Lorem Ipsum Dolor

Publication bias

Bioinformatics journal club
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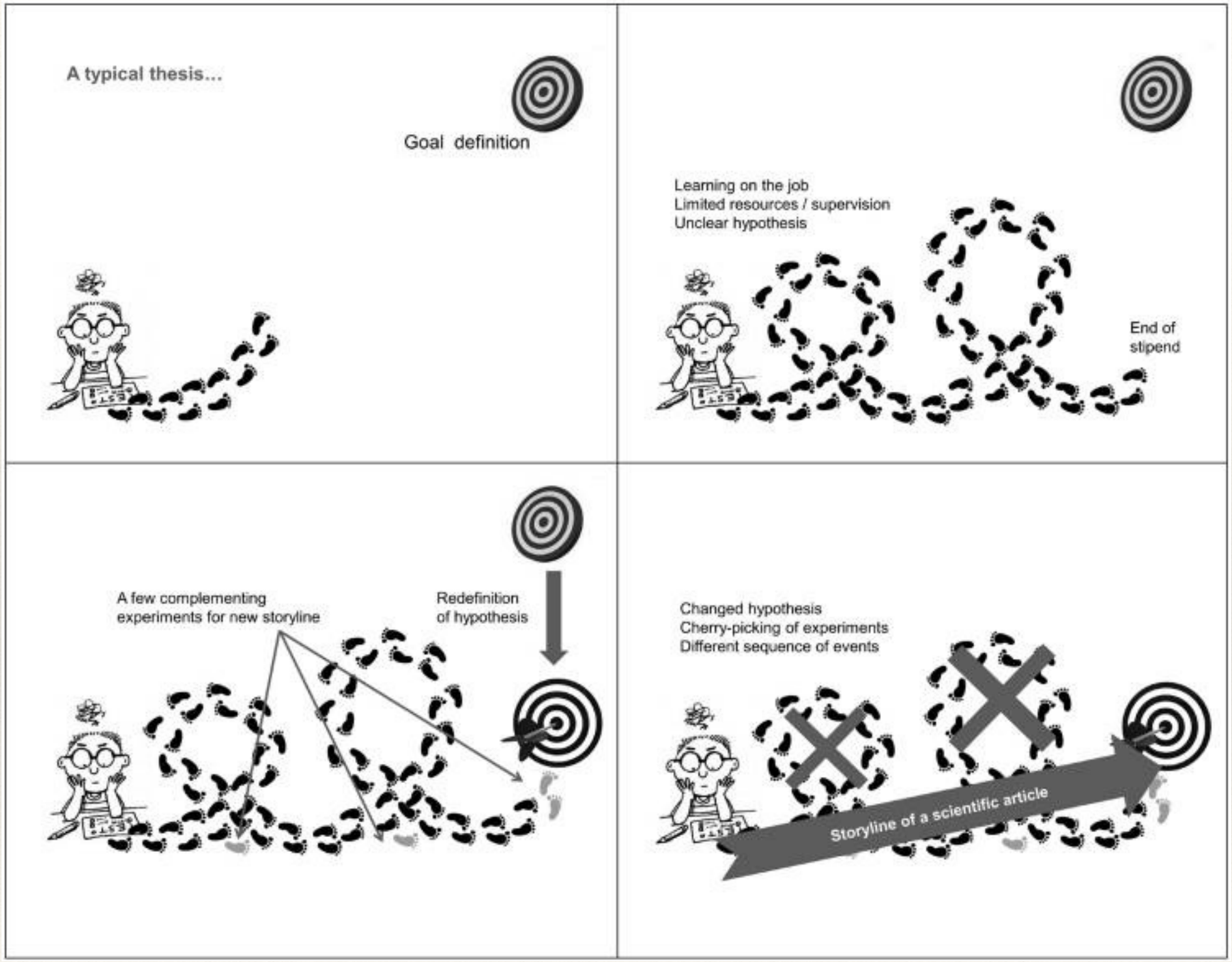
Publication bias

- Positive results have a greater chance of being published
- Statistically significant outcomes have greater chance of being published

Where the bias comes from - authors

- The file drawer effect - **researchers** don't bother to publish negative results
- If several associations were studied, only the positive associations are published
- The data is analysed from a different angle to find statistically significant and/or positive associations
- Studies with negative results are published in journals with lower impact factor



ALTEX. 2013;30(3):275-91.

Look back in anger - what clinical studies tell us about preclinical work.

Hartung T.

Where the bias comes from - editors

- Journal **editors** reject studies with negative results
- Studies with results not in concordance with previously published results are less likely to be accepted
- or studies on “unsexy” topics
- Studies not from geographical interest of readers or in poor English are less likely to be published

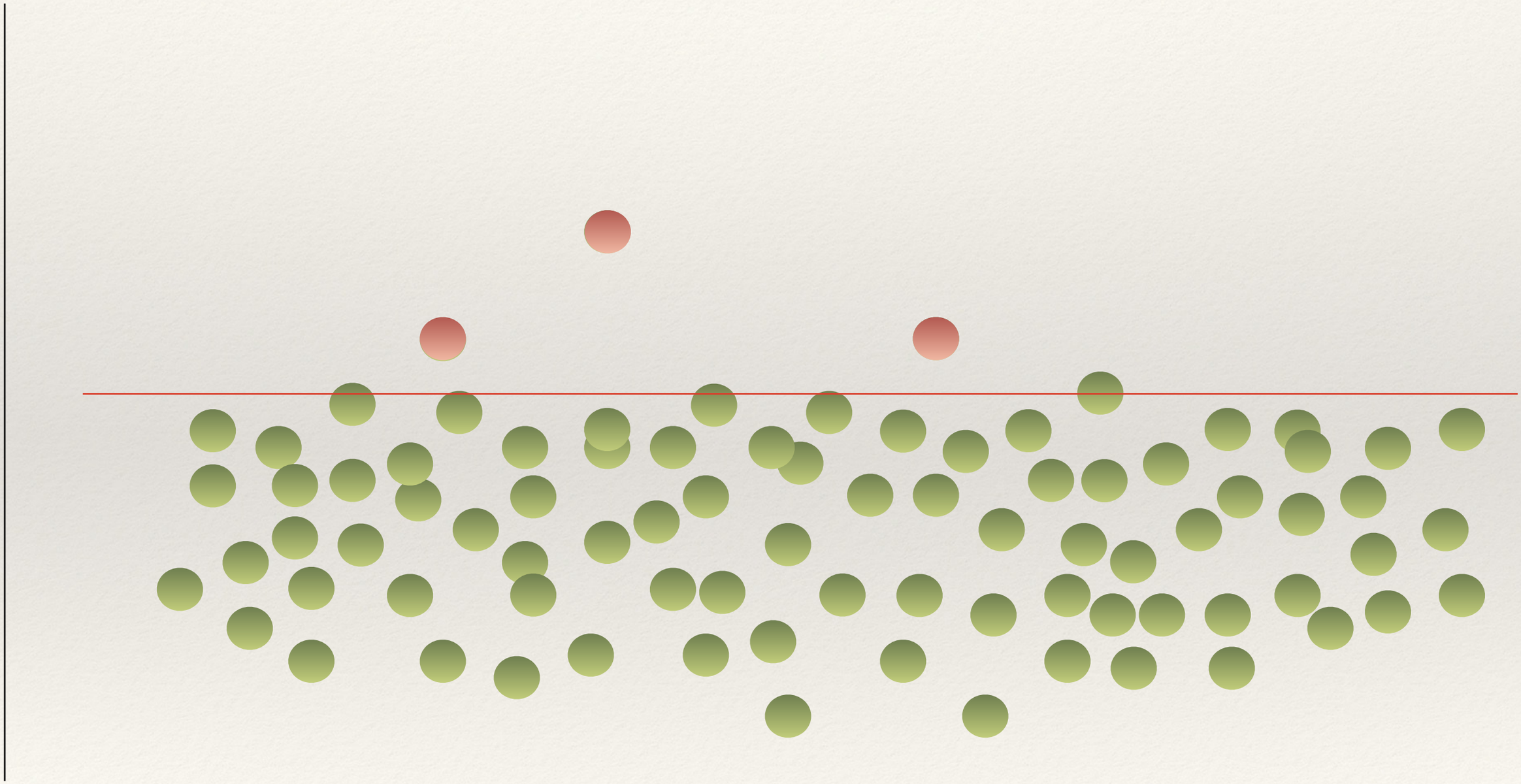
Where the bias comes from- reviewers and funders

- **Reviewers** reject studies with negative results
- Reviewers reject studies not in concordance with their own published results
- Study **sponsors** (pharmaceutical companies) don't allow the publication of undesired results (no effect or negative effect)
- Researchers are evaluated and funded based on publications in high impact journals - pressure to publish a lot and in top journals (no place for negative results)

Bias in meta-analyses

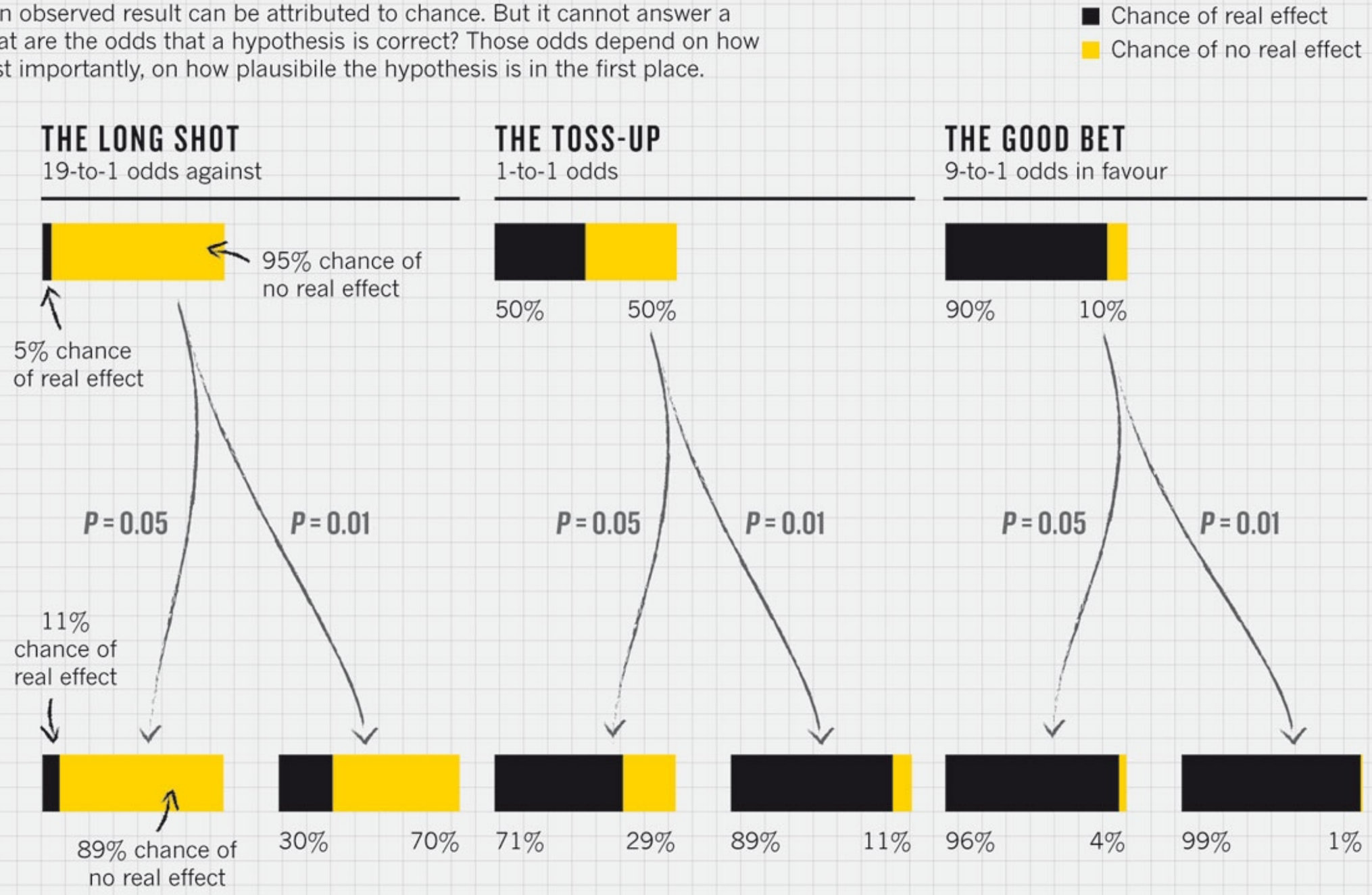
- Publication bias
- Selection bias
  - Language bias
  - Location bias

Extreme example



PROBABLE CAUSE

A *P* value measures whether an observed result can be attributed to chance. But it cannot answer a researcher's real question: what are the odds that a hypothesis is correct? Those odds depend on how strong the result was and, most importantly, on how plausibile the hypothesis is in the first place.



Before the experiment
The plausibility of the hypothesis — the odds of it being true — can be estimated from previous experiments, conjectured mechanisms and other expert knowledge. Three examples are shown here.

The measured *P* value
A value of 0.05 is conventionally deemed 'statistically significant'; a value of 0.01 is considered 'very significant'.

After the experiment
A small *P* value can make a hypothesis more plausible, but the difference may not be dramatic.

Nuzzo, R. Nature 14.02.2014 "Statistical errors"

PLOS One, Nov 2014, issue 11

Publication bias in recent meta-analyses

Michal Kicinski

Purpose of the study

- Did **statistically significant outcomes with positive effect of the treatment** (clinical trials)
- or **plausible statistically significant outcomes** (observational studies) have a greater probability to be included in recent meta-analyses than other outcomes?

Study design

- Meta-analyses that included at least 30 effect sizes from individual studies
- Published between 2008 and 2012 in BMJ, JAMA, Lancet and PLOS Medicine

Methods

- Clinical trials: RR - ratio of the probability of including statistically significant results favouring the treatment to the probability of including other results
- Observational studies: RR - ratio of the probability of including plausible statistically significant results to the probability of including other results
- They created a Bayesian selection model to describe the process of study selection.

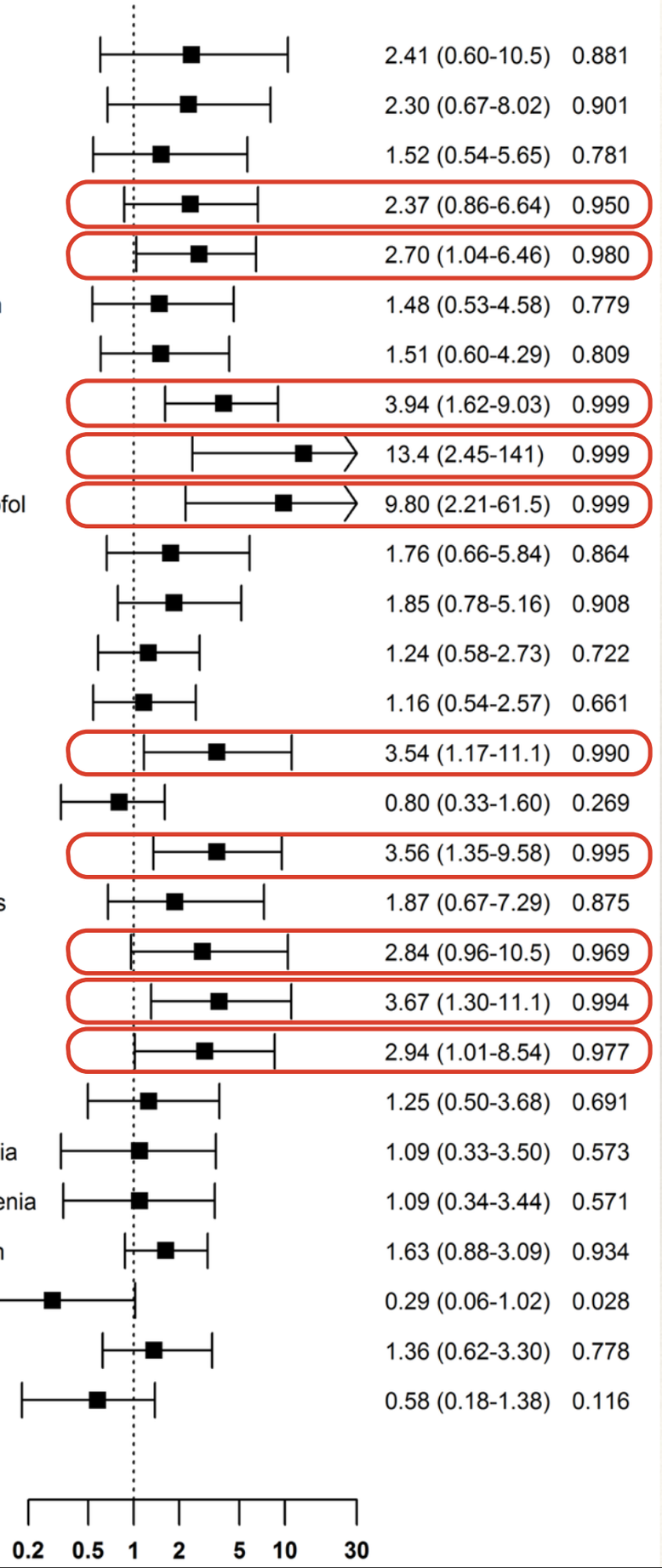
Model testing on simulated data

- The estimate of RR gave a correct idea about the existence of a publication bias
- The RR tended to be underestimated when the mean effect size was small
- The RR tended to be overestimated when the mean effect size was large
- Compared to other methods the Bayesian model was more sensitive and specific

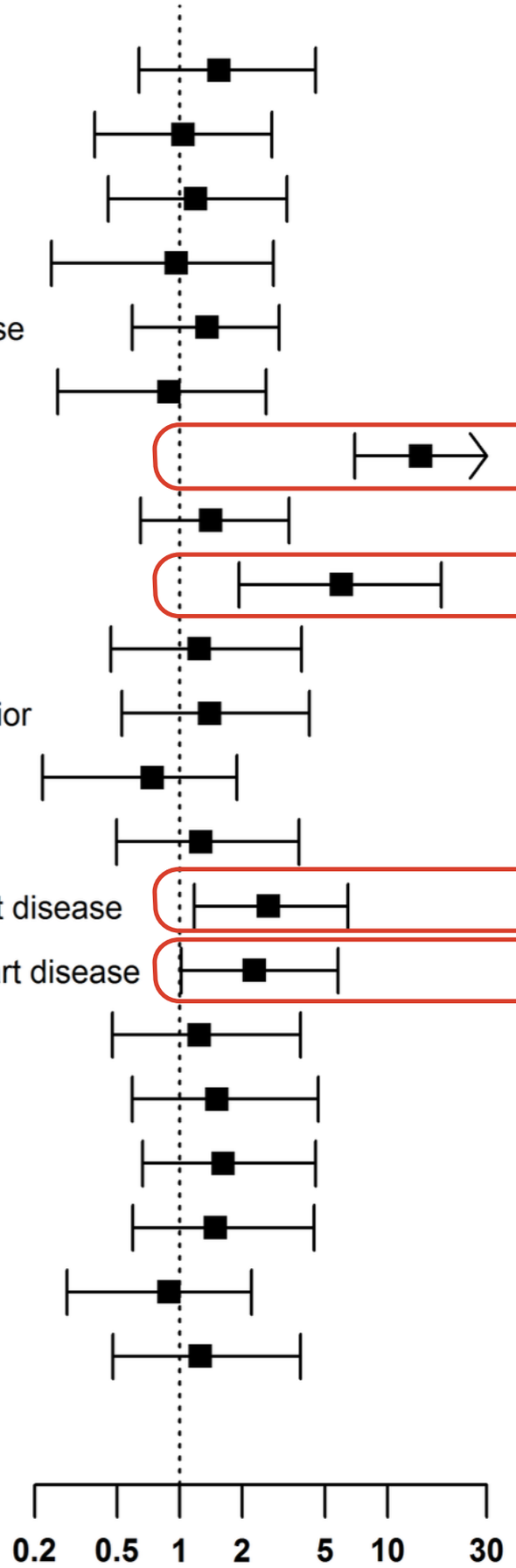
Results

- 20 reports including 49 meta-analyses were used
- 28 large meta-analyses of clinical trials
- 19 large meta-analyses of observational studies

Reference	Investigated association	RR (95% CI)	P(RR>1)
Bangalore, 2011	Angiotensin receptor blockers and myocardial infarction	2.41 (0.60-10.5)	0.881
Bangalore, 2011	Angiotensin receptor blockers and mortality	2.30 (0.67-8.02)	0.901
Bangalore, 2011	Angiotensin receptor blockers and heart failure	1.52 (0.54-5.65)	0.781
Beswick, 2008	Interventions to improve physical functioning and not living at home	2.37 (0.86-6.64)	0.950
Beswick, 2008	Interventions to improve physical functioning and risk of death	2.70 (1.04-6.46)	0.980
Beswick, 2008	Interventions to improve physical functioning and hospital admission	1.48 (0.53-4.58)	0.779
Beswick, 2008	Interventions to improve physical functioning and physical function	1.51 (0.60-4.29)	0.809
Hempel, 2012	Probiotic use and antibiotic-associated diarrhea	3.94 (1.62-9.03)	0.999
Jalota, 2011	Adding lidocaine and the risk of pain on injection of propofol	13.4 (2.45-141)	0.999
Jalota, 2011	Pretreatment with lidocaine and the risk of pain on injection of propofol	9.80 (2.21-61.5)	0.999
Ker, 2012	Tranexamic acid in surgery and the risk of blood transfusion	1.76 (0.66-5.84)	0.864
Law, 2009	Beta blockers and coronary heart disease	1.85 (0.78-5.16)	0.908
Law, 2009	Drugs other than beta blockers and coronary heart disease	1.24 (0.58-2.73)	0.722
Law, 2009	Single drug blood pressure treatment and coronary heart disease	1.16 (0.54-2.57)	0.661
Law, 2009	Single drug blood pressure treatment and stroke	3.54 (1.17-11.1)	0.990
Law, 2009	Blood pressure decrease and coronary heart disease	0.80 (0.33-1.60)	0.269
Law, 2009	Blood pressure decrease and stroke	3.56 (1.35-9.58)	0.995
Leucht, 2012	Antipsychotic drugs and relapse of schizophrenia up to three months	1.87 (0.67-7.29)	0.875
Leucht, 2012	Antipsychotic drugs and relapse of schizophrenia four to six months	2.84 (0.96-10.5)	0.969
Leucht, 2012	Antipsychotic drugs and relapse of schizophrenia	3.67 (1.30-11.1)	0.994
Leucht, 2012	Antipsychotic drugs and leaving the study early due to any reason	2.94 (1.01-8.54)	0.977
Leucht, 2012	Antipsychotic drugs and leaving the study early due to inefficacy	1.25 (0.50-3.68)	0.691
Leucht, 2009	Risperidone vs 1st gen. drugs and overall symptoms of schizophrenia	1.09 (0.33-3.50)	0.573
Leucht, 2009	Risperidone vs 1st gen. drugs and negative symptoms of schizophrenia	1.09 (0.34-3.44)	0.571
Tricco, 2012	Quality improvement strategies in diabetes and glycated hemoglobin	1.63 (0.88-3.09)	0.934
Tricco, 2012	Quality improvement strategies in diabetes and LDL	0.29 (0.06-1.02)	0.028
Tricco, 2012	Quality improvement strategies in diabetes and systolic BP	1.36 (0.62-3.30)	0.778
Tricco, 2012	Quality improvement strategies in diabetes and diastolic BP	0.58 (0.18-1.38)	0.116



Reference	Investigated association	RR (95% CI)	P(RR>1)
Botteri, 2008	Smoking and colorectal cancer incidence	1.54 (0.64-4.52)	0.818
Botteri, 2008	Smoking and colorectal cancer mortality	1.04 (0.39-2.77)	0.538
Brien, 2011	Alcohol consumption and high density lipoprotein cholesterol	1.19 (0.45-3.28)	0.657
Brien, 2011	Alcohol consumption and triglycerides	0.96 (0.24-2.83)	0.467
Clarke, 2012	C677T polymorphism of the MTHFR gene and coronary heart disease	1.35 (0.59-3.01)	0.777
De Boer, 2009	Cancer survivors vs healthy people and unemployment	0.89 (0.26-2.60)	0.401
Hemingway, 2010	C-reactive protein level and cardiovascular events	14.4 (6.97-30.7)	1.000
Norman, 2012	Child physical abuse and anxiety	1.41 (0.65-3.36)	0.813
Norman, 2012	Child physical abuse and depressive disorders	6.01 (1.92-18.1)	0.999
Norman, 2012	Child physical abuse and alcohol problem drinking	1.24 (0.46-3.87)	0.681
Norman, 2012	Child physical abuse and sexually transmitted infections/risky behavior	1.39 (0.53-4.20)	0.751
Norman, 2012	Child neglect and sexually transmitted infections/risky behavior	0.74 (0.22-1.88)	0.258
Norman, 2012	Child neglect and drug use	1.26 (0.49-3.75)	0.693
Palomaki, 2010	9p21 single-nucleotide polymorphism (2 vs 1 at-risk allele) and heart disease	2.68 (1.17-6.45)	0.990
Palomaki, 2010	9p21 single-nucleotide polymorphism (no vs 1 at-risk allele) and heart disease	2.29 (1.01-5.78)	0.977
Pan, 2011	Depression and stroke incidence	1.24 (0.47-3.81)	0.684
Renehan, 2008	BMI and postmenopausal breast cancer	1.51 (0.59-4.64)	0.800
Ronksley, 2011	Alcohol consumption and coronary heart disease incidence	1.62 (0.66-4.51)	0.845
Ronksley, 2011	Alcohol consumption and coronary heart disease mortality	1.48 (0.59-4.42)	0.799
Ronksley, 2011	Alcohol consumption and all-cause mortality	0.89 (0.29-2.22)	0.385
Ziegelbauer, 2012	Sanitation facilities and infection with soil-transmitted helminths	1.25 (0.48-3.82)	0.684



How to decrease publication bias?

- Prospective public registration of clinical trials (and observational studies) as a condition for publication and registration of trial results
- Publication of “negative results” (not statistically significant)