POSSIBLE NON-SCIENTIFIC BIAS IN THE LITERATURE DATABASE

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Bias

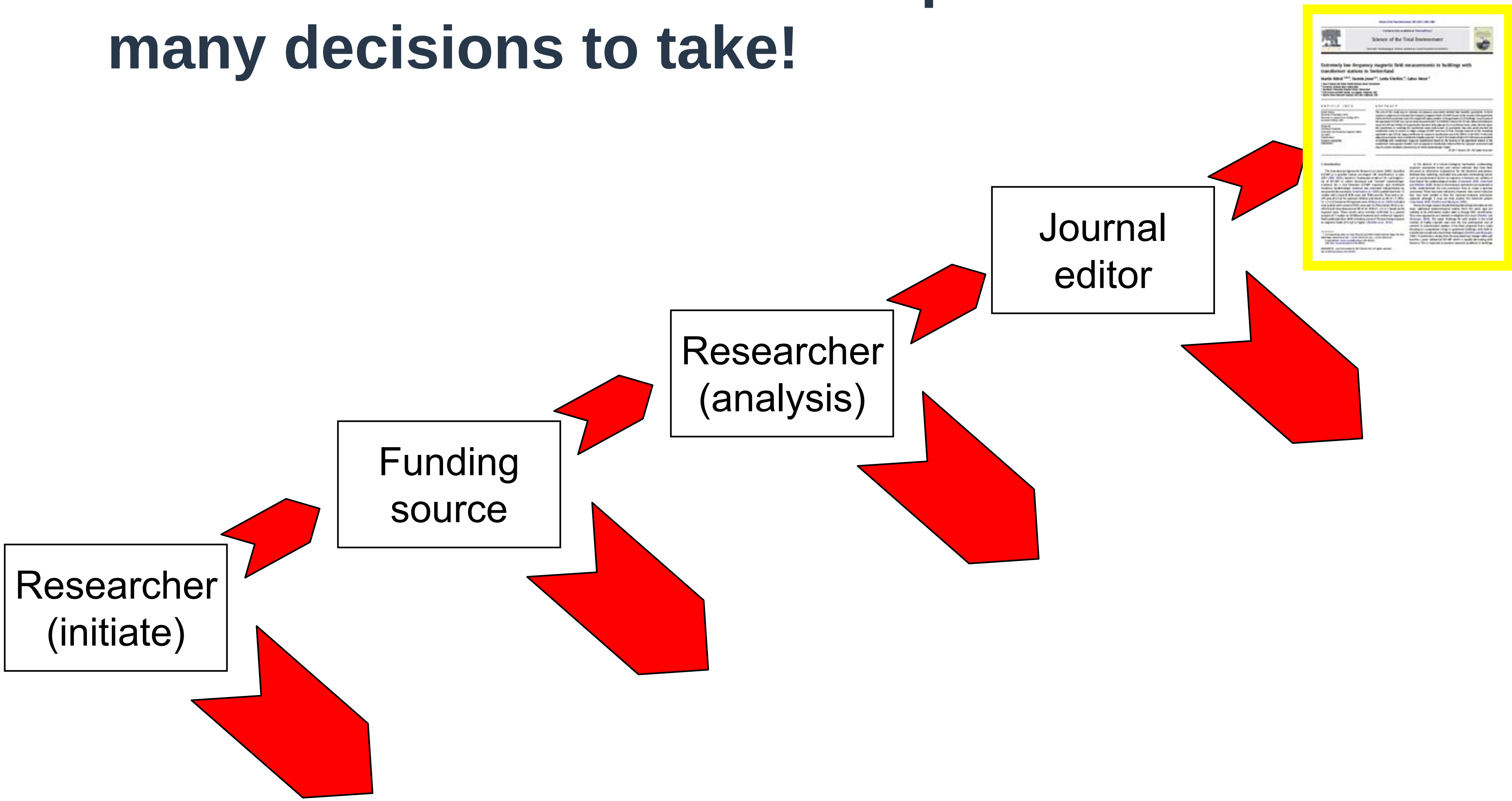
- **Bias** is an inclination to present or hold a partial perspective at the expense of (possibly equally valid) alternatives. Bias can come in many forms. (http://en.wikipedia.org/wiki/Bias)

- Question: In relation to EMF health research, are studies demonstrating an association over or underrepresented?

- Problem: I (we) do not know the truth about the association.

Sterne & Smith, BMJ, 2001

From the research idea to a publication: many decisions to take!



Initiating research

- Personal interests: competency, career, plausibility, etc

Example plausibility

- Epidemiological studies on male reproduction
- Quite a few epidemiological studies conducted (La Vignera et al., J Androl., 2011)
- Striking that…
  1. …use of mobile phones applied as an exposure proxy
  2. …rarely presented in the BioEM research community

Initiating research

- Personal interests: competency, career, plausibility, etc
- Comparative advantage of the host institution: competency, existing resources, synergies, etc
- Expectations: societal context, knowledge gap, etc
- Funding opportunities
- Feasibility
- Public health relevance
- …

Each researcher weights differently!!!

Example feasibility

- Use of mobile phones vs. brain tumour/Alzheimer's disease
- Brain tumour: >20 epidemiological studies
- Alzheimer's disease: 1 epidemiological study
- Both are…
  1. … equally biologically (un)plausible
  2. … related to exposure of the head from mobile phone
  3. … of high public health relevance

Example feasibility

- Feasibility of brain tumour studies: ***high***
  1. well diagnosed
  2. cancer registries
  3. exposure recall is assumed to be reliable
  4. large choice of animal models

- Feasibility of Alzheimer‘s disease studies: ***low***
  1. unclear diagnosis (autopsy)
  2. no registries
  3. exposure recall is impossible
  4. small choice of animal models

Funding source

- Quality of the proposal
- Public health relevance
- Scientific impact
- …
- Interests of the funder?
  1. Industrial/commercial sources
  2. Federal/public sources
  3. Private/"independent" sources

firewall, public foundations with industrial money

Systematic review on the effect of source of funding

- Van Nierop et al., Comp Rend Phys, 2010
- Methods
  1. Experimental studies of mobile phone use on health
  2. Published between 1995 and 2009
  3. Outcome: reporting of a significant effect in the abstract
  4. Funding sources: industry, public, mixed (e.g. firewall, public foundations with industrial money), not reported
  5. Data extracted by two researchers independently

Selected studies

	Industry	Public	Mixed	Not reported	Total
1995–2/2005*	12 (20%)	11 (19%)	14 (24%)	22 (37%)	59 (100%)
2/2005–2009	9 (12%)	33 (44%)	14 (19%)	19 (25%)	75 (100%)
Total	21 (16%)	44 (33%)	28 (21%)	41 (30%)	134 (100%)

*Huss et al, EHP, 2007

Odds ratio for reporting an effect in the abstract

	Industry	Public	Mixed	Not reported
1995–2/2005*	0.33 (0.04-3.06)	1 (referent)	2.00 (0.54–7.39)	3.67 (1.12–12.05)
2/2005–2009	0.29 (0.05–1.59)	1 (referent)	1.43 (0.26–7.7)	1.71 (0.35–8.42)
Total (crude)	0.55 (0.17–1.77)	1 (referent)	2.33 (0.89–6.14)	3.50 (1.41–8.66)
Total (adjusted*)	0.20 (0.05–0.85)	1 (referent)	1.89 (0.68–5.27)	3.11 (1.20–8.05)

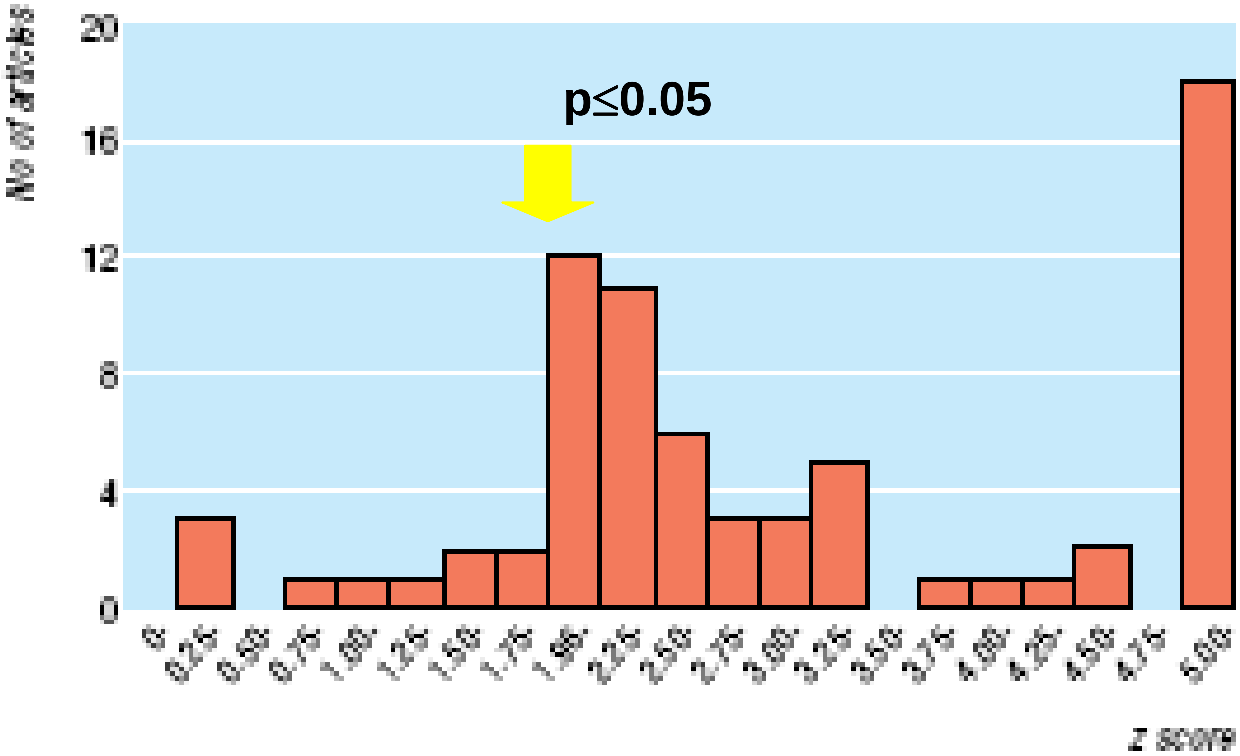
*for year of publication

- The proportion of studies indicating effects declined in 1995–2009, regardless of funding source.
- Studies with mixed funding were of highest quality, studies that did not report funding of lowest (Huss et al, EHP, 2007)

Analysis and Reporting

- Many decisions made by the researcher:
  1. A lot of data available in a study (in particular epi studies)
  2. Various suitable analytical approaches
  3. Various outcomes and exposure measures (e.g. continuous, categories with various cut-points, etc
  4. Many findings -> what to report?
- Data mining vs. waste of resources
- Good epidemiological practice:
  1. Analysis plan
  2. To evaluate consistency of findings and to be transparent about it
  3. To be transparent about primary and secondary analyses
- It is likely that all decisions are in favour of reporting an association compared to report a lack of association.

Distribution of p-values in a random sample of 73 epidemiological studies



P value	No of articles
<0.0001	23
0.0001-	5
0.001-	9
0.01-	12
0.02-	7
0.03-	4
0.04-	3
0.05-	2
0.1-	2
0.2-	6

Distribution of P values for first primary result in each article and corresponding absolute values of standardised normal deviates z (two sided P=0.05, 0.01, 0.001, and 0.0001 correspond to z=1.96, 2.58, 3.29, and 3.89, respectively)

from Pocock et al., BMJ 2004

What is the likelihood for a true association for an association reported to be significant?

- P-value is type I error rate
- Assuming a significance level of p=0.05 indicates that one out of 20 research results is false positive.
- Is this really true?
- Evaluation by Sterne & Smith, BMJ (2001), based on the assumption that:
    1. 10% of tested hypotheses are correct.
    2. average power of the studies is 50%.

Result of experiment	No true association	True association	Total
Accept null hypothesis	855	50	905
Reject null hypothesis	45	50	95
Total	900	100	1000

→ not all of them may be published

→ 45 out of 95 (=47%) are false alarms.

Sterne & Smith, BMJ, 2001

Proportion of false positive significant results with three different criteria for significance

Power of study (proportion (%) of time we reject null hypothesis if it is false)	Percentage of "significant" results that are false positives		
	P=0.05	P=0.01	P=0.001
80% of ideas correct (null hypothesis false)			
20	5.9	1.2	0.10
50	2.4	0.5	0.05
80	1.5	0.3	0.03
50% of ideas correct (null hypothesis false)			
20	20.0	4.8	0.50
50	9.1	2.0	0.20
80	5.9	1.2	0.10
10% of ideas correct (null hypothesis false)			
20	69.2	31.0	4.30
50	47.4*	15.3	1.80
80	36.0	10.1	1.10
1% of ideas correct (null hypothesis false)			
20	96.1	83.2	33.10
50	90.8	66.4	16.50
80	86.1	55.3	11.00

* corresponds to previous table

Sterne & Smith, BMJ, 2001

Journal‘s decision to publish or not to publish

- Criteria of peer and editorial review
  1. scientific quality
  2. quality of reporting
  3. public health relevance
  4. attitude of the reviewers/editors
  5. editor: impact for the journal

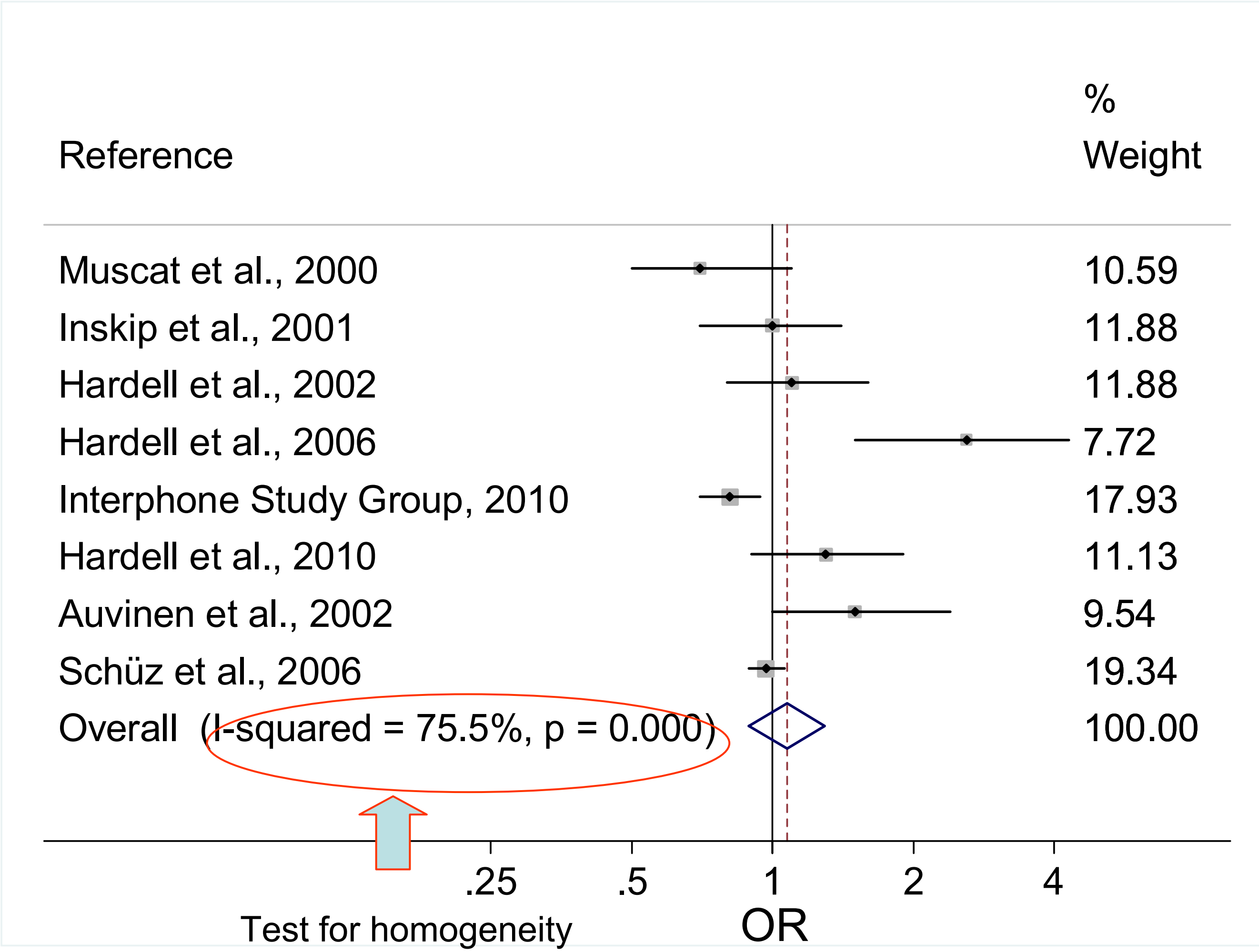
Journal's decision to publish or not to publish

- EMF problem
  1. Lack of biological mechanism -> no justification for reporting lack of association
  2. Reasons for publication of “no-effect studies”: public concerns, previous positive findings
- Small study problem
  1. A small study that does not find an association: power is questioned and thus -> not worth to be published
  2. A small study with an association: power was obviously high enough -> worth to be published (e.g. labelled as pilot study or “interesting observation”)

Evaluating publication bias

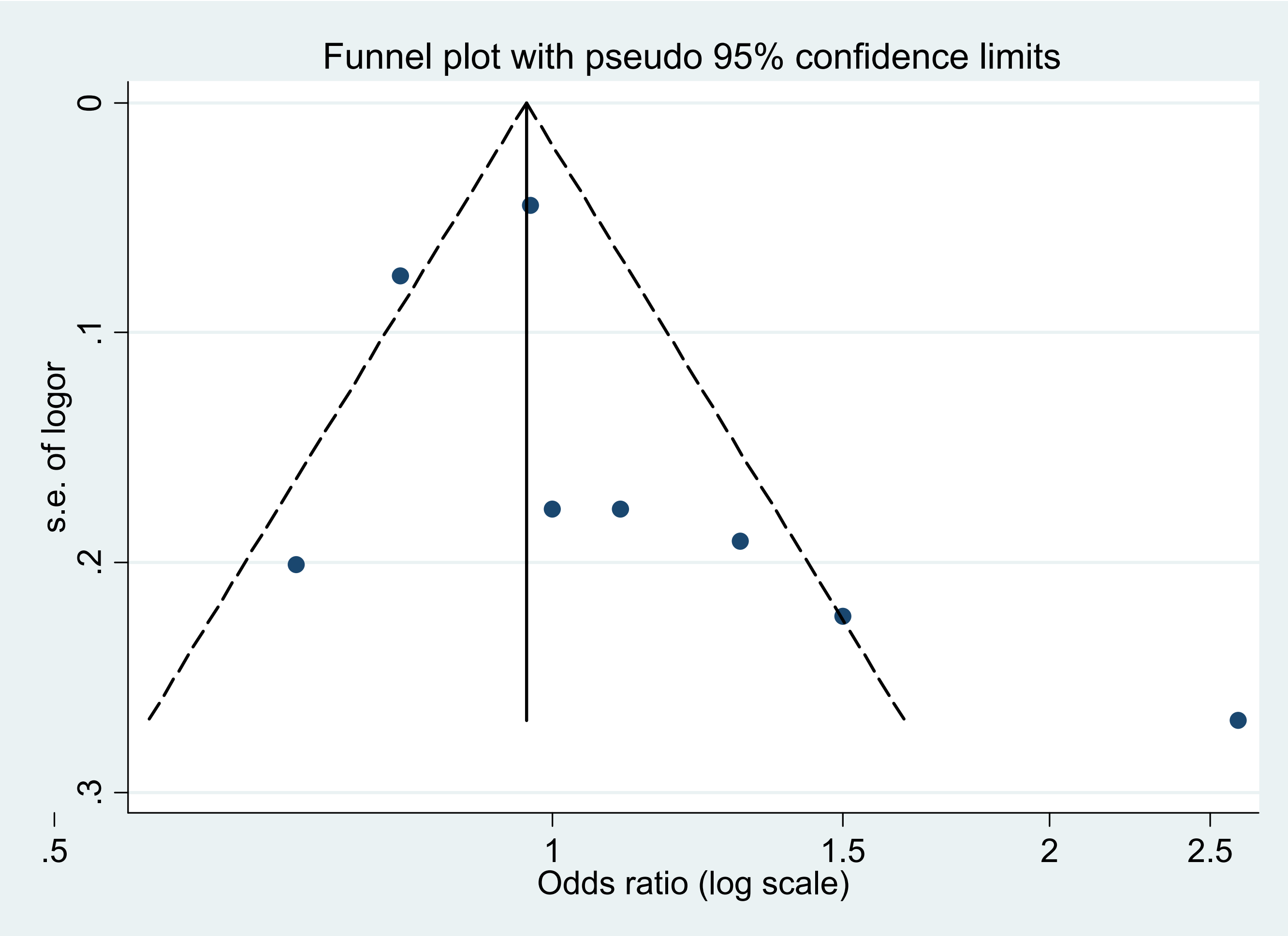
- Methods to evaluate publication bias assume that there is an association between precision of an effect estimate, the effect size and the likelihood for publication
  1. Precise effect estimates are from large studies -> likelihood of publication does not (only marginally) depend on the observed association.
  2. Imprecise effect estimates are from small studies, -> more likely to be published in case of an association
- Funnel plot: plotting effect estimates vs. standard error of effect estimate
- Various tests for estimating bias from funnel plots: Egger test, Harbord's modified test, Peters' test, or Begg and Mazumdar test
- Homogeneity tests

Meta-analysis: risk for glioma vs. ever having used a mobile phone



Repacholi et al, BioEM, 2012

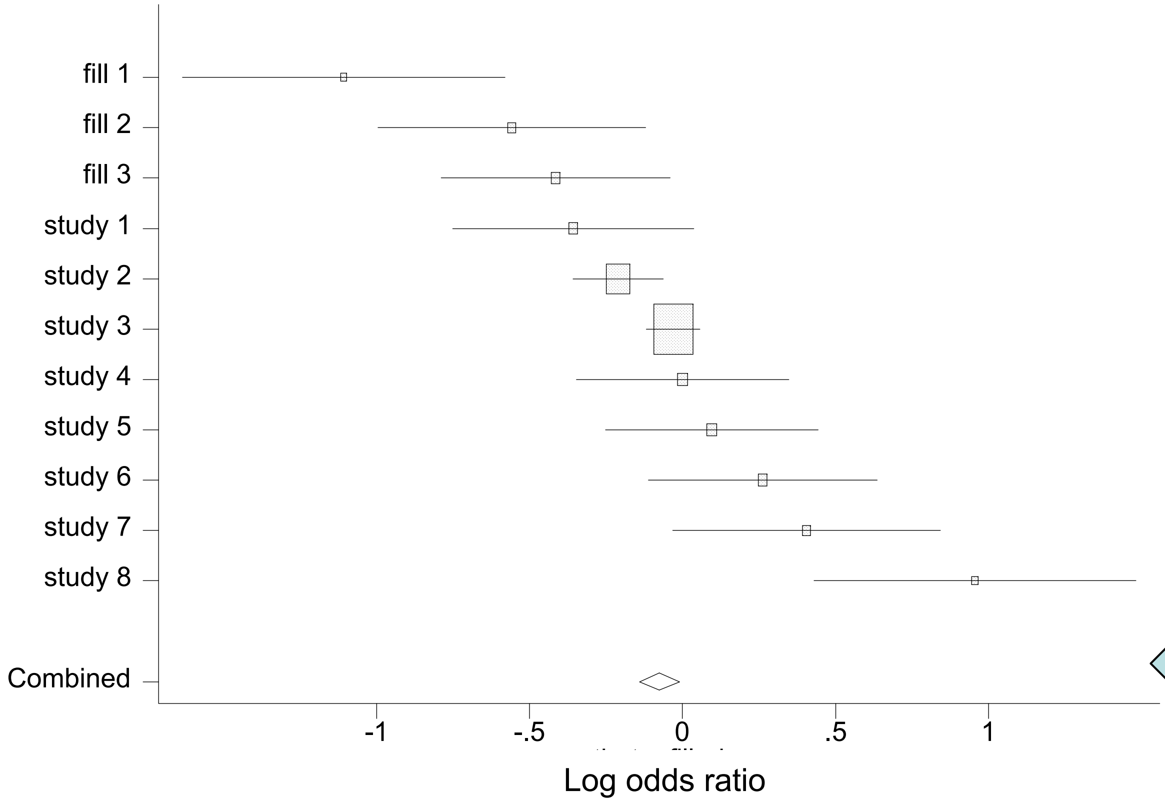
Funnel plot: glioma and mobile phone studies



Some asymetry but not strong (p for puplication bias=0.22)

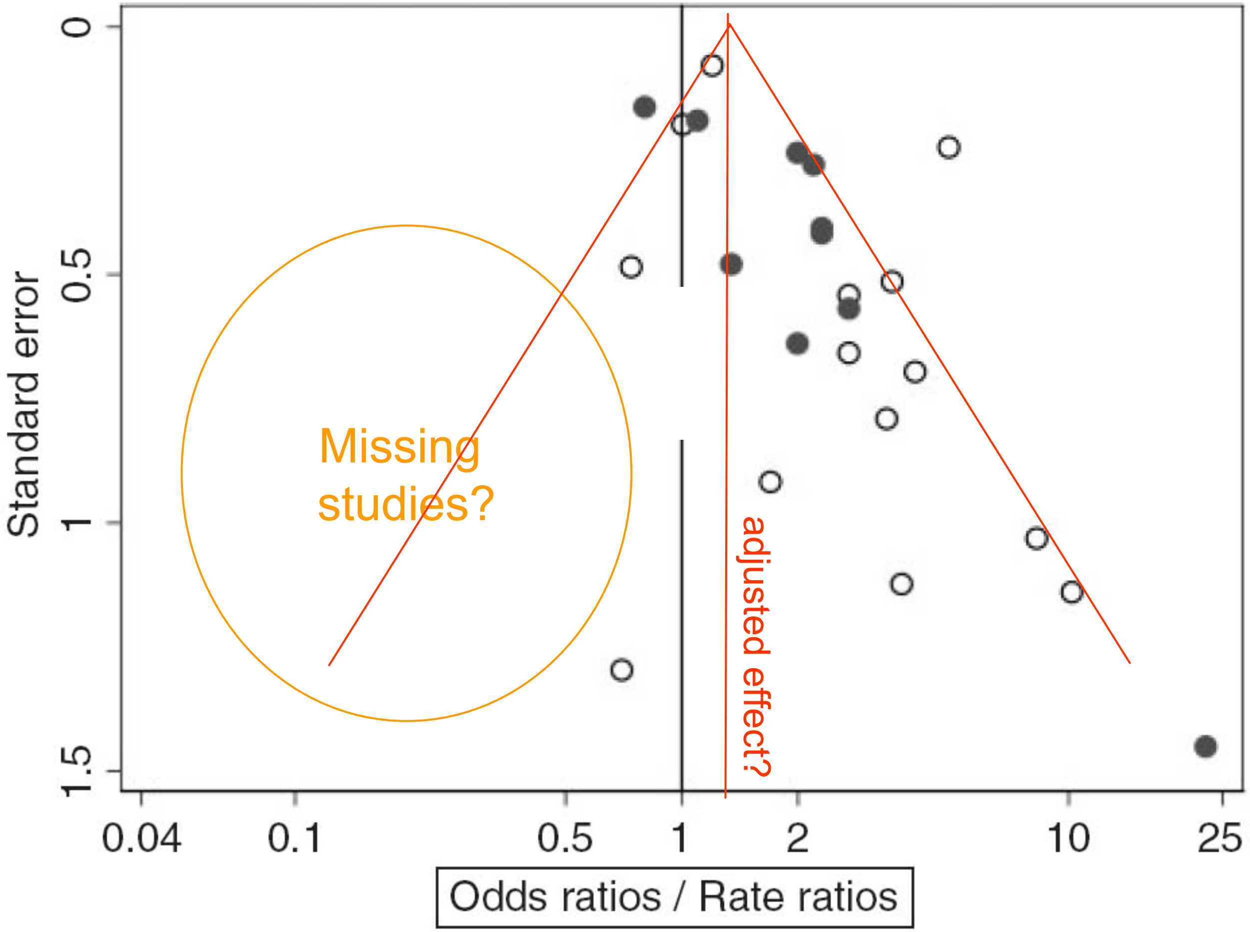
Correcting for publication bias

Use of data augmentation technique to estimate the number and outcomes of missing studies, and adjusts the meta-analysis to incorporate the theoretical missing studies.



adjusted OR=0.92
(before: OR=1.07)

An example for strong indication of publication bias: occupational ELF-MF and Alzheimer's Disease



○ Case-Control study

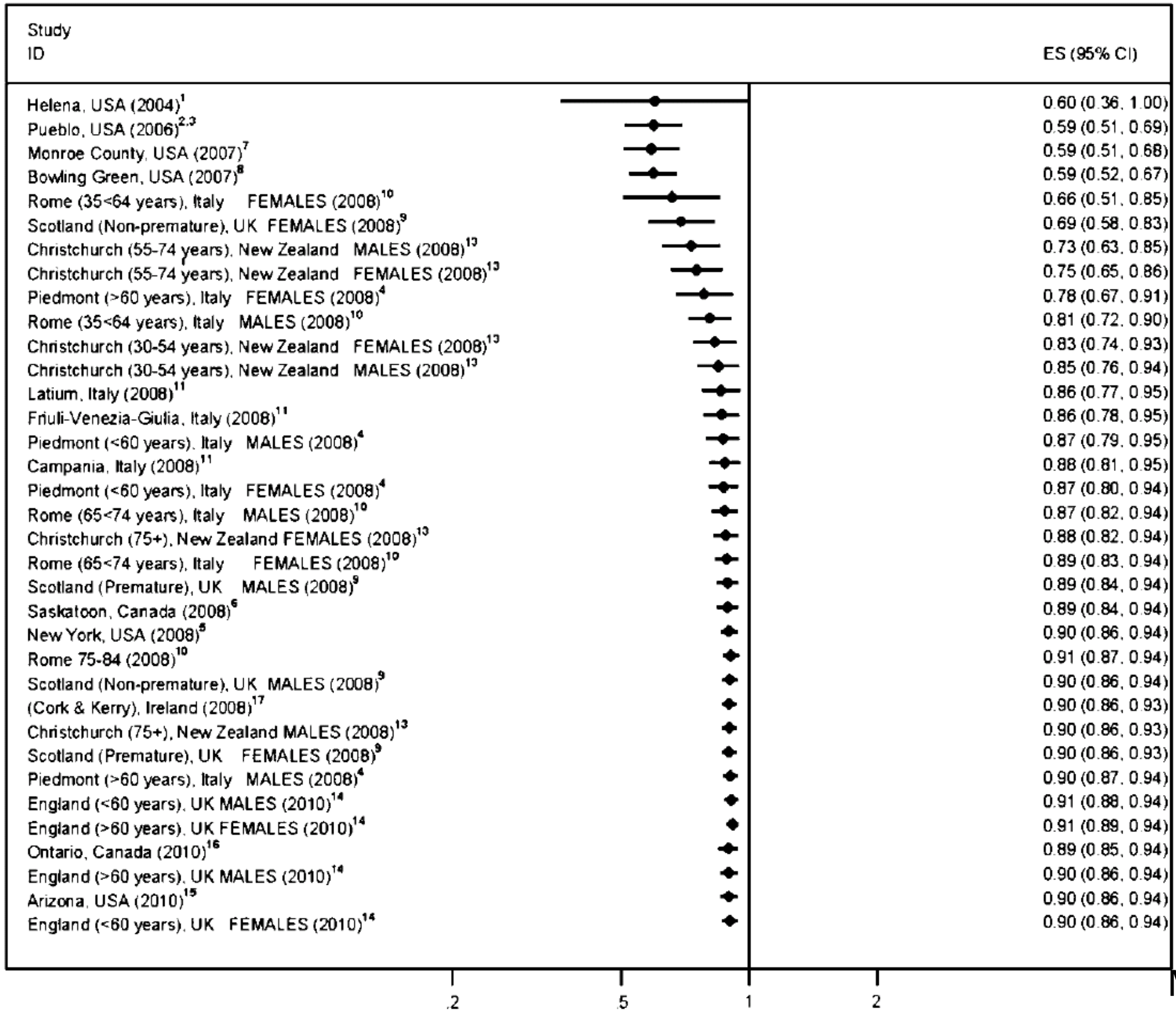
ORpooled: 2.03
(95%CI 1.38−3.00)
Heterogeneity test 0.004;

● Cohort study

RRpooled: 1.62
(95%CI 1.16−2.27)
Heterogeneity test 0.016

Garcia et al.,
Int J Epi 2008

Cumulative meta-analysis: effect of comprehensive smoke-freelegislation on acute coronary events



A common pattern in cumulative meta-analysis. First studies are small and effect is large. Later studies cannot confirm to the same extent.

Mackay et al. Postgrad Med J 2011

Direction of bias

- It is likely that most decisions in the process of conducting EMF research are in favour of publishing an association compared to report a lack of association.
- Exceptions may be:
  1. Strong attitudes of editors or reviewers
  2. Exposure misclassification
  3. Lack of data due to infeasibility

- There is nothing wrong with publishing “interesting observations”. That is how science moves forward. However, be aware of the possibility of false positive results.
- **Important!** Follow-up of early positive associations is a must

Conclusion

- Human tend to recognize patterns (and not lack of patterns).
- There are consistent indications that medical literature tends to accentuate positive associations.
- It is likely that positive findings are also overrepresented in EMF health research, however, opposite bias cannot be completely ruled out for specific topics.

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Sterne & Smith, BMJ, 2001