Meta analysis Tutorial

National and Kapodistrian
UNIVERSITY OF ATHENS

Author: Belias Michael

Student in MSc in Biostatistics

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Meta analysis

Contents

1 Meta analysis Basics

Meta Analysis is quantitative methodology used for combining researches that have a common subject, in order to make an overall conclusion.

As in many statistical methods Metanalysis has advantages and disadvantages.

pros:

- Provides an objective synthesis of many related studies or experiments for a particular problem, in order to drive a single overall conclusion.
- This methodology allows an partiality (BIAS) assessment.

cons:

- one number cannot summarise a research field": A good meta analysis will model variability in true effect sizes and model the uncertainty of estimates.
- "the file drawer problem invalidates meta-analysis": Funnel plots and related tools allows you to see whether sample size is related to effect size in order to check for publication bias. Good meta-analyses endeavour to obtain unpublished studies. This issue is shared with narrative studies.
- "Mixing apples and oranges": Good meta-analyses provide a rigorous coding system for categorising included studies and justifying the inclusion and exclusion of studies in the meta-analysis. After studies have been classified, moderator analysis can be performed to see whether effect sizes vary across study type.
- "Important studies are ignored": You can code for the evaluated quality of the studies. Large samples can be given greater weighting.
- "meta analysis can disagree with randomised trials":
- "meta-analyses are performed poorly": This is merely an argument for improving the standards of meta-analytic methods.
- "Is a narrative review better?": Many of the critiques of meta-analysis (e.g., publication bias) are shared by narrative reviews. It is just that the methods of inference are less explicit and less rigorous in narrative reviews.

2 Which Metanalysis method to use?

A common question in Metanalysis is `which analysis to use?` It all depends on what type of Data we have and if we want a Fixed, Random or Mixed Effects model.

Type of data	Effect measure	Fixed-effect methods	Random-effects methods
Dichotomous	Odds ratio (OR)	Mantel-Haenszel	Mantel-Haenszel
		Inverse variance	Inverse variance
		Peto	
	Risk ratio (RR)	Mantel-Haenszel	Mantel-Haenszel
		Inverse variance	Inverse variance
	Risk difference (RD)	Mantel-Haenszel	Mantel-Haenszel
		Inverse variance	Inverse variance
Continuous	Mean difference (MD)	Inverse variance	Inverse variance
	Standardized mean difference (SMD)	Inverse variance	Inverse variance
O – E and Variance	*User-specified*	Peto	None
Generic inverse variance	*User-specified*	Inverse variance	Inverse variance
Other data	*User-specified*	None	None

Some notes:

- An "effect" could be almost any aggregate statistic of interest:

    - Mean, Mean difference, Mean change (Continuous)
    - Risk ratio, Odds ratio, Risk difference (Dichotomous)
    - Incidence rate, Prevalence, Proportion (Dichotomous)
    - Correlation (Continuous)

- Conventional meta-analytic models assume normality of ESs.

- To normalize ESs, a log-transform is common.

Some examples and basic calculation of the ESs are.

Suppose we have an 2x2 matrix (dichotomous variable) like below:

	Treatment	Control	Total(Diseased or Not)
Disease = Yes	a	b	a+b
Disease = No	c	d	c+d
Total(arm)	a+c	b+d	N

Then the statistical results depending the measure are:

- Log-Odds Ratio:

  - $\log(\text{OR}) = log(\frac{a*d}{b*c})$
  - $\text{SD}(\log(\text{OR})) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

- Log-Relative Risk:

  - $\log(\text{RR}) = log(\frac{a/a+b}{c/c+d})$
  - $\text{SD}(\log(\text{RR})) = \sqrt{\frac{1}{a} + \frac{1}{c} + \frac{1}{a+b} + \frac{1}{c+d}}$

- Risk Difference:

  - $\log(\text{RR}) = \sqrt{\frac{a}{a+b} - \frac{c}{c+d}}$
  - $\text{SD}(\log(\text{RD})) = \sqrt{\frac{a*b}{(a+b)^3} - \frac{cxd}{(c*d)^3}}$

Sometimes we measure the person time so the 2x2 matrix is:

	Treatment	Control	Total
Events	a	b	c(Total Events)
Person Time	T0	T1	Tall(Total Time)

Then we may get:

- Incidence rate

  - $\log(\text{IR}) = \frac{a/T_0}{b/T_1}$
  - $\text{SD}(\log(\text{IR})) = \sqrt{\frac{1}{a} + \frac{1}{b}}$

- Prevalence

- Proportion

3 Fixed Effects Model

The fixed effects model approach is the simplest one and assumes that all included studies have zero τ^2 heterogeneity because it assumes that they investigate the same population, use the same variable and outcome definitions, etc. In Mathematical perception if :

- we have i = 1, ... , k studies
- have y_i and corresponding v_i
- we assume that

  - $y_i|\theta_i \sim N(\theta_i, v_i)$
  - $y_i = \theta_i + \epsilon_i$

- and approx. 95% CI for $\theta_i : y_i \pm 1.96\sqrt{v_i}$

where y_i denotes the observed effect in the i-th study, θ_i the corresponding (unknown) true effect, ϵ_i is the sampling error and $\epsilon_i \sim N(0, v_i)$. This assumption is rarely true, because researches are subject to various sources of heterogeneity. As we may immediately understand the treatment effects may be different because of deviation such as regional, dosage levels, study conditions etc. The fixed effects model is a weighted average of all the studies gathered. The weights are calculated by a variety of methods, most popular are :

- The Inverse Variance
- Mantel-Haenszel
- Peto (an Inverse Variance weighting method on different OR)

The **beta_full_prac1.dta** file contains results from 20 randomized clinical trials on the use of beta-blockers for the prevention of esophageal bleeding in patients with cirrhosis.

The file is described below:

Table 3: The 20 randomized clinical trials

id	Ttotal	Tcases	Ctotal	Ccases	quality
1	35	3	36	22	6
2	56	5	53	30	38
3	16	5	18	6	31
4	23	3	22	9	0
5	49	11	46	31	38
6	53	19	60	9	52
7	53	17	60	26	75
8	71	10	69	29	71
9	41	12	41	14	81
10	21	1	20	3	63
11	42	9	41	13	75

id	Ttotal	Tcases	Ctotal	Ccases	quality
12	33	13	35	14	71
13	143	31	138	23	68
14	55	20	51	19	58
15	73	13	72	13	83
16	13	3	16	12	NA
17	21	3	28	5	NA
18	18	4	19	1	NA
19	22	6	24	2	NA

- The `Ttotal` variable shows the total amount of patients in the `treatment` group.
- The `Tcases` variable shows the number of cases in the `treatment` group.
- The `Ctotal` variable shows the total amount of patients in the `Cases` group.
- The `Ccases` variable shows the number of cases in the `Cases` group.
- The quality variable contains a score of "quality" of each study based on several criteria (quality of randomization, compliance, patient withdrawals, etc.). The range of the variable that ranges from 0 to 100 (higher values indicate better quality studies) whereas for studies published only as abstracts there is no recorded value. Other variables are described by the corresponding variable labels.

3.1 Inverse Variance Method

A good package for Metanalysis is the `metafor` package, which provides a more step by step procedure on calculating the Effect Size and it's pooled Estimate. Firstly we shall calculate effect sizes (in our case Odds Ratios) and outcome measures we are interested in, using the `escalc()` function. The `escalc()` function main option is the measure, in which we declare the E.S. or outcome measure that will be calculated. Since we choose the Odds Ratio we need to provide the a, b etc from each 2x2 matrix.

For example for the ith study the matrix is:

	Treatment	Control	Total
Disease = Yes	a (Tcases)	b (Ccases)	a+b (TotCases)
Disease = No	c (Tnocases)	d (Cnocases)	c+d (TotNocases)
	a+c (Ttotal)	b+d (Ctotal)	N (Total)

So we input the a, b, c, d, n1 (a+b),n2 (c+d) needed to calculate the log-OR for each study, resulting in the following output.

Table 5: Log-Scale Odds Ratios, Variance, Standard Error and 95% CI bounds

yi	vi	sei	zi	ci.lb	ci.ub
-2.8191087	0.4814665	0.6938778	-4.0628315	-4.1790843	-1.4591332
-2.5880909	0.2964194	0.5444442	-4.7536389	-3.6551818	-1.5210000
-0.0953102	0.5409091	0.7354652	-0.1295917	-1.5367955	1.3461752
-1.5293952	0.5713675	0.7558886	-2.0233078	-3.0109096	-0.0478808
-1.9656279	0.2161496	0.4649189	-4.2278939	-2.8768522	-1.0544035
1.1526795	0.2127623	0.4612616	2.4989711	0.2486233	2.0567357
-0.4820416	0.1544746	0.3930326	-1.2264673	-1.2523713	0.2882881
-1.4867051	0.1758762	0.4193760	-3.5450414	-2.3086669	-0.6647434
-0.2256096	0.2262817	0.4756908	-0.4742780	-1.1579464	0.7067271
-1.2611312	1.4421569	1.2008984	-1.0501565	-3.6148487	1.0925863
-0.5320278	0.2540515	0.5040352	-1.0555370	-1.5199187	0.4558630
-0.0253178	0.2459707	0.4959543	-0.0510487	-0.9973704	0.9467348
0.3249262	0.0933605	0.3055496	1.0634158	-0.2739399	0.9237924
-0.0383189	0.1624530	0.4030546	-0.0950712	-0.8282914	0.7516536
-0.0168071	0.1874620	0.4329688	-0.0388183	-0.8654104	0.8317961
-2.3025851	0.7666667	0.8755950	-2.6297375	-4.0187198	-0.5864504
-0.2657032	0.6323671	0.7952152	-0.3341274	-1.8242962	1.2928899
1.6376088	1.3769841	1.1734497	1.3955509	-0.6623103	3.9375279
1.4170660	0.7746212	0.8801257	1.6100723	-0.3079486	3.1420807

The output:

- `yi`: log-OR of the studies
- `vi`: The Variance of the OR
- `sei`: The Standard Error (the square root of the above measure)
- `zi`: The Z-statistic for the significance
- `ci.lb`: The Lower bound C.I.
- `ci.ub`: The Upper bound C.I.

Since everything is calculated in the log scale, we need to exponentiate the measures we are interested.

Table 6: First 5 studies Odds Ratio with 95% bounds of each study

yi	ci.lb	ci.ub
0.0596591	0.0153125	0.2324377
0.0751634	0.0258568	0.2184933
0.9090909	0.2150692	3.8426997
0.2166667	0.0492469	0.9532474
0.1400679	0.0563117	0.3484002

For the overall Fixed effects model with IV weights we may use the `rma` function. The `rma` function takes as an input the y_i, v_i that are calculated by the `ecalc` function we used before the ES we are calculating , the method `fixed` in this case while the digits option is needed for declaring in which decimal shall we round the results.

```
res <- rma(yi   ## log(OR)
           ,vi ## Var(log(OR))
           , data=dat ## Output Dataset of ecalc
           , measure="OR", method="FE",
           digits = 3)
summary(res)



Fixed-Effects Model (k = 19)

  logLik  deviance       AIC       BIC      AICc
 -47.456    80.213    96.911    97.856    97.147


Test for Heterogeneity:
Q(df = 18) = 80.213, p-val < .001
```

```
Model Results:

estimate       se     zval     pval    ci.lb     ci.ub
  -0.481    0.119   -4.043    <.001   -0.714    -0.248       ***


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

In the summary above we may observe that the overall Fixed Effects model Estimate is log_Odds: -0.481 (0.62 exponentiated) with 95% C.I. (-0.71,-0.25) , [0.49,0.78] exponentiated. The result is statistically significant in the 5% level of significance since p-value<.001. The summary also suggests that the studies are Heterogeneous since Q Test for Heterogeneity p-value<.001.

The test of heterogeneity is a χ^2 test with k= 18 degrees of freedom where k is the number of the studies minus 1.

The forest plot is a good graphical method in order to present the Effect Sizes, the CIs and the weights of each study. In our case we have the *default* Inverse-Variance weighting method.

Forest Plot with Weights

dies		Weights	Odds Ratios [95% CI]
Study 1		2.94%	0.06 [0.02 , 0.23]
Study 2		4.77%	0.08 [0.03 , 0.22]
Study 3		2.61%	0.91 [0.22 , 3.84]
Study 4		2.47%	0.22 [0.05 , 0.95]
Study 5		6.54%	0.14 [0.06 , 0.35]
Study 6		6.64%	3.17 [1.28 , 7.82]
Study 7		9.15%	0.62 [0.29 , 1.33]
Study 8		8.04%	0.23 [0.10 , 0.51]
Study 9		6.25%	0.80 [0.31 , 2.03]
Study 10		0.98%	0.28 [0.03 , 2.98]
Study 11		5.56%	0.59 [0.22 , 1.58]
Study 12		5.75%	0.97 [0.37 , 2.58]
Study 13		15.14%	1.38 [0.76 , 2.52]
Study 14		8.70%	0.96 [0.44 , 2.12]
Study 15		7.54%	0.98 [0.42 , 2.30]
Study 16		1.84%	0.10 [0.02 , 0.56]
Study 17		2.24%	0.77 [0.16 , 3.64]
Study 18		1.03%	5.14 [0.52 , 51.29]
Study 19		1.82%	4.12 [0.73 , 23.15]
FE Model		100.00%	0.62 [0.49 , 0.78]

0.01　　0.59　　51.29

Odds Ratio (log scale)
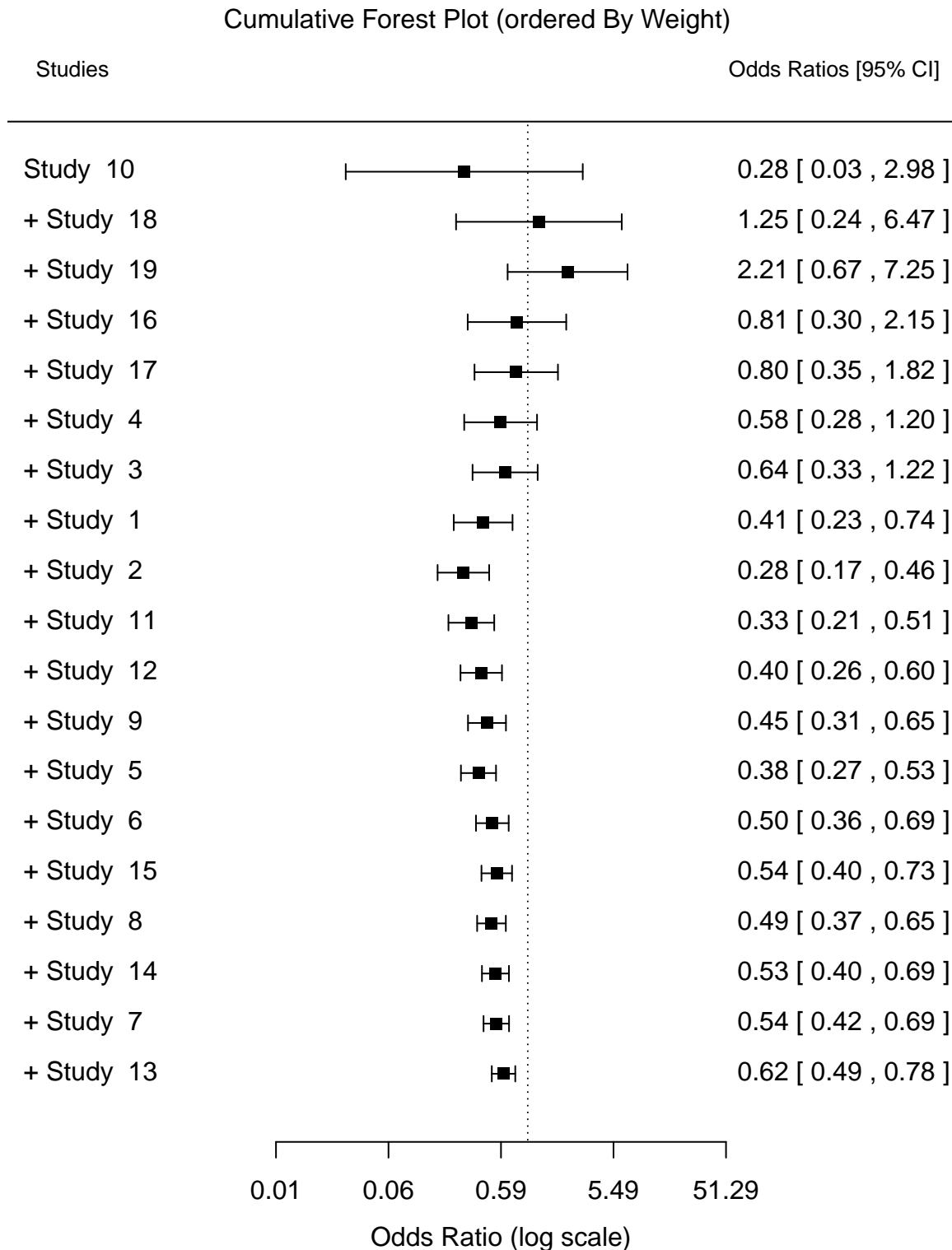
Further more we may draw the cumulative Forest plot to better observe the pooled effect size how this is changes by adding one by one the studies. It is common to use an ordering (for example the size of each study, or it's Variance etc.)

Cumulative Forest Plot (ordered By Weight)

Studies		Odds Ratios [95% CI]
Study 10		0.28 [0.03 , 2.98]
+ Study 18		1.25 [0.24 , 6.47]
+ Study 19		2.21 [0.67 , 7.25]
+ Study 16		0.81 [0.30 , 2.15]
+ Study 17		0.80 [0.35 , 1.82]
+ Study 4		0.58 [0.28 , 1.20]
+ Study 3		0.64 [0.33 , 1.22]
+ Study 1		0.41 [0.23 , 0.74]
+ Study 2		0.28 [0.17 , 0.46]
+ Study 11		0.33 [0.21 , 0.51]
+ Study 12		0.40 [0.26 , 0.60]
+ Study 9		0.45 [0.31 , 0.65]
+ Study 5		0.38 [0.27 , 0.53]
+ Study 6		0.50 [0.36 , 0.69]
+ Study 15		0.54 [0.40 , 0.73]
+ Study 8		0.49 [0.37 , 0.65]
+ Study 14		0.53 [0.40 , 0.69]
+ Study 7		0.54 [0.42 , 0.69]
+ Study 13		0.62 [0.49 , 0.78]

0.01   0.06   0.59   5.49   51.29

Odds Ratio (log scale)

Finally we may draw a funnel plot, that shows the observed effect sizes or outcomes on the x-axis against some measure of precision of the observed effect sizes or outcomes on the y-axis. Based on Sterne and Egger (Sterne and Egger, 2001), the recommended choice for the y-axis is the standard error (in decreasing order) and this is also the default for the funnel() function in the metafor package. In the absence of publication bias and heterogeneity, one would

then expect to see the points forming a funnel shape, with the majority of the points falling inside of the pseudo-confidence region with bounds $\hat{\theta} \pm SE$, where $\hat{\theta}$ is the estimated effect or outcome based on the fixed-effects model and SE is the standard error value from the y-axis. With other measures of precision for the y-axis, the expected shape of the funnel can be rather different. The plot below shows a variety of choices for the y-axis and how this impacts the shape of the funnel plot (and the form of the pseudo-confidence region). Furthermore we can add various levels of significance in order to create a Contour-like Funnel-plot.

Various levels of statistical significance of the points/studies are indicated by the shaded regions. In particular, the unshaded (i.e., white) region in the middle corresponds to p-values greater than .10, the Gray-shaded region corresponds to p-values between .10 and .05, the dark Gray-shaded region corresponds to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values below .01. Funnel plots drawn in this way are more useful for detecting publication bias due to the suppression of non-significant findings.

Standard Error

Sampling Variance

Inverse Standard Error

Inverse Sampling Variance
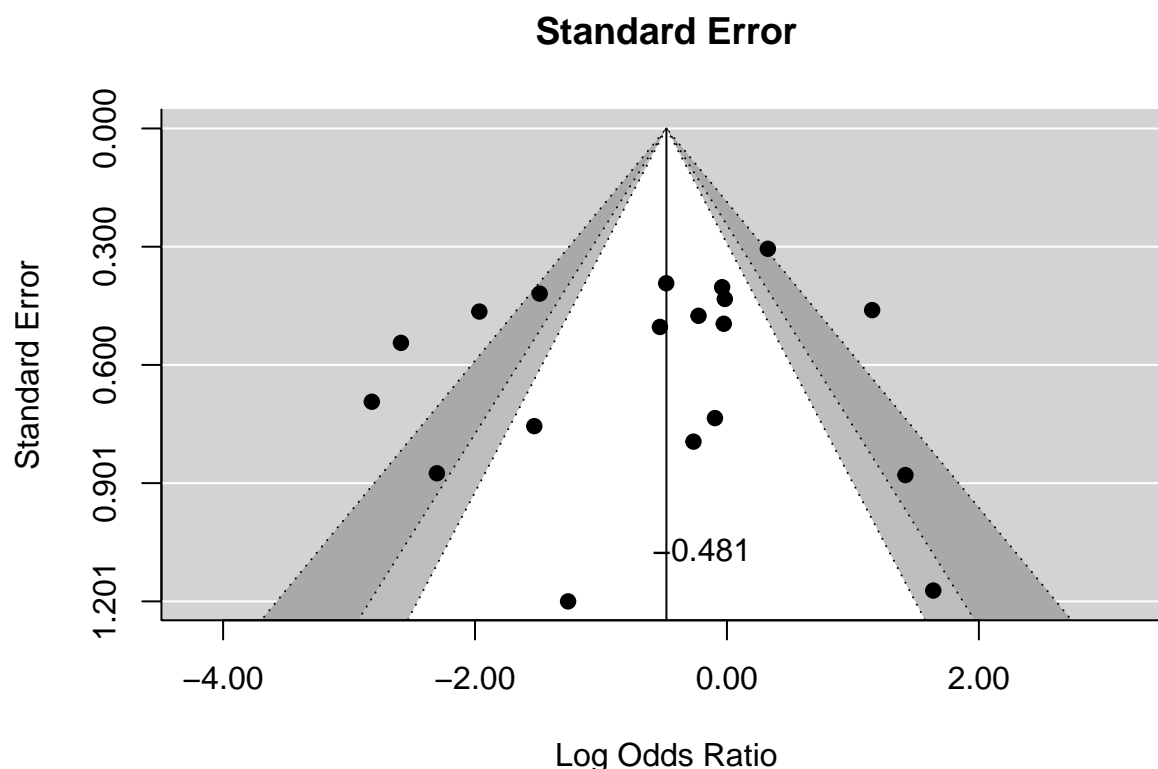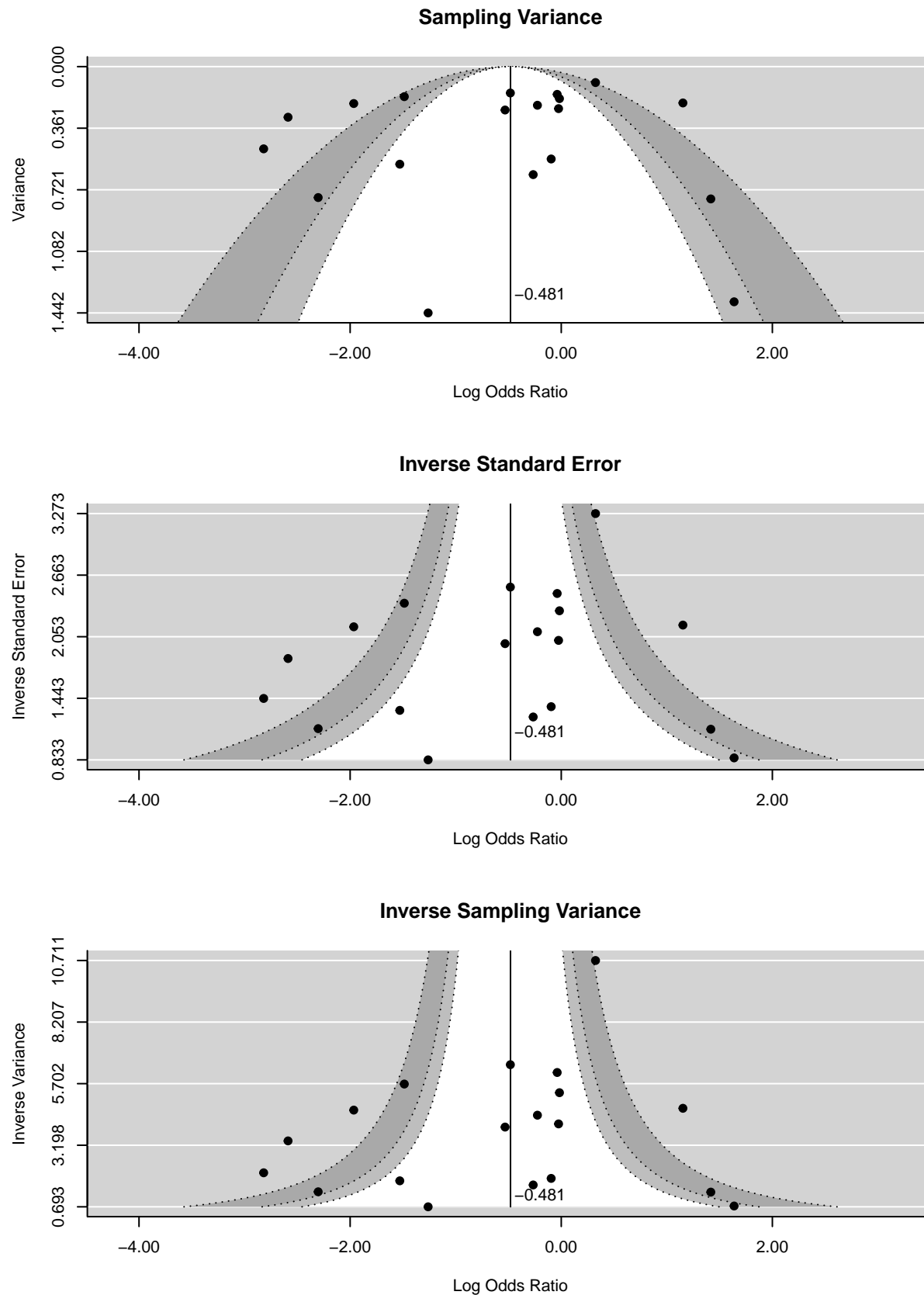
3.2   Mantel-Haenszel Method

In `metafor` package the *default* method is the Inverse-Variance as shown before. Sometime it is better to use in Metanalysis the M-H method, because of it's simplicity plus some statistical packages have Mantel-Haenszel Method as a default. The procedure is not the same, because we do not need to calculate the Effect sizes with the `escalc` function and store them into a Data-Set. The `rma.mh` needs the $a_i, b_i, c_i, d_i, n1_i$, and $n2_i$ of the 2x2 matrix, the measure (OR(default), RR,RD,IRD,IRR, etc).

```
res<-rma.mh("OR", ai = Meta_data$Tcases, bi =  Meta_data$Tnocases,
            ci =  Meta_data$Ccases,  di = Meta_data$Cnocases,
            n1i = Meta_data$Ttotal , n2i = Meta_data$Ctotal ,
            digits = 3  )
res
```

```
Fixed-Effects Model (k = 19)


Test for Heterogeneity:
Q(df = 18) = 80.366, p-val < .001


Model Results (log scale):

estimate       se      zval      pval     ci.lb      ci.ub
  -0.527    0.109    -4.827     <.001    -0.741     -0.313


Model Results (OR scale):

estimate    ci.lb     ci.ub
   0.590    0.477     0.731


Cochran-Mantel-Haenszel Test:    CMH = 24.078, df = 1,  p-val < .001
Tarone's Test for Heterogeneity: X^2 = 89.652, df = 18, p-val < .001
```

In the summary above we may observe that the overall Fixed Effects model Estimate is log_Odds: -0.527 (0.59 exponentiated) with 95% C.I. (-0.74,-0.31) , [0.48,0.73] exponentiated. The result is statistically significant in the 5% level of significance since p-value<.001. The summary also suggests that the studies are Heterogeneous since Q Test for Heterogeneity p-value<.001.

The Mantel-Haenszel summary estimates also the Cochran-Mantel-Haenszel Test and the Tarone's Test for Heterogeneity. Cochran-Mantel-Haenszel Test hypothesis is a chi-squared test with Hypothesis testing:

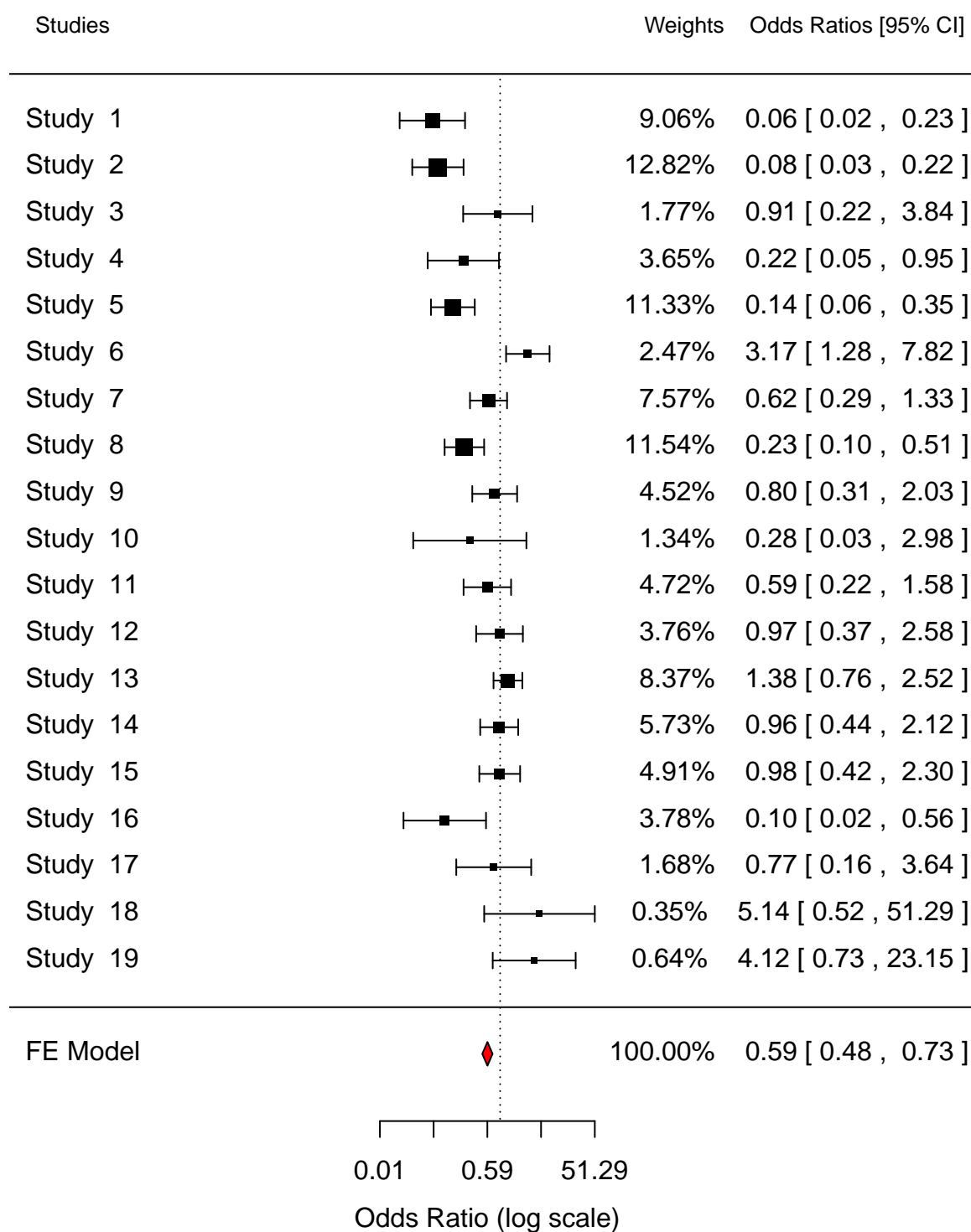H_0: Two nominal variables are conditionally independent in each stratum (2x2 matrix)

H_1: otherwise

The Tarone's Test for Heterogeneity is similar with the Q-test.

The forest plot is obviously a bit different also because the weights are calculated with another method described in the next chapter(4.3) .
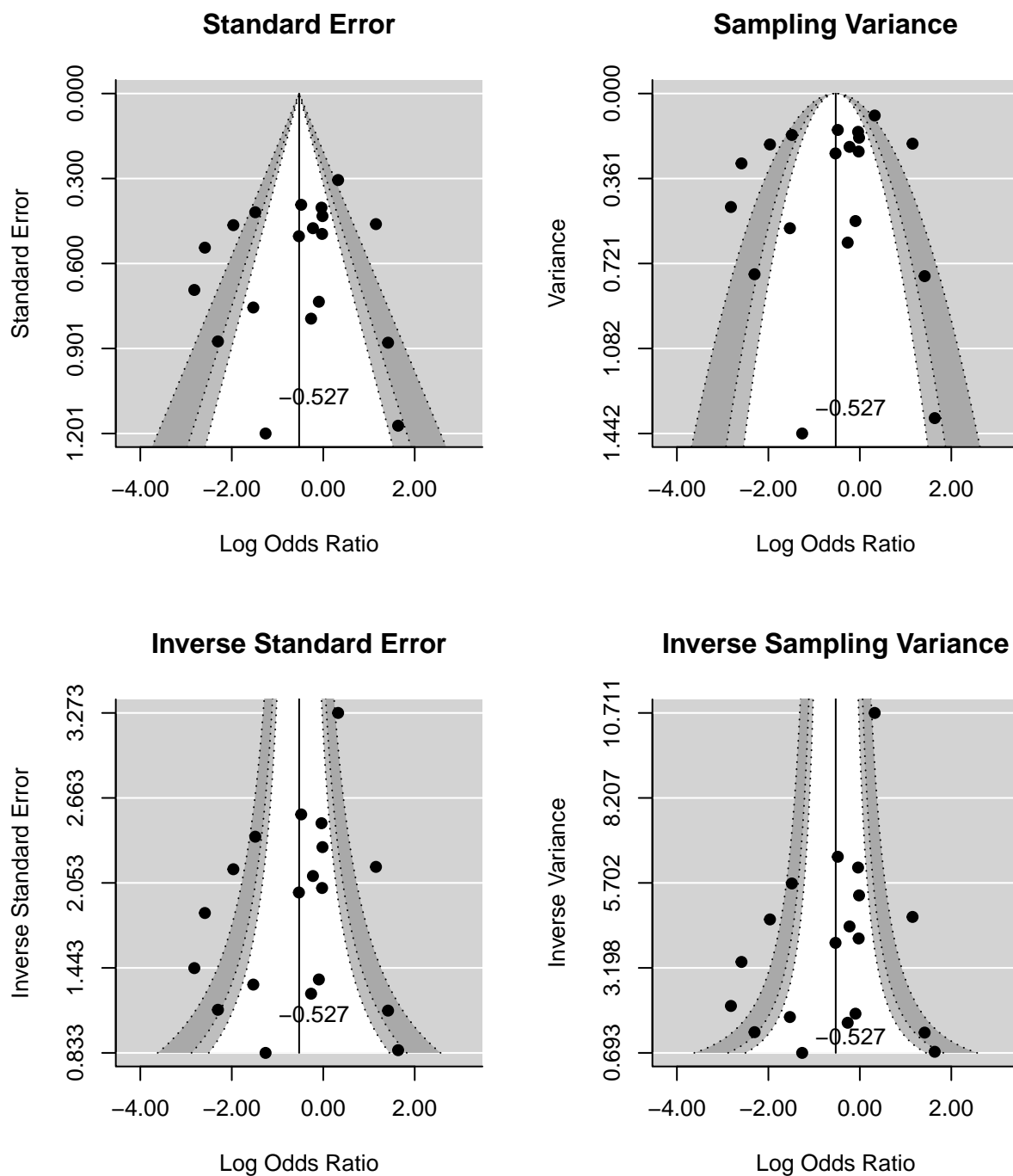
Mantel–Haenszel Forest Plot with Weights

Studies	Weights	Odds Ratios [95% CI]
Study 1	9.06%	0.06 [0.02 , 0.23]
Study 2	12.82%	0.08 [0.03 , 0.22]
Study 3	1.77%	0.91 [0.22 , 3.84]
Study 4	3.65%	0.22 [0.05 , 0.95]
Study 5	11.33%	0.14 [0.06 , 0.35]
Study 6	2.47%	3.17 [1.28 , 7.82]
Study 7	7.57%	0.62 [0.29 , 1.33]
Study 8	11.54%	0.23 [0.10 , 0.51]
Study 9	4.52%	0.80 [0.31 , 2.03]
Study 10	1.34%	0.28 [0.03 , 2.98]
Study 11	4.72%	0.59 [0.22 , 1.58]
Study 12	3.76%	0.97 [0.37 , 2.58]
Study 13	8.37%	1.38 [0.76 , 2.52]
Study 14	5.73%	0.96 [0.44 , 2.12]
Study 15	4.91%	0.98 [0.42 , 2.30]
Study 16	3.78%	0.10 [0.02 , 0.56]
Study 17	1.68%	0.77 [0.16 , 3.64]
Study 18	0.35%	5.14 [0.52 , 51.29]
Study 19	0.64%	4.12 [0.73 , 23.15]
FE Model	100.00%	0.59 [0.48 , 0.73]

0.01   0.59   51.29

Odds Ratio (log scale)

And we can draw the same funnel plots:

3.3 Peto Method

Another method for pooling odds ratios across the strata of the 2x2 matrices is Peto's method, not mathematically equal to the classical odds ratio. The Peto odds ratio can cause bias, especially when there is a substantial difference between the treatment and control group sizes, but it performs well in many situations.

```
res<-rma.peto("OR", ai = Meta_data$Tcases,
          bi =  Meta_data$Tnocases,
          ci =  Meta_data$Ccases,
          di = Meta_data$Cnocases,
          n1i = Meta_data$Ttotal ,
          n2i = Meta_data$Ctotal ,digits = 3)
summary(res)
```

```
Fixed-Effects Model (k = 19)

  logLik  deviance       AIC       BIC      AICc
 -48.554    86.061    99.108   100.053    99.344


Test for Heterogeneity:
Q(df = 18) = 86.061, p-val < .001


Model Results (log scale):

estimate       se      zval      pval     ci.lb     ci.ub
  -0.549    0.111    -4.962     <.001    -0.766    -0.332


Model Results (OR scale):

estimate     ci.lb     ci.ub
   0.578     0.465     0.717
```

4 Calculate Fixed-Effects Models by hand

4.1 Effect size calculation and CI bounds

We will calculate "by hand" the fixed-effects summary estimator of Odds Ratio using data on the number of patients with and without occurrence of bleeding in each arm of the respective study. The Odds Ratio is calculated from the **2x2 matrix** of each study.

	Treatment	Control	Total
Disease = Yes	a (Tcases)	b (Ccases)	a+b (TotCases)
Disease = No	c (Tnocases)	d (Cnocases)	c+d(TotNotCases)
	a+c (Ttotal)	b+d (Ctotal)	N

with the following type : $OR = (a * d)/(b * c)$ and is used in the Inverse-Variance and Mantel-Haenszel method, while in Peto there is another calculation of the OR.

As we can see in our Data-Set we miss the c_i and d_i but we can easily count them subtracting the cases from the total number of patients.

```
Meta_data$TotCases=with(Meta_data,Tcases + Ccases)

Meta_data$Tnocases = with(Meta_data,Ttotal-Tcases)
Meta_data$Cnocases = with(Meta_data,Ctotal-Ccases)
Meta_data$TotNoCases=with(Meta_data,Tnocases + Cnocases)
```

Now we can easily calculate the Odds Ratio of each study.

```
Meta_data$OR=with(Meta_data,(Tcases* Cnocases)/( Ccases* Tnocases))
```

The Variance and Standard Error is easily calculated in the log-scale. We know that the $\log(\text{Variance}) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$ and that the Standard Error is the square root of the Variance.

```
Var_logOR=1/Meta_data$Tcases+1/Meta_data$Tnocases+
  1/Meta_data$Ccases+1/Meta_data$Cnocases

SE_logOR=sqrt(Var_logOR)
logOR=log(Meta_data$OR)
```

So we can calculate the 95% C.I. in exponentiated form.

```
##qnorm(0.975) = 1.96
Meta_data$Lower95 = exp(logOR- qnorm(0.975)*SE_logOR)
Meta_data$Upper95 = exp(logOR+ qnorm(0.975)*SE_logOR)
```

Table 8: Odds Ratios of each study with 95% C.I.

ID	Odds Ratios	Lower 95% Bound	Upper 95% Bound
1	0.06	0.02	0.23
2	0.08	0.03	0.22
3	0.91	0.22	3.84
4	0.22	0.05	0.95
5	0.14	0.06	0.35
6	3.17	1.28	7.82
7	0.62	0.29	1.33
8	0.23	0.10	0.51
9	0.80	0.31	2.03
10	0.28	0.03	2.98
11	0.59	0.22	1.58
12	0.98	0.37	2.58
13	1.38	0.76	2.52
14	0.96	0.44	2.12
15	0.98	0.42	2.30
16	0.10	0.02	0.56
17	0.77	0.16	3.64
18	5.14	0.52	51.29
19	4.12	0.73	23.15

4.2 Weight Calculation

4.2.1 Inverse-Variance weight calculation

To find the overall Estimate of the Odds Ratios we need to calculate the weight of each research. The *default* method used to calculate the summary estimator in the `rma` function is `inverse-variance` the weights have to be calculated by the formula:

$$W_i = \frac{\frac{1}{V_i}}{\sum_{i=1}^{k} \frac{1}{V_i}} :$$

```
Wi <- 1/res$vi
Wi <- Wi/sum(Wi, na.rm = TRUE)
```

Table 9: Odds Ratios of each study with 95% C.I. and Weights

ID	Odds Ratios	Weights (I-V method)	Lower 95% Bound	Upper 95% Bound
1	0.06	5.02 %	0.02	0.23
2	0.08	7.33 %	0.03	0.22
3	0.91	2.34 %	0.22	3.84
4	0.22	2.75 %	0.05	0.95
5	0.14	7.24 %	0.06	0.35
6	3.17	6.48 %	1.28	7.82
7	0.62	8.19 %	0.29	1.33
8	0.23	8.67 %	0.1	0.51
9	0.8	5.5 %	0.31	2.03
10	0.28	1.13 %	0.03	2.98
11	0.59	5.01 %	0.22	1.58
12	0.98	5.05 %	0.37	2.58
13	1.38	13.39 %	0.76	2.52
14	0.96	7.6 %	0.44	2.12
15	0.98	6.57 %	0.42	2.3
16	0.1	2.27 %	0.02	0.56
17	0.77	2.05 %	0.16	3.64
18	5.14	1.36 %	0.52	51.29
19	4.12	2.06 %	0.73	23.15

Finally we get an weighted average of the Odds Ratios and we have the pooled I-V estimate

$$= \bar{logOR}_{pooledIV} = \frac{\sum_{i=1}^{k} w_i logOR_i}{\sum_{i=1}^{k} w_i}, \text{ which means: } \bar{logOR}_{pooledIV} = \frac{w_1 logOR_1 + w_2 logOR_2 + \cdots + w_n logOR_n}{w_1 + w_2 + \cdots + w_n} =$$

-0.6329484 $\Rightarrow exp(\bar{logOR}_{pooledIV}) = 0.53$

4.3 Mantel-Haenszel weight calculation

In STATA the *default* weight calculation method is the Mantel-Haenszel which is calculated as shown below:

- $W_i = \frac{(b_i * c_i)}{N_i}$

The b_i, c_i (Ccases,Tnocases) are already available. All we need to calculate are the total number of patients both in treatment and Control in each study (N_i).

```
Meta_data$Total= Meta_data$Ctotal+ Meta_data$Ttotal
```

Now we can calculate the above weights:

```
Meta_data$Weight= Meta_data$Ccases* Meta_data$Tnocases/Meta_data$Total
```

If we calculate the weights this way they add up to 109.49 so a better

```
Meta_data$Relative_Weight = Meta_data$Weight*100/sum(Meta_data$Weight)
```

Table 10: Weights and Relative Weights of the Studies

ID	Weights	Relative Weights
1	9.9154930	9.0560686
2	14.0366972	12.8200679
3	1.9411765	1.7729252
4	4.0000000	3.6533004
5	12.4000000	11.3252312
6	2.7079646	2.4732520
7	8.2831858	7.5652415
8	12.6357143	11.5405150
9	4.9512195	4.5220730
10	1.4634146	1.3365733
11	5.1686747	4.7206803
12	4.1176471	3.7607504
13	9.1672598	8.3726884
14	6.2735849	5.7298225
15	5.3793103	4.9130591
16	4.1379310	3.7792763
17	1.8367347	1.6775359
18	0.3783784	0.3455825
19	0.6956522	0.6353566

Now let's calculate the M-H pooled OR of all the researches.

```
[1] 0.5902876
```

4.4   Peto Method and Weights

The Peto method is calculating the Peto Odds Ratio a different approach than the classical Odds Ratio. In the typical 2x2 OR=$\frac{a*d}{b*c}$ while in the Peto method we first calculate:

- The Expected= $\frac{(a+b)(a+c)}{N}$
- The Variance equals $\frac{(a+b)(c+d)(a+c)(b+d)}{n^2(n-1)}$
- and finally the $\hat{OR}_{Peto} = exp(\frac{O-E}{V})$

In order to calculate by hand using the Peto method we need to estimate the $\hat{OR}_{Peto.pooled}$ which as

```
Meta_data$Expected= (Meta_data$TotCases)*(Meta_data$Ttotal)/Meta_data$Total
Meta_data$Variance= Meta_data$Ttotal*Meta_data$Ctotal*Meta_data$TotNoCases*Meta_data$Tot

Meta_data$OR = exp((Meta_data$Tcases - Meta_data$Expected)/(Meta_data$Variance) )
```

5 Random effects model

Most cases the Fixed-Effects model would be completely wrong, both Mathematically and Intuitively. In the Random- Effects modeling we assume that for various reasons (Differences in methods and sample characteristics) heterogeneity exists and we treat it as purely random. The Heterogeneity is symbolized with τ^2, which we have seen in the summaries of the Fixed-Eggects Models. Mathematical perception if :

- we have i = 1, . . . , k studies
- have y_i and corresponding v_i
- we assume that

  - $y_i|\theta_i \sim N(\theta_i, v_i)$
  - $\theta_i = \mu + u_i$
  - $y_i = \mu + u_i + \epsilon_i$

- and approx. 95% CI for $\theta_i : y_i \pm 1.96\sqrt{v_i}$

where y_i denotes the observed effect in the i-th study, θ_i the corresponding (unknown) true effect, ϵ_i is the sampling error and $\epsilon_i \sim N(0, v_i)$ and $u_i \sim N(0, \tau^2)$. Furthemore, because of the calculation of the τ^2 and the addition to the model, the weights change completely and sometimes this is used for reducing the weight of a study with a very small Variance (large Studies). In the following example we will demonstrate clearly the difference that may occur if we have a big study in our Meta-Analysis and the necessity of a random effects model. The `magnes.dta` file contains results from 16 randomized clinical trials that were designed to investigate the effect of magnesium intake on mortality of patients with acute myocardial infarction. The file is described below:

trial	trialnam	year	tot1	dead1	tot0	dead0
1	Morton	1984	40	1	36	2
2	Rasmussen	1986	135	9	135	23
3	Smith	1986	200	2	200	7
4	Abraham	1987	48	1	46	1
5	Feldstedt	1988	150	10	148	8
6	Schechter	1989	59	1	56	9
7	Ceremuzynski	1989	25	1	23	3
8	Bertschat	1989	22	0	21	1
9	Singh	1990	76	6	75	11
10	Pereira	1990	27	1	27	7
11	Schechter 1	1991	89	2	80	12
12	Golf	1991	23	5	33	13
13	Thogersen	1991	130	4	122	8
14	LIMIT-2	1992	1159	90	1157	118
15	Schechter 2	1995	107	4	108	17
16	ISIS-4	1995	29011	2216	29039	2103

- The first column shows the year the study was conducted.
- The columns named `tot` are showing the total amount of patients in Treatment (1) and Control (0), while
- The `dead` columns shows the diseased in Treatment (1) and Control (0).

We shall calculate the summary estimator for the death's Odds Ratio and create the corresponding forest-plot both in fixed (Inverse Variance method) and random effects (DerSimonian-Laird) approach. First we have the Fixed-effects model.

```
Fixed-Effects Model (k = 16)

  logLik  deviance       AIC       BIC      AICc
 -30.111    47.059    62.222    62.994    62.508


Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001


Model Results:

estimate       se     zval     pval     ci.lb     ci.ub
   0.015    0.031    0.484    0.629    -0.045     0.075


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```
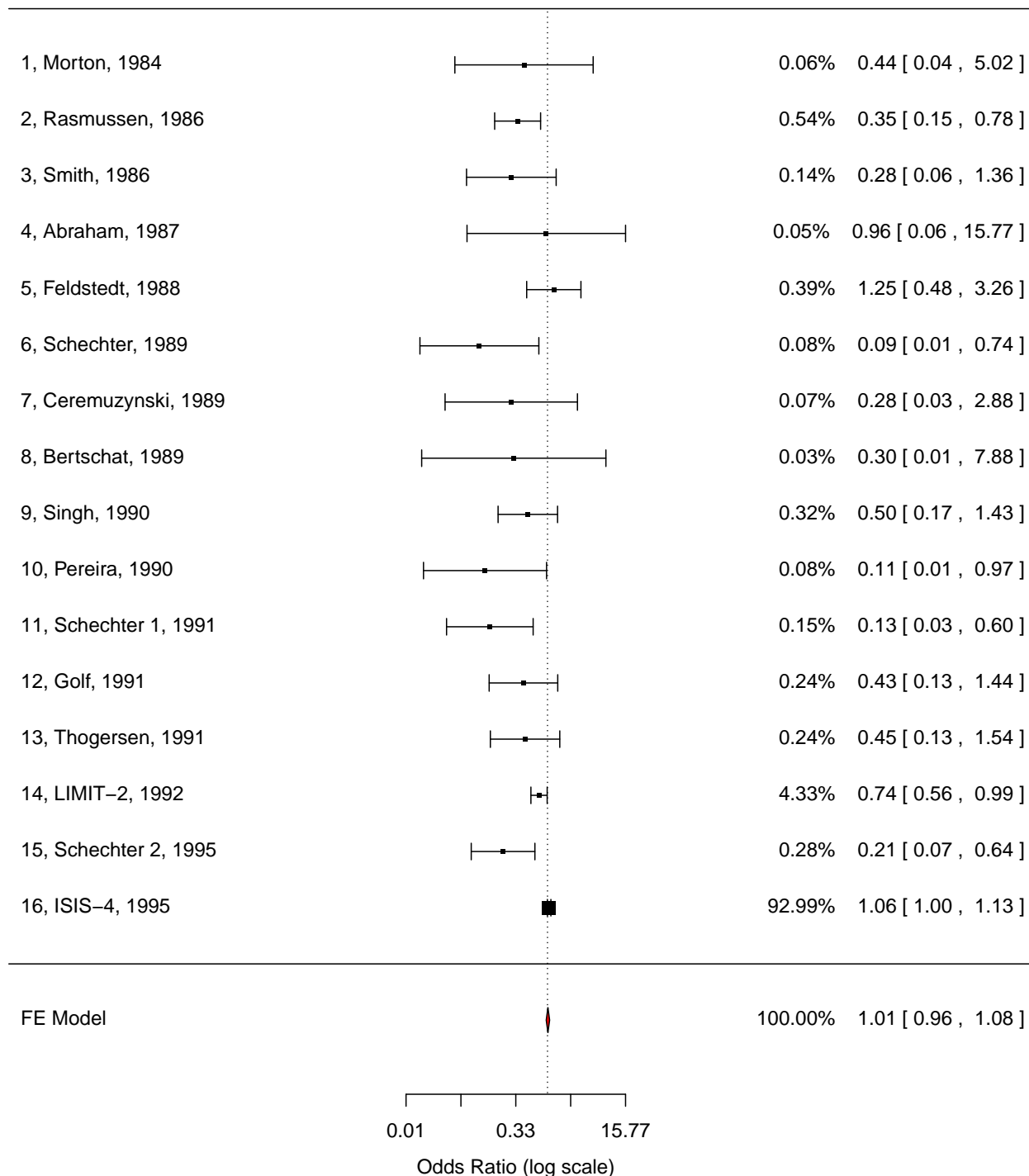
In the summary above we may observe that the overall Fixed Effects model Estimate is log_Odds: 0.015 (1.01 exponentiated) with 95% C.I. (-0.05,0.07) , [0.96,1.08] exponentiated. The result is not statistically significant in the 5% level of significance since p-value = 0.629 . The summary also suggests that the studies are Heterogeneous since Q Test for Heterogeneity p-value<.001. Let's have a look in the forest plot.

1, Morton, 1984	0.06%	0.44 [0.04 , 5.02]
2, Rasmussen, 1986	0.54%	0.35 [0.15 , 0.78]
3, Smith, 1986	0.14%	0.28 [0.06 , 1.36]
4, Abraham, 1987	0.05%	0.96 [0.06 , 15.77]
5, Feldstedt, 1988	0.39%	1.25 [0.48 , 3.26]
6, Schechter, 1989	0.08%	0.09 [0.01 , 0.74]
7, Ceremuzynski, 1989	0.07%	0.28 [0.03 , 2.88]
8, Bertschat, 1989	0.03%	0.30 [0.01 , 7.88]
9, Singh, 1990	0.32%	0.50 [0.17 , 1.43]
10, Pereira, 1990	0.08%	0.11 [0.01 , 0.97]
11, Schechter 1, 1991	0.15%	0.13 [0.03 , 0.60]
12, Golf, 1991	0.24%	0.43 [0.13 , 1.44]
13, Thogersen, 1991	0.24%	0.45 [0.13 , 1.54]
14, LIMIT−2, 1992	4.33%	0.74 [0.56 , 0.99]
15, Schechter 2, 1995	0.28%	0.21 [0.07 , 0.64]
16, ISIS−4, 1995	92.99%	1.06 [1.00 , 1.13]
FE Model	100.00%	1.01 [0.96 , 1.08]

Odds Ratio (log scale)

As we may observe there is a study (ISIS-4) that has nearly the 93% of the total weight and although it seems that all the studies have a lower than 1 odds ratio this study pulls the overall pooled MH Odds Ratio to above 1. Although it seems to be a ptotective effect the ISIS is resulting to a non-significant result.

5.1 DerSimonian-Laird estimator

A good solution is to use the Random-Effects model, that will reduce the weight of this study. The default estimator is the DerSimonian-Laird,.

```
Random-Effects Model (k = 16; tau^2 estimator: DL)

  logLik  deviance       AIC       BIC      AICc
 -19.700    26.238    43.400    44.946    44.324

tau^2 (estimated amount of total heterogeneity): 0.224 (SE = 0.247)
tau (square root of estimated tau^2 value):      0.473
I^2 (total heterogeneity / total variability):   68.13%
H^2 (total variability / sampling variability):  3.14

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:

estimate       se     zval      pval    ci.lb     ci.ub
  -0.728    0.196   -3.706     <.001   -1.112    -0.343        ***


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

In the summary above we may observe that the overall Random Effects model Estimate is log(Odds Ratio)= -0.7276 (0.4831 exponentiated) with 95% C.I. (-1.11,-0.34) , [0.33,0.71] exponentiated.

The result is statistically significant in the 5% level of significance since p-value < .0001.

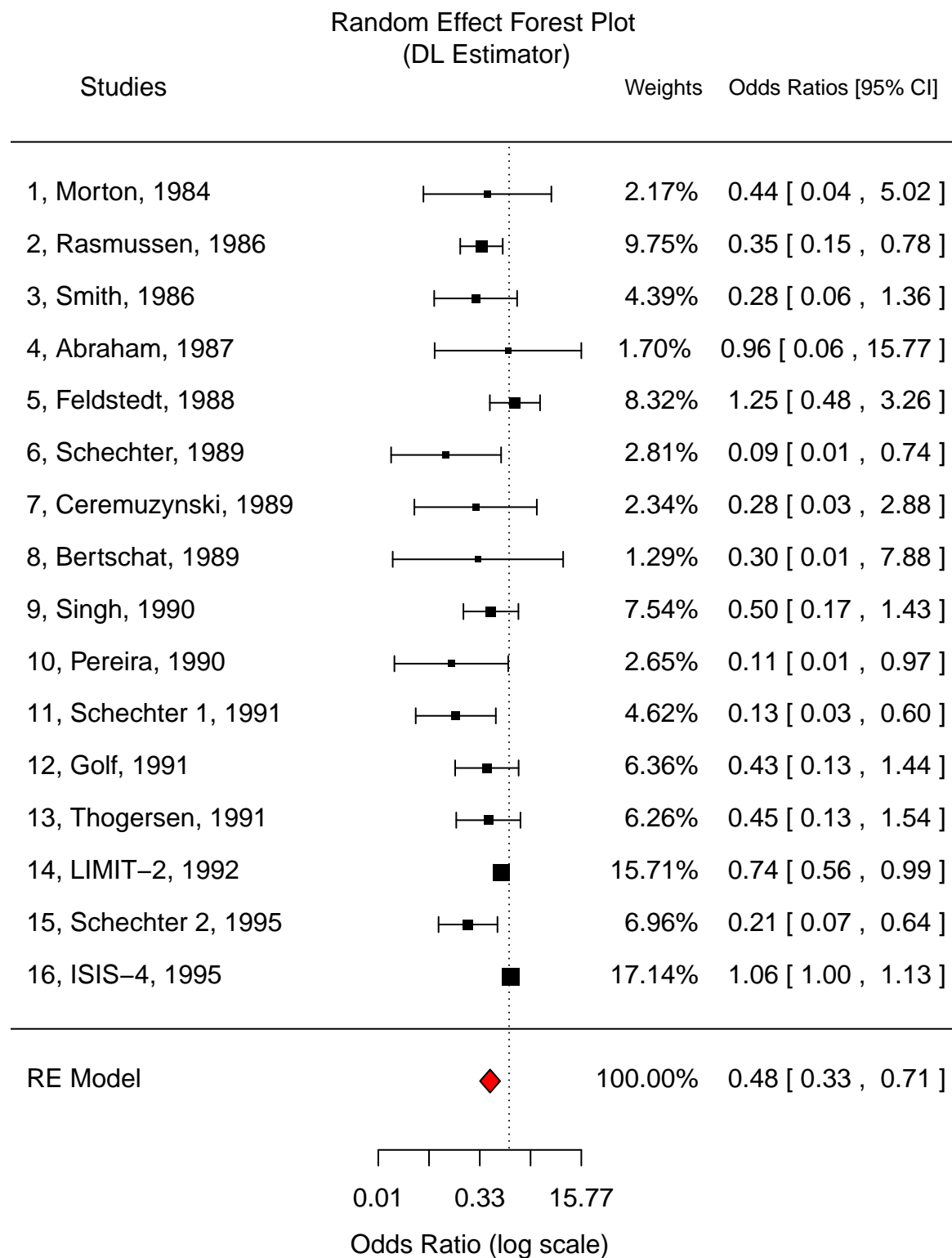The Cochran's test for Heterogeneity is the same as before.

In the Random effects model there are some outputs that need attention.

The amount of heterogeneity is calculated $\tau^2 = 0.224 \Rightarrow \tau = sqrt(0.224) = 0.473$, the $I^2 = (Q - df)/Q * 100\%$ where Q is Cochran's heterogeneity statistic and df the degrees of freedom. The I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, while larger values show increasing heterogeneity. Finally the H^2 is a measure of variability

The forest plot is a little bit different also. The weights have changed and now ISIS-4 has a weight nearly 17%.
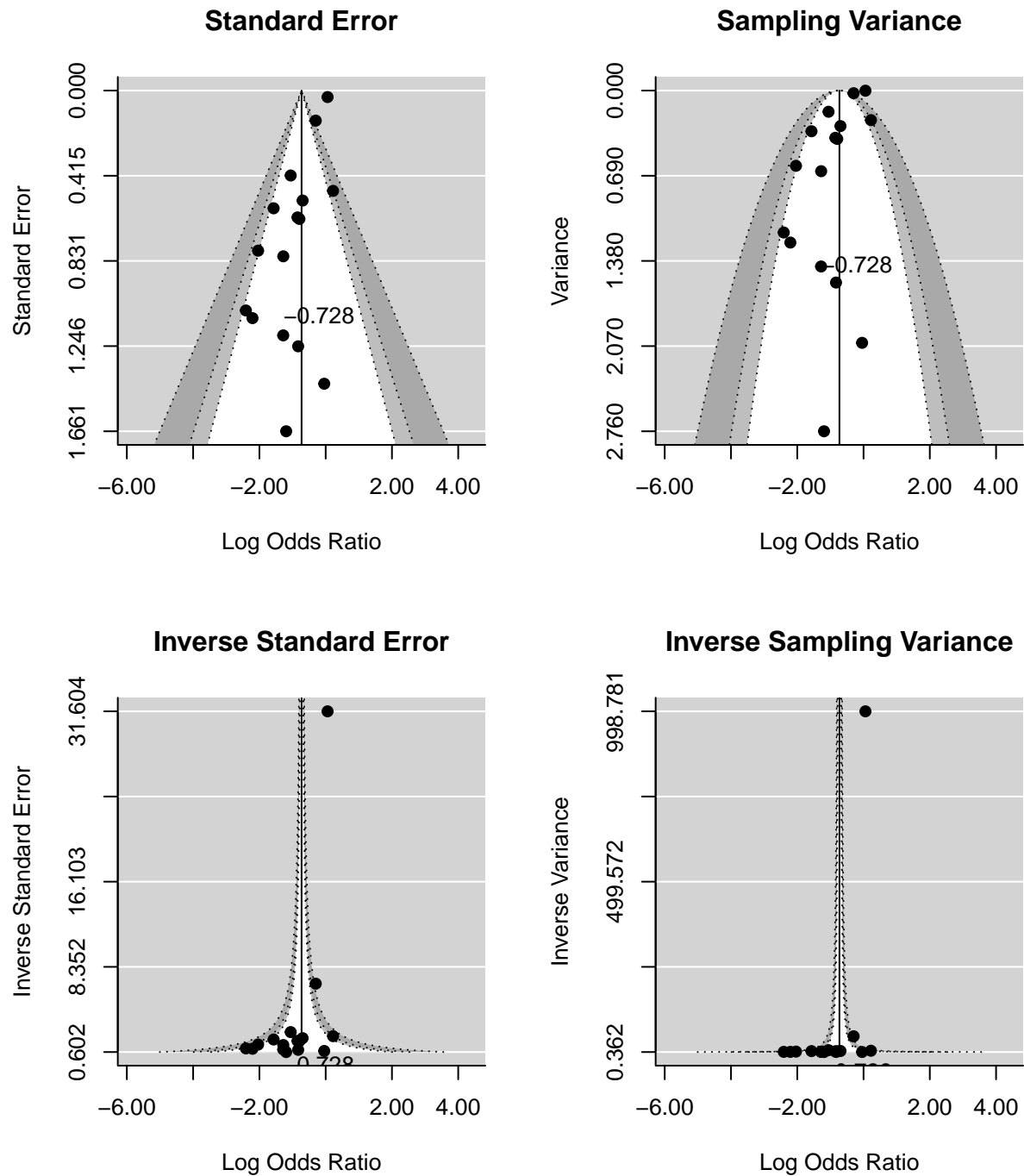
Random Effect Forest Plot
(DL Estimator)

Studies		Weights	Odds Ratios [95% CI]
1, Morton, 1984		2.17%	0.44 [0.04 , 5.02]
2, Rasmussen, 1986		9.75%	0.35 [0.15 , 0.78]
3, Smith, 1986		4.39%	0.28 [0.06 , 1.36]
4, Abraham, 1987		1.70%	0.96 [0.06 , 15.77]
5, Feldstedt, 1988		8.32%	1.25 [0.48 , 3.26]
6, Schechter, 1989		2.81%	0.09 [0.01 , 0.74]
7, Ceremuzynski, 1989		2.34%	0.28 [0.03 , 2.88]
8, Bertschat, 1989		1.29%	0.30 [0.01 , 7.88]
9, Singh, 1990		7.54%	0.50 [0.17 , 1.43]
10, Pereira, 1990		2.65%	0.11 [0.01 , 0.97]
11, Schechter 1, 1991		4.62%	0.13 [0.03 , 0.60]
12, Golf, 1991		6.36%	0.43 [0.13 , 1.44]
13, Thogersen, 1991		6.26%	0.45 [0.13 , 1.54]
14, LIMIT−2, 1992		15.71%	0.74 [0.56 , 0.99]
15, Schechter 2, 1995		6.96%	0.21 [0.07 , 0.64]
16, ISIS−4, 1995		17.14%	1.06 [1.00 , 1.13]
RE Model		100.00%	0.48 [0.33 , 0.71]

0.01   0.33   15.77

Odds Ratio (log scale)

Standard Error

Sampling Variance

Inverse Standard Error

Inverse Sampling Variance

What is the difference between the results of Fixed versus Random effects model?

In the fixed effects analysis ISIS-4 study takes a huge burden compared to the others because ISIS has a much larger size As a result the final pooled MH odds ratio is calculated mainly out of this study. On the other hand in the random effects analysis the weight of this study is much smaller and comparable with the LIMIT-2 study which is approximately 30 times smaller. This affected pooled OR because it is calculated "more" uniformly by all the studies.

Let's see the difference into the calculation of the Empirical Bayes Estimate a

Note however that the Empirical Bayes estimate the effect of ISIS-4 study is essentially the same as the individual assessment of the study (the very small within-study variance results in shrinkage effect is negligible).

```
                        pred pi.lb pi.ub
1, Morton, 1984         0.48  0.19  1.21
2, Rasmussen, 1986      0.40  0.21  0.76
3, Smith, 1986          0.42  0.18  0.98
4, Abraham, 1987        0.52  0.20  1.33
5, Feldstedt, 1988      0.76  0.38  1.53
6, Schechter, 1989      0.37  0.15  0.91
7, Ceremuzynski, 1989 0.45  0.18  1.13
8, Bertschat, 1989      0.47  0.18  1.22
9, Singh, 1990          0.49  0.24  1.01
10, Pereira, 1990       0.38  0.15  0.96
11, Schechter 1, 1991 0.34  0.15  0.79
12, Golf, 1991          0.46  0.21  1.00
13, Thogersen, 1991     0.47  0.22  1.03
14, LIMIT-2, 1992       0.71  0.54  0.94
15, Schechter 2, 1995 0.34  0.16  0.73
16, ISIS-4, 1995        1.06  0.99  1.12
```

Shrinkage Effect of studies
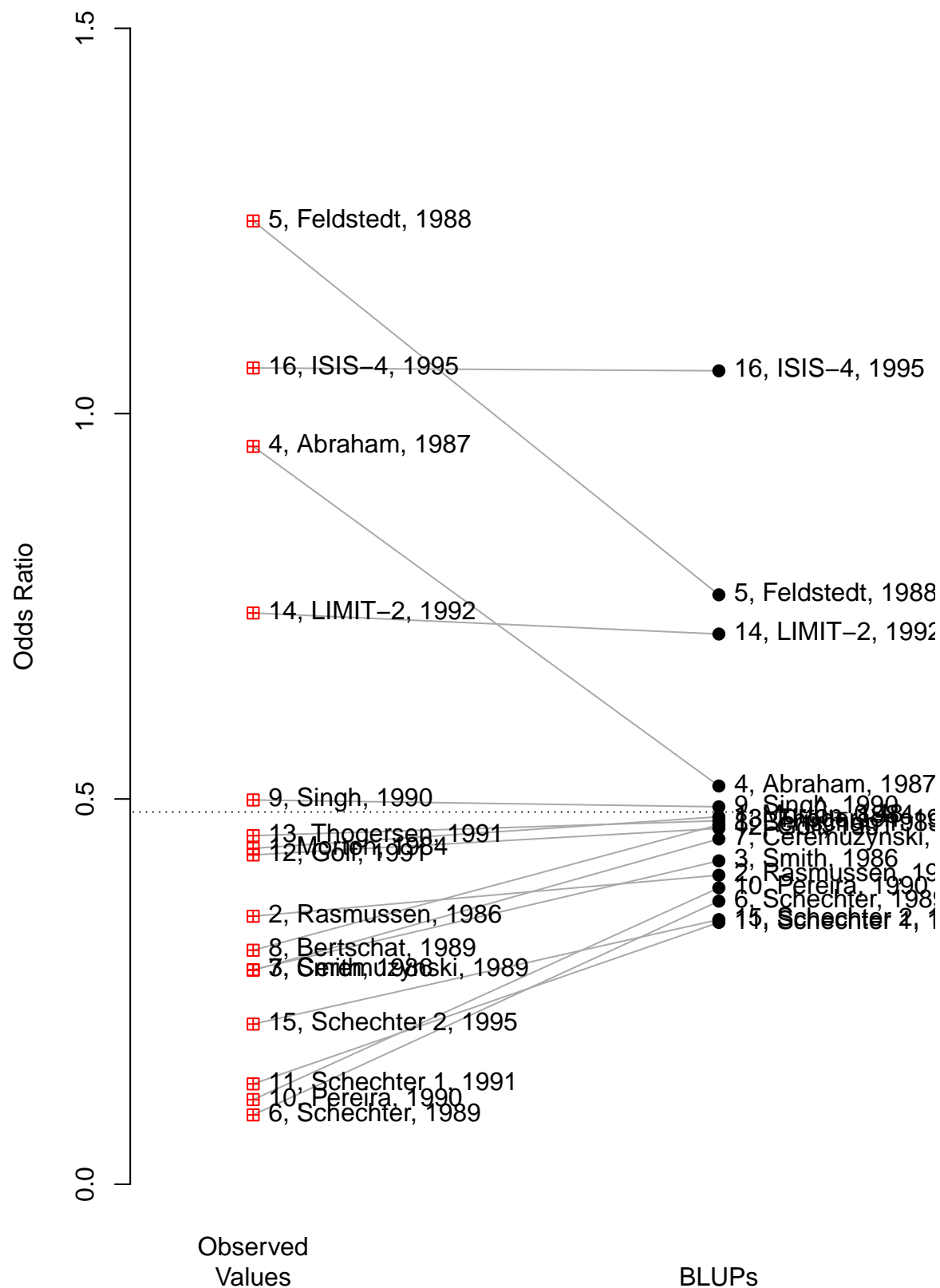
6 Calculation Random-Effects by hand

6.1 DerSimonian-Laird (default) estimator

The weights in the DerSimonian-Laird method are calculated through the following equations.
$W_i = \frac{1}{v_i + \tau^2}$ and then we calculate as usual a weighted average for the log(OR)=$\bar{logOR} = \frac{\sum_1^k W_i * OR_i}{\sum_1^k W_i} \Rightarrow \bar{OR} = exp(logOR))$

```
wi=1/(res$vi + res$tau2)
exp(sum(wi*res$yi)/sum(wi))
```

```
[1] 0.4830752
```

6.1.1   Other Estimators

The DerSimonian-Laird estimation is the most simple of all and is the default method in R, Stata and SAS. But there are other estimation methods :

- Hedges ('variance component estimator' or 'Cochran estimator') estimator
- Hunter-Schmidt estimator
- Sidik-Jonkman estimator
- maximum-likelihood estimator
- restricted maximum-likelihood estimator
- empirical Bayes estimator

```
$`DerSimonian-Laird`

Random-Effects Model (k = 16; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.224 (SE = 0.247)
tau (square root of estimated tau^2 value):      0.473
I^2 (total heterogeneity / total variability):   68.13%
H^2 (total variability / sampling variability):  3.14

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:

estimate      se     zval     pval    ci.lb    ci.ub
  -0.728   0.196   -3.706    <.001   -1.112   -0.343        ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


$Hedges

Random-Effects Model (k = 16; tau^2 estimator: HE)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.406)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001
```

```
Model Results:


estimate        se      zval      pval      ci.lb      ci.ub
   0.015     0.031     0.484     0.629     -0.045     0.075


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1



$`Paule-Mandel`

Random-Effects Model (k = 16; tau^2 estimator: PM)

tau^2 (estimated amount of total heterogeneity): 0.177 (SE = 0.198)
tau (square root of estimated tau^2 value):      0.420
I^2 (total heterogeneity / total variability):   62.76%
H^2 (total variability / sampling variability):  2.69

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:


estimate        se      zval      pval      ci.lb      ci.ub
  -0.691     0.184    -3.756     <.001    -1.051     -0.330       ***


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1



$`Hunter-Schmid`

Random-Effects Model (k = 16; tau^2 estimator: HS)

tau^2 (estimated amount of total heterogeneity): 0.029 (SE = 0.007)
tau (square root of estimated tau^2 value):      0.170
I^2 (total heterogeneity / total variability):   21.63%
H^2 (total variability / sampling variability):  1.28

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:
```

```
estimate         se      zval      pval      ci.lb      ci.ub
  -0.373      0.112    -3.330     <.001     -0.593     -0.154        ***


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1



$`Sidik-Jonkman`

Random-Effects Model (k = 16; tau^2 estimator: SJ)

tau^2 (estimated amount of total heterogeneity): 0.313 (SE = 0.162)
tau (square root of estimated tau^2 value):      0.560
I^2 (total heterogeneity / total variability):   74.95%
H^2 (total variability / sampling variability):  3.99

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001


Model Results:

estimate         se      zval      pval      ci.lb      ci.ub
  -0.776      0.216    -3.592     <.001     -1.200     -0.353        ***


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1



$`Maximum Likelihood `

Random-Effects Model (k = 16; tau^2 estimator: ML)

tau^2 (estimated amount of total heterogeneity): 0.254 (SE = 0.193)
tau (square root of estimated tau^2 value):      0.504
I^2 (total heterogeneity / total variability):   70.80%
H^2 (total variability / sampling variability):  3.42

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001


Model Results:

estimate         se      zval      pval      ci.lb      ci.ub
  -0.746      0.203    -3.669     <.001     -1.145     -0.348        ***
```

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


$`Restricted Maximum Likelihood`

Random-Effects Model (k = 16; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.293 (SE = 0.229)
tau (square root of estimated tau^2 value):      0.541
I^2 (total heterogeneity / total variability):   73.64%
H^2 (total variability / sampling variability):  3.79

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:

estimate        se      zval      pval      ci.lb      ci.ub
  -0.767     0.212    -3.619     <.001     -1.182     -0.351        ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


$`Empirical Bayes `

Random-Effects Model (k = 16; tau^2 estimator: EB)

tau^2 (estimated amount of total heterogeneity): 0.177 (SE = 0.198)
tau (square root of estimated tau^2 value):      0.420
I^2 (total heterogeneity / total variability):   62.76%
H^2 (total variability / sampling variability):  2.69

Test for Heterogeneity:
Q(df = 15) = 47.059, p-val < .001

Model Results:

estimate        se      zval      pval      ci.lb      ci.ub
  -0.691     0.184    -3.756     <.001     -1.051     -0.330        ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Objects res.DL , res.HE, and res.PM include the results when using the Paule-Mandel, Cochran, and DerSimonian-Laird estimators (the Cochran estimator is referred to as the Hedges estimator in the metafor package).Next, we obtain the results using the empirical Bayes (res.EB) , maximum-likelihood (res.ML) and restricted maximum-likelihood estimators (res.REML) , the Hunter-Schmidt estimator (res.HS) , and the Sidik-Jonkman (res.SJ) estimator.

The next two models (res.CA2 and res.DL2) use the generalized Q-statistic estimator of τ^2 (referred to as the general method-of-moments estimator in the paper), where the weights are set equal to the usual (random-effects model) inverse-variance weights, once using the Cochran and once using the DerSimonian-Laird estimator values. This will provide us with the two-step Cochran and two-step DerSimonian-Laird estimator values. However, note that the weights specified are used not only to estimate τ^2 but also to estimate μ the average effect. If we now want to use the usual inverse-variance weights but using the two-step estimator values, we have to fit each model one more time, but this time with specified values for τ^2 as obtained from the two-step procedure.

Finally, to obtain the improved Sidik-Jonkman estimator, we must use the control argument to set the initial estimate of τ^2 to that of the Cochran estimator, which then gets updated using the method described by Sidik and Jonkman.

```
        tau     mu     se
DL    0.4732 0.4831 0.1963
HE    0.0000 1.0149 0.0305
PM    0.4202 0.5012 0.1839
HS    0.1701 0.6885 0.1121
SJ    0.5598 0.4602 0.2161
ML    0.5040 0.4741 0.2034
REML  0.5410 0.4646 0.2118
EB    0.4202 0.5012 0.1839
SJ2   0.0000 1.0149 0.0305
CA2   0.4732 0.4831 0.1963
DL2   0.3983 0.5099 0.1786
```

References

Sterne, J.A., Egger, M., 2001. Funnel plots for detecting bias in meta-analysis. Journal of Clinical Epidemiology 54, 1046–1055.