Class 11: Meta-Analysis for Binary Outcome

R section EPH 705

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Overview

Class 11: Meta-Analysis for Binary Outcome

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Object:
Introduction
Effect sizes and standard error
Coding reliability
Steps in a meta-analysis
Homogeneity test

R Example

Exercise

1. Object:
   - Introduction
   - Effect sizes and standard error
   - Coding reliability
   - Steps in a meta-analysis
   - Homogeneity test
2. R Example
3. Exercise

Introduction

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- The term "meta-analysis" was coined by Gene V. Glass, who was the first modern statistician to formalize the use of the term meta-analysis. He states *"my major interest currently is in what we have come to call ...the meta-analysis of research. The term is a bit grand, but it is precise and apt ... Meta-analysis refers to the analysis of analyses"*
- *Terms viewed as interchangeable include Systematic review, Research synthesis and Quantitative review*

Advantages

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- Results can be generalized to a larger population
- The precision and accuracy of estimates can be improved as more data is used. This, in turn, may increase the statistical power to detect an effect.
- Inconsistency of results across studies can be quantified and analyzed. For instance, does inconsistency arise from sampling error, or are study results (partially) influenced by between-study heterogeneity.
- Hypothesis testing can be applied on summary estimates,
- Moderators can be included to explain variation between studies,
- The presence of publication bias can be investigated

Problem: Publication bias

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Another potential pitfall is the reliance on the available body of published studies, which may create exaggerated outcomes due to publication bias, as studies which show negative results or insignificant results are less likely to be published. For example, pharmaceutical companies have been known to hide negative studies and researchers may have overlooked unpublished studies such as dissertation studies or conference abstracts that did not reach publication. This is not easily solved, as one cannot know how many studies have gone unreported

Problem: Publication bias

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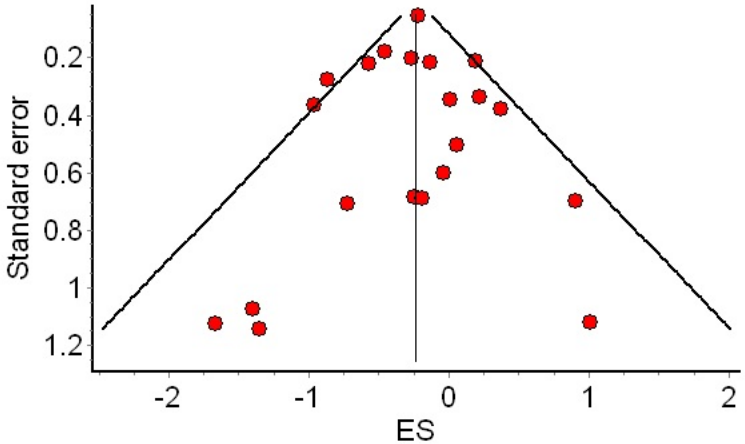
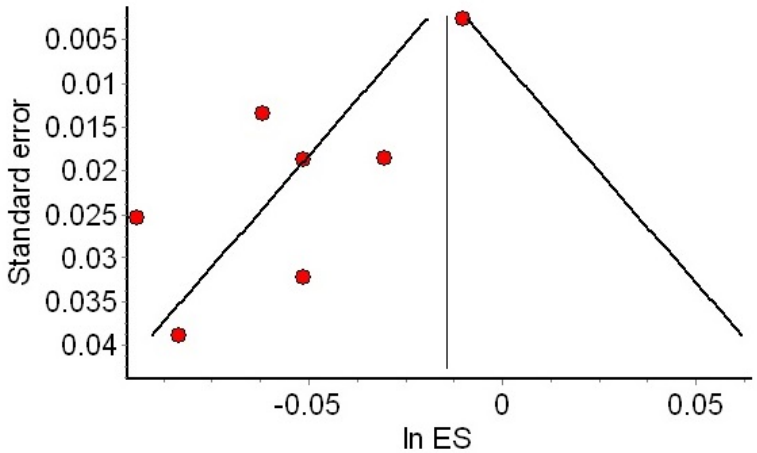


A funnel plot expected without the file drawer problem. The largest studies converge at the tip while smaller studies show more or less symmetrical scatter at the base



A funnel plot expected with the file drawer problem. The largest studies still cluster around the tip, but the bias against publishing negative studies has caused the smaller studies as a whole to have an unjustifiably favorable result to the hypothesis

Recall:Cochran–Mantel–Haenszel statistics

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In statistics, the Cochran-Mantel-Haenszel test (CMH) is a test used in the analysis of stratified or matched categorical data. We consider a binary outcome variable such as case status (e.g. lung cancer) and a binary predictor such as treatment status (e.g. smoking). The observations are grouped in strata. The stratified data are summarized in a series of 2×2 contingency tables, one for each strata. The ith such contingency table is:

	Treatment	No treatment	Row total
Case	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
Column total	M_{1i}	M_{2i}	T_i

The common odds-ratio of the K contingency tables is defined as:

$$R = \frac{\sum_{i=1}^{K} \frac{A_i D_i}{T_i}}{\sum_{i=1}^{K} \frac{B_i C_i}{T_i}},$$

Recall: Cochran–Mantel–Haenszel statistics

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The null hypothesis is that there is no association between the treatment and the outcome. More precisely, the null hypothesis $H_0 : R = 1$ and the alternative hypothesis is $H_1 : R \neq 1$. The test statistic is:

$$\xi_{CMH} = \frac{\sum_{i=1}^{K}(A_i - \frac{N_{1i}M_{1i}}{T_i})^2}{\sum_{i=1}^{K}\frac{N_{1i}N_{2i}M_{1i}M_{2i}}{T_i^2(T_i-1)}}.$$

It follows a χ^2 distribution with degree of freedom $K - 1$ asymptotically under the null hypothesis.

	Treatment	No treatment	Row total
Case	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
Column total	M_{1i}	M_{2i}	T_i

Effect size and standard error

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- Why Effect size?

	Treatment	No treatment	Row total
Case	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
Column total	M_{1i}	M_{2i}	T_i

- Odds ratio (OR): $SE_{LogOR_i} = \sqrt{\frac{1}{A_i} + \frac{1}{B_i} + \frac{1}{C_i} + \frac{1}{D_i}}$
- Risk Ratio (RR): $SE_{LogRR_i} = \sqrt{\frac{1}{A_i} + \frac{1}{N_{1i}} + \frac{1}{C_i} + \frac{1}{N_{2i}}}$
- Risk Difference (RD): $SE_{RD} = \sqrt{\frac{A_i * B_i}{N_{1i}} + \frac{C_i * D_i}{N_{2i}}}$

Effect size and standard error

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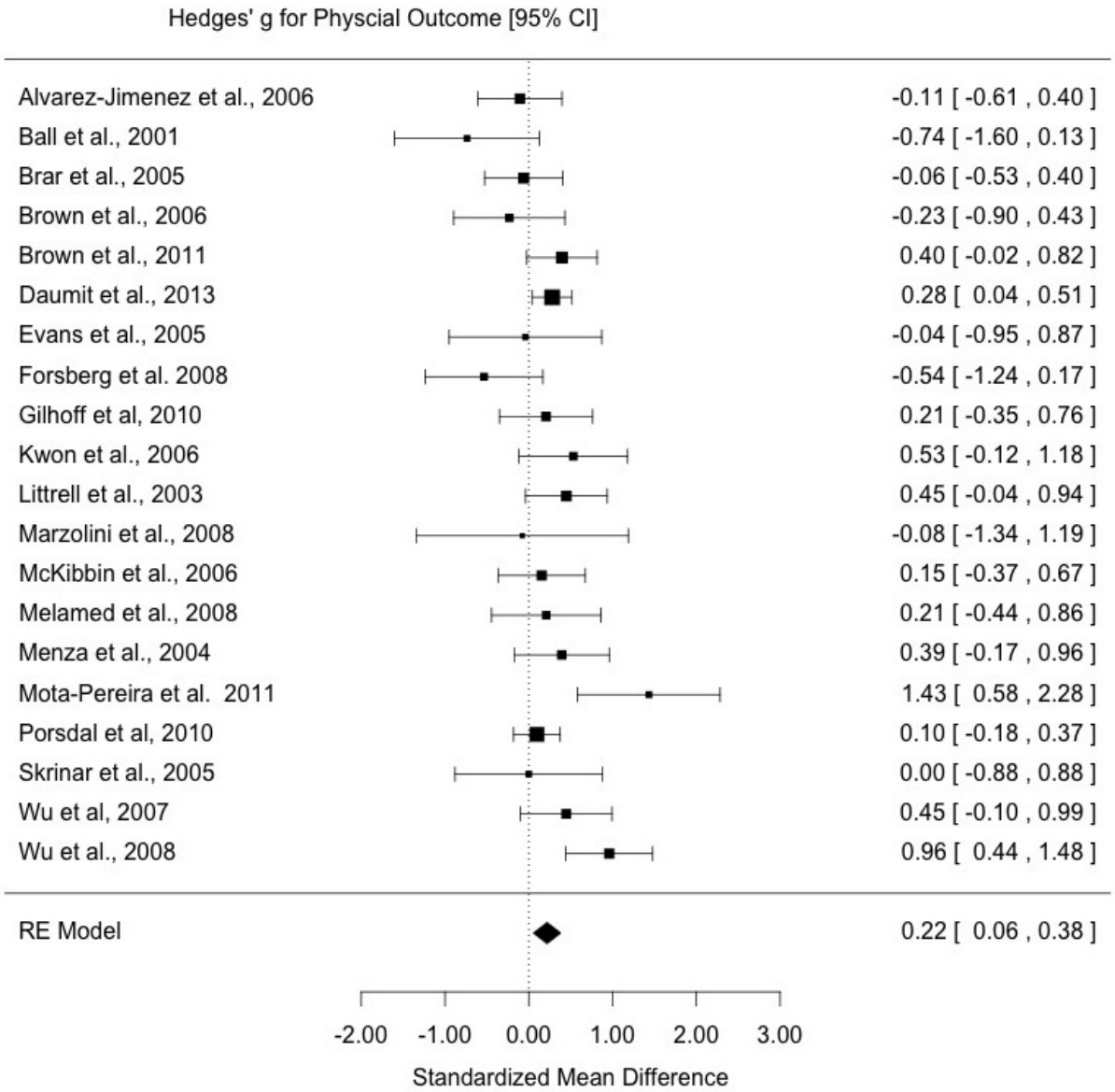

Coding reliability: Agreement rate

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- Require double-code study information.
- Agreement rate $= \frac{\text{Num of studies with same codings}}{\text{Total Num of studies}}$

Coding reliability: Cohen's Kappa Statistic

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Cohen's kappa coefficient, κ, is a statistic which measures inter-rater agreement for qualitative (categorical) items. It is generally thought to be a more robust measure than simple percent agreement calculation, since κ takes into account the possibility of the agreement occurring by chance. Cohen's kappa measures the agreement between two raters who each classify N items into C mutually exclusive categories.
The definition of κ is:

$$\kappa \equiv \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

where p_o is the relative observed agreement among raters (identical to accuracy), and p_e is the hypothetical probability of chance agreement, using the observed data to calculate the probabilities of each observer randomly saying each category. If the raters are in complete agreement then $\kappa = 1$. If there is no agreement among the raters other than what would be expected by chance (as given by p_e), $\kappa \leq 0$. For categories k, number of items N and n_{ki} the number of times rater i predicted category k:

$$p_e = \frac{1}{N^2} \sum_k n_{k1} n_{k2}$$

Coding reliability:Cohen's Kappa Statistic

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Suppose that you were analyzing data related to a group of 94 people applying for a grant. Each grant proposal was read by two readers and each reader either said "Yes" or "No" to the proposal. Suppose the disagreement count data were as follows, where A and B are readers, data on the main diagonal of the matrix (top left-bottom right) the count of agreements and the data off the main diagonal, disagreements:

		B	
		Yes	No
A	Yes	a	b
	No	c	d

e.g.

		B	
		Yes	No
A	Yes	20	5
	No	10	15

Coding reliability: Cohen's Kappa Statistic

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The observed proportionate agreement is:

$$p_o = \frac{a+d}{a+b+c+d} = \frac{20+15}{50} \approx 0.70$$

To calculate p_e (the probability of random agreement), the expected probability that both would say yes at random is:

$$p_{\text{Yes}} = \frac{a+b}{a+b+c+d} \cdot \frac{a+c}{a+b+c+d} = 0.5 * 0.6 = 0.3$$

Similarly:

$$p_{\text{No}} = \frac{c+d}{a+b+c+d} \cdot \frac{b+d}{a+b+c+d} = 0.5 * 0.4 = 0.2$$

Overall random agreement probability is the probability that they agreed on either Yes or No, i.e.:

$$p_e = p_{\text{Yes}} + p_{\text{No}} = 0.3 + 0.2 = 0.5$$

So now applying our formula for Cohen's Kappa we get:

$$\kappa = \frac{p_o - p_e}{1 - p_e} = \frac{0.70 - 0.50}{1 - 0.50} = 0.40$$

Steps in a meta-analysis

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Exercise

- Formulation of the problem
- Search of literature
- Selection of studies ('incorporation criteria')
  1. Based on quality criteria, e.g. the requirement of randomization and blinding in a clinical trial
  2. Selection of specific studies on a well-specified subject, e.g. the treatment of breast cancer.
  3. Decide whether unpublished studies are included to avoid publication bias (file drawer problem)
- Decide which dependent variables or summary measures are allowed. For instance:
- Homogeneity test: selection of a meta-regression statistical model: e.g. simple regression, fixed-effect meta-regression or random-effect meta-regression.

Search of literature

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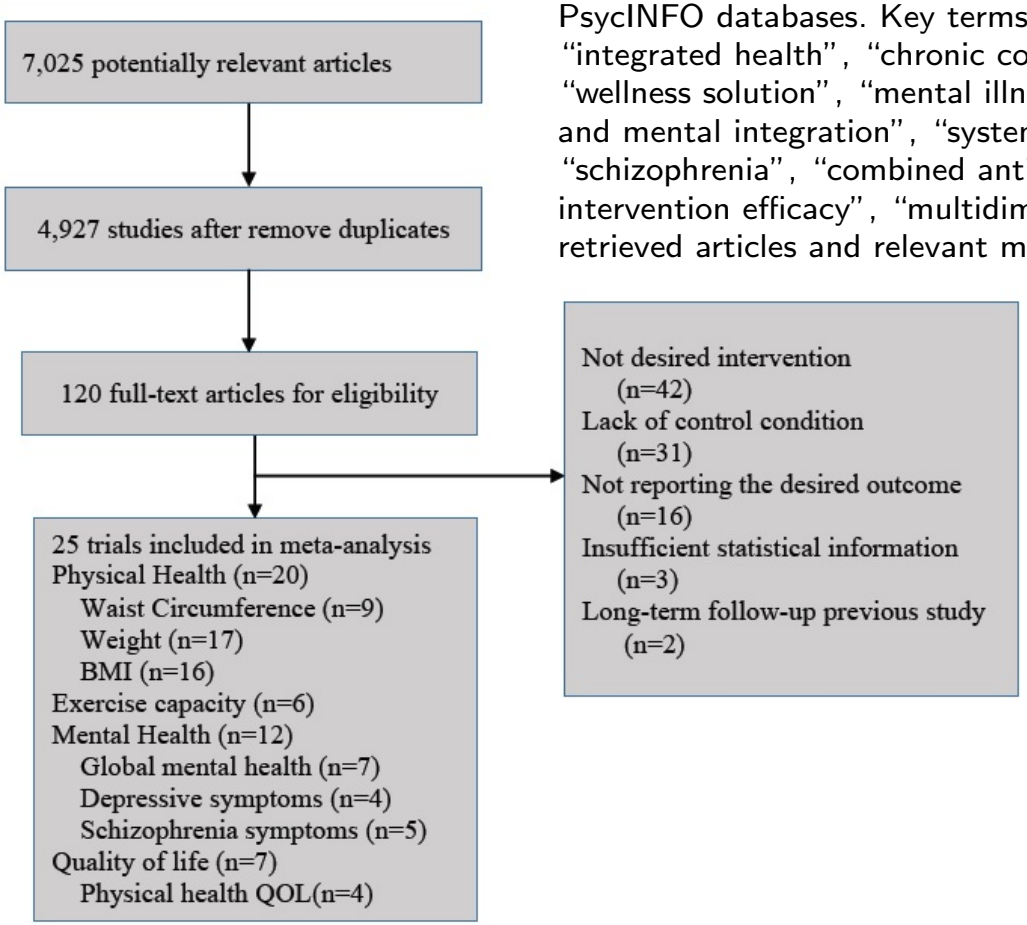
Figure 1. Flow of study selection



Psychosocial/Behavioral Interventions for People with Mental Illness: An electronic database search was conducted from earliest record to September 2016 using MEDLINE, EMBASE, CLINAHL, BNI and PsycINFO databases. Key terms used in electronic searches included "integrated health", "chronic conditions", "lifestyle intervention", "wellness solution", "mental illness", "psychiatric conditions", "physical and mental integration", "systematic health intervention", "schizophrenia", "combined antipsychotic treatment", "interactive intervention efficacy", "multidimensional clinic study". Reference lists of retrieved articles and relevant meta-analysis studies were also searched.

Selection of studies

Figure 1. Inclusion criteria

Design
- Experimental study or quasi experimental study

Participants
- Adults, aged 18 years or greater
- DSM, EPDS or other diagnosis of a mental illness

Interventions
- Psychosocial/Behavioral Intervention

Outcome measures
- Physical Health, e.s., WC, BMI, WT, physical health QOL

Breslow-Day statistic in homogeneity test of odds ratio

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In Statistical Methods of Cancer Research; Volume 1 (https://www.iarc.fr/en/publications/pdfs-online/stat/sp32/SP32.pdf) The analysis of case-control studies the authors Breslow and Day derive a statistic to test for the homogeneity of combining strata into an odds ratio (equation 4.30). Given the value of the statistic, the test determines if it is appropriate to combine strata together and compute a single odds ratio.

	Disease present	Disease absent	Totals
Risk factor present (success)	A	B	R1
Risk factor absent (failure)	C	D	R2
Totals	C1	C2	N

the odds ratio for getting a disease with a risk factor compared to not having the risk factor is:

$$\psi = (A * D)/(B * C)$$

Breslow-Day statistic in homogeneity test of odds ratio

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if we have multiple contingency tables (for example, we stratify by age group), we can use the Mantel-Haenzel estimate to compute the odds ratio across all I strata:

$$\psi_{mh} = \frac{\sum_{i=1}^{I} A_i D_i / N_i}{\sum_{i=1}^{I} B_i C_i / N_i}.$$

For each contingency table we have $R1 = A + B, R2 = C + D$ and $C1 = A + C$, so we can express the expected odds ratio for that table in terms of the totals:

$$\psi_{mh} = \frac{AD}{BC} = \frac{\tilde{A}(R2 - C1 + \tilde{A})}{(R1 - \tilde{A})(C1 - \tilde{A})}$$

	Disease present	Disease absent	Totals
Risk factor present (success)	A	B	R1
Risk factor absent (failure)	C	D	R2
Totals	C1	C2	N

which gives a quadratic equation for $\tilde{A}$. Let a be the solution to this quadratic equation (only one root gives a reasonable answer).

Breslow-Day statistic in homogeneity test of odds ratio

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Thus a reasonable test for the adequacy of the assumption of a common odds ratio is to sum up the squared deviation; of observed and fitted values, each standardized by its variance:

$$\chi^2 = \sum_{i=1}^{I} \frac{(a_i - A_i)^2}{V_i}$$

where the variance is:

$$V_i = \left(\frac{1}{A_i} + \frac{1}{B_i} + \frac{1}{C_i} + \frac{1}{D_i} \right)^{-1}$$

	Disease present	Disease absent	Totals
Risk factor present (success)	A	B	R1
Risk factor absent (failure)	C	D	R2
Totals	C1	C2	N

If the homogeneity assumption is valid, and the size of the sample is large relative to the number of strata, this statistic follows an approximate chi-square distribution on $I - 1$ degrees of freedom and thus a p-value can be determined.

Breslow-Day statistic in homogeneity test of odds ratio

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If instead we divide the I strata into H groups and we suspect the odds ratios are homogeneous within groups but not between them, Breslow and Day give an alternative statistic (equation 4.32):

$$\chi^2 = \sum_{h=1}^{H} \frac{\left(\sum_{i \in h} a_i - A_i\right)^2}{\sum_{i \in h} V_i}$$

	Disease present	Disease absent	Totals
Risk factor present (success)	A	B	R1
Risk factor absent (failure)	C	D	R2
Totals	C1	C2	N

where the i summations are over strata in the hth group with the statistic being chi-square with only $H - 1$ degrees of freedom (I assume a different Mantel-Haenzel estimate is computed within each group).

Studies on the Effectiveness of the BCG Vaccine Against Tuberculosis

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Results from 13 studies examining the effectiveness of the Bacillus Calmette-Guerin (BCG) vaccine against tuberculosis.

variable	discreption
trial	trial number
author	author(s)
year	publication year
tpos	# of TB positive cases in the treated (vaccinated) group
tneg	# of TB negative cases in the treated (vaccinated) group
cpos	# of TB positive cases in the control (non-vaccinated) group
cneg	# of TB negative cases in the control (non-vaccinated) group
ablat	absolute latitude of the study location (in degrees)
alloc	method of treatment allocation (random, alternate, or systematic assignment)

Calculating Effect size

```
library(metafor)
### load BCG vaccine data
dat <- get(data(dat.bcg))
### calculate log relative risks and corresponding sampling variances
dat <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat.bcg)
head(dat)
```

```
##   trial               author year tpos  tneg cpos  cneg ablat     alloc
## 1     1              Aronson 1948    4   119   11   128    44    random
## 2     2     Ferguson & Simes 1949    6   300   29   274    55    random
## 3     3      Rosenthal et al 1960    3   228   11   209    42    random
## 4     4    Hart & Sutherland 1977   62 13536  248 12619    52    random
## 5     5 Frimodt-Moller et al 1973   33  5036   47  5761    13 alternate
## 6     6      Stein & Aronson 1953  180  1361  372  1079    44 alternate
##         yi     vi
## 1 -0.8893 0.3256
## 2 -1.5854 0.1946
## 3 -1.3481 0.4154
## 4 -1.4416 0.0200
## 5 -0.2175 0.0512
## 6 -0.7861 0.0069
```

display the random-effects meta-analysis result

```
### random-effects model
library(metafor)
```

```
## Loading required package: Matrix
```

```
## Loading 'metafor' package (version 1.9-9). For an overview
## and introduction to the package please type: help(metafor).
```

```
res <- rma(yi, vi, data=dat)
res
```

```
##
## Random-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.3132 (SE = 0.1664)
## tau (square root of estimated tau^2 value):      0.5597
## I^2 (total heterogeneity / total variability):   92.22%
## H^2 (total variability / sampling variability):  12.86
##
## Test for Heterogeneity:
## Q(df = 12) = 152.2330, p-val < .0001
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##  -0.7145   0.1798  -3.9744   <.0001  -1.0669  -0.3622      ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
### average relative risk with 95% CI
predict(res, transf=exp)
```

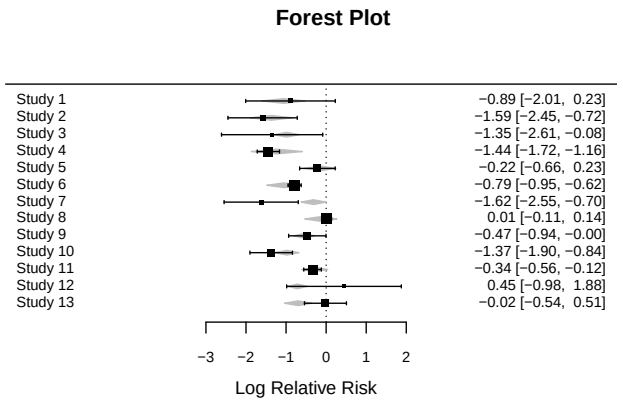
display the meta-regression result

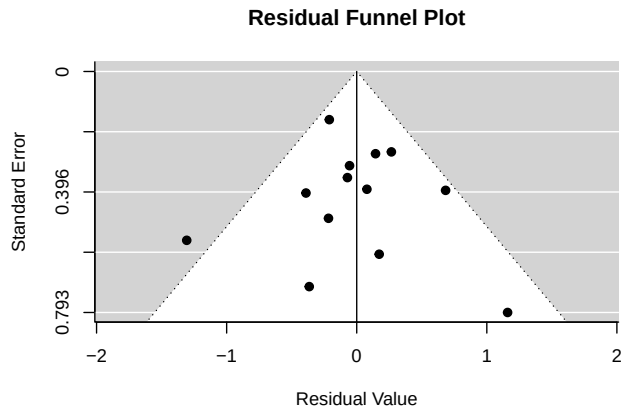
```
library(metafor)
res <- rma(yi, vi, mods = ~ ablat + year, data=dat)
res
```

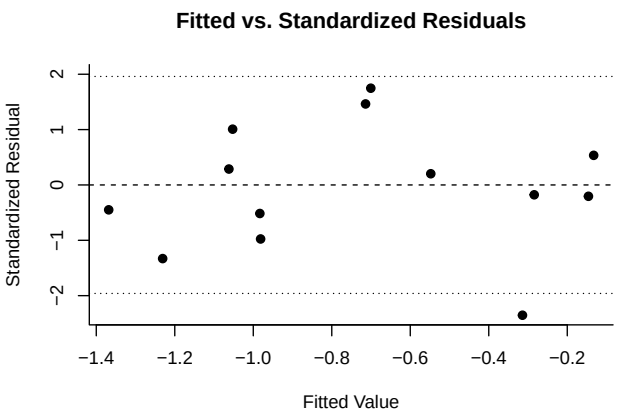
```
##
## Mixed-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of residual heterogeneity):     0.1108 (SE = 0.0845)
## tau (square root of estimated tau^2 value):             0.3328
## I^2 (residual heterogeneity / unaccounted variability): 71.98%
## H^2 (unaccounted variability / sampling variability):   3.57
## R^2 (amount of heterogeneity accounted for):            64.63%
##
## Test for Residual Heterogeneity:
## QE(df = 10) = 28.3251, p-val = 0.0016
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 12.2043, p-val = 0.0022
##
## Model Results:
##
##          estimate       se     zval    pval     ci.lb    ci.ub
## intrcpt   -3.5455  29.0959  -0.1219  0.9030  -60.5724  53.4814
## ablat     -0.0280   0.0102  -2.7371  0.0062   -0.0481  -0.0080  **
## year       0.0019   0.0147   0.1299  0.8966   -0.0269   0.0307
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

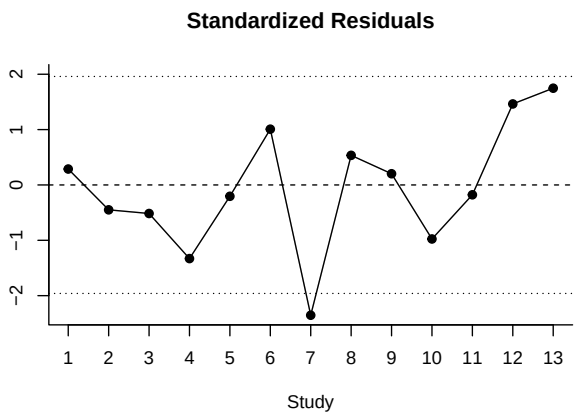
Forest and Funnel Plot

```
library(metafor)
plot(res)
```









In class exercise

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Using the same data but conduct meta-analysis using Odds Ratio

Take home exercise

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Using the same data but conduct meta-analysis using Risk Difference

Class over

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