Random effects meta-analysis

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Fixed-effect inverse-variance-weighted average (1)

- Require from each of k studies:
  - estimate of treatment effect, y_i
  - estimate of variance of estimate, v_i
  - (When using ratio measures, natural log of the ratio is used)

- Combine the estimates using a weighted average

- Take weight = inverse variance:

$$w_i = 1 / v_i$$

- It is intuitively sensible to give more weight to the bigger studies

Application to risk ratios

	Event	No event	Total
Treatment A	r_{Ai}	f_{Ai}	n_{Ai}
Treatment B	r_{Bi}	f_{Bi}	n_{Bi}

- From each trial:
  - Log risk ratio $$y_i = \ln RR_i = \ln \frac{r_{Ai}/n_{Ai}}{r_{Bi}/n_{Bi}}$$
  - Variance of log risk ratio ≈ $$v_i = \frac{1}{r_{Ai}} - \frac{1}{n_{Ai}} + \frac{1}{r_{Bi}} - \frac{1}{n_{Bi}}$$
  - Weight $$w_i = \frac{1}{v_i}$$

Application to Roumen 2008

	Event	No event	Total
Treatment A	11	63	74
Treatment B	19	54	73

- From each trial:
  - Log risk ratio $$y_i = \ln RR_i = \ln \frac{11/74}{19/73} = \ln 0.571 = -0.56$$
  - Variance of log risk ratio ≈ $$v_i = \frac{1}{11} - \frac{1}{74} + \frac{1}{19} - \frac{1}{73} = 0.116$$
  - Weight $$w_i = \frac{1}{0.116} = 8.6$$

Fixed-effect inverse-variance-weighted average

- Summary estimate μ

$$\mu = \frac{\sum w_i y_i}{\sum w_i}$$

- A standard error is: $SE(\mu) = \sqrt{1/\sum w_i}$
- 95% confidence interval for the summary estimate:

$$\mu - 1.96\sqrt{1/\sum w_i} \text{ to } \mu + 1.96\sqrt{1/\sum w_i}$$

y_i can be anything! logOR, logRR, RD, logHR, mean difference, standardised mean difference etc.

Fixed-effect inverse-variance

Study	r1	n1	r2	n2
Kosaka 2005	3	102	32	356
Eriksson 1991	17	181	16	79
Tuomilehto 2001	27	265	59	257

in R: `poolRR<-metabin(r1,n1,r2,n2,studlab=Study,sm="RR",`

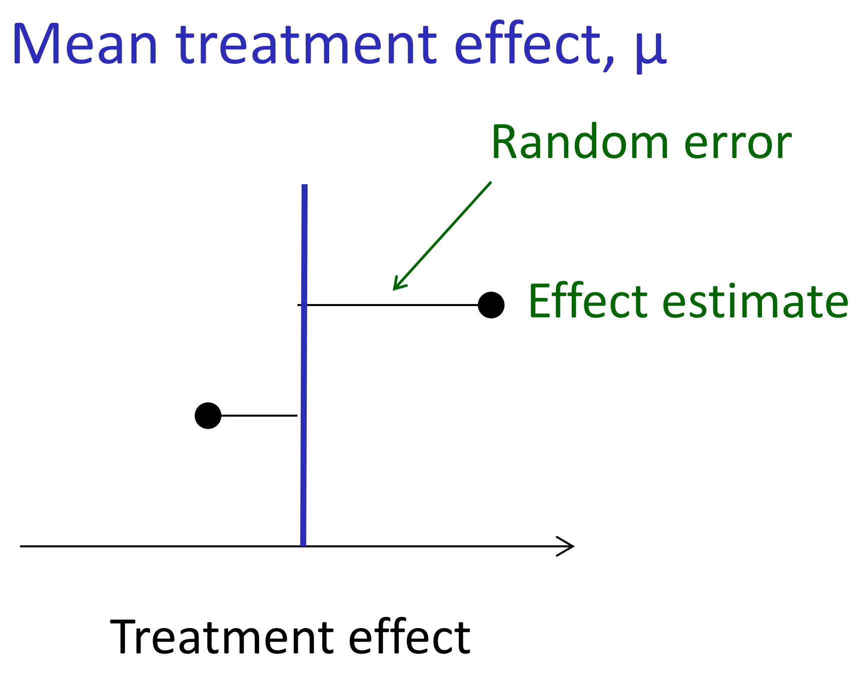
`summary(poolRR)`

Mantel-Haenszel

```
                      RR            95%-CI      z  p-value
Fixed effect model    0.6036 [0.5496; 0.6631] -10.54 < 0.0001
Random effects model 0.6264 [0.5425; 0.7234]  -6.37 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.0244; H = 1.34 [1.00; 1.85]; I^2 = 43.9% [0.0%; 70.7%]

Test of heterogeneity:
     Q d.f. p-value
 21.39   12  0.0449
```

Interpretation of fixed-effect meta-analysis results

- assume all studies share an identical true treatment effect
- estimate this single treatment effect

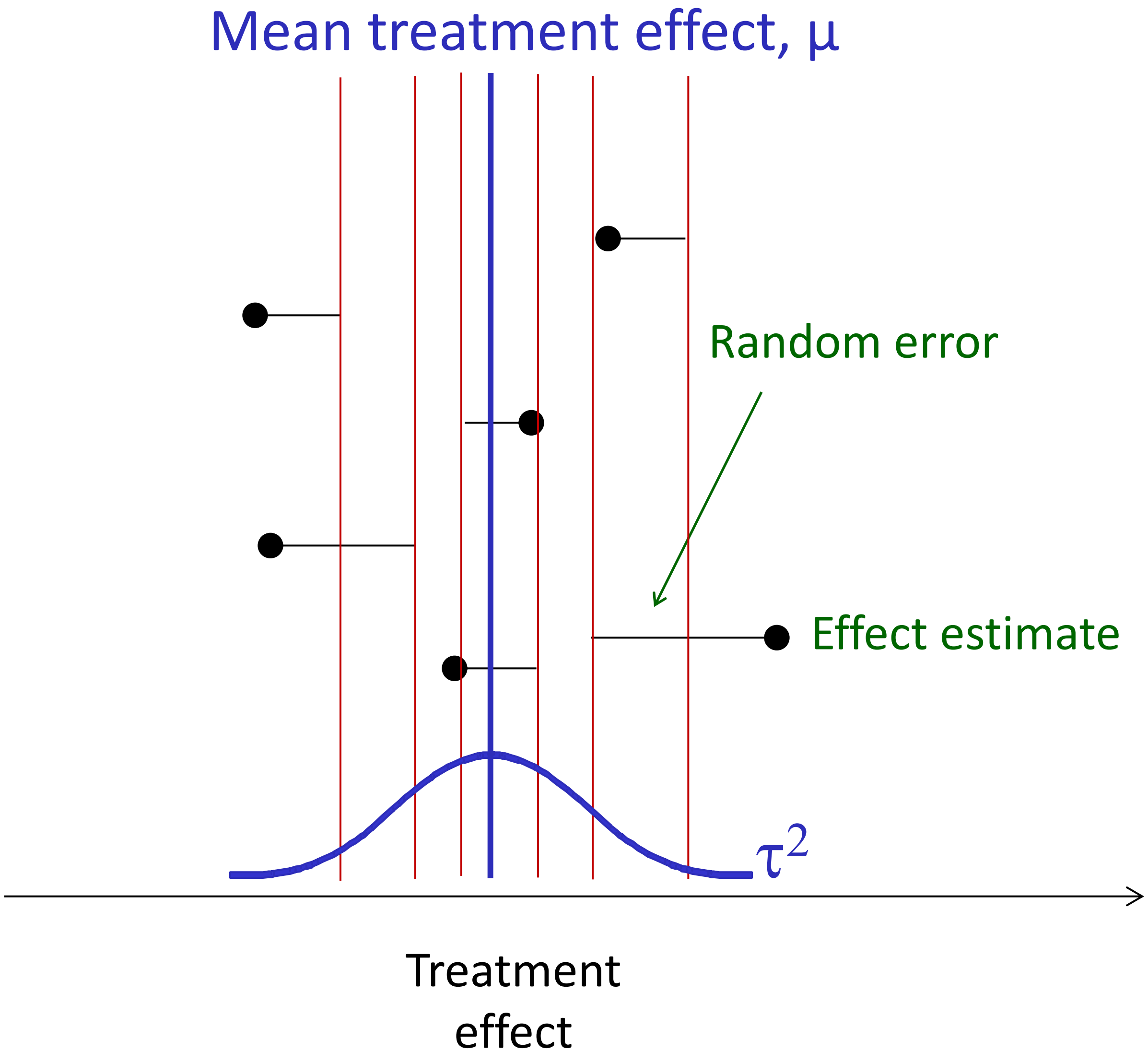


Interpretation of fixed-effect meta-analysis results

- The confidence interval for the summary odds ratio reflects *within-study errors only*
- Variation across studies (heterogeneity) is ignored
- So the following yield exactly the same result

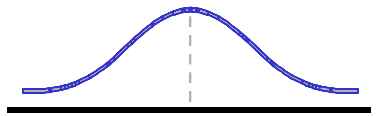
- Many of us feel uncomfortable about this

Random-effects meta-analysis



Random-effects meta-analysis

- We suppose the *true* treatment effect in each study is randomly, normally distributed across studies
  - with variance τ^2 ("tau-squared")



- Estimate the between-study variance τ^2, and use this to modify the weights used to calculate the summary estimate

- The most common estimate of τ^2 is called the DerSimonian and Laird estimate, or method of moments estimate
  - but other (better) estimators are available

Random-effects meta-analysis (3)

Random-effects estimate: $$\mu = \frac{\sum w_i^* y_i}{\sum w_i^*}$$

where $$w_i^* = \frac{1}{v_i + \tau^2}$$

A standard error is: $SE(\mu) = \sqrt{1/\sum w_i^*}$

95% confidence interval for the summary estimate:

$$\mu - 1.96\sqrt{1/\sum w_i^*} \text{ to } \mu + 1.96\sqrt{1/\sum w_i^*}$$

Identifying heterogeneity : test

- To test the null hypothesis that the true treatment effect is the same in all studies we can calculate a *heterogeneity statistic*:

$$Q = \sum w_i (y_i - \mu)^2$$

- To calculate a P value, Q is compared with the χ^2 distribution on (k – 1) degrees of freedom (k is no. of studies).
- The greater the average weighted squared distance between the individual study log risk ratio y_i and the summary log risk ratio μ, the more evidence against the null hypothesis that the true treatment effect is the same in all studies.

Identifying heterogeneity: τ^2

- The between-studies variance, τ^2 is estimated as part of the random-effects meta-analysis
- It provides a useful measure of the true extent of heterogeneity across studies
- Methods to estimate τ^2
  - **DerSimonian and Laird** estimator is default; method.tau="DL”
  - **Paule-Mandel**;method.tau="PM"(Paule and Mandel,1982)
  - Restrictedmaximum-likelihood;method.tau="REML" (Viechtbauer, 2005)
- Simulations and empirical analyses suggest that for both dichotomous and continuous data PM and for continuous data REML are better alternatives (Veroniki et al., Res Synth Meth 2015)

Example: Compare estimators of τ^2

Inverse variance RE method

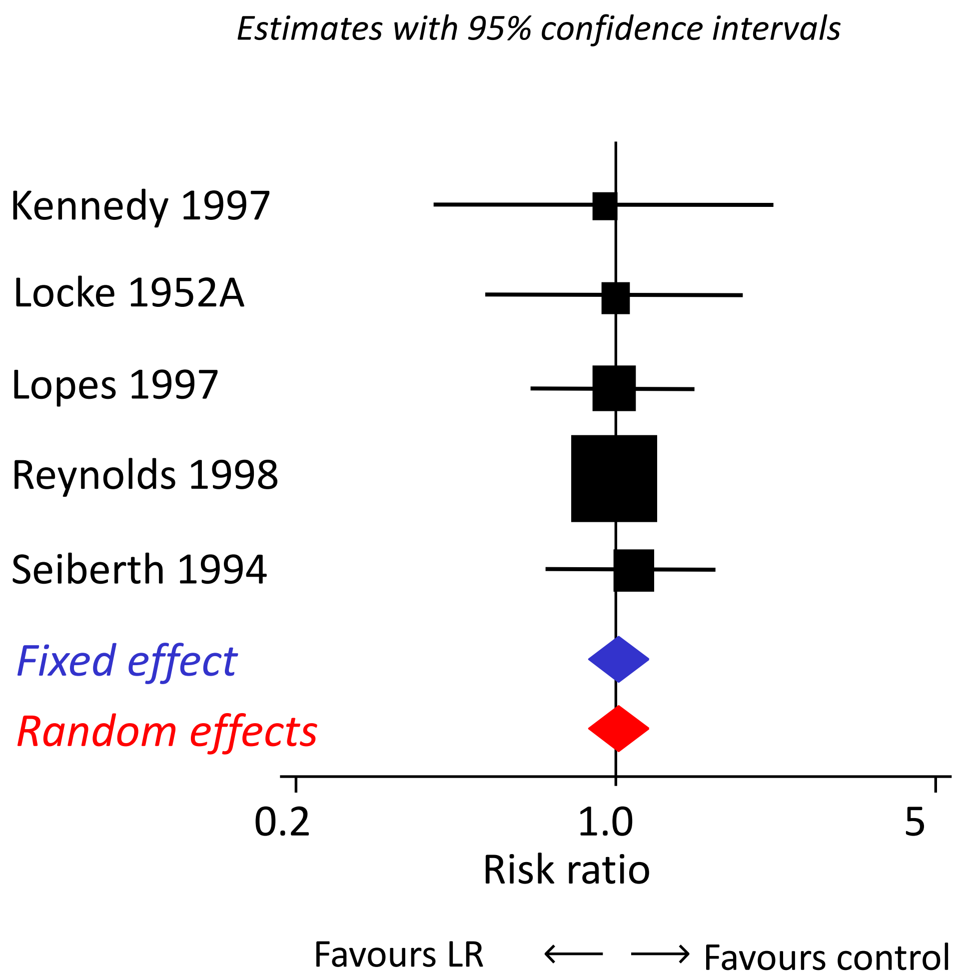
DerSimonian and Laird

```
                          RR            95%-CI     z  p-value
Random effects model 0.6264 [0.5425; 0.7234] -6.37 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.0244; H = 1.34 [1.00; 1.85]; I^2 = 43.9% [0.0%; 70.7%]

Test of heterogeneity:
     Q d.f. p-value
 21.39   12  0.0449
```

Paule-Mandel

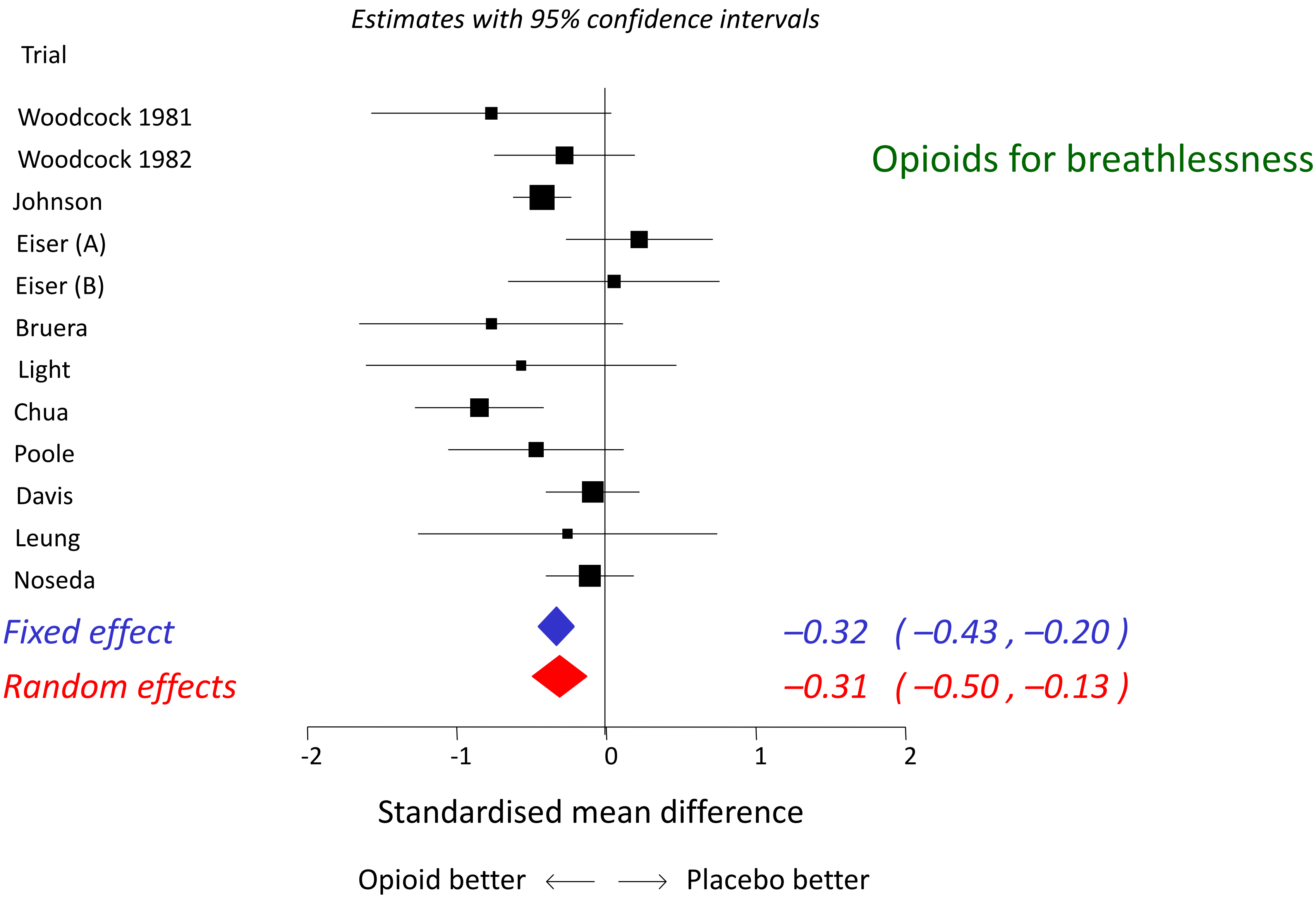
```
                          RR            95%-CI     z  p-value
Random effects model 0.6269 [0.5489; 0.7160] -6.89 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.0174; H = 1.34 [1.00; 1.85]; I^2 = 43.9% [0.0%; 70.7%]

Test of heterogeneity:
     Q d.f. p-value
 21.39   12  0.0449
```

Fixed versus random effects: Identical results

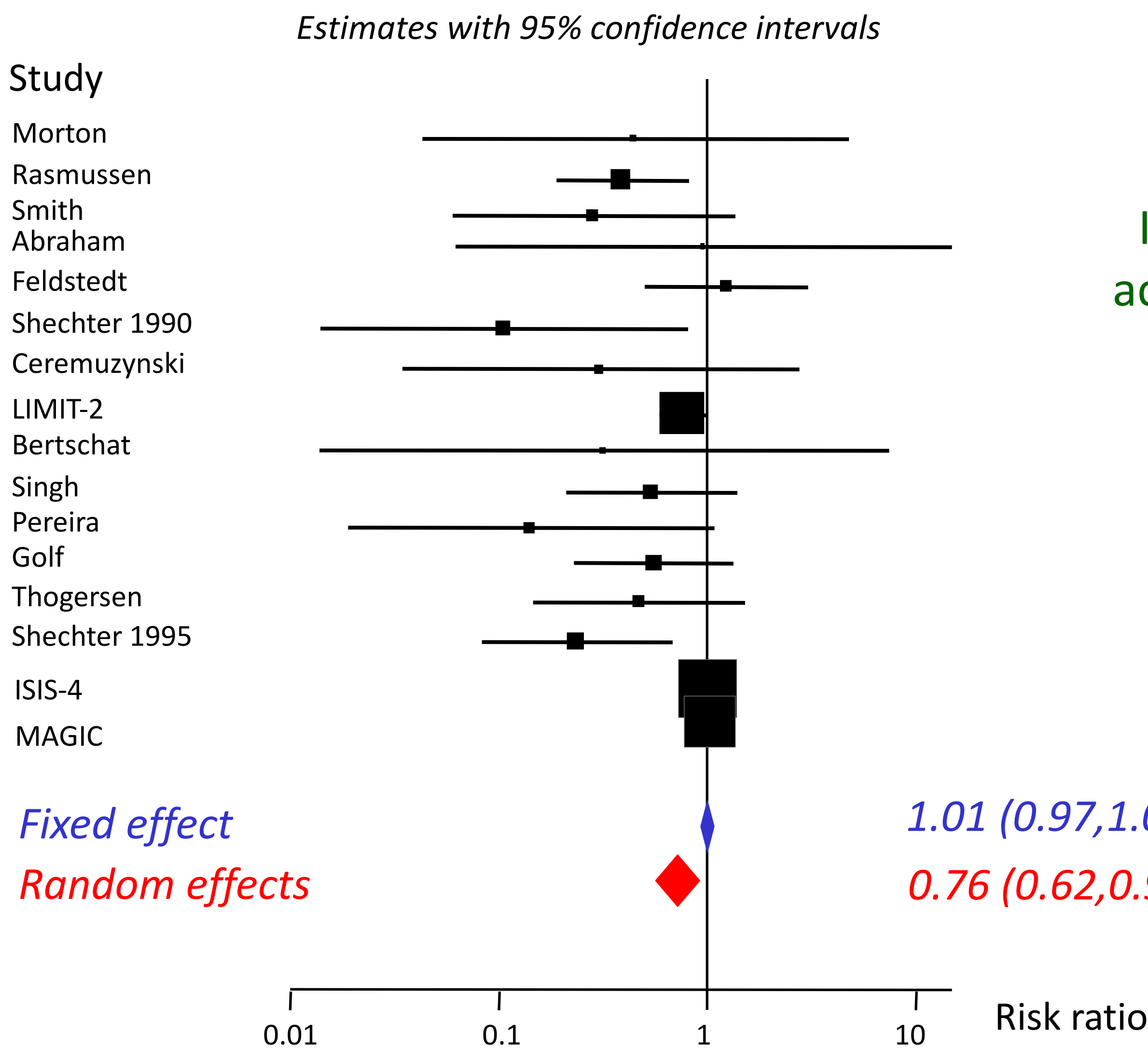


Early light reduction for preventing retinopathy of prematurity

Fixed versus random effects: Slightly different results



Fixed versus random effects: Very different results



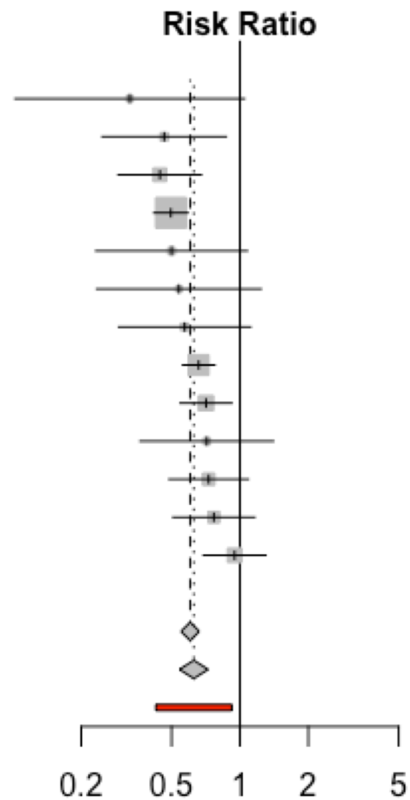
IV magnesium for acute MI (mortality)

Add random-effects prediction interval

forest(poolRR, prediction=T)

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%-CI	Weight (fixed)	Weight (random)
Kosaka 2005	3	102	32	356	0.33	[0.10; 1.05]	1.7%	1.5%
Eriksson 1991	17	181	16	79	0.46	[0.25; 0.87]	2.6%	4.3%
Tuomilehto 2001	27	265	59	257	0.44	[0.29; 0.68]	7.1%	7.7%
US DPP 2002	155	1079	313	1082	0.50	[0.42; 0.59]	36.9%	16.6%
Sakane 2011	9	152	18	152	0.50	[0.23; 1.08]	2.1%	3.1%
Penn 2009	7	51	13	51	0.54	[0.23; 1.24]	1.5%	2.7%
Roumen 2008	11	74	19	73	0.57	[0.29; 1.11]	2.3%	3.9%
China Da Qunq 1997	188	438	90	138	0.66	[0.56; 0.77]	16.2%	17.1%
Ramachandran 2006	52	133	75	136	0.71	[0.55; 0.92]	8.8%	12.8%
Bhopal 2014	12	85	17	86	0.71	[0.36; 1.40]	2.0%	3.8%
Saito 2011	35	311	51	330	0.73	[0.49; 1.09]	5.8%	8.2%
Shek 2014	33	225	43	225	0.77	[0.51; 1.16]	5.1%	7.8%
Davies 2016	64	447	67	443	0.95	[0.69; 1.30]	7.9%	10.7%
Fixed effect model		**3543**		**3408**	**0.60**	**[0.55; 0.66]**	**100.0%**	**--**
Random effects model					**0.63**	**[0.54; 0.72]**	**--**	**100.0%**
Prediction interval						**[0.43; 0.92]**		

Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0251$, $p = 0.04$



Prediction intervals

- Prediction intervals portray the actual heterogeneity across studies

- An interval within which the true effect size in a similar study (from the same distribution) is predicted to lie

$$\mu - t_{k-1,0.025}\sqrt{SE(\mu)^2 + \tau^2} \text{ to } \mu + t_{k-1,0.975}\sqrt{SE(\mu)^2 + \tau^2}$$

This is a generic approach

- Suppose we have an estimate of some quantity, y_i, and we know its variance, v_i
- Then we can perform a meta-analysis as a weighted average

FE: $$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i} \qquad SE(\hat{\theta}) = \sqrt{\frac{1}{\sum w_i}}$$

RE: $$\hat{\mu} = \frac{\sum w_i^* y_i}{\sum w_i^*} \qquad SE(\hat{\mu}) = \sqrt{\frac{1}{\sum w_i^*}}$$

- For example, for binary data, y_i could be a log odds ratio or a risk difference
  - we (almost) always work on the log scale for ratio measures
- Note: these methods ignore uncertainty in τ^2