Statistical considerations in indirect comparisons and network meta-analysis

Said Business School, Oxford, UK

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THE COCHRANE COLLABORATION®

Handout S2-L

Review of standard meta-analysis methods & Introduction to indirect comparison

Tianjing Li

Handbook Chapter 9 in a nutshell

analyses (91) analysis (67) characteristics (46) clinical (53) cochrane (34) combined (32) comparisons (33) consider (33) continuous (42) control (35) data (161) dichotomous (45) difference (156) effect (244) error (41) estimate (45) events (114) example (65) fixed-effect (35) heterogeneity (107) important (36) intervention (159) investigate (56) log (30) measures (44) meta-analyses (34) meta-analysis (168) meta-regression (31) methods (75) number (60) observed (43) odds (106) outcome (74) participants (51) random-effects (48) ratio (168) results (104) review (103) revman (37) risk (183) scales (31) section (114) standard (86) statistical (110) studies (218) subgroup (52) summary (55) systematic (34) treatment (37) trials (48) value (31)

Fixed-effect Model

Fixed-effect Model Assumes a Common ("True") Effect Size

Under the fixed-effect model, we assume

- All studies share a common ("true") effect size (θ)
- All factors that could influence the effect size are the same in all studies
- All observed variation reflects sampling error
- Study weights are assigned proportional to the inverse of within studies variance

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

Fixed-effect Model – True Effects and Sampling Error

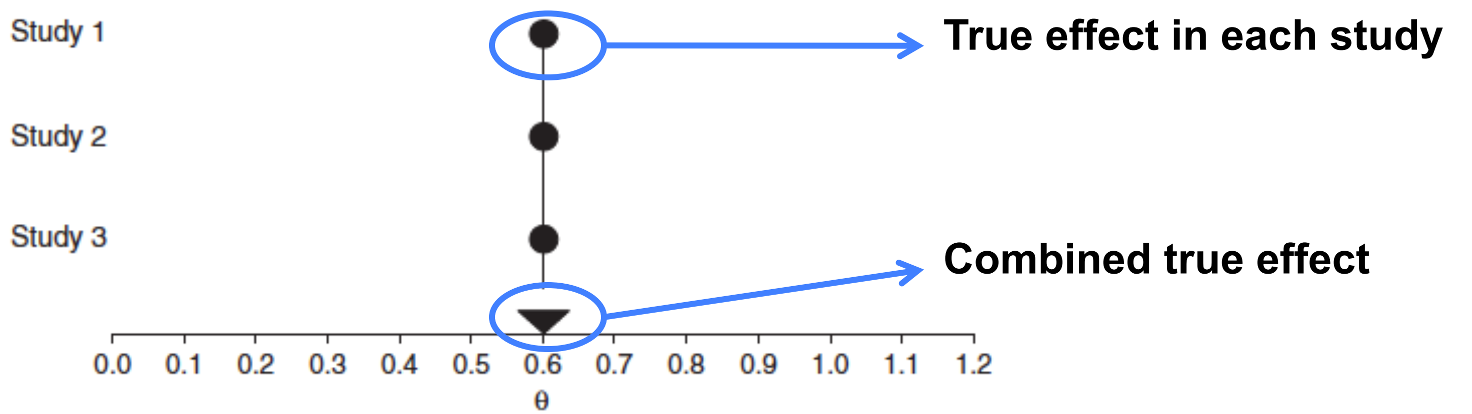


Figure 11.1 Fixed-effect model – true effects.

The observed effect size varies from one study to the next only because of the random errors inherent in each study.

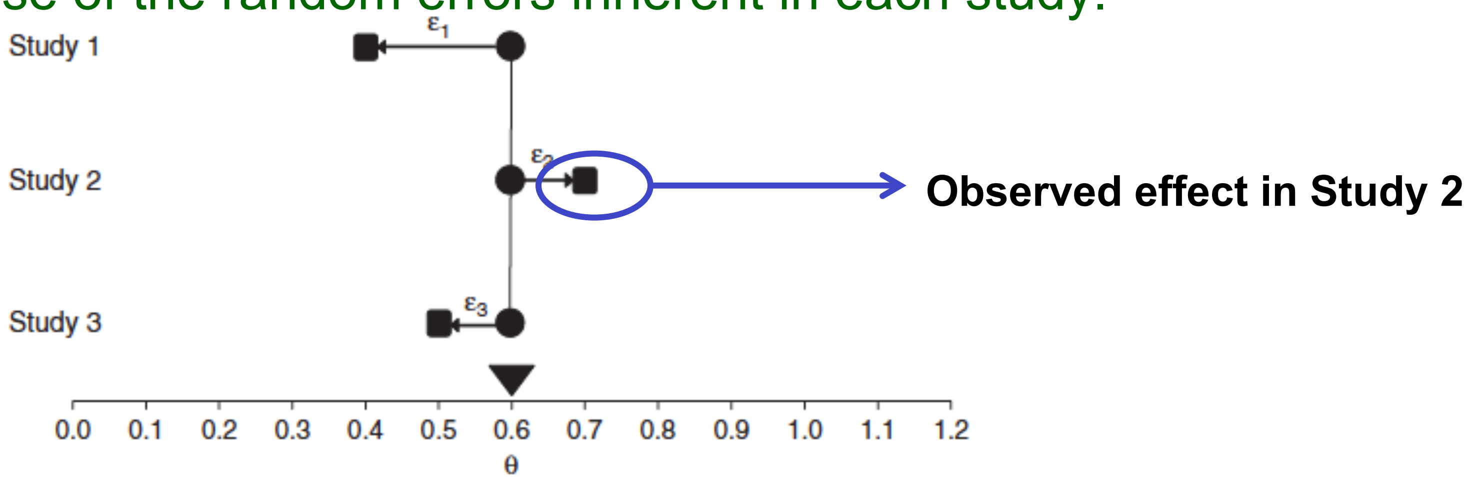
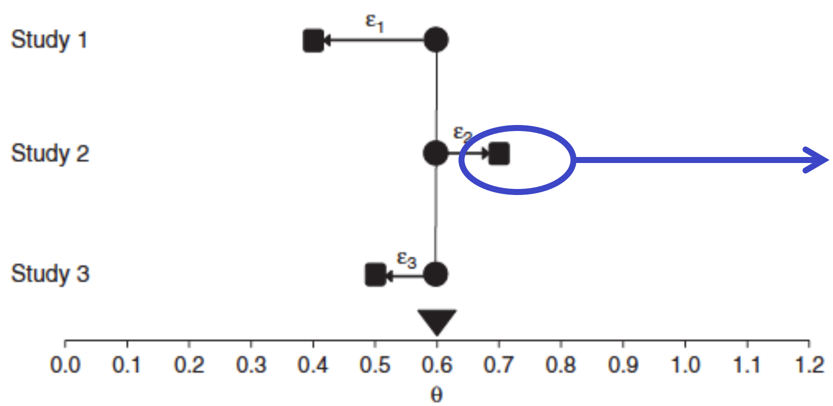


Figure 11.2 Fixed-effect model – true effects and sampling error.

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

Fixed-effect Model – True Effects and Sampling Error

The observed effect size varies from one study to the next only because of the random error inherent in each study.



Observed effect in Study 2, denoted as Y_2

Figure 11.2 Fixed-effect model – true effects and sampling error.

The sampling error (ε_i) is -0.20, 0.10, and -0.10 respectively in Study 1, 2, and 3.

Y_1= 0.60-0.20 =0.40
Y_2= 0.60+0.10=0.70
Y_3= 0.60-0.10 =0.50

More generally, the observed effect *Yi* for any study is given by the population mean plus the sampling error in that study.

$$Y_i = \theta + \varepsilon_i$$

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

- One source of variance (ie, random errors inherent in the study)
- The width of the normal curve is based on the variance in that study.

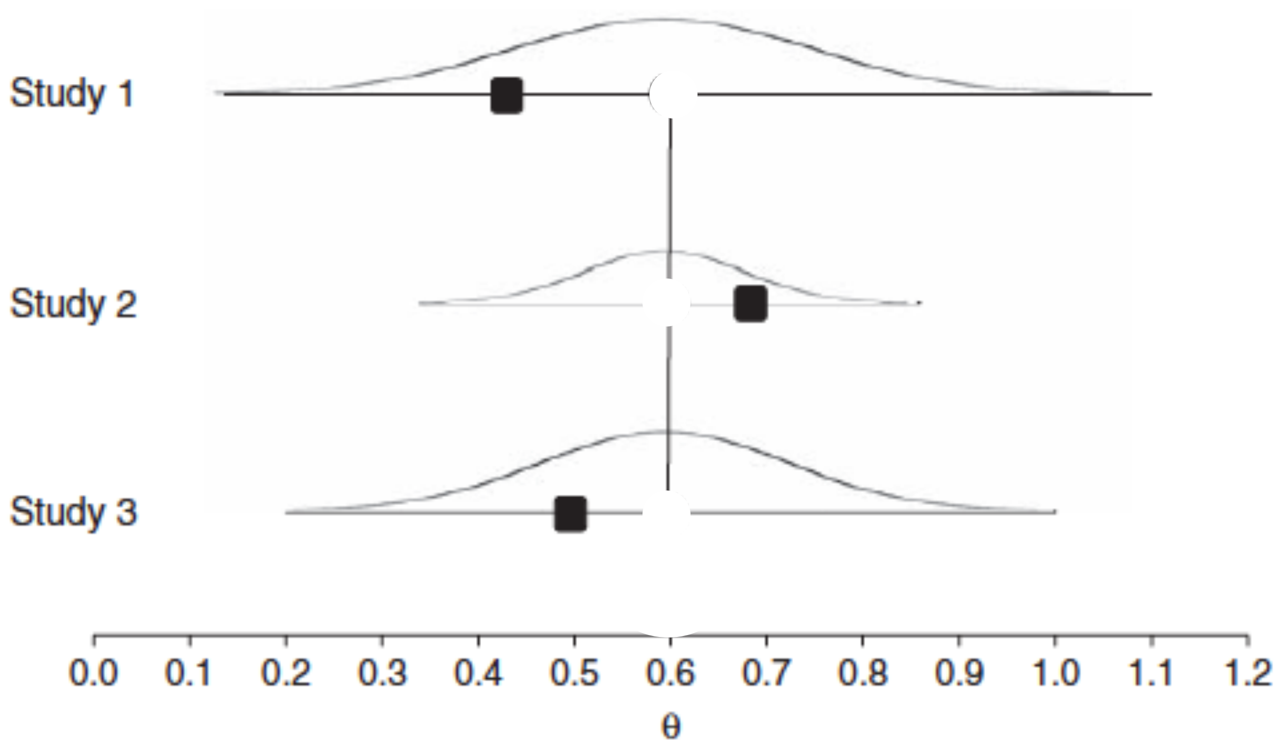


Figure 11.3 Fixed-effect model – distribution of sampling error.

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

Performing a Fixed-effect Meta-analysis

Start with the observed effects and try to estimate the population effect through computing a weighted mean.

- **Weight** assigned to each study in a ***fixed-effect*** meta-analysis is

$$W_i = \frac{1}{V_{Y_i}}$$

V_{yi} is the within study variance for study *i*

- **Weighted mean (*M*)** is computed as

$$M = \frac{\sum Y_i W_i}{\sum W_i}$$

- **Variance of the summary effect (*V_M*)** is estimated as

$$V_M = \frac{1}{\sum W_i}$$

- **Standard error of the summary effect (*SE_M*)** is estimated as

$$SE_M = \sqrt{V_M}$$

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

Random-effects Model

Is the Assumption Underlying a FE Model Plausible?

- Fixed-effect models assume that the studies are *identical* and the true effect size is *exactly the same* in all studies.

In reality…

- Studies usually differ in the mix of participants and in the implementations of interventions etc.
- There may be *different effect sizes* underlying different studies.

Borenstein M et al. Chapter 12. Random-Effects Models. Introduction to Meta-analysis. 2009

Is the Assumption Underlying a FE Model Plausible?

- For example, the magnitude of the impact of an educational intervention might vary depending the class size, the age, and other factors, which are likely to vary from study to study.
- We may or may not know for sure whether these characteristics are actually related to the size of effect.
- Nevertheless, logic suggests that such factors do exist and will lead to variations in the magnitude of the effect.

Borenstein M et al. Chapter 12. Fixed-Effects Models. Introduction to Meta-analysis. 2009

Heterogeneity and a Distribution of True Effects

- Careful qualitative synthesis of the data indicates that clinical and methodological diversities usually exist and may lead to variations in the magnitude of the effect.

- Instead of assuming there is one common true effect (as in a fixed-effect model), shall we assume that there is a distribution of true effects?

Borenstein M et al. Chapter 12. Fixed-Effects Models. Introduction to Meta-analysis. 2009

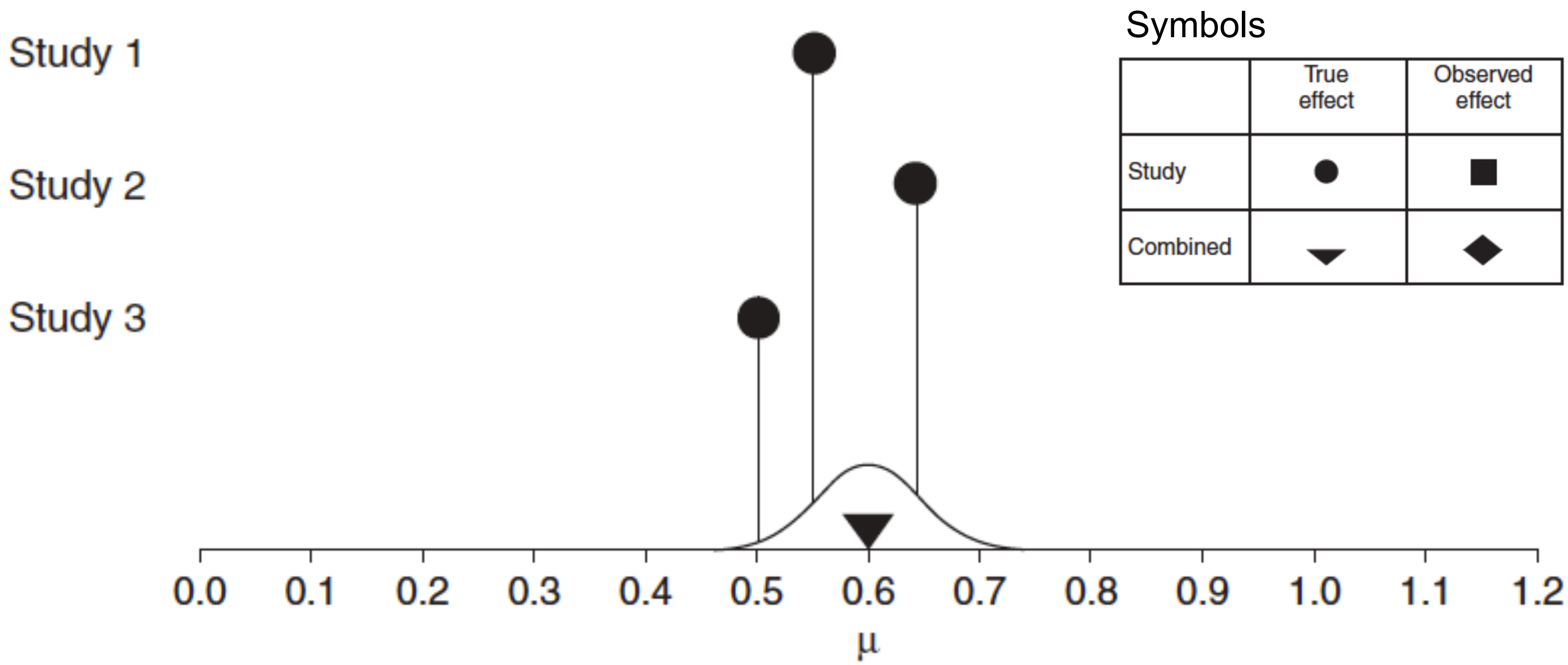


Figure 12.2 Random-effects model – true effects.

Borenstein M et al. Chapter 12. Random-Effects Models. Introduction to Meta-analysis. 2009

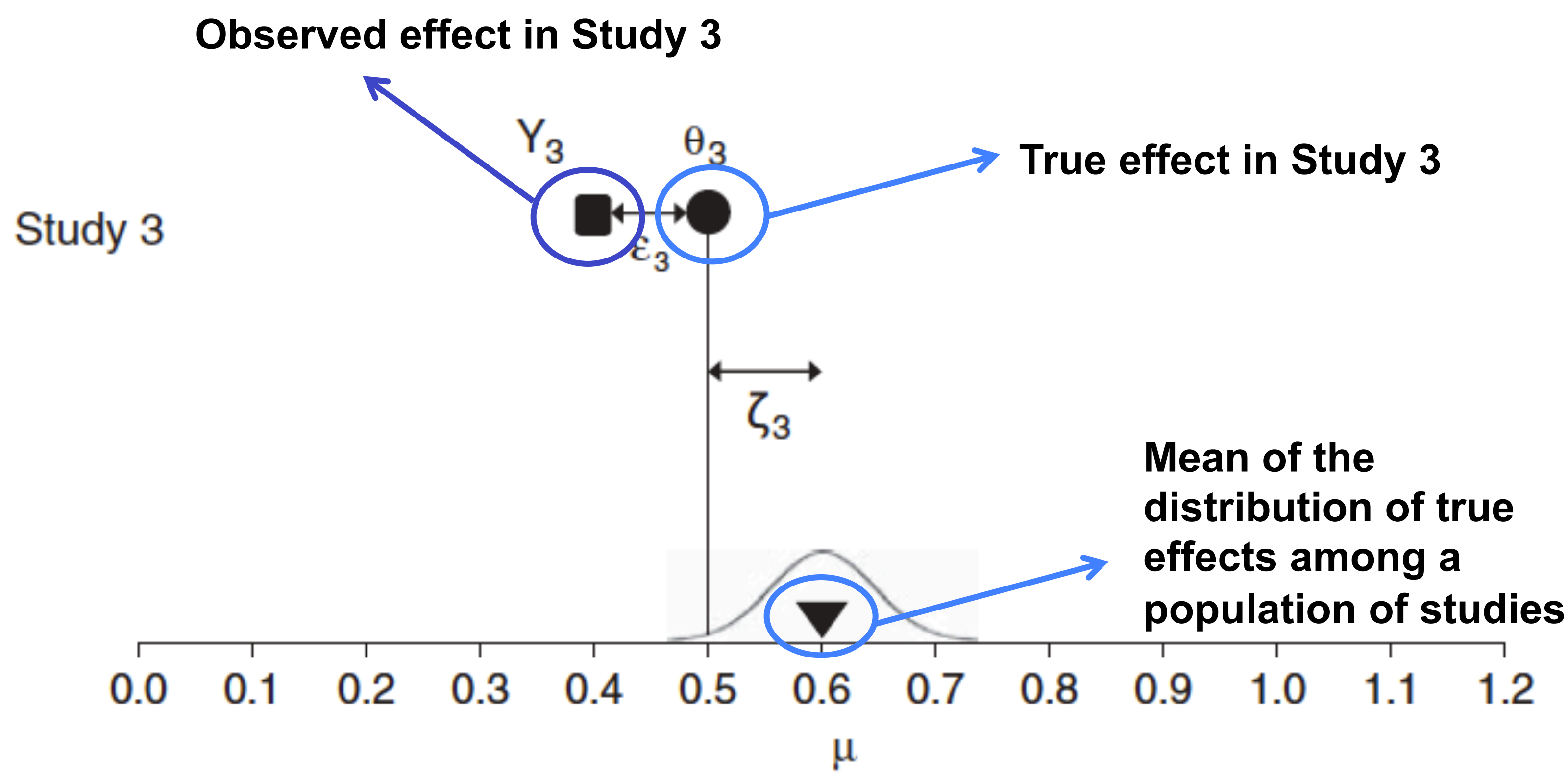
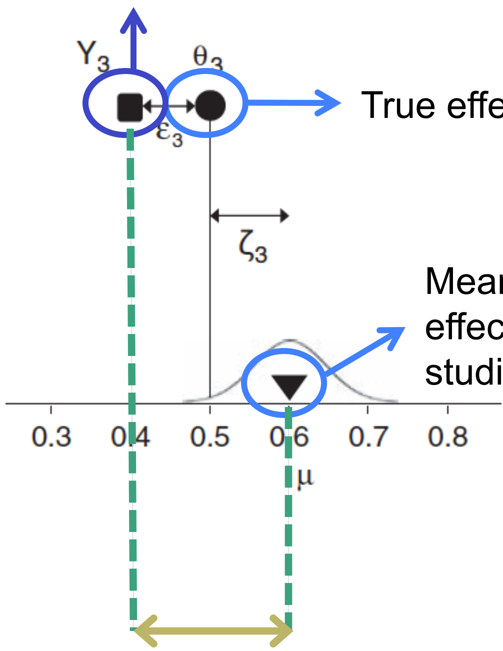


Figure 12.3 Random-effects model – true and observed effect in one study.

Borenstein M et al. Chapter 12. Random-Effects Models. Introduction to Meta-analysis. 2009

Observed effect in Study 3: $Y_3 = \mu + \zeta_3 + \varepsilon_3 = 0.4$



True effect in Study 3: $\mu + \zeta_3 = 0.5$

Mean of the distribution of true effects among a population of studies: $\mu = 0.6$

Symbols

	True effect	Observed effect
Study	●	■
Combined	▼	◆

The distance between the overall mean and the observed effect in any given study consists of two distinct parts:

- True variation in effect sizes (ζ_i)
- Sampling error (ε_i)

More generally, the observed effect *Yi* for any study is given by the grand mean, the deviation of the study's true effect from the grand mean, and the sampling error in that study.

$$Y_i = \mu + \zeta_i + \varepsilon_i$$

Borenstein M et al. Chapter 12. Random-Effects Models. Introduction to Meta-analysis. 2009

Random-effects Model – Two Sources of Variance

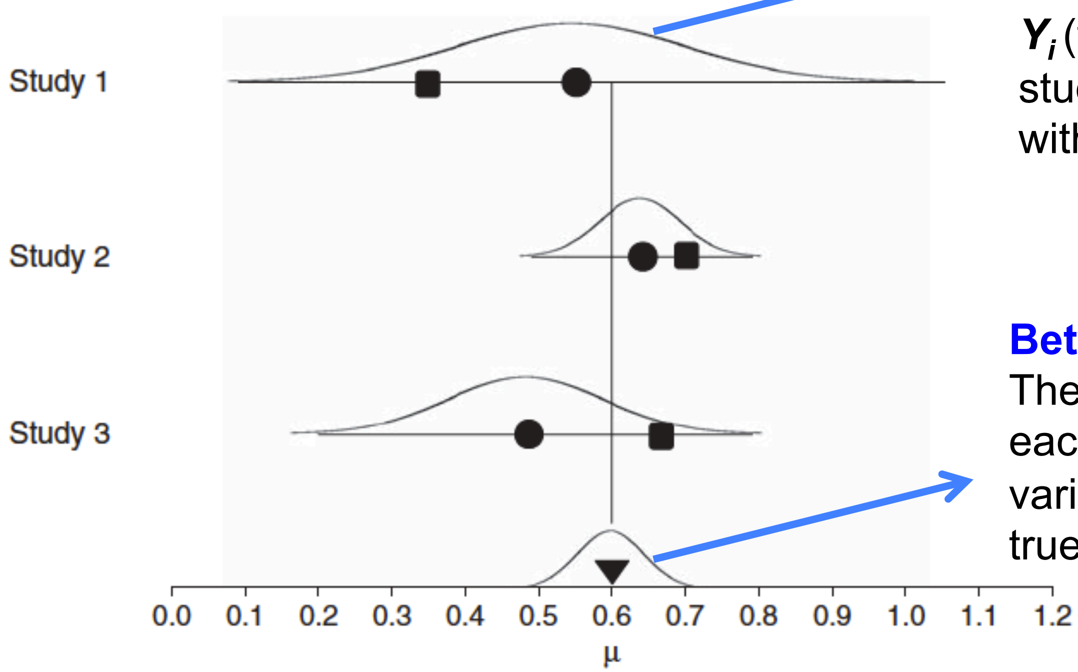


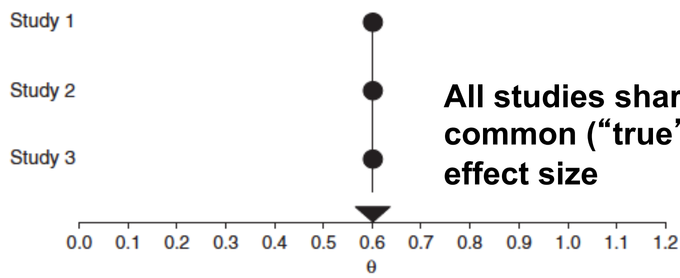
Figure 12.4 Random-effects model – between-study and within-study variance.

Within studies variance:
The distance from $\boldsymbol{\theta_i}$ (the circles) to $\boldsymbol{Y_i}$ (the square) depends on within study variance (ie., random errors within study) $\boldsymbol{V_{Yi}}$

Between studies variance:
The distance from $\boldsymbol{\mu}$ (the triangle) to each $\boldsymbol{\theta_i}$ (the circles) depends on the variance of the distribution of the true effects across studies, called $\boldsymbol{\tau^2}$

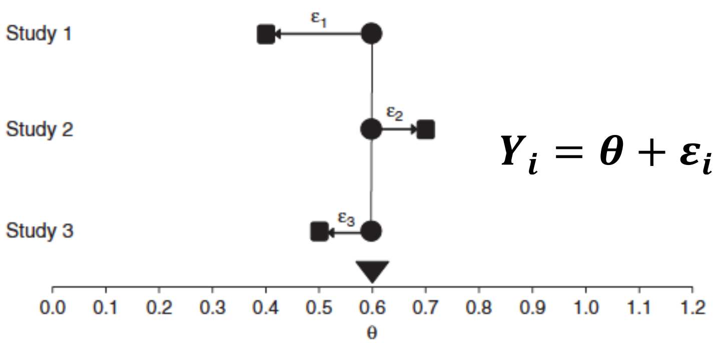
Borenstein M et al. Chapter 12. Random-Effects Model. Introduction to Meta-analysis. 2009

Fixed-effect Versus Random-effects



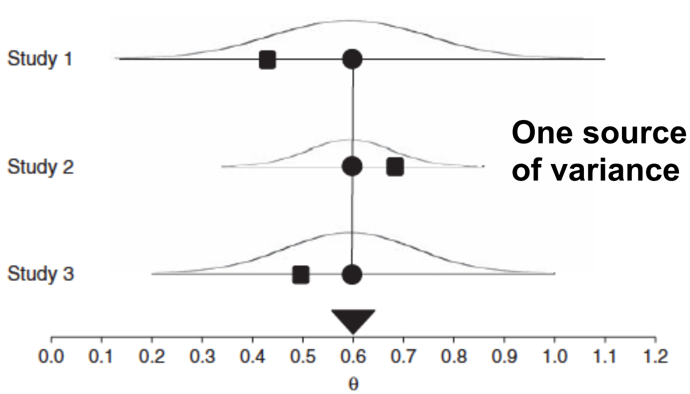
All studies share a common ("true") effect size

Figure 11.1 Fixed-effect model – true effects.



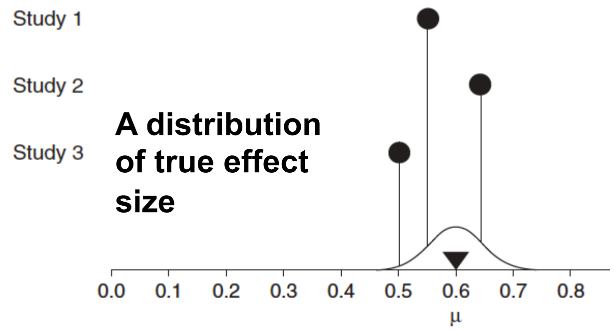
$$Y_i = \theta + \varepsilon_i$$

Figure 11.2 Fixed-effect model – true effects and sampling error.



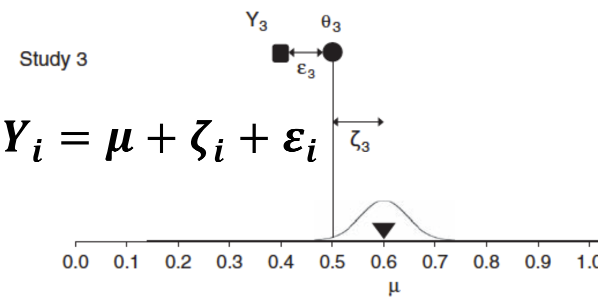
One source of variance

Figure 11.3 Fixed-effect model – distribution of sampling error.



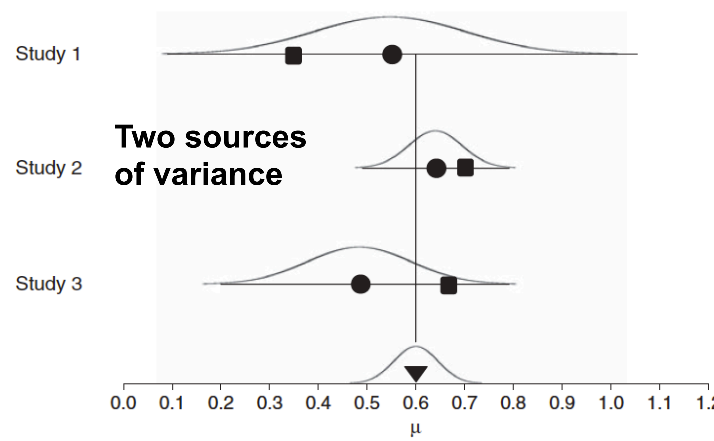
A distribution of true effect size

Figure 12.2 Random-effects model – true effects.



$$Y_i = \mu + \zeta_i + \varepsilon_i$$

Figure 12.3 Random-effects model – true and observed effect in one study.



Two sources of variance

Figure 12.4 Random-effects model – between-study and within-study variance.

Performing a Random-effects Meta-analysis

Analysis goal

- In an actual meta-analysis, we start with the observed effects and try to estimate the population effect.

- Goal is to use the collection of Y_i to estimate the overall mean μ.

How?

- Overall mean is calculated as a weighted average; the weight assigned to each study is the inverse of that study's variance.

- The variance now includes the ***within*** studies variance plus the estimate of the ***between*** studies variance.

Borenstein M et al. Chapter 12. Random-Effects Model. Introduction to Meta-analysis. 2009

Performing a Random-effects Meta-analysis

Start with the observed effects and try to estimate the population effect through computing a weighted mean.

- **Weight** assigned to each study in a ***random-effects*** meta-analysis is

$$W_i^* = \frac{1}{V_{Y_i}^*}$$

$$V_{Y_i}^* = V_{Y_i} + T^2$$

$V_{Y_i}^*$ is the within studies variance for study *i* plus the estimate of between studies variance T^2

- **Weighted mean (*M**):** $M^* = \dfrac{\sum Y_i W_i^*}{\sum W_i^*}$

- **Variance of the summary effect (V_{M^*}):** $V_{M^*} = \dfrac{1}{\sum W_i^*}$

- **Standard error of the summary effect (SE_{M^*}):** $SE_{M^*} = \sqrt{V_{M^*}}$

Borenstein M et al. Chapter 12. Random-Effects Model. Introduction to Meta-analysis. 2009

τ^2 is the between studies variance. Its estimate is denoted as T^2.

DerSimonian and Laird Method (Method of Moment)

$$\boldsymbol{T^2 = \frac{Q - df}{C}}$$

$$Q = \sum_{i=1}^{k} W_i \,(Y_i - M^*)^2 = \sum_{i=1}^{k} W_i \,Y_i^{\,2} - \frac{(\sum_{i=1}^{k} W_i \,Y_i)^2}{\sum_{i=1}^{k} W_i}$$

$$df = k - 1$$

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

A caveat: if the number of studies is small, then the estimate of the τ^2 will have poor precision.

DerSimonian and Laird Method 1986

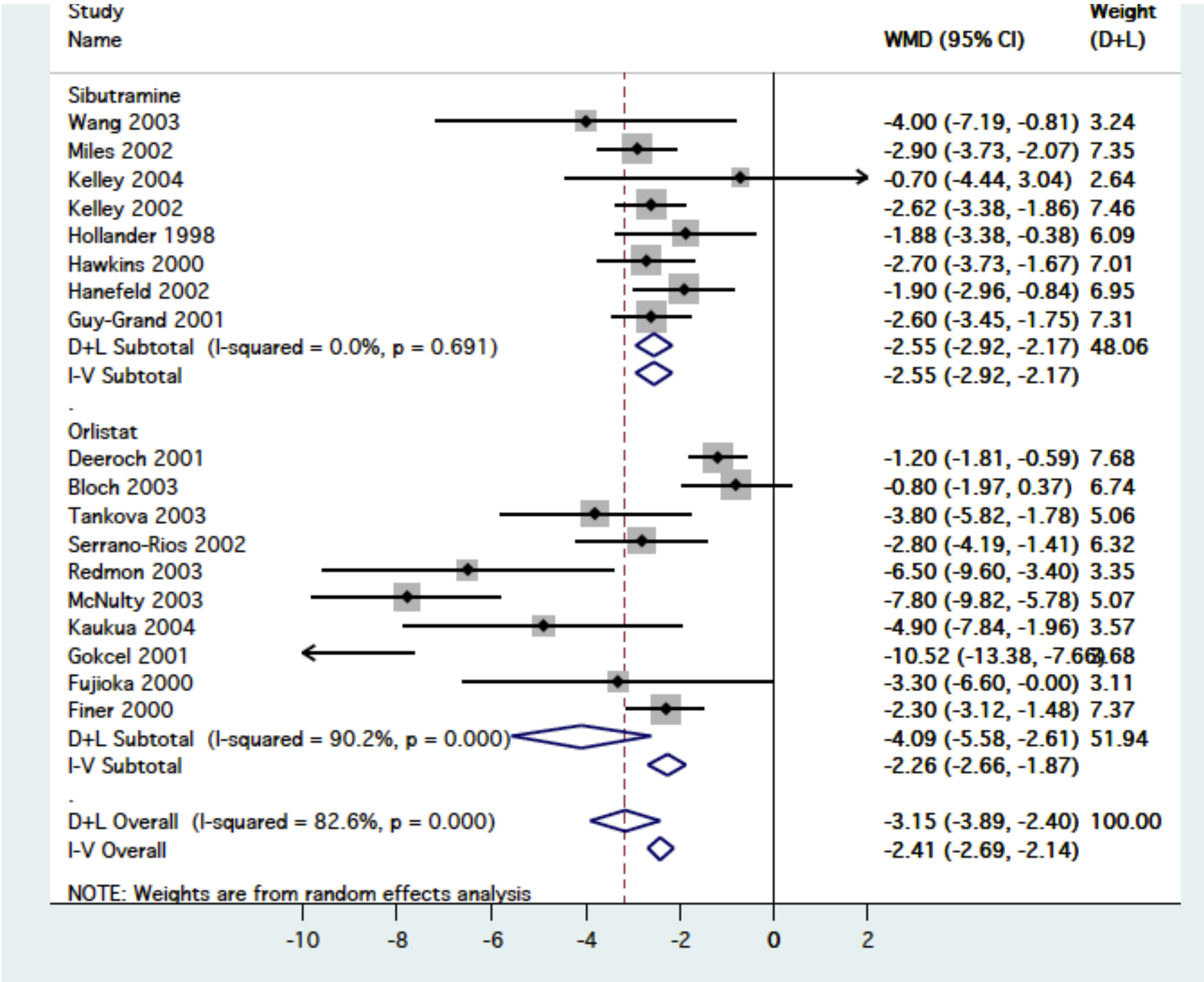
Pharmacotherapy for Weight Loss in Adults with Type 2 Diabetes

		Weigh Loss Drug			Placebo		
		Total	Mean	SD†	Total	Mean	SD
	Variable name	n_treat	mean_treat	sd_treat	n_plc	mean_plc	sd_plc
Drug Name	Study Name						
Sibutramine	Finer 2000	43	-2.4	2.03	40	-0.1	1.77
	Fujioka 2000	60	-3.7	9.22	61	-0.4	9.29
	Gokcel 2001	29	-9.61	7.38	25	0.91	2.47
	Kaukua 2004	102	-7.3	10.71	108	-2.4	11.02
	McNulty 2003	49	-8.0	6.3	46	-0.2	3.39
	Redmon 2003	27	-7.30	6.76	27	-0.8	4.68
	Serrano-Rios 2002	68	-4.5	4.12	65	-1.7	4.03
	Tankova 2003	53	-6.5	5.31	42	-2.7	4.73
Orlistat	Bloch 2003	38	-2.3	2.8	38	-1.5	2.4
	Deeroch 2001	126	-2.6	2.47	126	-1.4	2.47
	Guy-Grand 2001	97	-3.9	3.4	96	-1.3	2.6
	Hanefeld 2002	189	-5.3	5.1	180	-3.4	5.3
	Hawkins 2000	119	-5.4	4.04	118	-2.7	4.02
	Hollander 1998	139	-6.19	6.01	115	-4.31	6.11
	Kelley 2002	137	-3.89	3.16	128	-1.27	3.17
	Kelley 2004	17	-10.1	5.77	22	-9.4	6.1
	Miles 2002	160	-4.7	3.79	139	-1.8	3.54
	Wang 2003	30	-7.0	6.36	31	-3.0	6.36

†Standard deviation

(Data extracted from Norris SL et al. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews 2005, Issue 1.*)

```
metan n_treat mean_treat sd_treat n_plc mean_plc sd_plc, by(drug) random
second(fixed) lcols (studyname) nostandard xlabel(-10,-8,-6,-4,-2,0,2)
force boxsca(150) texts(100)
```



Three Measures of Statistical Heterogeneity

- Q
- I^2 statistic
- T^2

Computing Q

$$Q = \sum_{i=1}^{k} W_i \, (Y_i - M^*)^2 = \sum_{i=1}^{k} \left(\frac{Y_i - M^*}{S_i}\right) = \sum_{i=1}^{k} W_i \, {Y_i}^2 - \frac{\left(\sum_{i=1}^{k} W_i \, Y_i\right)^2}{\sum_{i=1}^{k} W_i}$$

- Q is a weighted sum of squares
- Q is a standardized measure (therefore not affected by the scale used)
- Under null hypothesis (i.e., all studies share a common effect size), Q follows a chi-squared distribution with df=k-1 (k is # of studies included in the meta-analysis).

The I^2 Statistic

What proportion of the observed variance reflects real differences in effect size?

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

If Q<df, I^2=0

$$I^2 = \left(\frac{Variance_{bet}}{Variance_{total}}\right) \times 100\%$$

- Can be viewed as (not exact)
- Allows us to discuss the amount of variance on a relative scale
- I^2 of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity

Higgins 2003

Tau-Squared Reflects the Actual Amount of Variation

τ^2 is the between studies variance, it's estimate is donated as T^2

DerSimonian and Laid Method (method of moment)

$$\boldsymbol{T^2 = \frac{Q - df}{C}}$$

$$Q = \sum_{i=1}^{k} W_i \,(Y_i - M^*)^2 = \sum_{i=1}^{k} W_i \, {Y_i}^2 - \frac{\left(\sum_{i=1}^{k} W_i \, Y_i\right)^2}{\sum_{i=1}^{k} W_i}$$

$$df = k - 1$$

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

A caveat: if the number of studies is small, then the estimate of the τ^2 will have poor precision

DerSimonian and Laid Method 1986

Measures of Heterogeneity

```
. metan n_treat mean_treat sd_treat n_plc mean_plc sd_plc, random

           Study     |     SMD   [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
1                    | -0.629      -1.144    -0.114          4.35
2                    | -0.789      -1.025    -0.553          6.88
3                    | -0.117      -0.751     0.516          3.51
4                    | -0.828      -1.079    -0.577          6.74
5                    | -0.310      -0.559    -0.062          6.76
6                    | -0.670      -0.932    -0.408          6.64
7                    | -0.365      -0.571    -0.160          7.14
8                    | -0.858      -1.153    -0.563          6.32
9                    | -0.486      -0.736    -0.235          6.74
10                   | -0.307      -0.759     0.146          4.86
11                   | -0.751      -1.170    -0.332          5.16
12                   | -0.687      -1.037    -0.337          5.80
13                   | -1.118      -1.693    -0.543          3.90
14                   | -1.528      -1.987    -1.070          4.81
15                   | -0.451      -0.725    -0.177          6.52
16                   | -1.856      -2.498    -1.213          3.45
17                   | -0.357      -0.716     0.003          5.71
18                   | -1.205      -1.673    -0.736          4.72
---------------------+---------------------------------------------------
D+L pooled SMD       | -0.701      -0.859    -0.544        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  66.49 (d.f. = 17) p = 0.000
  I-squared (variation in SMD attributable to heterogeneity) =  74.4%
  Estimate of between-study variance Tau-squared =  0.0792

  Test of SMD=0 : z=   8.74 p = 0.000
```

- CI from a RE meta-analysis describes uncertainty in the location of the mean of systematically different effects in the different studies.
- It does not describe the degree of heterogeneity among studies!

Q=66.49

I-squared=74.4%

Tau-squared=0.0792

Meta-regression and subgroup analysis

Introduction to Meta-regression

- In primary studies we use regression to assess the relationship between one or more covariates and a dependent variable.

- The same approach can be used with meta-analysis, except that
  - **Unit of analysis** (each observation in the regression model): **individual study** rather than individual participants
  - **Dependent variable: the summary estimate (effect size) in each primary study** rather than outcomes measured in individual participants
  - **Covariates: at level of the study** rather than the level of the participant

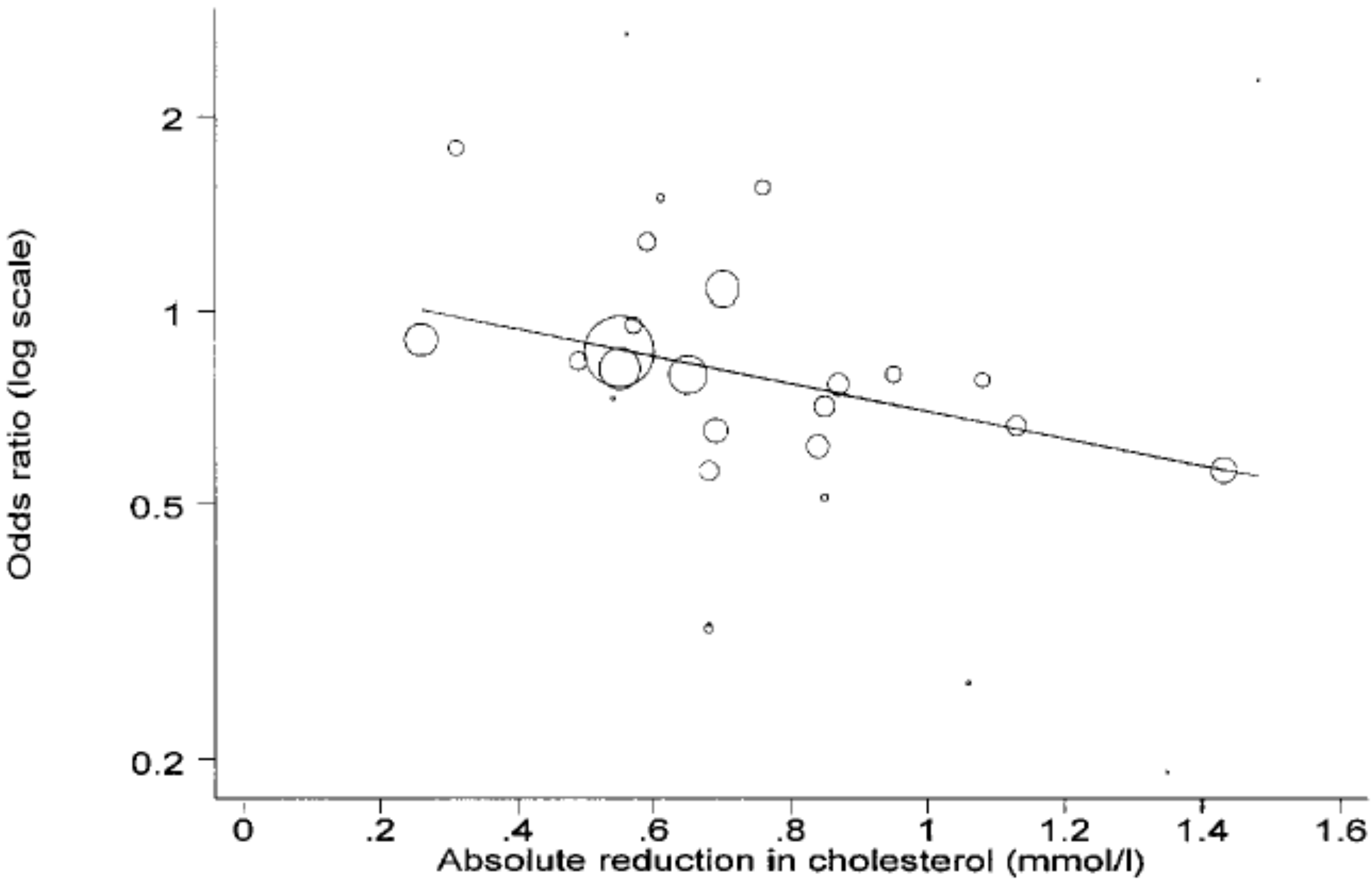
Why do a Meta-regression?

- Examine the relationship between study-level characteristics and effect size
    - ***Study potential effect modification:***

      Does the intervention effect (association) vary with different population or study characteristics?

- Explore and explain between study variation

Estimated ORs of coronary heart disease in 28 cholesterol reduction RCTs



Thompson SG, et al. Stat Med 1999;18:2693-708

Introduction to Meta-regression

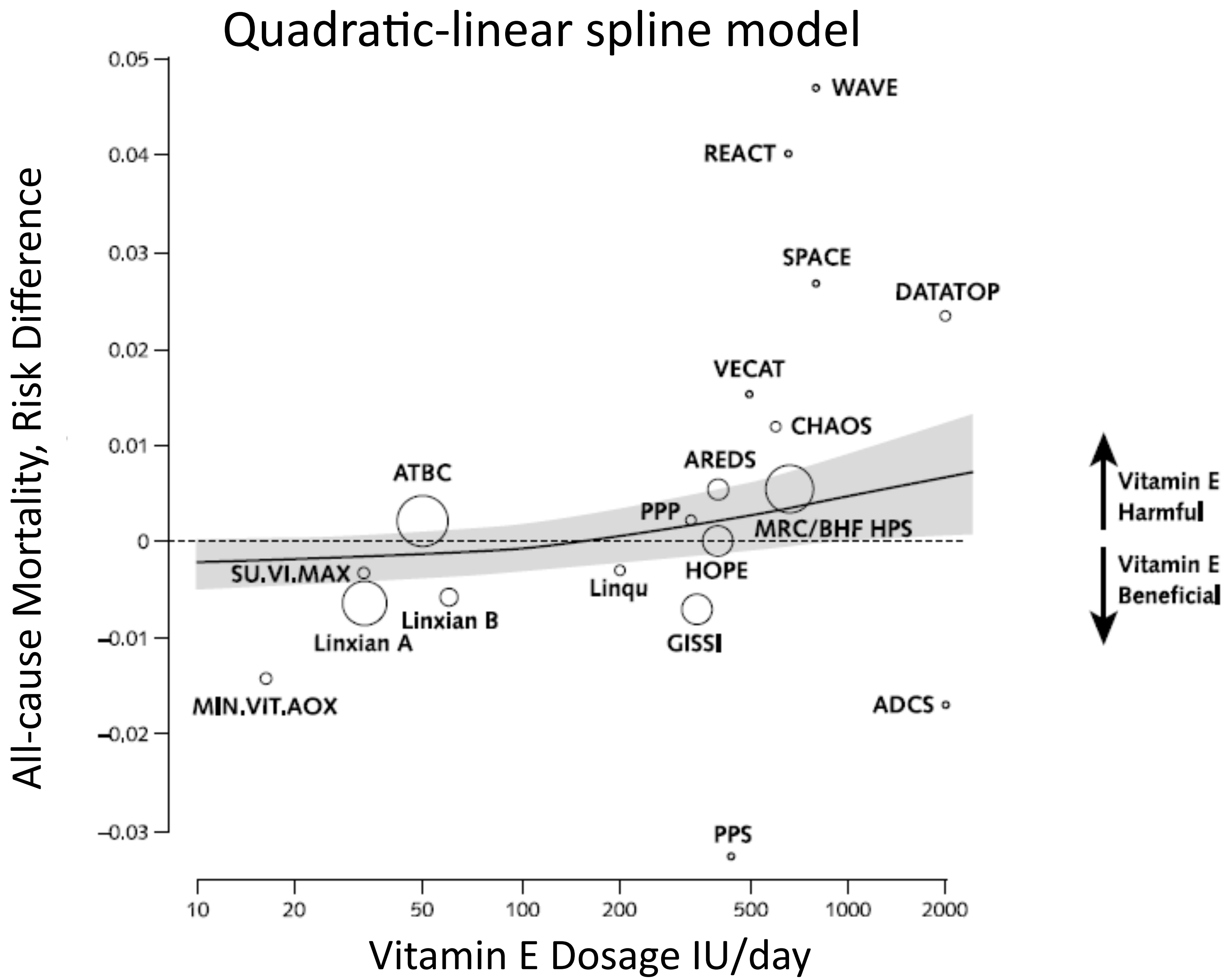
- Coefficient interpretation:

  How outcome variable (the intervention effect) changes on average with a unit change in the explanatory variable (the potential effect modifier).

- Larger studies have more influence on the relationship than smaller studies, since studies are weighted by the precision of their respective effect estimate.

- Both categorical (e.g., dummy-coded) and continuous variables can be used as covariates.
  - **Subgroup analysis:** a special case of meta-regression in which covariates are categorical

Meta-regression – Vitamin E and All-cause Mortality

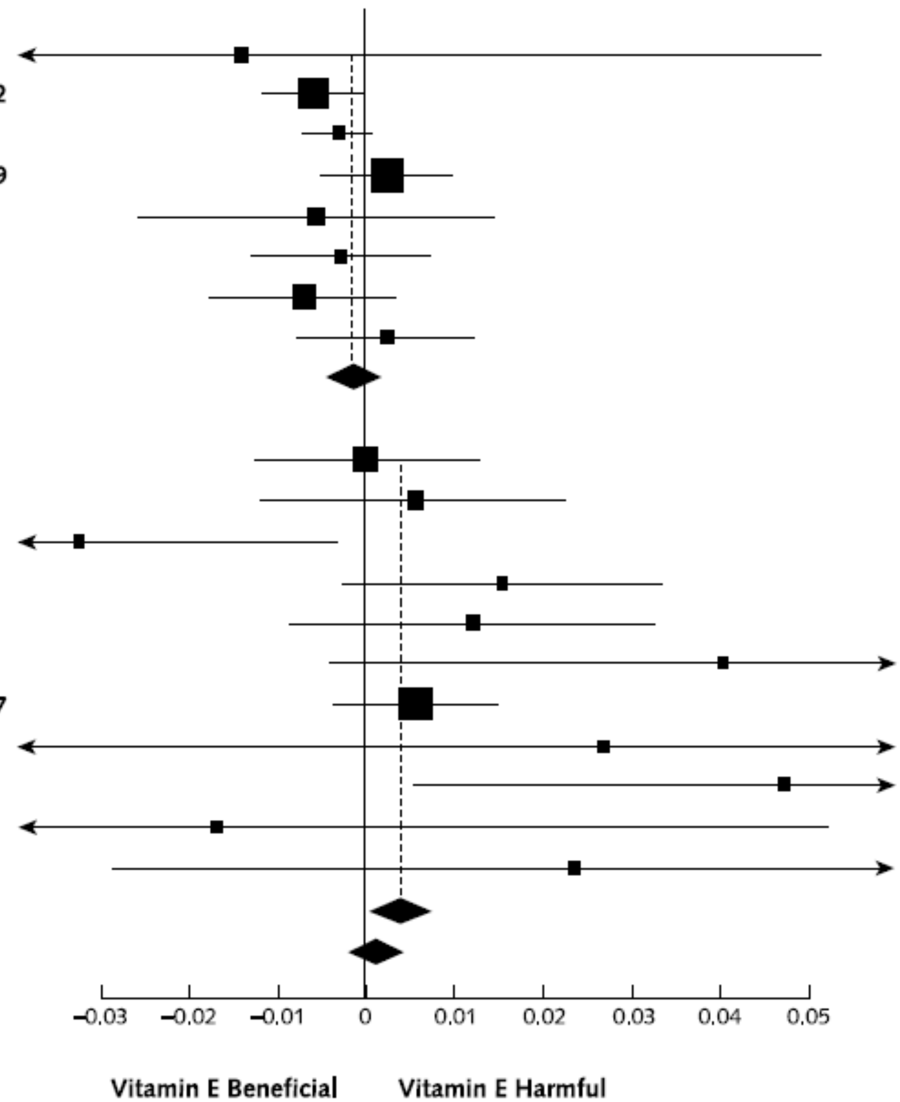


Miller ER III, et al. Ann Intern Med 2005;142:37-46

Subgroup Analysis – Vitamin E and All-cause Mortality

Study, Year (Reference)	Vitamin E Dosage, *IU/d*	Deaths/Participants, *n/n* Vitamin E	Control
Low-dosage vitamin E			
MIN.VIT.AOX, 1999 (35)	16.5	100/361	106/364
Linxian A, 1993 (36)	33	1018/14 792	1109/14 792
SU.VI.MAX, 2004 (37)	33	76/6481	98/6536
ATBC, 1994 (38, 39)	50	1800/14 564	1770/14 569
Linxian B, 1993 (40)	60	157/1657	167/1661
Linqu, 2001 (41)	200	38/1706	43/1705
GISSI, 1999 (42)	330	488/5666	529/5668
PPP, 2001 (43)	330	72/2231	68/2264
Total (low dosage)			
High-dosage vitamin E			
HOPE, 2000 (44)	400	535/4761	537/4780
AREDS, 2001 (45)	400	251/2370	240/2387
PPS, 1994 (46)	440	15/433	29/431
VECAT, 2004 (47)	500	20/595	11/598
CHAOS, 1996 (8, 9)	600	68/1035	52/967
REACT, 2002 (48)	660	9/149	3/148
MRC/BHF HPS, 2002 (49)	660	1446/10 269	1389/10 267
SPACE, 2000 (50)	800	31/97	29/99
WAVE, 2002 (51)	800	16/212	6/211
ADCS, 1997 (52)	2000	19/170	22/171
DATATOP, 1998 (53)	2000	73/399	64/401
Total (high dosage)			
Total for all studies			

All-Cause Mortality Risk Difference (95% CI)



Miller ER III, et al. Ann Intern Med 2005;142:37-46

Conducting a Meta-regression

Bacillus Calmette-Guérin (BCG) Vaccine to Prevent Tuberculosis Dataset

		Vaccinated		Control				
ID	Study	TB	No TB	TB	No TB	RR[1]	SE(lnRR)	Latitude[2]
1	Ferguson_1949	6	300	29	274	0.205	0.441	55
2	Hart_1977	62	13536	248	12619	0.237	0.141	52
3	Aronson_1948	4	119	11	128	0.411	0.571	44
3	Stein_1953	180	1361	372	1079	0.456	0.083	44
4	Rosenthal_1961	17	1699	65	1600	0.254	0.270	42
4	Rosenthal_1960	3	228	11	209	0.260	0.644	42
5	Comstock_1976	27	16886	29	17825	0.983	0.267	33
5	Comstock_1969	5	2493	3	2338	1.562	0.730	33
6	Coetzz_1968	29	7470	45	7232	0.625	0.238	27
7	Vandiviere_1973	8	2537	10	619	0.198	0.472	19
8	Comstock_1974	186	50448	141	27197	0.712	0.111	18
9	Frimodt_1973	33	5036	47	5761	0.804	0.226	13
9	TB Preventiaon Trial_1980	505	87886	499	87892	1.012	0.063	13

1. RR <1.0 indicates the vaccine decreased the risk of TB.
2. The higher the latitude the farther away the study location was from the equator (used as surrogate for climates).

Colditz, et al. JAMA 1994;271:698-702; Borenstein, et al. Introduction to Meta-analysis. Chapter 20.

Heterogeneous Treatment Effects across Studies

```
. metan t_tb t_no_tb c_tb c_no_tb,rr randomi label(namevar=author)
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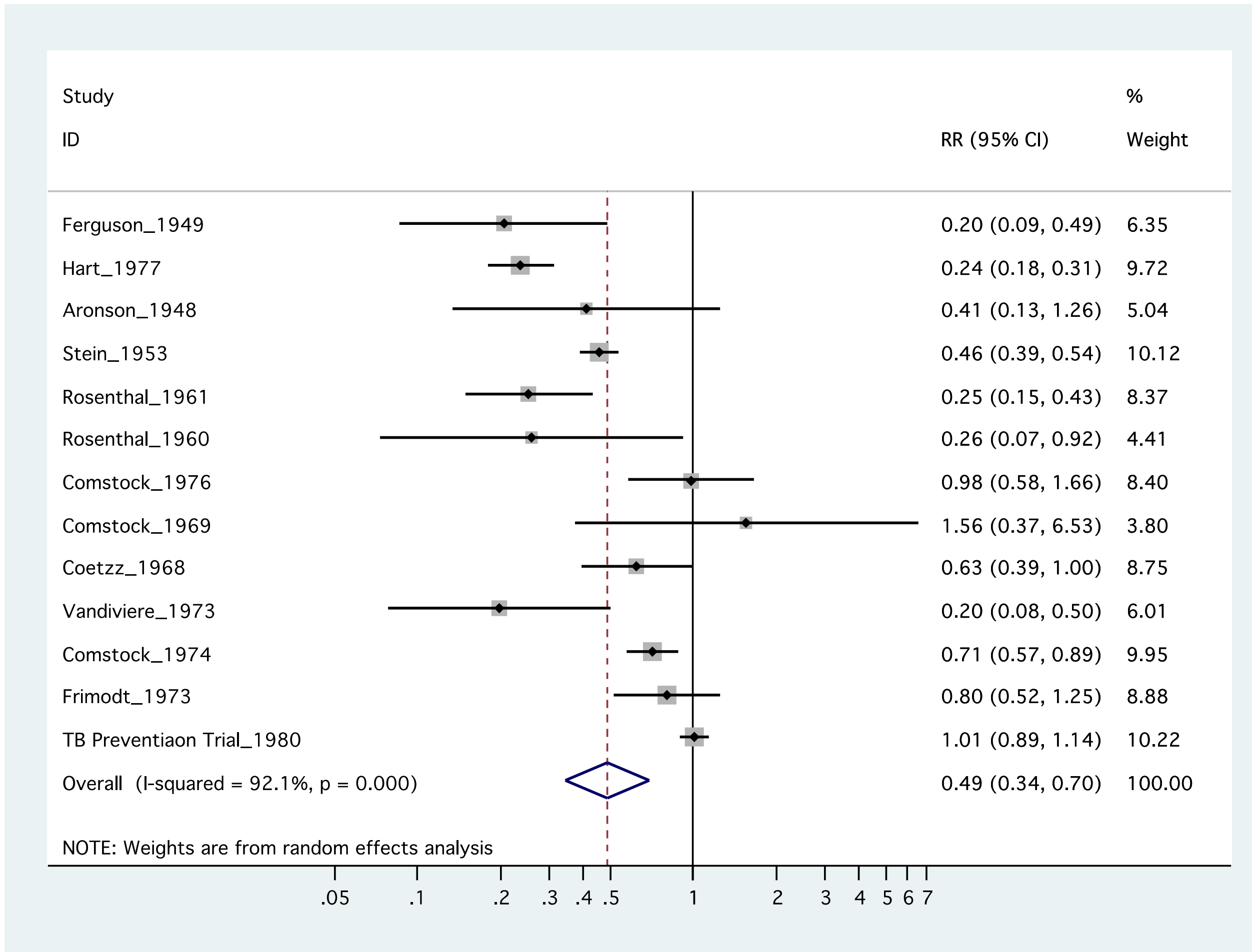


X_H^2 = chi-squared for heterogeneity = 152.23 (d.f.=12) p=0.000

I^2 (variation in RR attributable to heterogeneity)=92.1%

Estimate of between-study variance Tau-squared =0.3088

Test of RR=1 : z=4.00 p =0.000

Meta-regression Model Specification

$$\ln(RR)_i = a + b * latitude_i + \mu_i + \varepsilon_i$$

$$\varepsilon_i \sim N(0, (se(\ln RR)_i)^2)$$

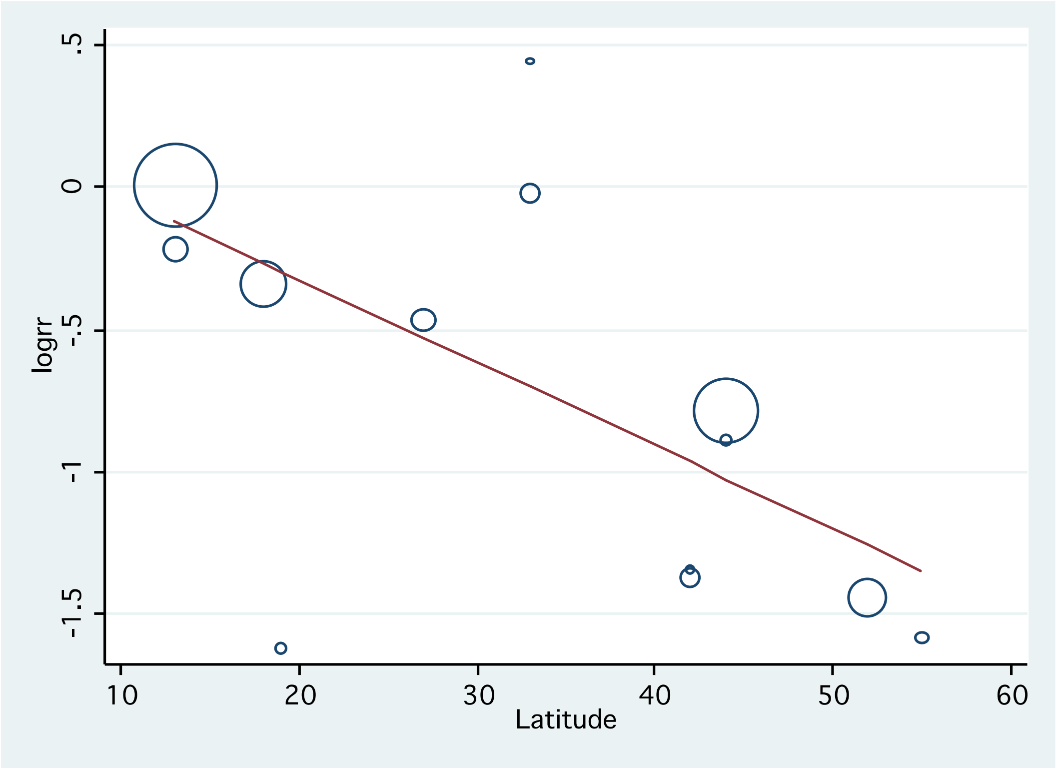
$$\mu_i \sim N(0, \tau^2)$$

- Parameters to estimate:

a – intercept, ln(RR) at latitude=0 (equator)

b – slope, the average change in ln(RR) for every unit change in latitude

τ^2 – between study variance



Interpreting the Coefficients from Meta-regression

```
. metareg logrr latitude, wsse(_selogES) mm graph

Meta-regression                                      Number of obs  =       13
Method of moments estimate of between-study variance tau2           =    .0633
% residual variation due to heterogeneity           I-squared_res  =   64.21%
Proportion of between-study variance explained       Adj R-squared  =   79.50%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
latitude	-.0292287	.0079378	-3.68	0.004	-.0466996	-.0117579
_cons	.2595437	.2738745	0.95	0.364	-.34325	.8623374

ln(RR)=0.2595437-0.0292287*latitude

Slope:

For each unit increase in latitude (moving farther away from equator), the ln(RR) measuring the BCG vaccine effectiveness decreased by 0.029 on average. The 95% CI for this estimate is (-0.047 to -0.012) and is statistically significant.

Or on a RR scale, exp(-0.0292287)=0.97

–Ratio of two RRs of outcome that are one unit apart in covariate of interest.

–(RR of TB at latitude b+1 unit)/(RR of TB at latitude b unit) = 0.97

Constant on a RR scale: exp(0.2595437)=1.30

At latitude=0 (i.e., equator), the estimated RR of TB was 1.30 (95% CI:0.71 to 2.37) on average comparing those receiving BCG vaccine vs. not receiving vaccine.

Could Latitude Explain Some of the Variation?

- Intercept only model

```
. metareg logrr, wsse(_selogES) mm

Meta-regression                                         Number of obs  =      13
Method of moments estimate of between-study variance    tau2           =   .3088
% residual variation due to heterogeneity               I-squared_res  =  92.12%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_cons	-.7141172	.1806966	-3.95	0.002	-1.107821	-.3204131

- With latitude in the model

```
. metareg logrr latitude, wsse(_selogES) mm graph

Meta-regression                                         Number of obs  =      13
Method of moments estimate of between-study variance    tau2           =   .0633
% residual variation due to heterogeneity               I-squared_res  =  64.21%
Proportion of between-study variance explained          Adj R-squared  =  79.50%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
latitude	-.0292287	.0079378	-3.68	0.004	-.0466996	-.0117579
_cons	.2595437	.2738745	0.95	0.364	-.34325	.8623374

- Proportion of total between-study variance explained by the model:

$$R^2 = \frac{\tau^2_{explained}}{\tau^2_{total}} = \frac{\tau^2_{total} - \tau^2_{unexplained}}{\tau^2_{total}} = 1 - \frac{\tau^2_{unexplained}}{\tau^2_{total}} = 1 - \left(\frac{0.0633}{0.3088}\right) = 0.7950$$

Variance(Heterogeneity) Explained by a Covariate

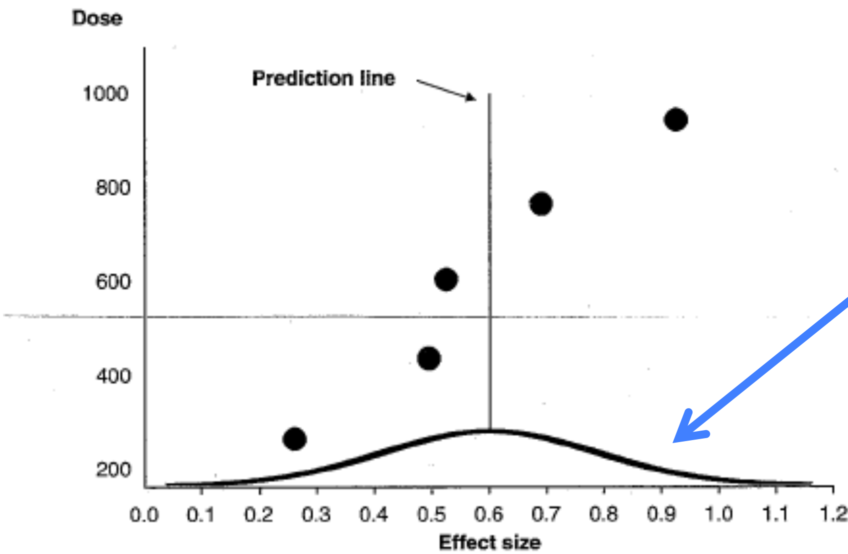


Figure 20.7 Between-studies variance (T^2) with no covariate.

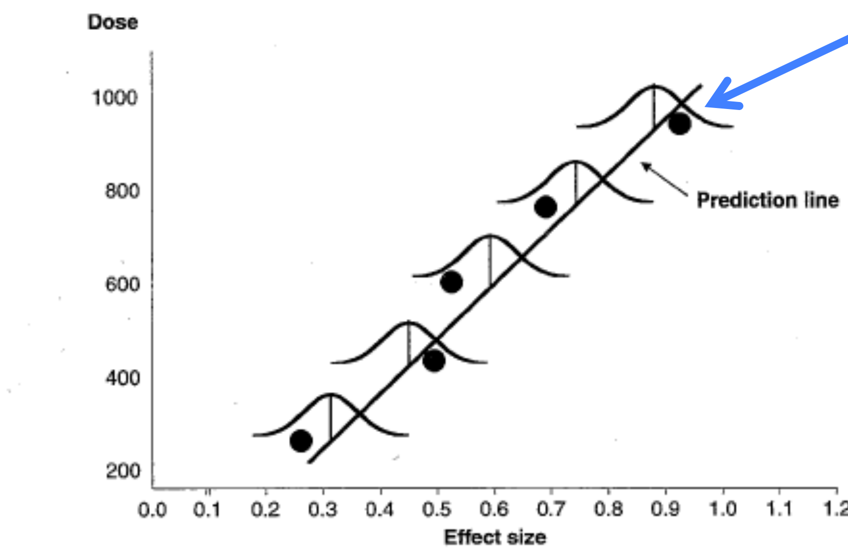


Figure 20.8 Between-studies variance (T^2) with covariate.

The spread of this distribution reflects the amount of between study variance (tau^2) without any covariate.

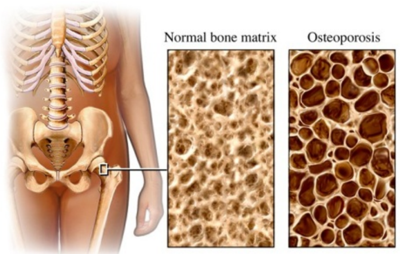
The spread of this distribution reflects the amount of between study variance with a covariate; assumed to be the same at each level of covariate.

The decrease in spread from the top to the bottom pane illustrates how a covariate explains some of the between-studies variance.

Borenstein, et al. Introduction to Meta-analysis. Chapter 20.

Introduction to Indirect Comparison

Which Treatment Should be Recommended?



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

A 67-year-old woman was referred by her primary care physician for treatment of osteoporosis and progressive bone loss. One year before the visit, the patient had discontinued hormone-replacement therapy. She had subsequently begun to experience midback pain and lost 1.5 inch in height. A x-ray scan has confirmed a diagnosis of osteoporosis. One year later, a second scan showed a further decrease of bone mineral density at the lumbar spine, as well as a compression fracture of the 11th thoracic vertebra.

Which treatment should be recommended?

Paraphrased from
Favus NEJM 2010

Treatment of Osteoporosis and Risk of Hip Fracture

- **Medical treatment:**
  Over 10 drugs/combination of drugs
  - ✓ Estrogen
  - ✓ Selective estrogen receptor modulators (SERMs)- Raloxifene
  - ✓ Calcium and/or vitamin D
  - ✓ Bisphosphonates, e.g., alendronate (Fosamax), risedronate (Actonel)
  - ✓ Other hormones, e.g., Teriparatide (Forteo)

- **Cost: ranges from $4 to $130 per month**

Where is the evidence?

Existing Evidence on the Treatment of Osteoporosis

14 Cochrane systematic reviews

Which interventions work? In Whom?

*"At a dose of 10 mg per day, **alendronate** results in **a statistically significant and clinically important reduction** in vertebral, non-vertebral, hip and wrist fractures (Wells 2010)."*

*"**No statistically significant reductions** in non-vertebral, hip, or wrist fractures were found, regardless of whether **etidronate** was used for primary or secondary prevention (Wells 2010)."*

*"**Vitamin D alone** appears **unlikely to be effective in preventing hip fracture**…**Vitamin D with calcium** **reduces hip fractures** (Avenell 2009)."*

Indirect comparison

- If we know how much taller is B to A and how much taller is C to A we know how much taller is B compared to C

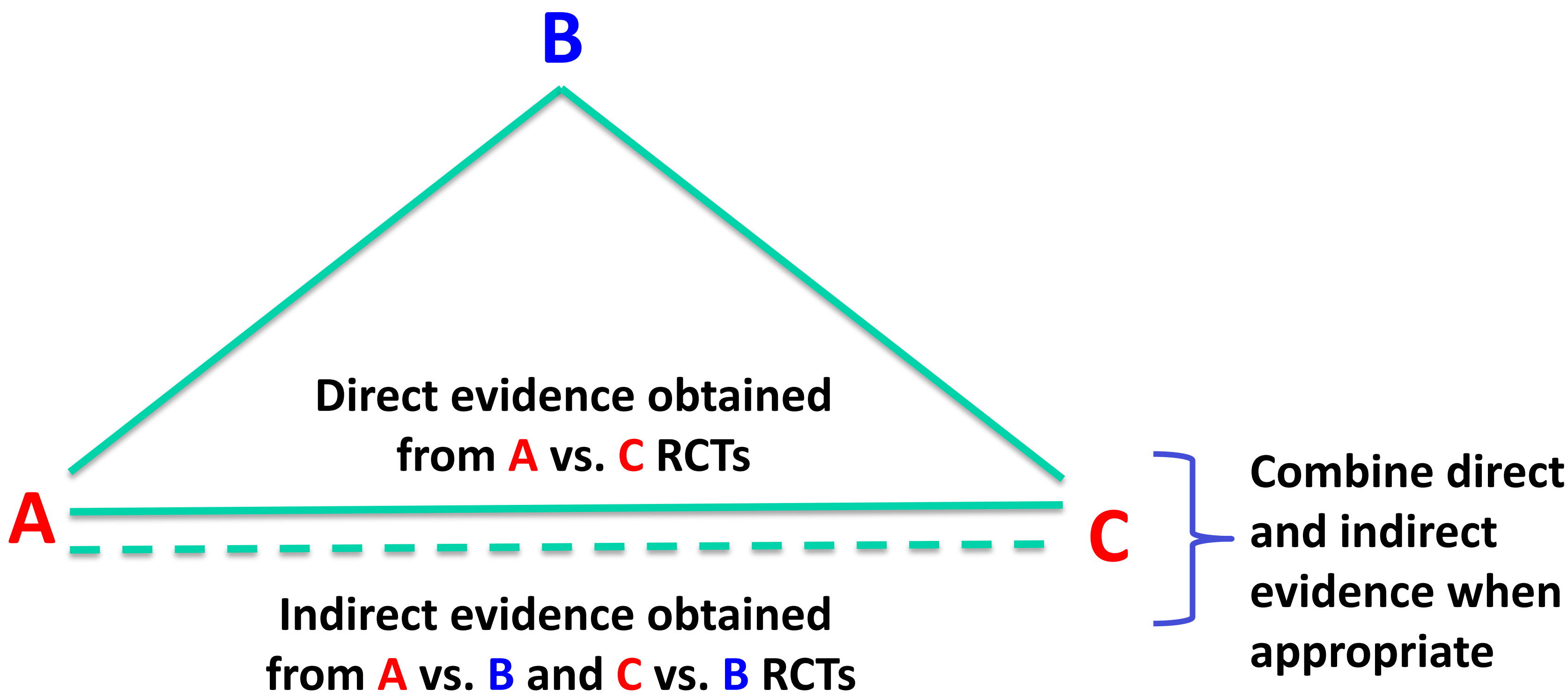
- For any pair B and C,

Typical (or mean) advantage of C over B =

advantage of C over A – advantage of B over A

Borrowed slide from G Salanti

Indirect Comparison and Network Meta-analysis Framework



Solid line: direct evidence
Dashed line: indirect evidence

Bucher 1997; Song 2003; Glenny 2005

Indirect Comparison Formulation – A Simple Example

Bupropion ⟷ Direct (9 RCTs) ⟷ Placebo ⟷ Direct (19 RCTs) ⟷ NRT*

$OR^{Direct}_{Bup\ vs.\ Pla} = \boxed{0.51}\ (0.36\ to\ 0.73); I^2 = 54\%$

$OR^{Direct}_{NRT\ vs.\ Pla} = \boxed{0.57}\ (0.48\ to\ 0.67); I^2 = 12\%$

Indirect (28 RCTs)

$$OR^{Indirect}_{Bup\ vs.\ NRT} = \frac{OR^{Direct}_{Bup\ vs.Pla}}{OR^{Direct}_{NRT\ vs.Pla}} = \frac{0.51}{0.57} = 0.90\ (0.61\ to\ 1.34)$$

On the log scale:

$$log\left(OR^{Indirect}_{Bup\ vs.\ NRT}\right) = log\left(OR^{Direct}_{Bup\ vs.Pla}\right) - log\left(OR^{Direct}_{NRT\ vs.Pla}\right)$$

$$Var\left[log\left(OR^{Indirect}_{Bup\ vs.\ NRT}\right)\right] = Var\left[log\left(OR^{Direct}_{Bup\ vs.Pla}\right)\right] + Var\left[log\left(OR^{Direct}_{NRT\ vs.Pla}\right)\right]$$

* NRT: Nicotine Replacement Therapy

Bucher 1997; Caldwell 2005; Glenny 2005; Song 2003; Song 2009

Statistical considerations in indirect comparisons and network meta-analysis

Said Business School, Oxford, UK

March 18-19, 2013