Statistical methods in EBM

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Statistical methods in meta-analysis

Meta-analysis is the quantitative, systematic summary of a collection of separate studies for the purpose of obtaining information that cannot be derived from any of the studies alone.
(Boissel JP et al., Eur J Clin Pharmacol 1988; 34 (6): 535-538)

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The example

British Journal of Surgery 1997, **84**, 750–759

Review

Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses

A. KOCH, S. BOUGES*, S. ZIEGLER, H. DINKEL, J. P. DAURES* and N. VICTOR

Here:

Restriction on the outcome „Deep vein thrombosis (DVT)“ from the group of orthopaedic surgery studies.

The data

Study		LMWH		UFH	
		N treated	N DVT	N treated	N DVT
Maroske	1985	40	7	40	7
Haas	1987	80	15	80	15
Lassen	1988	118	35	122	34
Planes	1988	124	15	113	27
Lassen	1989	68	14	71	23
Monreal	1989	46	14	44	6
Reilmann	1989	68	8	71	6
Eriksson	1991	67	19	69	25
Freick	1991	55	5	55	12
Levine	1991	333	50	332	61
GHAT	1992	169	45	172	47

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The data

Planes 1988

	DVT: Yes	DVT: No	Σ
LMWH	**15**		**124**
UFH	**27**		**113**
Σ			

The data

Planes 1988

	DVT: Yes	DVT: No	Σ
LMWH	**15**	109	**124**
UFH	**27**	86	**113**
Σ	42	195	237

$$OR = \frac{15 \times 86}{27 \times 109} = 0.44$$

The data

Study		OR	95% CI	p	Fixed effect model weights (IV)
Maroske	1985	1.00	0.32 to 3.17	1	0.03
Haas	1987	1.00	0.45 to 2.21	1	0.07
Lassen	1988	1.09	0.62 to 1.91	0.76	0.13
Planes	1988	0.44	0.22 to 0.88	0.02	0.09
Lassen	1989	0.54	0.25 to 1.17	0.12	0.07
Monreal	1989	2.77	0.95 to 8.04	0.06	0.04
Reilmann	1989	1.44	0.47 to 4.41	0.52	0.03
Eriksson	1991	0.70	0.34 to 1.44	0.33	0.08
Freick	1991	0.36	0.12 to 1.10	0.07	0.03
Levine	1991	0.78	0.52 to 1.18	0.25	0.25
GHAT	1992	0.97	0.60 to 1.56	0.88	0.18

Calculating the overall estimate

The summary (overall, meta-analytic) estimator for the treatment effect is a **weighted average** of the estimates from the single studies.

Two Models:

1. **Fixed Effects (FEM)**
   Assumption of homogeneity (all studies have the same underlying true treatment effect), weights are inverse variances from the single studies
2. **Random Effects (REM)**
   Underlying treatment effects vary according to a normal distribution, weights are corrected for the variance of this normal distribution

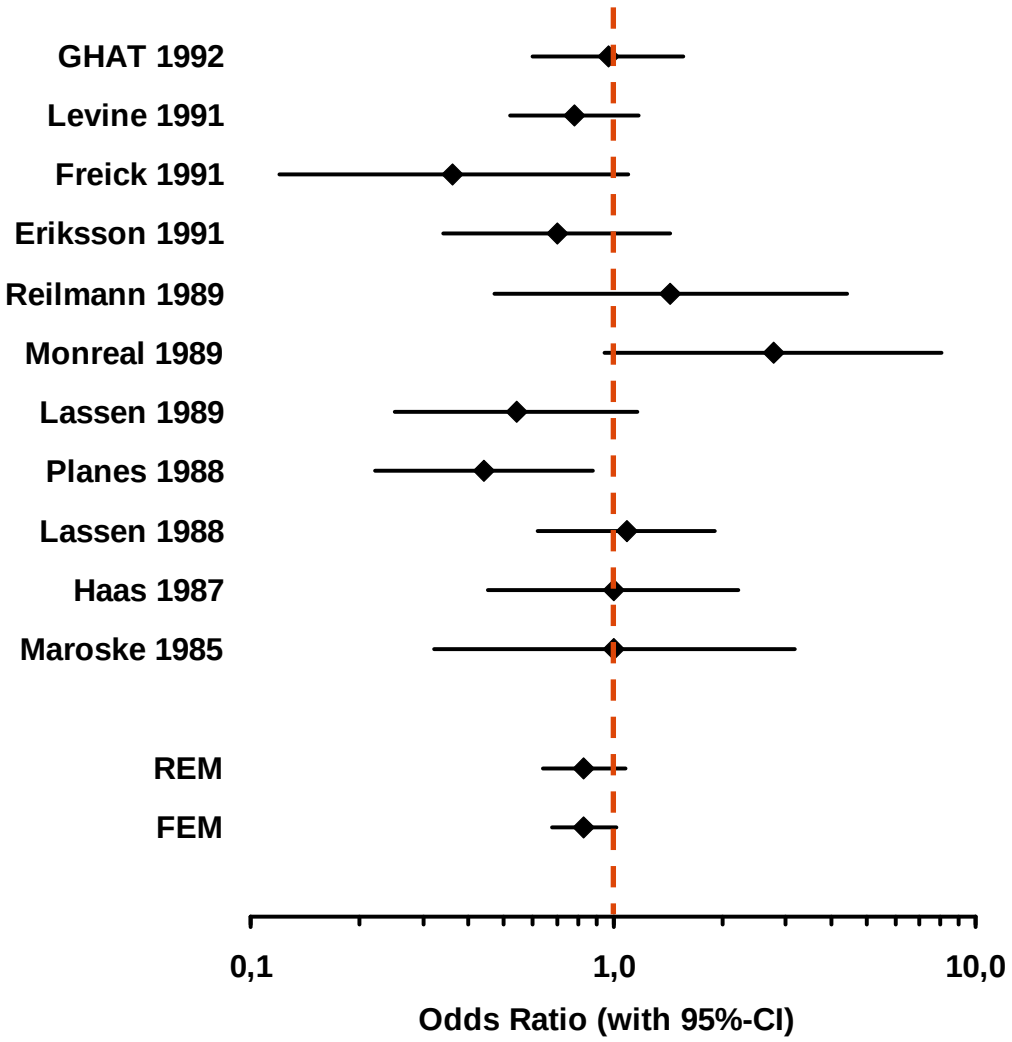
Calculating the overall estimate

Results:

OR (FEM): 0.83 [0.68; 1.02], p=0.079

OR (REM): 0.83 [0.64; 1.08], p=0.170

Forest-Plot


GHAT 1992
Levine 1991
Freick 1991
Eriksson 1991
Reilmann 1989
Monreal 1989
Lassen 1989
Planes 1988
Lassen 1988
Haas 1987
Maroske 1985
REM
FEM
0,1
1,0
10,0
Odds Ratio (with 95%-CI)

What about the assumption of homogeneity?

Two Methods:

1. **Testing for homogeneity**
   Test is known to have low power. Maybe allow a more liberal α
   (here: p=0.156)
2. **Report I^2**
   I^2 =0%: No heterogeneity
   I^2 =100%: Maximal heterogeneity
   (here: I^2=31 % [0 %, 66 %])

My recommendation:
Explain heterogeneity from a clinical viewpoint.

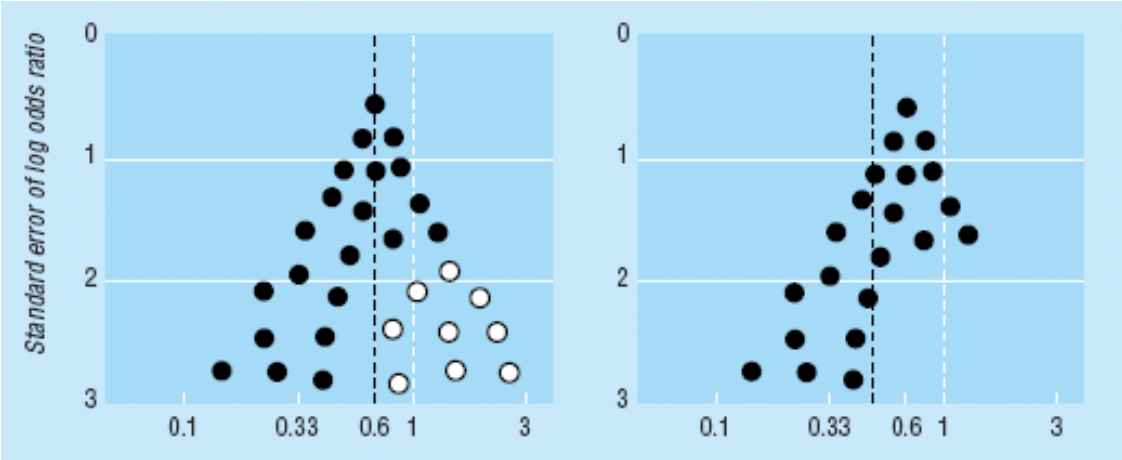
Why did we use the odds ratio?

- Mainly convenience
- Some small mathematical advantages
- However, OR is criticized for its limited interpretability
- As a sensitivity analysis:
  Calculate overall estimates also for the RR and the RD
  RD (FEM): -2.9 % [-6.1 %; 0.2 %], p=0.071
  RR (FEM): 0.87 [0.75; 1.02], p=0.089

What about publication bias?

Def.: Selective reporting of trials depending on study results

Graphical diagnostic: Funnel-plot

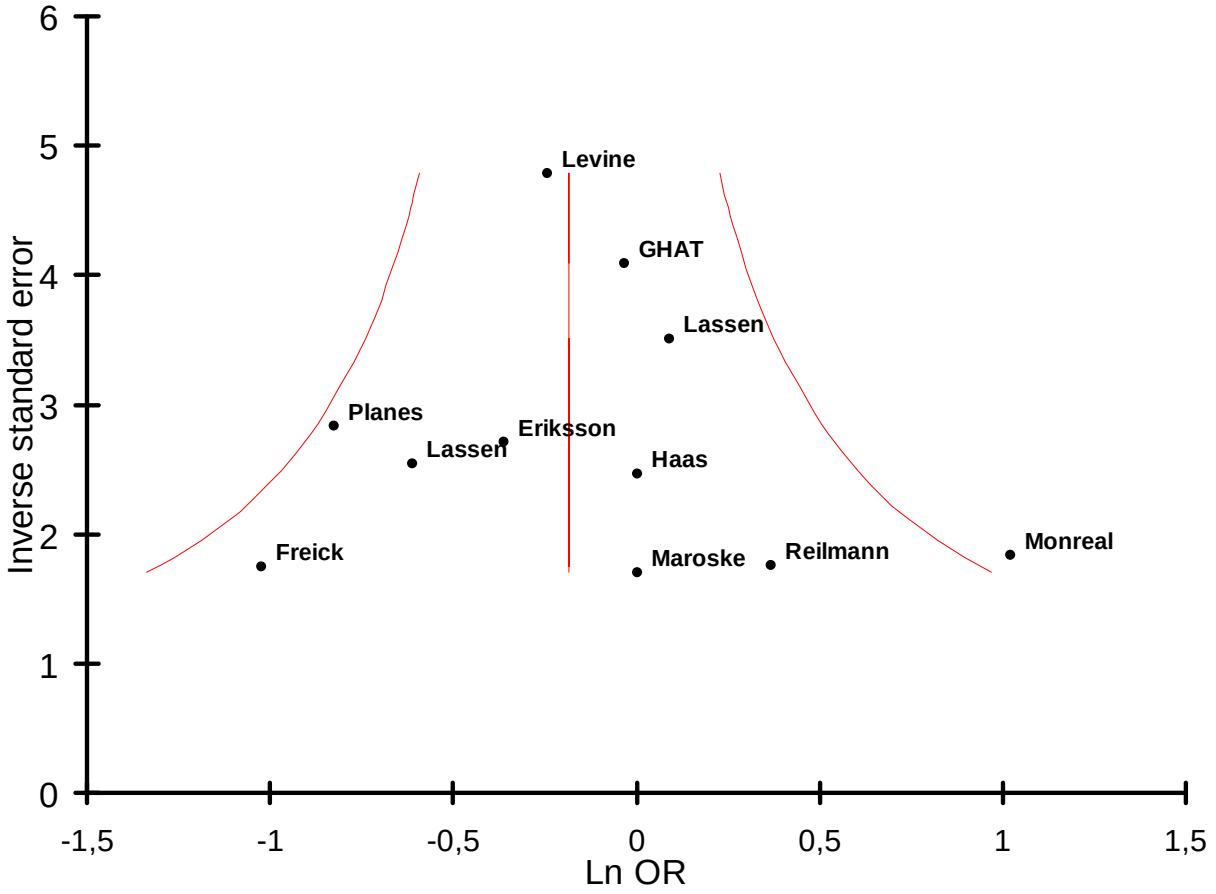


Sterne JA et al., BMJ. 2001;323(7304):101-5.

Funnel-plot **without** **with**
publication bias

What about publication bias?

No indication of publication bias in our meta-analysis!



More things to say

- Take care with rare events. Do no longer use FE or RE models. Use the Mantel-Haenszel method instead.
- Meta-analysis works analogously for continuous outcomes (measure treatment effect by mean differences) or survival outcomes (measure treatment effect by hazard ratios)
- Not every systematic review must contain a meta-analysis! Sometimes studies are too heterogeneous to be combined!
- Software: MIX (http://www.mix-for-meta-analysis.info/), runs within MS EXCEL