Meta-analysis

A Summary of Summaries

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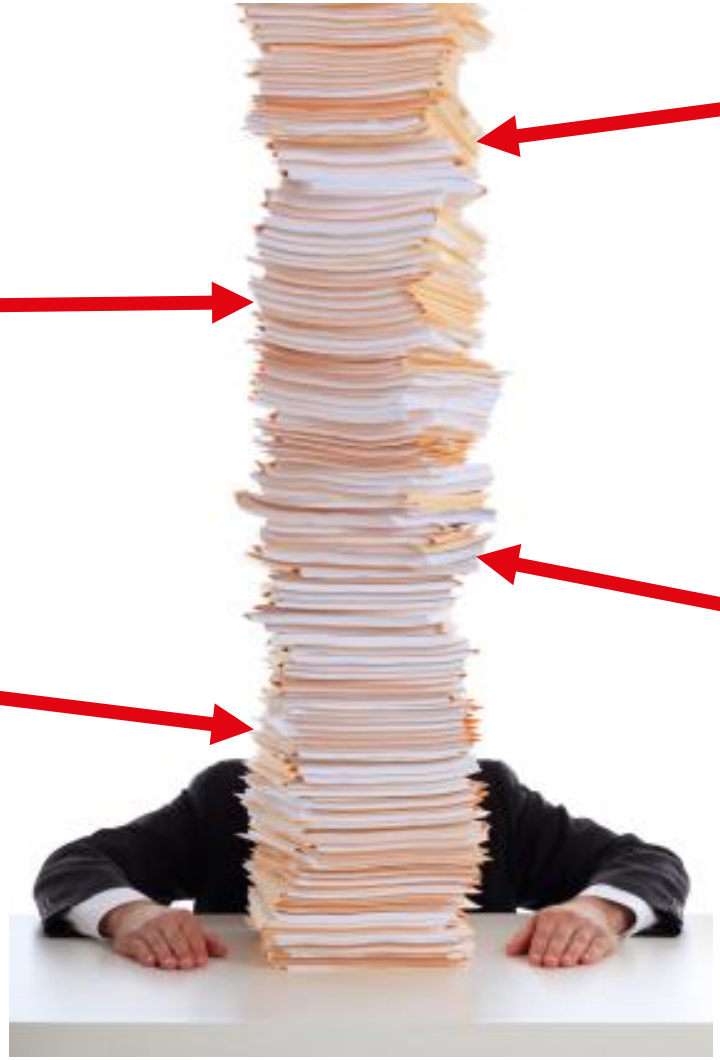
The Task



Different Methods

Different Countries

Different Decades

Different
Experimental Design

W Meta-Analysis

Summarize or combine information from multiple studies to obtain information that is applicable to a larger population

How is Meta-analysis different from mixed models?

It's all about assumptions…

Homoscedasticity vs. Heteroscedasticity

- Previously assumed the variance of the errors (ε_i) was a constant value
  - Homoscedastic
- Even in a mixed-model, the errors are usually assumed to have a constant variance
- In meta-analysis, we know that is not true because each observation has a different SE
  - Heteroscedastic

$$\sigma^2\{\varepsilon_i\} = \sigma^2$$

$$\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$$

$$\varepsilon_i \sim N\left(0, \sigma_{\varepsilon_i}^2\right)$$

Two approaches to Heteroscedasticity

metafor package

Use sampling variances collected from the literature ← Variance is known

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2\right)$$

Variance is know up to a constant → Collected sampling variances are multiplied by an estimated residual variance

lme4, nlme

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2 \sigma_R^2\right)$$

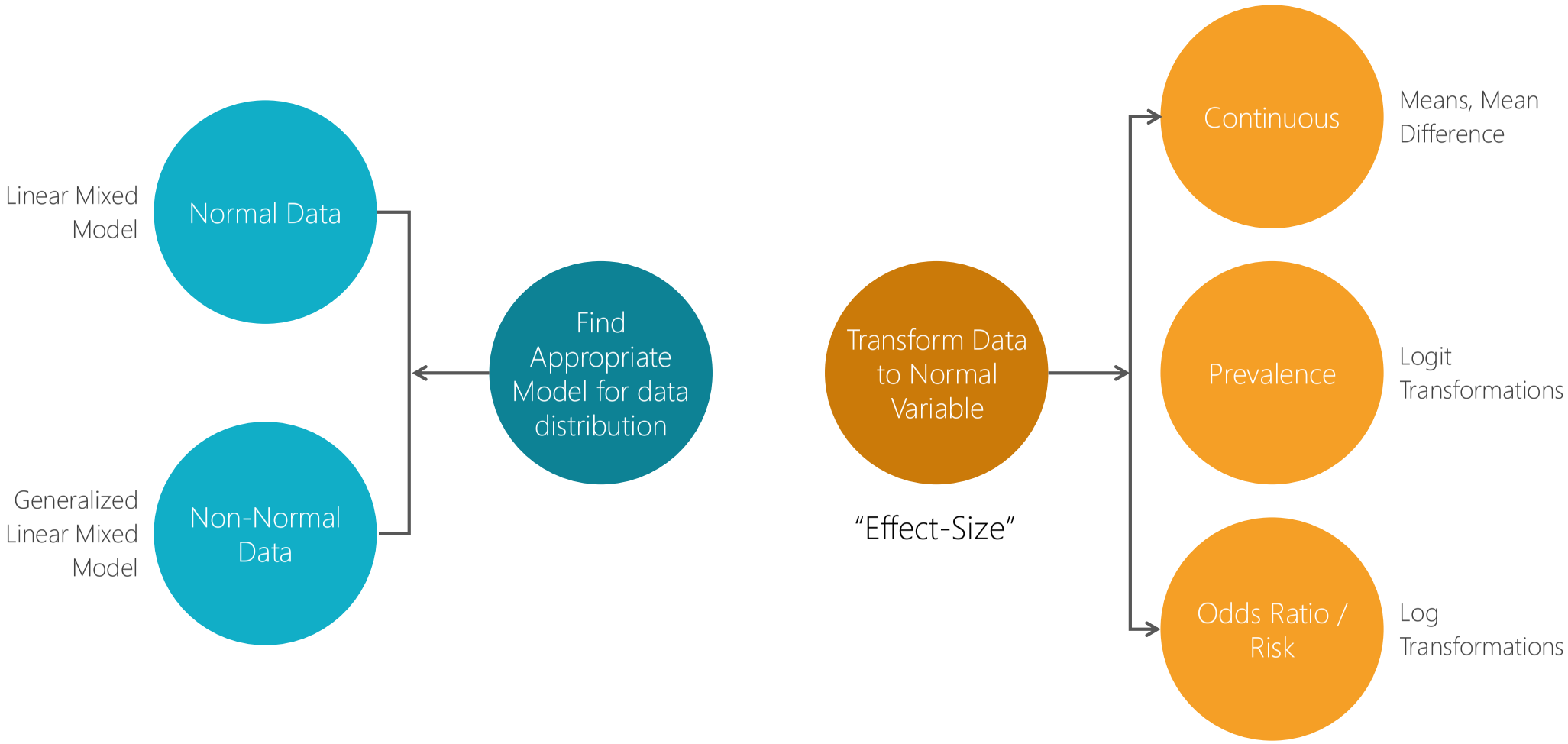
Types of Data

Variable Type	Example Measurements	Range	Distribution	Comments
Continuous	Milk production, Excretion, Concentrations, rates	$-\infty$, ∞ (real numbers)	Normal	Physiological range is often limited to $(0, \infty)$
Counts	Number of event occurrences (e.g. visits to bunk,	0 , ∞ (integers)	Poisson	Need to specify unit of time associated with event data
Prevalence/Risk	Disease Incidence, Conception	[0, 1] / $[0, \infty]$ (real numbers)	Binomial, Multinomial	

Check your Data

Even when reported data is, on the surface, the same estimate or measurement, differences in methods of collection, chemical analysis, statistical model, and units can create large differences in the relationship of the reported value to the underlying 'true' value. Being aware of these differences is key to conducting a sound meta-analysis so always check, and double check your data!

Two approaches to Meta-Data



W Effect Size

Provide a **common metric** to compare the direction and strength of a relationship between variables **across studies**

(Berben et al., 2012. Int. J. of Nursing Studies)

Effect Size Examples

Reported Metrics

- Continuous variables
  - Milk production
  - body weight gain
  - fecal N
  - FA concentration in milk or blood
  - Cortisol concentration in feces

- Check the units and methods of collection!

Effect Size

- Treatment mean: $\bar{X}_1$
- Mean difference : $\mathrm{MD}_{1-2} = \bar{X}_1 - \bar{X}_2$
- Standardized Mean Difference: $\mathrm{sMD}_{1-2} = \frac{\bar{X}_1 - \bar{X}_2}{s_{pooled}}$

Standard Error

- Treatment mean: s_1
- Mean difference : $s_{MD} = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$
- St. Mean Difference:

$$s_{sMD} = \sqrt{\frac{n_1 + n_2}{n_1 n_2} + \frac{s\mathrm{MD}_{1-2}^2}{2(n_1 + n_2)}}$$

Effect Size Examples

Reported Metrics

- Counts of Events/Non-events
  - Disease Incidence
  - Conception

	Disease	No Disease	Sample Size
Treatment	t_1	t_2	n_1
Control	c_1	c_2	n_2

Effect Size

- Logit Prevalence: $\ln\left(\frac{t_1/n_1}{1-t_1/n_1}\right)$
- Log Odds Ratio: $\ln\left(\frac{t_1/t_2}{c_1/c_2}\right) = \ln\left(\frac{t_1 c_2}{t_2 c_1}\right)$
- Log Risk Ratio: $\ln\left(\frac{t_1/n_1}{c_1/n_2}\right) = \ln\left(\frac{t_1 n_2}{c_1 n_1}\right)$

Standard Error

- logitPrevalence: $\frac{1}{n_1+n_2} + \frac{1}{(n_1+n_2)\left(1-t_1/n_1\right)}$
- lnOR: $s_{sMD} = \sqrt{\frac{1}{t_1} + \frac{1}{t_2} + \frac{1}{c_1} + \frac{1}{c_2}}$
- lnRR: $s_{MD} = \sqrt{\frac{t_2}{t_1(n_1)} + \frac{c_2}{c_1(n_2)}}$

The Study Effect

- The study effect is analogous to a random effect as we have previously interpreted it.
- Can be a random effect on the overall mean (**intercept**) or a random effect on the overall mean and the treatment effect (**intercept and slope**)

<u>Eg. Random Intercept Model</u>

$$\sigma^2(Y_{ij}) = u + \sigma^2_{\varepsilon_i}$$

$$u_i \sim N(0, \sigma^2_u)$$

Otherwise it is very similar!

With some differences…

Meta-Analysis

What's the objective?

What information will the summary provide and how will it be used?

- Global Hypothesis testing
  - Combines outcomes of many studies for increased power and application to a broader population
- Prediction of a Biological response
  - Kind of like a Meta-regression which usually applies to a wider range of the independent variables.
- Secondary Measurement Summaries
  - Routinely measured values that are not the focus of the study can be summarized to lead to new hypotheses
- Parameterization of Mechanistic models
  - This can be similar to the objective of the biological response summarization but with a specific, quantitative application of the estimate

Meta-Analysis

What's the Objective?

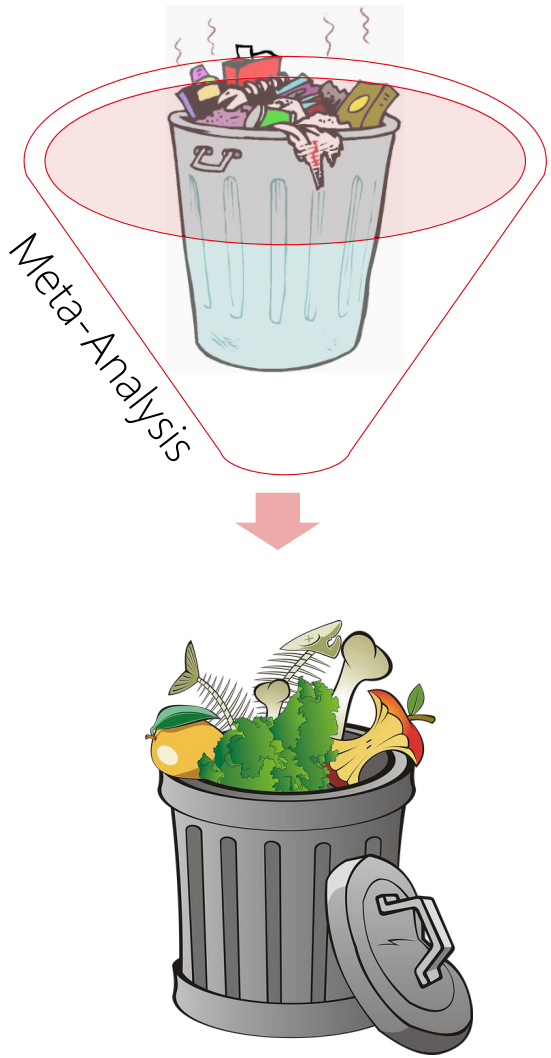
Before beginning, it's important to know how the model results will be used.

Data Exploration + Cleaning

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Data Exploration

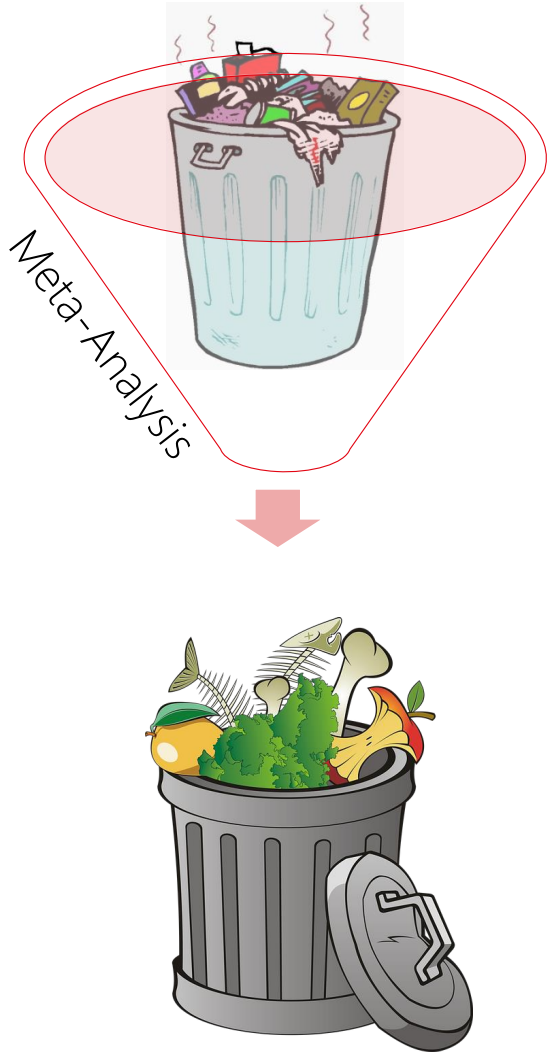
- Extension of the same data assessments used for regression
  - Additional data checking and cleaning to ensure accuracy and consistency
  - Account for intra-study vs. inter-study aspects of the data



Data Exploration

Data Cleaning

- Does each study include the minimal observations/reported measurements to meet the objectives.
- Expert review methods and quality of data
- Re-check data for accuracy of data transfer



Data Exploration

Sparse Data

Are there enough observations on all factor levels of the predictor variables? Are there a lot of studies with only two factor levels?

In this example there are only 2 observations for 'Treatment C'

Study	A	B	C	D	E
1	+	+	+		
2		+		+	+
3	+	+			
4		+	+		+
5	+			+	+
6	+	+		+	
7		+		+	+

Data Exploration

- If there is a curvilinear response, you need to ensure there are enough studies that have at least 3 factor levels

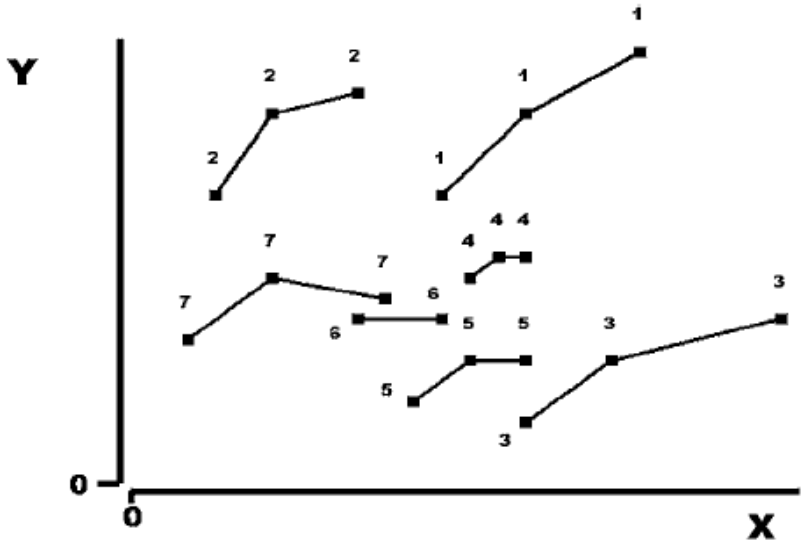


Figure 2 Example of a curvilinear intrastudy effect in the presence of a linear negative interstudy effect.

Sauvant et al., 2008

Data Exploration

- If the Intra-study Variability is low, you may choose to create a cut off for the lower limit of the predictor variable SE
  - However, this is not necessary if using a random effects model

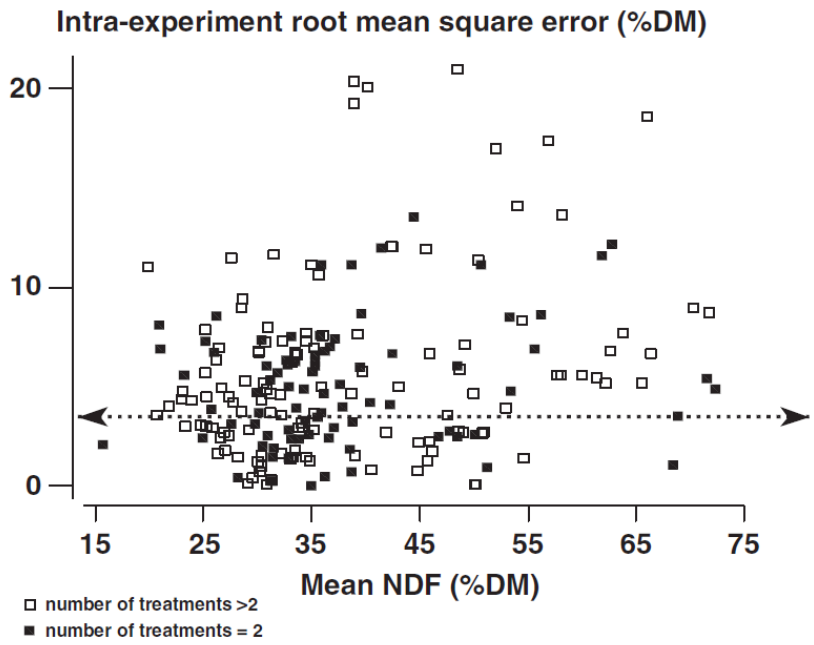
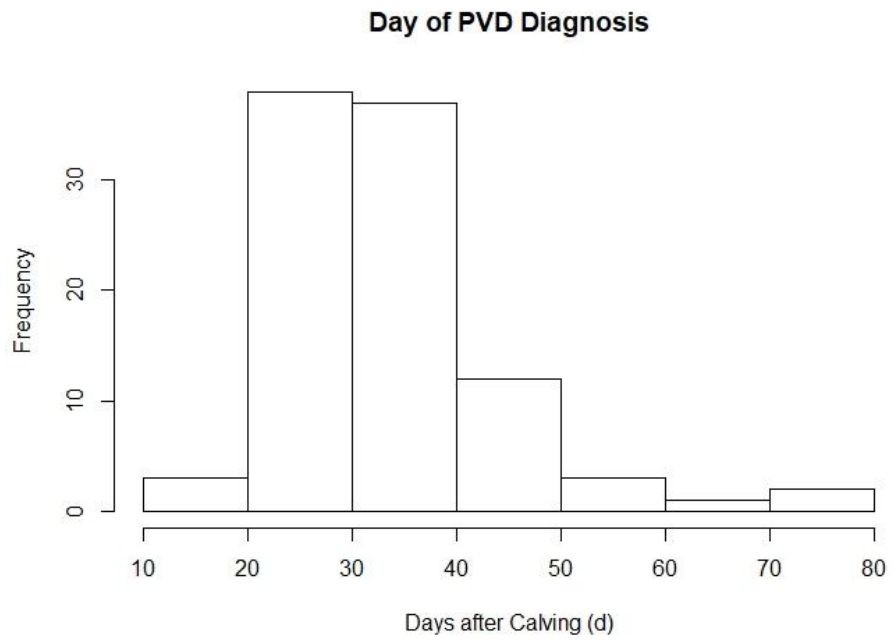


Figure 5 Intrastudy root mean square error of dietary neutral detergent fiber (NDF) and mean NDF of experiments designed to study the effects of NDF in cattle.

Sauvant et al., 2008

Data Exploration

- For continuous predictor variables, what does the distribution look like?
- Estimates will be more precise for values of the predictor variable that occur more frequently



Data Exploration

- Leverage – the influence of an observation on predicting the slope/response with respect to the predictor variable
  - The farther away from the mean, the higher the leverage is

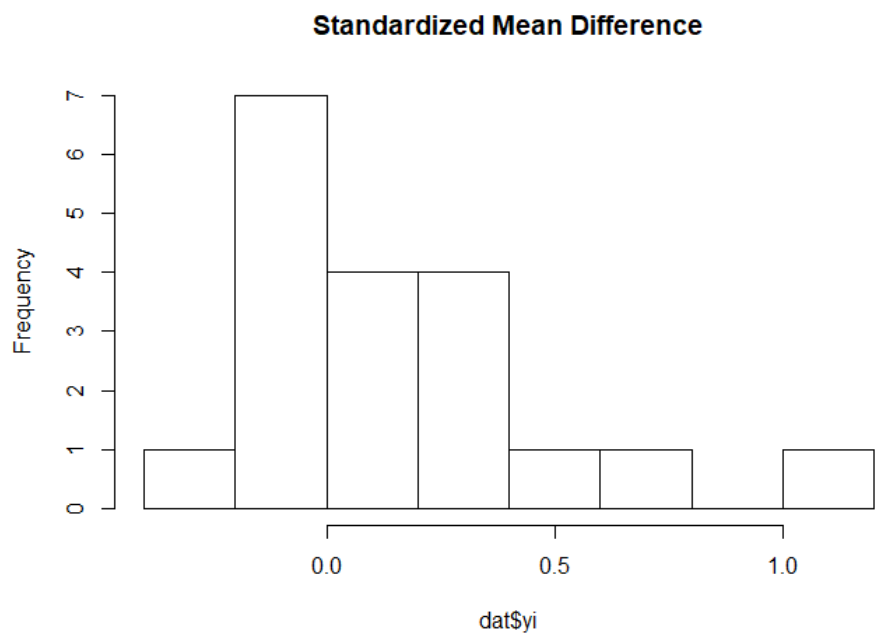
$$h_i = 1/n + (X_i - X_m)^2 / \Sigma(X_i - X_m)^2$$

- May choose to remove observations with high outlier leverage

Data Exploration

IQ Example

- Standardized mean difference of IQ scores
  - Analogous to any meta-analysis of continuous variables
  - 19 observations
- Effect Size =
  - $\frac{\bar{X}_1 - \bar{X}_2}{s_{pooled}}$
- Potential Fixed Effects:
  - Weeks of interaction with teacher (0-24)
  - Testing setting (group v. individual)
  - Tester blindness (blind v. aware)



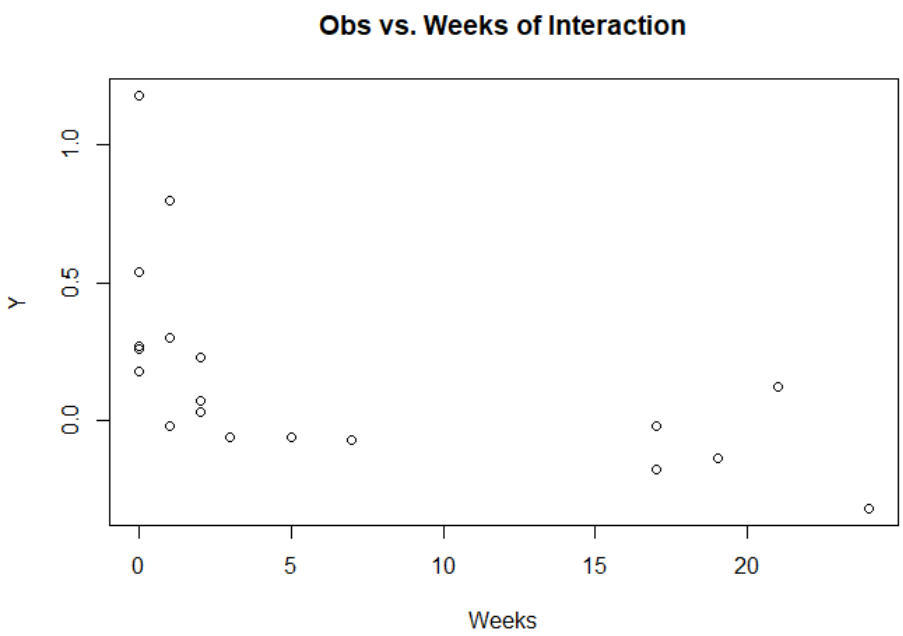
Data Exploration

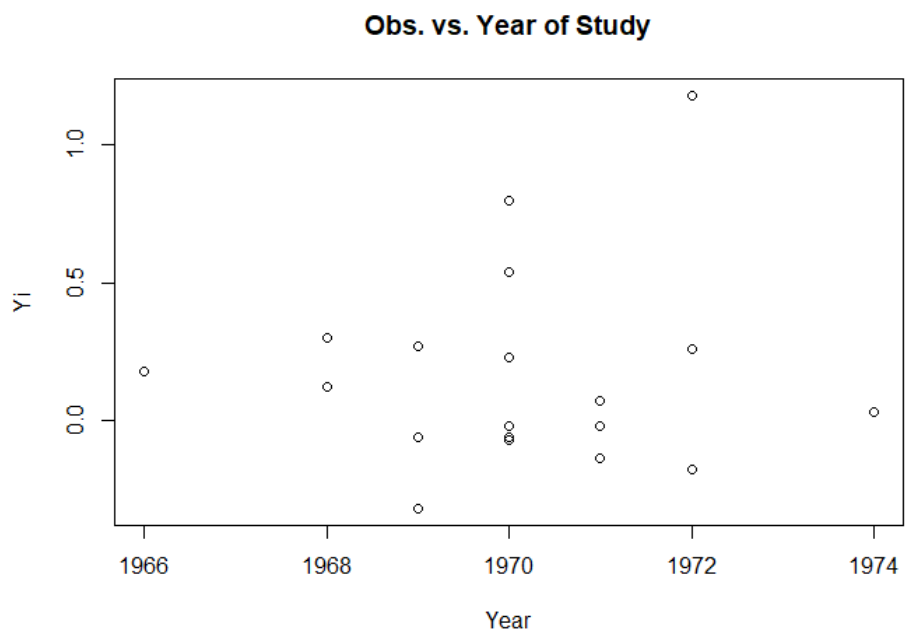
IQ Example

	study	author	year	weeks	setting	tester	n1i	n2i	yi	vi	sei
1	1	Rosenthal et al.	1974	2	group	aware	77	339	0.03	0.0156	0.12489996
2	2	Conn et al.	1968	21	group	aware	60	198	0.12	0.0216	0.14696938
3	3	Jose & Cody	1971	19	group	aware	72	72	-0.14	0.0279	0.16703293
4	4	Pellegrini & Hicks	1972	0	group	aware	11	22	1.18	0.1391	0.37296112
5	5	Pellegrini & Hicks	1972	0	group	blind	11	22	0.26	0.1362	0.36905284
6	6	Evans & Rosenthal	1969	3	group	aware	129	348	-0.06	0.0106	0.10295630
7	7	Fielder et al.	1971	17	group	blind	110	636	-0.02	0.0106	0.10295630
8	8	Claiborn	1969	24	group	aware	26	99	-0.32	0.0484	0.22000000

Data Exploration

IQ Example



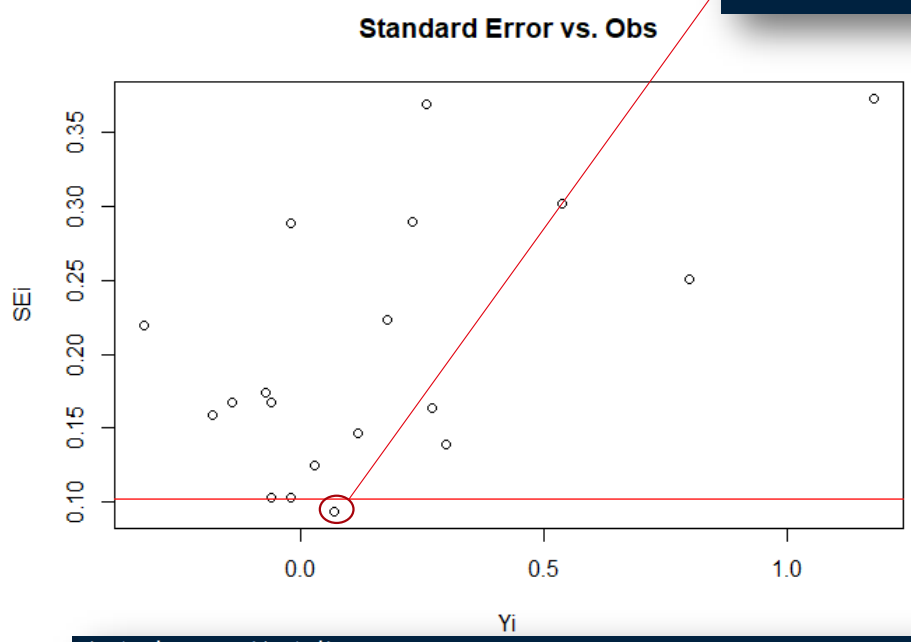


Data Exploration

IQ Example

- Should this observation be removed?

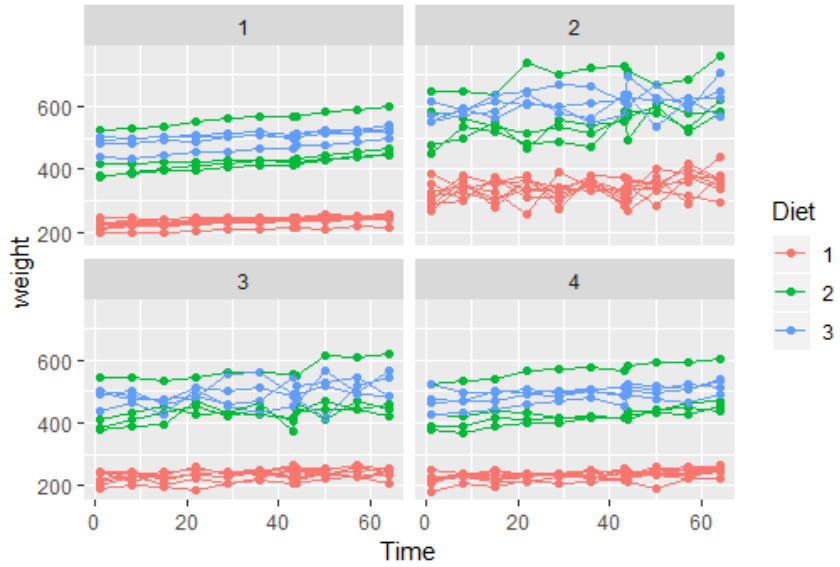
```
study              author year
   18 Fleming & Anttonen 1971
```




```
dat$sei = sqrt(dat$vi)
plot(sei~yi, dat, xlab = ("Yi"), ylab = "SEi", main = "Standard Error vs. Obs")
sei.q05 = quantile(dat$sei, 0.05)
abline(h = sei.q05, col = "red")
dat[which(dat$sei < sei.q05), c("study", "author", "year")]
```

Rat Growth Example

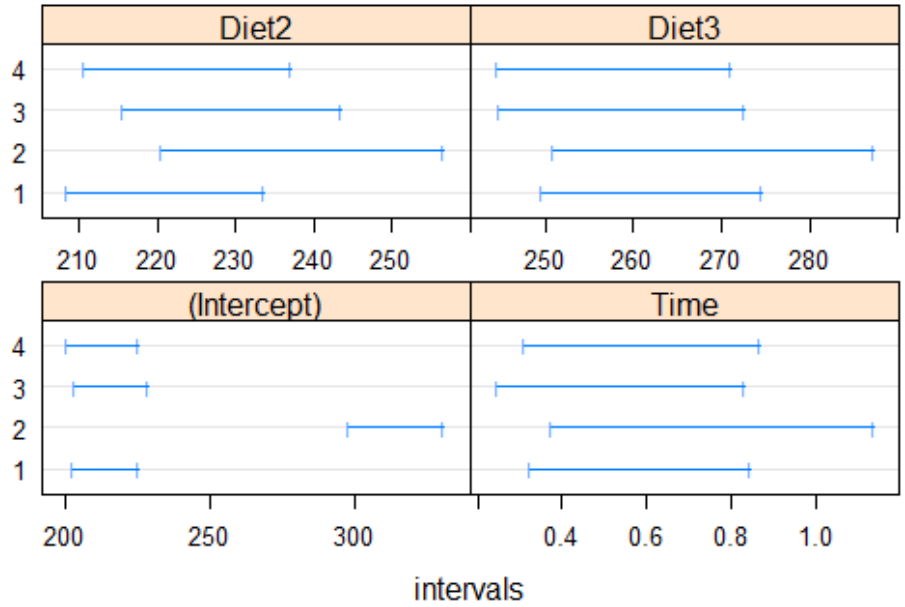
- Now have 4 studies with the same diets but conducted in different locations with different strains and different methodologies



Dose Example

- Is there a study effect?

```
lm.studies = lmList(weight ~ Time + Diet |study, data = datnew )
cints = confint(lm.studies)
plot(cints)
```



Meta-Analysis

What's the Objective?

Before beginning, it's important to know how the model results will be used.

Data Exploration

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Model Fitting

metafor vs. linear models, fixed vs. random effects models, choice of weights

- Lme4/nlme vs. metafor

Two Fitting Methods

```
res.fe <- rma(yi, vi, data=dat, method="FE")
res.fe
```

```
res.lm <- lm(yi ~ 1, weights = 1/vi, data=dat)
summary(res.lm)
```

metafor package

Use sampling variances collected from the literature ← Variance is known

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2\right)$$

Variance is know up to a constant → Collected sampling variances are multiplied by an estimated residual variance

lme4, nlme

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2 \sigma_R^2\right)$$

The choice of package to use in R to fit your meta-analysis depends on your theoretical approach to the variance structure of the data.

Two Fitting Methods

Linear Mixed Model

Normal Data

```
yi = log(1/(1-pvd$Prevalence...))
```

Find Appropriate for data distribution

Generalized Linear Mixed Model

Non-Normal Data

```
esdat<- escalc(measure = "PFT", xi = Prevalence...,
               ni = Sample.Size, data = pvd , add = 0)
```

Transform Data to Normal Variable

"Effect-Size"

Continuous

Means, Mean Difference

Prevalence

Logit Transformations

Odds Ratio / Risk

Log Transformations

OR, if your data is not normal, the choice may depend on the ease/ability to represent your data in a GLM model or transform the data yourself

Fixed Effects Model – IQ Example

```
> fe.met <- rma(yi, vi, data = dat, method = "FE")
> summary(fe.met)

Fixed-Effects Model (k = 19)

  logLik  deviance       AIC       BIC      AICc
 -3.4588   35.8295    8.9176    9.8620    9.1529

Test for Heterogeneity:
Q(df = 18) = 35.8295, p-val = 0.0074

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.0604  0.0365  1.6553  0.0979  -0.0111  0.1318  .
```

Model:

$$y_i = \theta + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

Two Fitting Methods
Metafor

Random Effects Model – IQ Example

```
> re.met <- rma(yi, vi, data = dat)
> summary(re.met)

Random-Effects Model (k = 19; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -3.7360    7.4721   11.4721   13.2528   12.2721

tau^2 (estimated amount of total heterogeneity): 0.0188 (SE = 0.0155)
tau (square root of estimated tau^2 value):      0.1372
I^2 (total heterogeneity / total variability):   41.86%
H^2 (total variability / sampling variability):  1.72

Test for Heterogeneity:
Q(df = 18) = 35.8295, p-val = 0.0074

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.0837  0.0516  1.6208  0.1051  -0.0175  0.1849
```

Model:

$$y_i = \theta + u_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

$$u_i \sim N(0, \sigma_s^2)$$

Mixed Effects Model – IQ Example

```
> me.met <- rma(yi~weeks, vi, data = dat)
> summary(me.met)

Mixed-Effects Model (k = 19; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -0.7144    1.4287    7.4287    9.9284    9.2749

tau^2 (estimated amount of residual heterogeneity):     0.0112 (SE = 0.0128)
tau (square root of estimated tau^2 value):             0.1057
I^2 (residual heterogeneity / unaccounted variability): 29.40%
H^2 (unaccounted variability / sampling variability):   1.42
R^2 (amount of heterogeneity accounted for):            40.63%

Test for Residual Heterogeneity:
QE(df = 17) = 27.6730, p-val = 0.0489

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 7.5094, p-val = 0.0061

Model Results:

         estimate      se    zval    pval    ci.lb    ci.ub
intrcpt    0.1942  0.0633  3.0649  0.0022   0.0700   0.3183  **
weeks     -0.0157  0.0057 -2.7403  0.0061  -0.0270  -0.0045  **
```

$$y_i = \theta + \beta X_i + u_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

$$u_i \sim N(0, \sigma_s^2)$$

Mixed Effects Model – IQ Example

Metafor

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> me.met <- rma(yi~weeks, vi, data = dat)
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         estimate      se     zval    pval    ci.lb    ci.ub
intrcpt    0.1942  0.0633   3.0649  0.0022   0.0700   0.3183  **
weeks     -0.0157  0.0057  -2.7403  0.0061  -0.0270  -0.0045  **
```

Assessing Heterogeneity

- In meta-analysis, heterogeneity refers to the amount of variation that is attributable to differences in studies
- There is no set number that can be used to indicate an 'acceptable amount' of heterogeneity because it is highly dependent on the system being studied
- Instead, heterogeneity is assessed in terms of
  - I^2: the amount of remaining heterogeneity as a proportion of the residual variance
  - R^2: the proportion of heterogeneity accounted for in the Full vs. Reduced model
  - Q-test – A Chi-squared test for the presence of heterogeneity

Two Fitting Methods
Metafor

TB Example

- 13 studies were collected of tuberculosis incidence for patients who were not vaccinated (control) and those who were (treatment)
- Observations from each study are from a 2 x 2 contingency table

$Study_i$	Vaccine	No-Vaccine
TB+	4	11
TB-	119	128

Log Odds Ratio: $\ln\left(\frac{t_1/t_2}{c_1/c_2}\right) = \ln\left(\frac{t_1 c_2}{t_2 c_1}\right) = \ln\left(\frac{4/119}{11/128}\right) = -0.939$

```
dat <- escalc(measure="OR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat)
```

Additional information is available on the year of the study, the latitude at which the study took place, and the method in which the vaccines were allocated to the patients (i.e. study design)

trial	author	year	tpos	tneg	cpos	cneg	ablat	alloc	yi	vi
1	Aronson	48	4	119	11	128	44	random	-0.93869414	0.357124952
2	Ferguson & Simes	49	6	300	29	274	55	random	-1.66619073	0.208132394
3	Rosenthal et al	60	3	228	11	209	42	random	-1.38629436	0.433413078
4	Hart & Sutherland	77	62	13536	248	12619	52	random	-1.45644355	0.020314413
5	Frimodt-Moller et al	73	33	5036	47	5761	13	alternate	-0.21914109	0.051951777

Fixed Effects Model – TB Example

```
> fe.mod <- rma(yi, vi, method = "FE", data = dat)
> summary(fe.mod)

Fixed-Effects Model (k = 13)

  logLik  deviance       AIC       BIC      AICc
-76.0290  163.1649  154.0580  154.6229  154.4216

Test for Heterogeneity:
Q(df = 12) = 163.1649, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.4361  0.0423  -10.3190  <.0001  -0.5190  -0.3533  ***
```

$$\widehat{y_i} = \ln(\widehat{\mathrm{OR}}_i) \rightarrow e^{\widehat{y_i}} = \widehat{\mathrm{OR}}_i$$

$$y_i = \theta + u_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

Two methods to back-transform the outputs

```
> predict(fe.mod, transf=exp)
   pred  ci.lb  ci.ub
 0.6465 0.5951 0.7024
> exp(fe.mod$beta); exp(fe.mod$ci.lb); exp(fe.mod$ci.ub)
             [,1]
intrcpt 0.6465278
[1] 0.5951285
[1] 0.7023662
```

**Note that the results are given in terms of the LOG odds ratio!!

Random Effects Model – TB Example

```
> re.mod <- rma(yi, vi, data = dat)
> summary(re.mod)

Random-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-12.5757   25.1513   29.1513   30.1211   30.4847

tau^2 (estimated amount of total heterogeneity):  0.3378 (SE = 0.1784)
tau (square root of estimated tau^2 value):       0.5812
I^2 (total heterogeneity / total variability):    92.07%
H^2 (total variability / sampling variability):   12.61

Test for Heterogeneity:
Q(df = 12) = 163.1649, p-val < .0001

Model Results:

estimate      se    zval    pval    ci.lb    ci.ub
 -0.7452  0.1860  4.0057  <.0001  -1.1098  -0.3806  ***
```

$$y_i = \theta + u_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

$$u_i \sim N(0, \sigma_s^2)$$

Two methods to back-transform the outputs

```
> predict(re.mod, transf=exp)
   pred  ci.lb  ci.ub  cr.lb  cr.ub
 0.4746 0.3296 0.6835 0.1435 1.5696
> exp(re.mod$beta); exp(re.mod$ci.lb); exp(re.mod$ci.ub)
             [,1]
intrcpt 0.4746499
[1] 0.3296296
[1] 0.6834719
```

Mixed Effects Model – TB Example

```
> me.mod <- rma(yi~ablat, vi, data = dat)
> summary(me.mod)

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -7.9358   15.8717   21.8717   23.0653   25.3002

tau^2 (estimated amount of residual heterogeneity):     0.0504 (SE = 0.0449)
tau (square root of estimated tau^2 value):             0.2246
I^2 (residual heterogeneity / unaccounted variability):
H^2 (unaccounted variability / sampling variability):   2.35
R^2 (amount of heterogeneity accounted for):            85.06%

Test for Residual Heterogeneity:
QE(df = 11) = 25.0954, p-val = 0.0088

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 25.2424, p-val < .0001

Model Results:

         estimate      se     zval    pval    ci.lb    ci.ub
intrcpt    0.3010  0.2146   1.4025  0.1608  -0.1197   0.7217
ablat     -0.0315  0.0063  -5.0242  <.0001  -0.0438  -0.0192  ***
```

$$y_i = \theta + \beta X_i + u_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \mathrm{SE}_i^2)$$

$$u_i \sim N(0, \sigma_s^2)$$

```
> predict(me.mod, transf=exp)
     pred  ci.lb  ci.ub  cr.lb  cr.ub
1  0.3374 0.2640 0.4313 0.2038 0.5585
2  0.2385 0.1681 0.3385 0.1359 0.4186
3  0.3594 0.2856 [illegible] 0.2187 0.5905
4  0.2622 0.1905 0.360[illegible] 0.1522 0.4516
5  0.8968 0.6741 1.193[illegible] 0.5307 1.5156
6  0.3374 0.2640 0.43[illegible] 0.2038 0.5585
7  0.7422 0.5874 0.[illegible]8 0.4509 1.2219
8  0.8968 0.6741 1.[illegible]932 0.5307 1.5156
9  0.5767 0.4772 0.[illegible]70 0.3571 0.9313
10 0.3594 0.2856 0.4522 0.2187 0.5905
11 0.7660 0.6015 0.[illegible]54 0.4636 1.2657
12 0.4773 0.3964 0.5747 0.2960 0.7697
13 0.4773 0.3964 0.5747 0.2960 0.7697
```

When using the predict() function on models with independent variables, it will return a prediction for each observed level of the independent variable

Mixed Effects Model – TB Example

```
> me.mod <- rma(yi~ablat, vi, data = dat)
> summary(me.mod)

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -7.9358   15.8717   21.8717   23.0653   25.3002

tau^2 (estimated amount of residual heterogeneity):     0.0504 (SE = 0.0449)
tau (square root of estimated tau^2 value):             0.2246
I^2 (residual heterogeneity / unaccounted variability):  97.99%
H^2 (unaccounted variability / sampling variability):   2.35
R^2 (amount of heterogeneity accounted for):            85.06%

Test for Residual Heterogeneity:
QE(df = 11) = 25.0954, p-val = 0.0088

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 25.2424, p-val < .0001

Model Results:

         estimate      se    zval    pval    ci.lb    ci.ub
intrcpt    0.3010  0.2146  1.4025  0.1608  -0.1197   0.7217
ablat     -0.0315  0.0063 -5.0242  <.0001  -0.0438  -0.0192  ***
```

Use the "newmods" input to supply values for the independent variables that you are interested in predicting

```
> predict(me.mod, newmods = newdat, transf=exp, addx = TRUE)
    pred  ci.lb  ci.ub  cr.lb  cr.ub X.intrcpt X.ablat
1 1.3513 0.8872 2.0580 0.7350 2.4842         1       0
2 0.9858 0.7197 1.3503 0.5738 1.6935         1      10
3 0.7192 0.5734 0.9020 0.4384 1.1799         1      20
4 0.5247 0.4365 0.6306 0.3256 0.8455         1      30
5 0.3828 0.3084 0.4750 0.2344 0.6250         1      40
6 0.2793 0.2070 0.3768 0.1640 0.4756         1      50
```

```
> exp(me.mod$beta[1] + me.mod$beta[2]*newdat)
[1] 1.3512556 0.9858001 0.7191843 0.5246764 0.3827744 0.2792507
```

Two Fitting Methods
lmer

Mixed Effects Model – Dose Example

Previous Mixed Effect Model – 1 Study

```
> me.mod.final = mod = lmer(weight ~ Time + Diet  + (1|Rat), data = dat)
> summary(me.mod.final)
Linear mixed model fit by REML ['lmerMod']
Formula: weight ~ Time + Diet + (1 | Rat)
   Data: dat

REML criterion at convergence: 1304.3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.5236 -0.5557 -0.0467  0.5667  3.0932

Random effects:
 Groups   Name        Variance Std.Dev.
 Rat      (Intercept) 1337.88  36.577
 Residual               66.85   8.176
Number of obs: 176, groups:  Rat, 16

Fixed effects:
             Estimate Std. Error t value
(Intercept) 244.06890   13.00477  18.768
Time          0.58568    0.03168  18.486
Diet2       220.98864   22.44958   9.844
Diet3       262.07955   22.44958  11.674

Correlation of Fixed Effects:
      (Intr) Time   Diet2
Time  -0.082
Diet2 -0.575  0.000
Diet3 -0.575  0.000  0.333
```

Meta-Analysis Model – 4 Studies

```
> meta.mod = lmer(weight ~ Time + Diet + (1|study) + (1|Rat:study),
+                 data = datnew, weights = 1/vi)
> summary(mod)
Linear mixed model fit by REML ['lmerMod']
Formula: weight ~ Time + Diet + (1 | Rat)
   Data: dat

REML criterion at convergence: 1304.3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.5236 -0.5557 -0.0467  0.5667  3.0932

Random effects:
 Groups   Name        Variance Std.Dev.
 Rat      (Intercept) 1337.88  36.577
 Residual               66.85   8.176
Number of obs: 176, groups:  Rat, 16

Fixed effects:
             Estimate Std. Error t value
(Intercept) 244.06890   13.00477  18.768
Time          0.58568    0.03168  18.486
Diet2       220.98864   22.44958   9.844
Diet3       262.07955   22.44958  11.674
```

Meta-Analysis

What's the Objective?

Before beginning, it's important to know how the model results will be used.

Data Exploration

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Model Fitting

metafor vs. linear models, fixed vs. random effects models, choice of weights

.

Designation of Variance Components

Variance (Weights)

- The variance heterogeneity is estimated based on the squared SE collected from the literature

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2\right)$$

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2 \sigma_R^2\right)$$

- These are often referred to as 'weights' although they are more appropriately thought of as components of the variance-covariance matrix

Variance (Weights)

What to do when:

1. The SE are not available?
2. There are very large or very small reported values for SE?
3. There are individual and pooled SE reported

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2\right)$$

$$\varepsilon_i \sim N\left(0, \mathrm{SE}_i^2 \sigma_R^2\right)$$

Variance (Weights)

What to do when:

1. The SE are not available?

There are other ways to infer the relative variability associated with each study, but they are not well supported by statistical theory:

- Sample Size – larger sample size → smaller expected variance
- Expert Opinion – can use knowledge of study methods and design to assign relative weights to each observation (not desirable)

Variance (Weights)

What to do when:

1. The SE are not available?
2. There are very large or very small reported values for SE?

An unusually small reported SE will cause problems in the fitting algorithm and skew results towards that observation. There is no standard methodology to deal with this but in practice, it is not uncommon to create a minimum cut-off for the SE.

- Establish a cutoff (e.g. 5 percentile of observations)
- Set all values below the cutoff to the cutoff value

Variance (Weights)

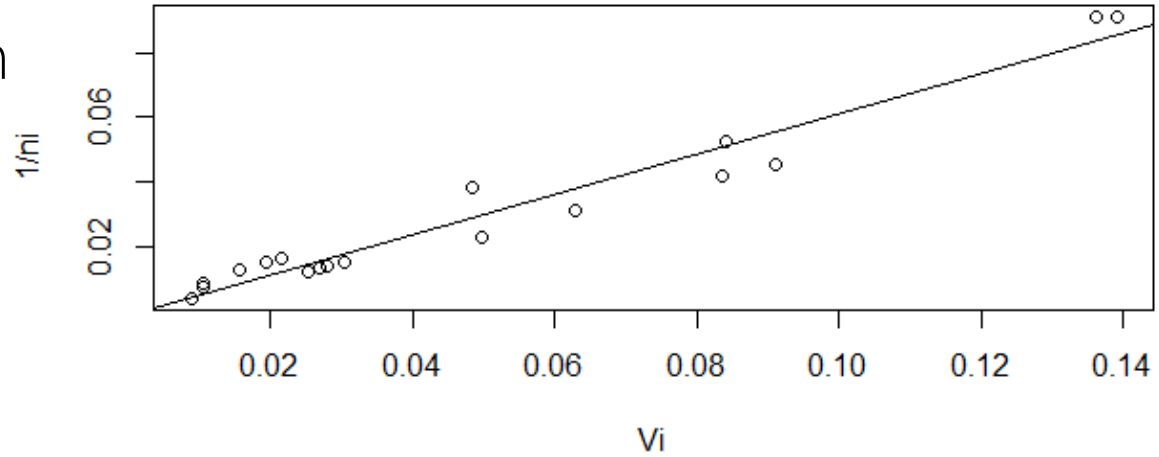
What to do when:

1. The SE are not available?
2. There are very large or very small reported values for SE?
3. There are individual and pooled SE reported

If each treatment SE is similar or the authors reported a test for homoscedasticity, the pooled SE is a good choice. If the original observations are homoscedastic but the observations are unbalanced due to missing data, the individual SE should be used if it is available.

Sample Size Variance Substitution – IQ Example

- How does use of sample size in place of reported variances affect the results?




```
> summary(dat$vi)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.00880 0.02045 0.02790 0.04842 0.07325 0.13910
```

```
> summary(1/dat$n1i)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.004292 0.013160 0.015385 0.028932 0.040064 0.090909
```

```
Call:
lm(formula = (1/dat$n1i) ~ dat$vi)

Residuals:
       Min         1Q     Median         3Q        Max
-0.0100189 -0.0023111 -0.0000579  0.0043969  0.0095427

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.001110   0.002071  -0.536    0.599
dat$vi       0.620434   0.033131  18.727 8.74e-13 ***
```

Sample Size Variance Substitution – IQ Example

Vi = sei^2

```
> me.met <- rma(yi~weeks, vi, data = dat)
> summary(me.met)

Mixed-Effects Model (k = 19; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -0.7144    1.4287    7.4287    9.9284    9.2749

tau^2 (estimated amount of residual heterogeneity):     0.0112 (SE = 0.0128)
tau (square root of estimated tau^2 value):             0.1057
I^2 (residual heterogeneity / unaccounted variability): 29.40%
H^2 (unaccounted variability / sampling variability):   1.42
R^2 (amount of heterogeneity accounted for):            40.63%

Test for Residual Heterogeneity:
QE(df = 17) = 27.6730, p-val = 0.0489

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 7.5094, p-val = 0.0061

Model Results:

         estimate      se    zval    pval    ci.lb    ci.ub
intrcpt    0.1942  0.0633  3.0649  0.0022    0.0700   0.3183  **
weeks     -0.0157  0.0057 -2.7403  0.0061   -0.0270  -0.0045  **
```

vi.Sub = 1/ni

```
Mixed-Effects Model (k = 19; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -1.7687    3.5375    9.5375   12.0371   11.3836

tau^2 (estimated amount of residual heterogeneity):     0.0327 (SE = 0.0181)
tau (square root of estimated tau^2 value):             0.1807
I^2 (residual heterogeneity / unaccounted variability): 66.61%
H^2 (unaccounted variability / sampling variability):   3.00
R^2 (amount of heterogeneity accounted for):            43.26%

Test for Residual Heterogeneity:
QE(df = 17) = 45.9214, p-val = 0.0002

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 8.7356, p-val = 0.0031

Model Results:

         estimate      se    zval    pval    ci.lb    ci.ub
intrcpt    0.2457  0.0710  3.4608  0.0005    0.1066   0.3848  ***
weeks     -0.0195  0.0066 -2.9556  0.0031   -0.0325  -0.0066   **
```

Meta-Analysis

What's the Objective?

Before beginning, it's important to know how the model results will be used.

Data Exploration

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Model Fitting

metafor vs. linear models, fixed vs. random effects models, choice of weights

.

Model Selection

How do you know which dependent variables should remain in the model?

Fixed Effects Selection – IQ Example

Add "Tester" Fixed effect

```
> me.met2 <- rma(yi~weeks + tester, vi, data = dat)
> summary(me.met2)

Mixed-Effects Model (k = 19; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
 -1.3419    2.6838   10.6838   13.7742   14.3202

tau^2 (estimated amount of residual heterogeneity):     0.0148 (SE = 0.0153)
tau (square root of estimated tau^2 value):             0.1215
I^2 (residual heterogeneity / unaccounted variability): 34.24%
H^2 (unaccounted variability / sampling variability):   1.52
R^2 (amount of heterogeneity accounted for):            21.60%

Test for Residual Heterogeneity:
QE(df = 16) = 27.4173, p-val = 0.0371

Test of Moderators (coefficient(s) 2:3):
QM(df = 2) = 7.3878, p-val = 0.0249

Model Results:

             estimate      se    zval    pval    ci.lb    ci.ub
intrcpt        0.1836  0.0843  2.1788  0.0293   0.0184   0.3487  *
weeks         -0.0158  0.0062 -2.5586  0.0105  -0.0279  -0.0037  *
testerblind    0.0356  0.1021  0.3487  0.7273  -0.1645   0.2357
```

Compare with an F-Test using MLE

```
> me.met.ML<- rma(yi~weeks , vi, data = dat, method = "ML")
> me.met.ML2 <- rma(yi~weeks + tester, vi, data = dat, method = "ML")
> anova(me.met.ML, me.met.ML2)
        df    AIC     BIC   AICc logLik    LRT   pval       QE  tau^2
Full     4 6.3235 10.1013 9.1807 0.838                  27.4173 0.0042
Reduced  3 4.5192  7.3525 6.1192 0.740  0.1956 0.6583 27.6730 0.0049
           R^2
Full
Reduced 13.63%
>
```

Fixed Effects Selection – TB Example

M_0: $y_i \sim \beta_0 + u_i + \varepsilon_i$

M_1: $y_i \sim \beta_0 + \beta_1 \mathrm{Lat}_i + u_i + \varepsilon_i$

M_2: $y_i \sim \beta_0 + \beta_1 \mathrm{Lat}_i + \beta_2 \mathrm{Year}_i + u_i + \varepsilon_i$

M_3: $y_i \sim \beta_0 + \beta_1 \mathrm{Lat}_i + \beta_2 \mathrm{Year}_i + \beta_3 \mathrm{Alloc}_i + u_i + \varepsilon_i$

Compare nested models with Chi-Squared Tests

```
> me.mod0 <- rma(yi, vi, data = dat, method = "ML")
> me.mod1 <- rma(yi~ablat, vi, data = dat, method = "ML")
> me.mod2 <- rma(yi~ablat + year, vi, data = dat, method = "ML")
> me.mod3 <- rma(yi~ablat + year + alloc, vi, data = dat, method = "ML")
> anova(me.mod3, me.mod2)
        df     AIC     BIC    AICc  logLik     LRT   pval      QE  tau^2   R^2
Full     6 25.2779 28.6676 39.2779 -6.6389                24.1712 0.0136
Reduced  4 21.8921 24.1519 26.8921 -6.9460  0.6142 0.7356 25.0721 0.0021 0.00%
> anova(me.mod2, me.mod1)
        df     AIC     BIC    AICc  logLik     LRT   pval      QE  tau^2
Full     4 21.8921 24.1519 26.8921 -6.9460                25.0721 0.0021
Reduced  3 19.9269 21.6217 22.5935 -6.9634  0.0348 0.8521 25.0954 0.0040
           R^2
Full
Reduced 46.64%
> anova(me.mod1, me.mod0)
        df     AIC     BIC    AICc   logLik     LRT   pval      QE  tau^2
Full     3 19.9269 21.6217 22.5935  -6.9634                25.0954 0.0040
Reduced  2 30.1455 31.2754 31.3455 -13.0728 12.2186 0.0005 162.1649 0.3025
           R^2
Full
Reduced 98.67%
```

Meta-Analysis

What's the Objective?

Before beginning, it's important to know how the model results will be used.

Data Exploration

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Model Fitting

Find the 'best' numerical relationship between the dependent and independent variables.

Model Selection

How do you know which dependent variables should remain in the model?

Similar to regular regression but often have fewer variables to work with

Meta-Analysis

What's the Objective?

Before beginning, it's important to know how the model results will be used.

Data Exploration

What data do you have to work with? What are their ranges? Patterns? Visual relationships?

Model Fitting

Find the 'best' numerical relationship between the dependent and independent variables.

Model Selection

How do you know which dependent variables should remain in the model?

Evaluation + Interpretation

Does the model follow all the assumption? How well does it perform?

What assumptions need to be checked?

Mostly the same!

Model Evaluation

- Normality ☑
- Constant Variance ☒
- Fit ☑
- Prediction ☑
- Publication Bias ☐

Publication Bias

Study name	Statistics for each study		Risk ratio and 95% CI	Weight (Fixed)
	Risk ratio	p-Value	0.01 0.10 1.00 10.00 100.00	Relative weight
Fontham et al., 1994	1.260	0.021		13.63
Brownson et al., 1992	0.970	0.786		10.90
Wu-Williams et al., 1990	0.790	0.063		8.48
Garfinkel, 1992	1.180	0.227		7.28
Cardenas et al., 1997	1.200	0.223		6.11
Lam et al., 1987	1.650	0.005		4.22
Hirayama, 1984	1.450	0.041		4.14
Sobue, 1990	1.060	0.751		4.06
Gao et al., 1987	1.190	0.361		3.77
Sun et al., 1996	1.160	0.437		3.76
Zaridze et al., 1995	1.660	0.011		3.43
Garfinkel et al., 1985	1.230	0.332		3.00
Wang et al., 1996	1.110	0.686		2.06
Shimizu et al., 1988	1.080	0.773		1.92
Pershagen et al., 1987	1.030	0.912		1.91
Koo et al., 1987	1.550	0.114		1.78
Akiba et al, 1986	1.520	0.138		1.72
Chan et al, 1982	0.750	0.308		1.72
Kabat et al., 1995	1.100	0.745		1.59
Trichopoulos, 1983	2.130	0.011		1.54
Du et al., 1993	1.190	0.561		1.53
Kalandidi et al., 1990	1.620	0.107		1.53
Lam, 1985	2.010	0.026		1.39
Stockwell et al., 1992	1.600	0.163		1.20
Geng et al., 1988	2.160	0.029		1.10
Liu et al., 1993	1.660	0.227		0.78
Liu et al., 1991	0.740	0.478		0.76
Buffler, 1984	0.800	0.611		0.71
Lee et al., 1986	1.030	0.949		0.63
Correa, 1983	2.070	0.127		0.60
Wu et al, 1985	1.200	0.705		0.59
Humble et al., 1987	2.340	0.116		0.47
Jockel, 1991	2.270	0.145		0.43
Kabat, 1984	0.790	0.686		0.40
Inoue et al., 1988	2.550	0.138		0.34
Brownson et al., 1987	1.520	0.547		0.28
Butler, 1988	2.020	0.339		0.25
	1.204	0.000		

Figure 30.1 Passive smoking and lung cancer – forest plot.

Borenstein et al., 2009

Publication Bias

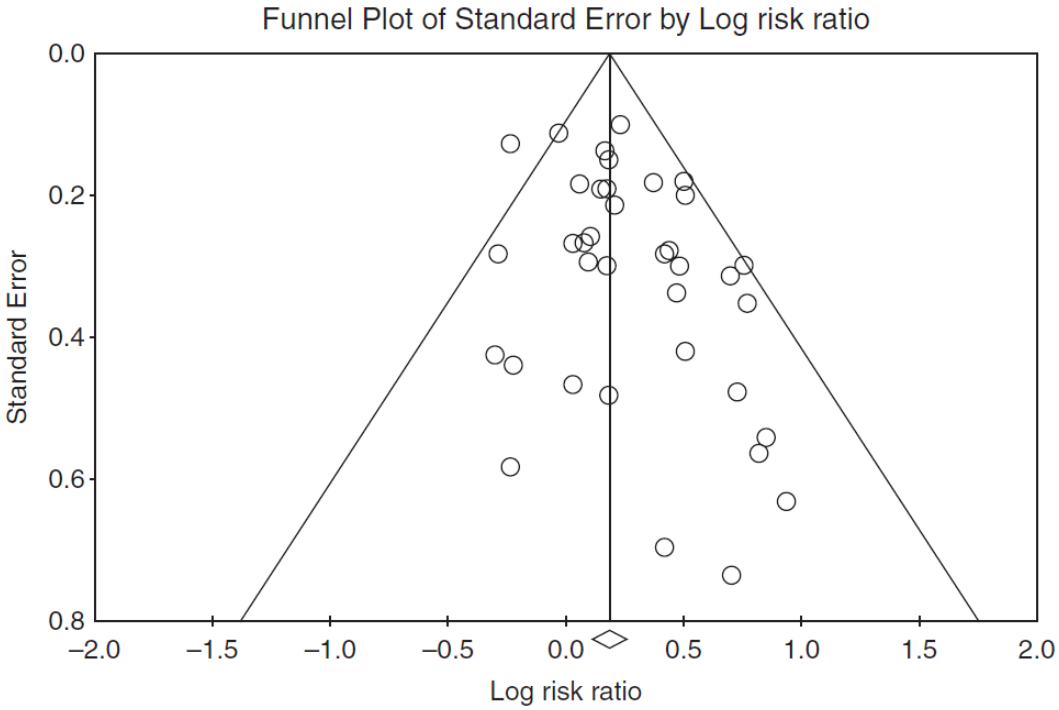
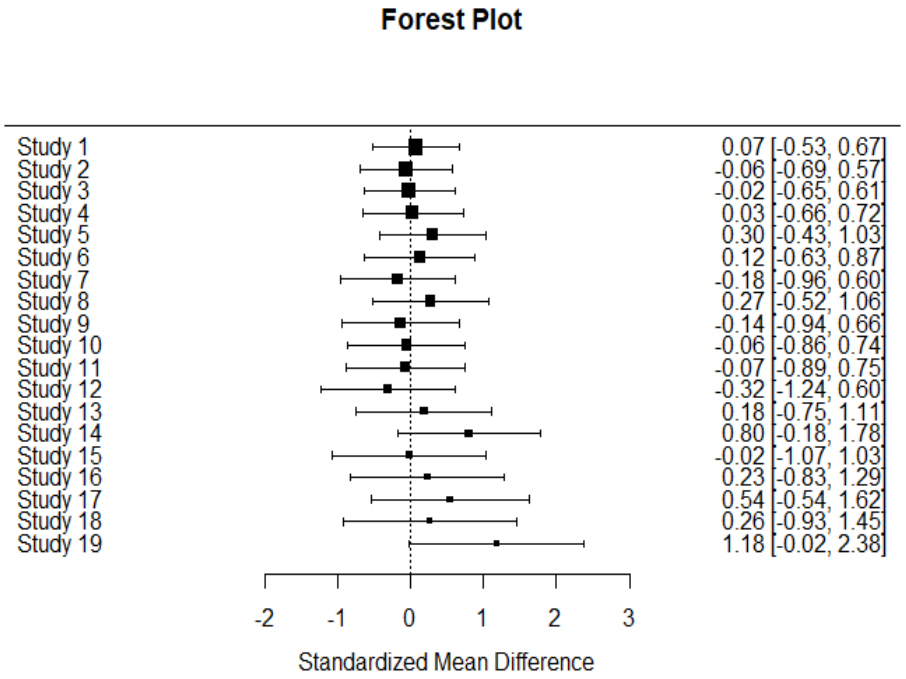


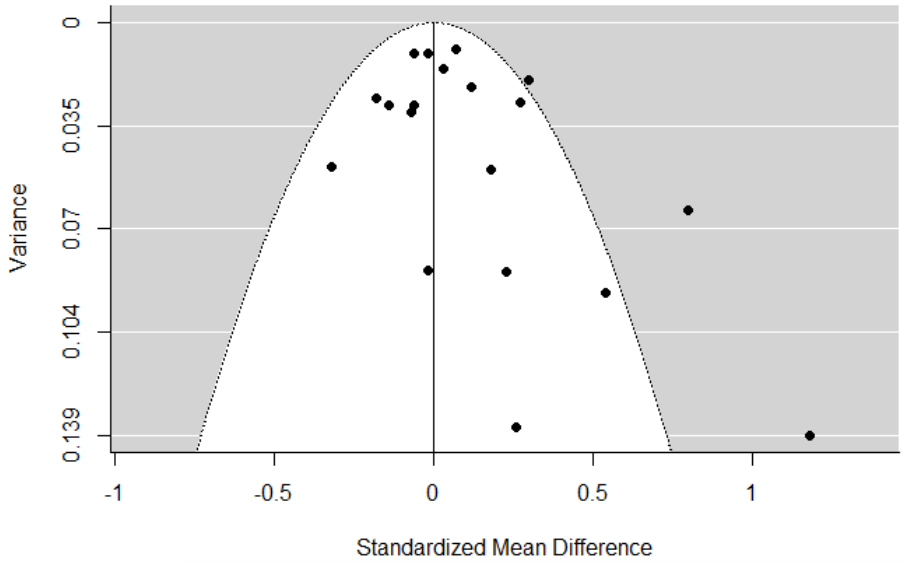
Figure 30.2 Passive smoking and lung cancer – funnel plot.

Borenstein et al., 2009

Publication Bias- IQ Example



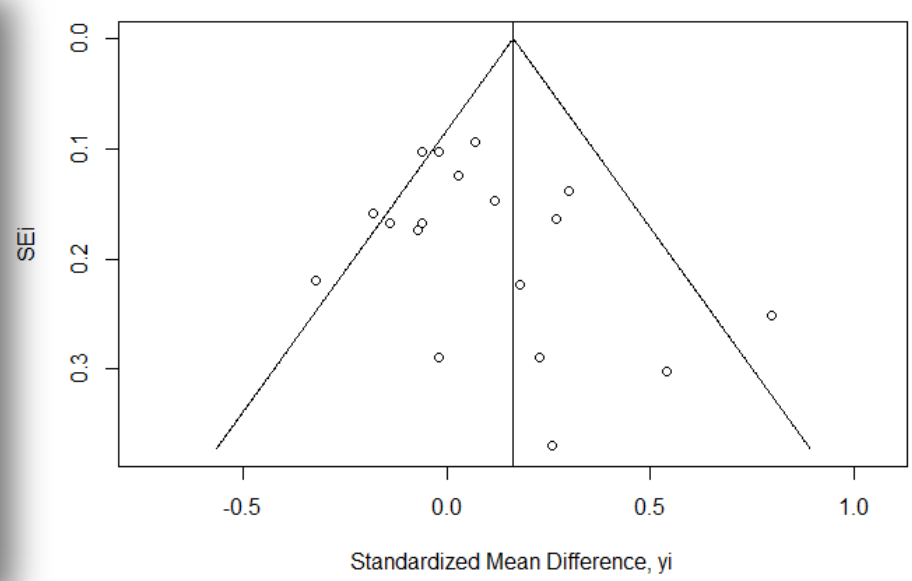

```
dat.sei.order = dat[order(dat$sei),]
forest(dat.sei.order$yi, vi = dat.sei.order$sei, main = "Forest Plot")
```




```
### Funnel Plot
funnel(x = dat$yi, vi = dat$vi, yaxis = "vi")
```

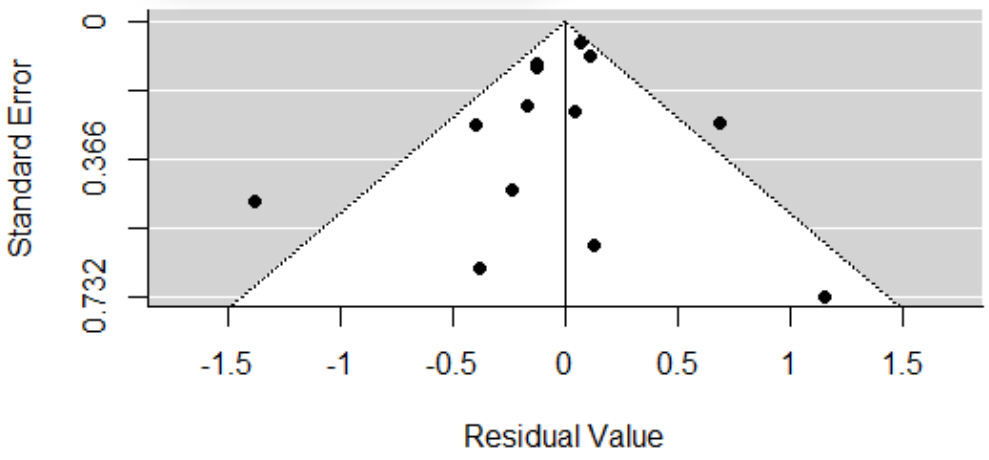
Publication Bias – IQ Example

```r
### create funnel plot manually

y.mean = mean(dat$yi) # or use meta-analysis estimate
sd.y = sd(dat$yi)
ylims = rev(range(dat$sei))
ylims[2] = 0

plot(dat$sei ~ dat$yi, ylim = ylims, xlim = c(y.mean -2.5*sd.y, y.mean+ 2.5*sd.y),
     xlab = "Standardized Mean Difference, yi",
     ylab = "SEi")
abline(v = y.mean)

#Store a vector of values that spans the range from 0
#to the max value of standard error in your dataset.
se.seq=seq(0, max(dat$sei), 0.001)

#Compute vectors of the lower-limit and upper limit values for
#the 95% CI region
ll95 = y.mean-(1.96*se.seq)
ul95 = y.mean+(1.96*se.seq)

## add lines
lines(se.seq~ll95)
lines(se.seq~ul95)
abline(v = y.mean)
```

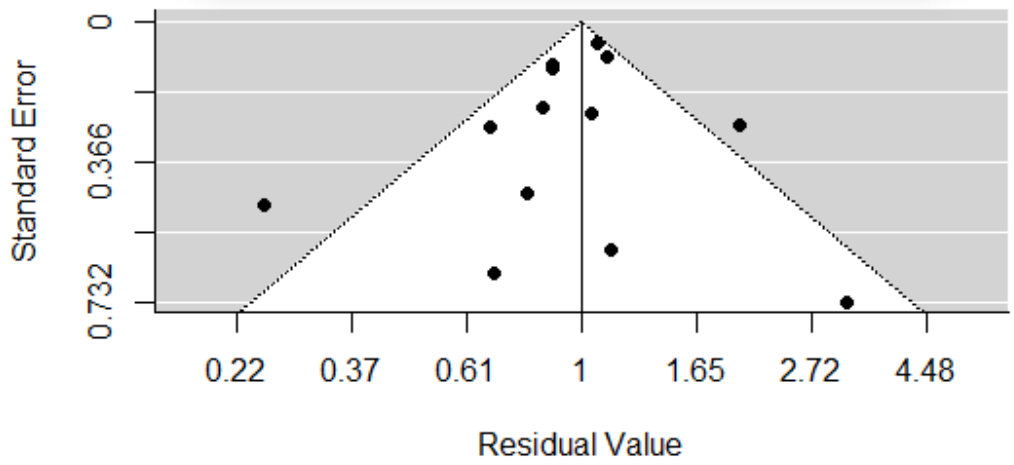


Publication Bias – TB Example

```
funnel(me.mod1)
```




```
funnel(me.mod1, atransf = exp)
```



Model Inference

- Interpret within the bounds of your data
- Make predictions with fixed effects (in general)
- Back transform the effect size to the units/value of interest
- Apply inferences to appropriate population

Your Turn!

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