oscar
- A 20 year follow-up study of women in an English village found higher survival amongst smokers than non-smokers
- Transplant receivers on highest doses of cyclosporine had higher probability of graft rejection than on lower doses
- Left-handers observed to die younger on average than right-handers
- Obese infarct survivors have better prognosis than non-obese

TARGET study

- Trial of more than 18,000 patients in osteoarthritis over one year or more
- Two sub-studies
  - Lumiracoxib v ibuprofen
  - Lumiracoxib v naproxen
- Stratified by aspirin use or not
- Analysis of cardiovascular(CV)events at one year


TARGET odds ratios CV event
Aspirin
Naproxen
Ibuprofen
Substudy II
Intercept
0
1
2
3
4
Odds Ratio

Moral

- What you don't see can be important
  - Actually this is a point Goldacre makes over and over but forgets
- The data may have arisen in a way which would bias naïve analyses
- We need to think about the publication bias carefully

Negative Thinking

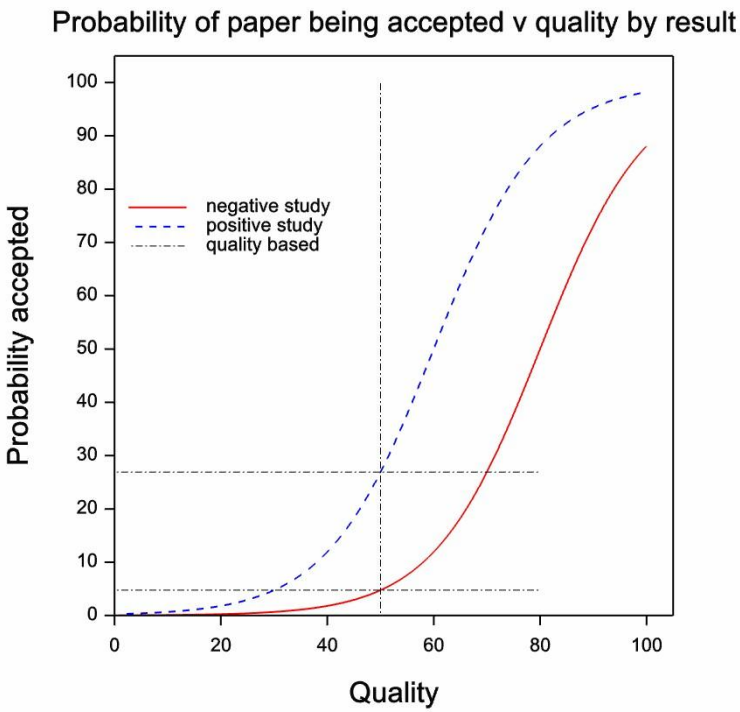
'In the light of all this, the data on what researchers say about their own behaviour is very revealing. In various surveys they have said that they thought there was no point in submitting negative results, because they would just be rejected by journals.' *Bad Pharma*, p36

- If authors act rationally they will make a decision based on the estimated probability of acceptance whether to submit or not
- In that case the relevant threshold for submission *is not a quality threshold but a probability threshold*
- Return to our graphical model of paper acceptance…

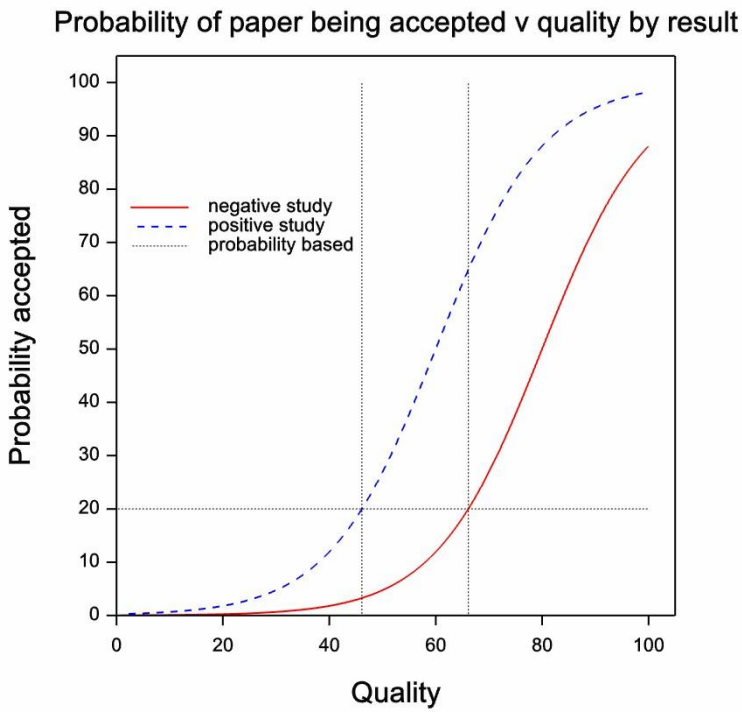
Minding your Ps and Qs

You Choose

Quality based

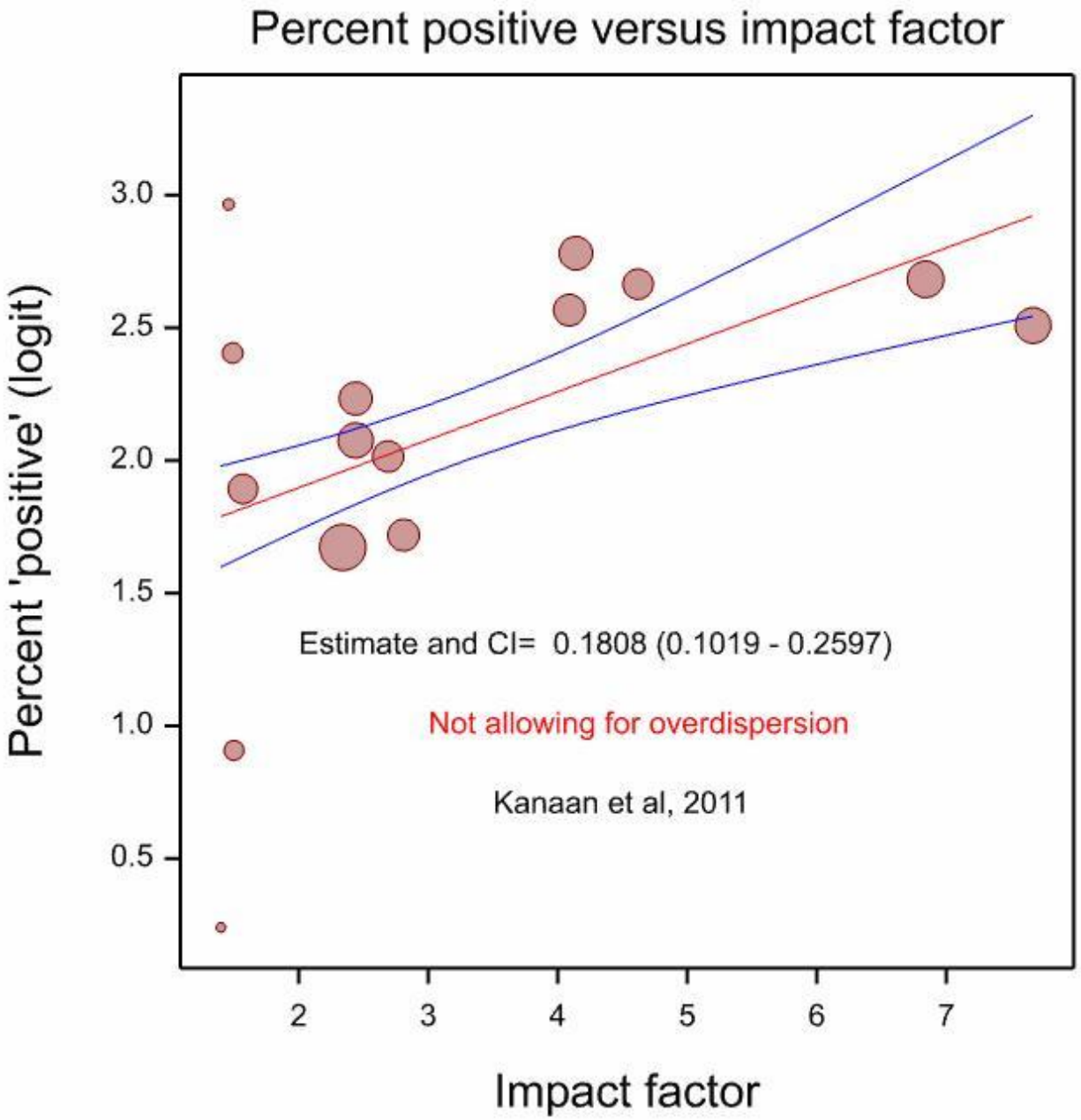


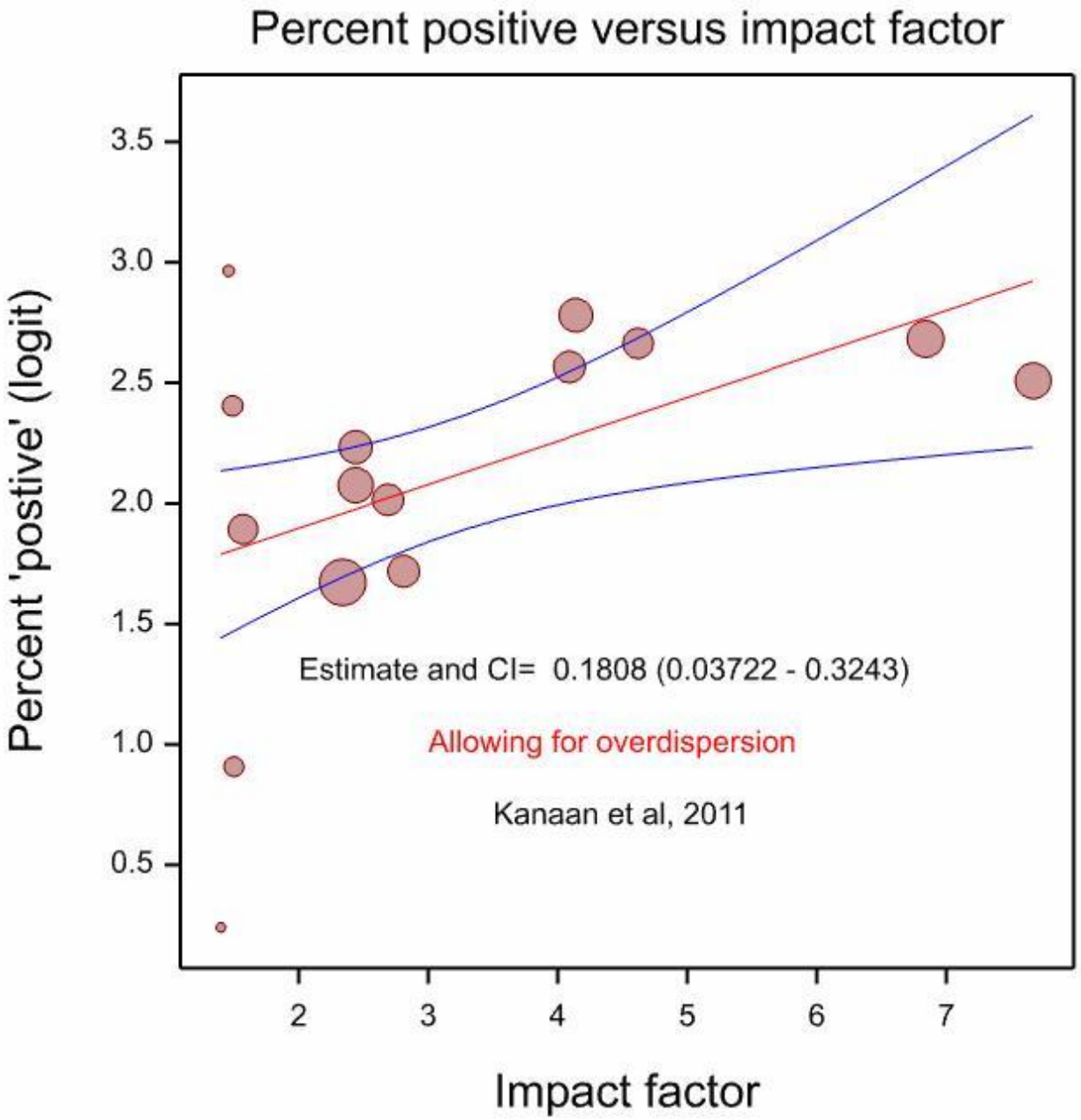
Probability based



Explanation of the meta-analysis

- Authors know there is a bias against negative studies
- Other things being equal they are much less likely to submit to a prestigious journal
- In consequence the *probability* of negative and positive studies being accepted is the same
- They differ in *quality*


Percent positive versus impact factor
Percent 'positive' (logit)
3.0
2.5
2.0
1.5
1.0
0.5
2
3
4
5
6
7
Impact factor
Estimate and CI= 0.1808 (0.1019 - 0.2597)
Not allowing for overdispersion
Kanaan et al, 2011


Percent positive versus impact factor
Percent 'postive' (logit)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2
3
4
5
6
7
Impact factor
Estimate and CI= 0.1808 (0.03722 - 0.3243)
Allowing for overdispersion
Kanaan et al, 2011

To Sum Up

- Comparing negative and positive studies the assumption has been made that (apart from the defining condition) like is being compared with like
- The data have been analysed as if they came from a randomised trial
- They don't
- There are data missing and these are missing 'not at random' to use the Rubin classification

How could we deal with the bias?

- One way would be to have randomised studies
- Provide reviewers with different randomised versions of the same manuscript
  - Conclusions changed to be positive or negative
- These are also mentioned briefly in *Bad Pharma*

What about quality?

'The same thing has been tried with papers submitted to the *BMJ*, *The Lancet*, *Annals of Internal Medicine* and the *Journal of Bone and Joint Surgery*. Again and again no effect was found.' *Bad Pharma* p34

- Is Goldacre right?
- Let us have a look at the *Journal of Bone and Joint Surgery*

Lynch et al, 2007

- All manuscripts about hip or knee arthroplasty submitted to *Journal of Bone and Joint Surgery*, American volume, over 17 months were evaluated
- Study design, quality and outcome were noted
- 209 Manuscripts reviewed

Lynch et al 2

‘Commercially funded and United States-based research is more likely to be published; good-quality studies with negative outcomes are not’

- Title is very revealing!
- No difference found in probability of acceptance positive and negative studies
- However significant difference in quality, negative versus positive p=0.003

Aristotelian theories of causality?

- Why did the chicken cross the road?
  - Because in response to various bio-physical stimuli its legs propelled it forward orthogonally to the road direction? (Efficient cause.)
  - To get to the other side? (Final cause)
- Why did the author submit to this journal?
  - Because the quality was right for this journal?
  - Because the probability of acceptance was right for this journal?

Who's Guilty?
Authors or Reviewers?

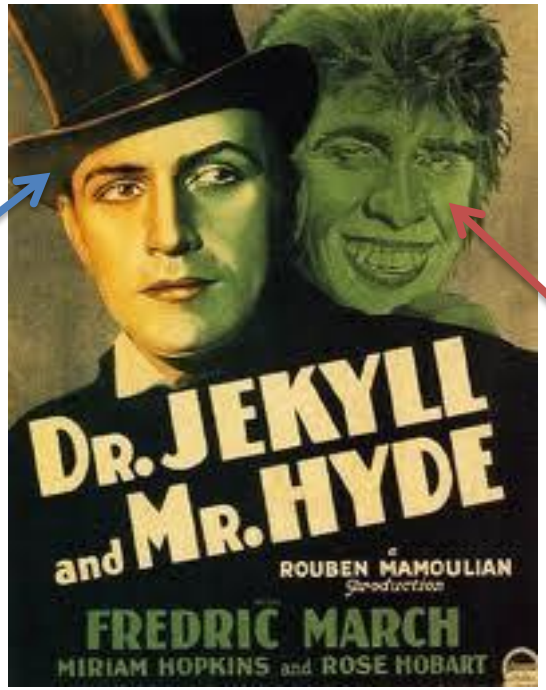
- The Goldacre view is that journals are blameless and authors are guilty
- But there is something very strange about this
- By and large these are the same people
  - albeit in different roles
- Can we believe that researchers as authors are biased against submitting negative papers but researchers as reviewers are not?

In Summary

- Authors tells us they are reluctant to submit negative papers because they fear rejection
- Authors are also reviewers
- It is logical for them to submit by quality of acceptance
- The empirical evidence show that submitted negative papers are of higher quality
- The experimental evidence shows that reviewers are less likely to accept negative papers
- Equal probability of acceptance of positive and negative studies does not show lack of bias

Would I submit this? No! Let's publish it!

How can I hide my negative result?



Just judge Jekyll

Horrible hypothesis tester Hyde

The Solution

- The responsibility for publishing must lie with the trialist *alone*
- Trialists must be come self-publishing
  - E.g on http://www.clinicaltrials.gov/
- We must abandon publishing in medical journals as a means of primary communication of trial results
- The journals should concentrate on reviews
- A further issue is should data be made available?

Advantage

- Time to publish will reduce
- Publications can be more complete
- Quality will be better
  - Stress on pre-specified analyses
  - Regulatory version is the published version
  - Elimination of in-expert interference by journal editors and their reviewers

Surely, publication and regulatory conflict is impossible?

To the Editor:
On October 4, 2001, the Antiviral Drugs Advisory Committee of the Food and Drug Administration (FDA) discussed 1 the results of the clinical trial reported by Walsh and colleagues in this issue of the *Journal*2

The authors present the unstratified analysis in their report. The plan for the primary analysis of this trial was defined prospectively as the evaluation of the overall stratified rate of response in terms of a five-part composite end point. The stratified analysis is the appropriate primary analysis, since patients were stratified at randomization according to their degree of risk of fungal infection and their receipt or nonreceipt of antifungal prophylaxis. The plannedanalysis also included stratification according to the duration of neutropenia before randomization

Powers, J. H., et al. (2002). "Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever." N Engl J Med **346(4): 289-290.**

Walsh, T. J., et al. (2002). "Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever." N Engl J Med **346(4): 225-234.**

Various initiatives are underway

- Bayer, Boehringer Ingelheim, GSK, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare
  - https://clinicalstudydatarequest.com/
- Pfizer
  - http://www.pfizer.com/research/clinical_trials/trial_data_and_results/data_requests/
- EMA policy statement
  - http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/06/WC500168342.pdf

Pros and cons of openness

Con

- Loss of proprietary information
- Proliferation of inexpert analysis of clinical trial
- Expense of managing system
- We may now have a file-draw analysis problem

Pro

- Gain of proprietary information from rivals
- More things may be discovered
- Gain in public trust?
- The file-draw trial problem was worse

Conclusion

- There is a third party in drug-regulation and this must be accepted
- There are differences between the views of the three parties
- Publication of all trials is inevitable
- Data release is inevitable
- There is a potential for conflict
- Prevention is better than cure
- Full & timely publications with documented pre-specifications will
  - Help minimise problems
  - And help disseminate valuable information about the effects of drugs

Finally

Statistics is a subject that many medics find easy but most statisticians find difficult.

Guernsey McPearson