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LECTURE 4: ASSESSING VARIATIONS IN EFFECT

Looking at Heterogeneity

- Pre-plan how you will do this in protocol
- Consider:
  - Heterogeneity due to clinical characteristics (clinical heterogeneity)
  - Heterogeneity due to methodological characteristics (methodological heterogeneity)
  - Heterogeneity in study effect estimates (statistical heterogeneity)
    - Cochran's Q = statistical test for presence
    - I^2 statistic = magnitude

Looking at heterogeneity

- Might dictate
  - Whether to combine the studies at all
    - Best evidence synthesis instead??
  - Meta-analysis model choice (fixed vs random)
  - What subgroup analyses / variables to include in meta-regression

Heterogeneity

First; examine clinical heterogeneity

- How different are patients, interventions, outcomes from study to study
  - Refer to summary table
  - Might examine initial forest plot
- Look at trial characteristics
  - E.G. Age, sex, baseline severity, etc
- Determine if there are any differences that preclude a meta-analysis

Vitamin D and Death

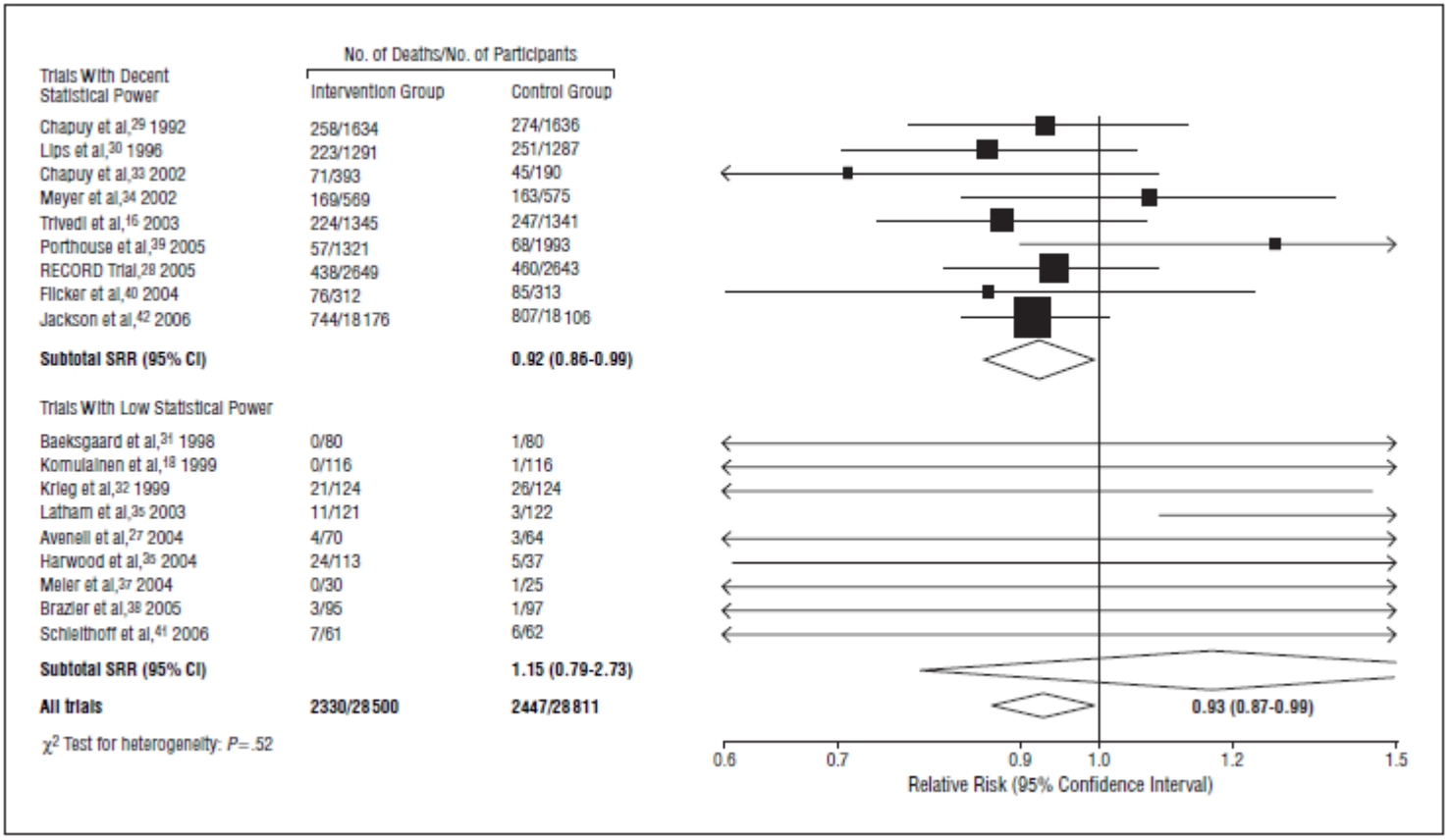


Figure. Meta-analysis of data on all-cause mortality in 18 randomized controlled trials with vitamin D. SRR indicates summary relative risk.

 Autier P. Arch Intern Med. 2007;167(16):1730-1737

ACL Prevention Summary Table

Study	Year of Publication	Study Design	Study Location	Follow-up Duration	Age Range (years)	Gender Ratio F:M	Type of Sport	Subject Unit Allocation	# in Control/ Intervention	Training Time
Cahill	1978	Cohort	Illinois	4 years	high school	all male	football	by season	1254/2481	80min @ descretion
Caraffa	1996	Cohort	Italy	3 seasons	n/a	n/a	soccer	by team	300/300	20 min per day
Gilchrest	2008	RCT	USA	3 months	mean 19.8	all female	soccer	by team	852/583	3x/wk
Kiani	2010	Cohort	Sweden	8 month	13-19 yrs	all female	soccer	by team	729/777	20-25m 2x/wk
Mandelbaum	2005	Cohort	California	2 years	14-18 yrs	all female	soccer	by team	1905/1041	20min @ discretion
Myklebust	2003	Cohort	Norway	3 years	n/a	all female	handball	by team	942/1705	15min 3x/wk
Olsen	2005	RTC	Norway	8 months	15-17 yrs	~ 8:1	handball	by team	879/958	15-20min 1x/wk
Pasanen	2008	RCT	Finland	6 months	mean 24 yrs	all female	floorball	by team	201/256	20-30m 1-3x/wk
Peterson	2005	Case control	Germany	8 weeks	16-18 yrs	all female	handball	by team	142/134	10min 3x/wk
Pfeiffer	2008	Cohort	USA	2 years	high school	all female	soccer/vball/ ball	by team	862/577	20min 2x/wk
Soderman	2000	RCT	Sweden	6 months	15-26yrs	all female	soccer	by team	100/131	10-15m 3x/wk
Steffen	2008	RCT	Norway	7 months	13-17yrs	all female	football	by team	1001/1091	10exc 1x/wk

Analyze and present results

If clinically heterogeneous

- A meta-analysis may not be warranted
  - Describe trials in a qualitative manner, considering trial design, methods, results etc
  - Best evidence synthesis

Or……

- Do a meta-analysis and make plans to explore the influence of these characteristics
  - pre-plan logical subgroup or meta-regression analyses

Analyze and present results

If clinically homogenous……check for **statistical heterogeneity**

- Are differences b/w trials > expected by chance?
- Cochran's Q = WSS= sum Wi $(Yi-M)^2$ (true variation and chance variation)
  - A test for the presence of statistical homogeneity (Ho= no difference between groups)
- Compared to the Chi-squared distribution
  - too little power with a collection of studies with small sample sizes
  - too much power with a collection of studies with large sample sizes
  - P usually set at 0.10 since has low power with small samples (as is mostly the case….SRs N=6-8 on average)

Q Test: Homogeneity Analysis

- Homogeneity analysis tests whether the assumption that all of the effect sizes are estimating the same population mean is a reasonable assumption.
- If homogeneity is rejected, the distribution of effect sizes is assumed to be heterogeneous.
  - Thus, a single mean ES not a good descriptor of the distribution
  - There are real between study differences, that is, studies estimate different population mean effect sizes.
  - Two options:
    - Fixed effects and model between study differences
      - Meta-regression
      - Analogue to the ANOVA
    - Fit a random effects model
      - Look for explanations for heterogeneity

Statistical heterogeneity

- I^2 = (Q-df / Q) x 100% = (variance between/variance total) x 100%
  - measure of the magnitude of statistical heterogeneity
  - proportion of inconsistency in individual studies that cannot be explained by chance (true variation only; between studies)
  - Rough guide for values of I-squared:
    - 0-40%: might not be important
    - 30-60%: may represent moderate heterogeneity*
    - 50-90%: may represent substantial heterogeneity*
    - 75-100%: considerable heterogeneity*
  - Not affected by number of studies
  - But as sample sizes increase, it will increase too, since variance within a larger study will ussually decrease, causing a larger weight for that study and therefore a larger Q value, and such a larger Isq
    - Overestimates heterogeneity with trials with large N

Q - The Homogeneity Statistic

Study	ES	w	w*ES	w*ES^2
1	-0.33	11.91	-3.93	1.30
2	0.32	28.57	9.14	2.93
3	0.39	58.82	22.94	8.95
4	0.31	29.41	9.12	2.83
5	0.17	13.89	2.36	0.40
6	0.64	8.55	5.47	3.50
7	-0.33	9.80	-3.24	1.07
8	0.15	10.75	1.61	0.24
9	-0.02	83.33	-1.67	0.03
10	0.00	14.93	0.00	0.00
		269.96	41.82	21.24

- Calculate a new variable that is the ES squared multiplied by the weight.
- Sum new variable.

Calculating Q

We now have 3 sums:

$$\sum w = 269.96$$
$$\sum (w \times ES) = 41.82$$
$$\sum (w \times ES^2) = 21.24$$

Q is can be calculated using these 3 sums:

$$Q = \sum (w \times ES^2) - \frac{\left[\sum (w \times ES)\right]^2}{\sum w} = 21.24 - \frac{41.82^2}{269.96} = 21.24 - 6.48 = 14.76$$

Interpreting Q

- Q is distributed as a Chi-Square
- df = number of ESs - 1
- Running example has 10 ESs, therefore, df = 9
- Critical Value for a Chi-Square with df = 9 @ p = 0.05 is: 16.92

- Since our Calculated Q (14.76) is less than 16.92, we **fail to reject** the null hypothesis of homogeneity.
- Thus, the variability across effect sizes does not exceed what would be expected based on sampling error.

Statistical Heterogeneity

- If the studies are statistically heterogeneous you need to determine how to proceed
  - Don't statistically combine
    - Do a qualitative systematic review
      - Describe trials and evidence narratively (best evidence synthesis)
  - Combine with a random effects model
  - Combine only those that are similar
  - Plan subgroup analyses to attempt to explain the heterogeneity

Analyze and present results

- If homogeneous (clinically and statistically) consider a meta-analysis (Statistically combining results)
  - If studies provide appropriate data it will be easy to turn into a meta-analysis (IPD or APD)

Vitamin D and Death

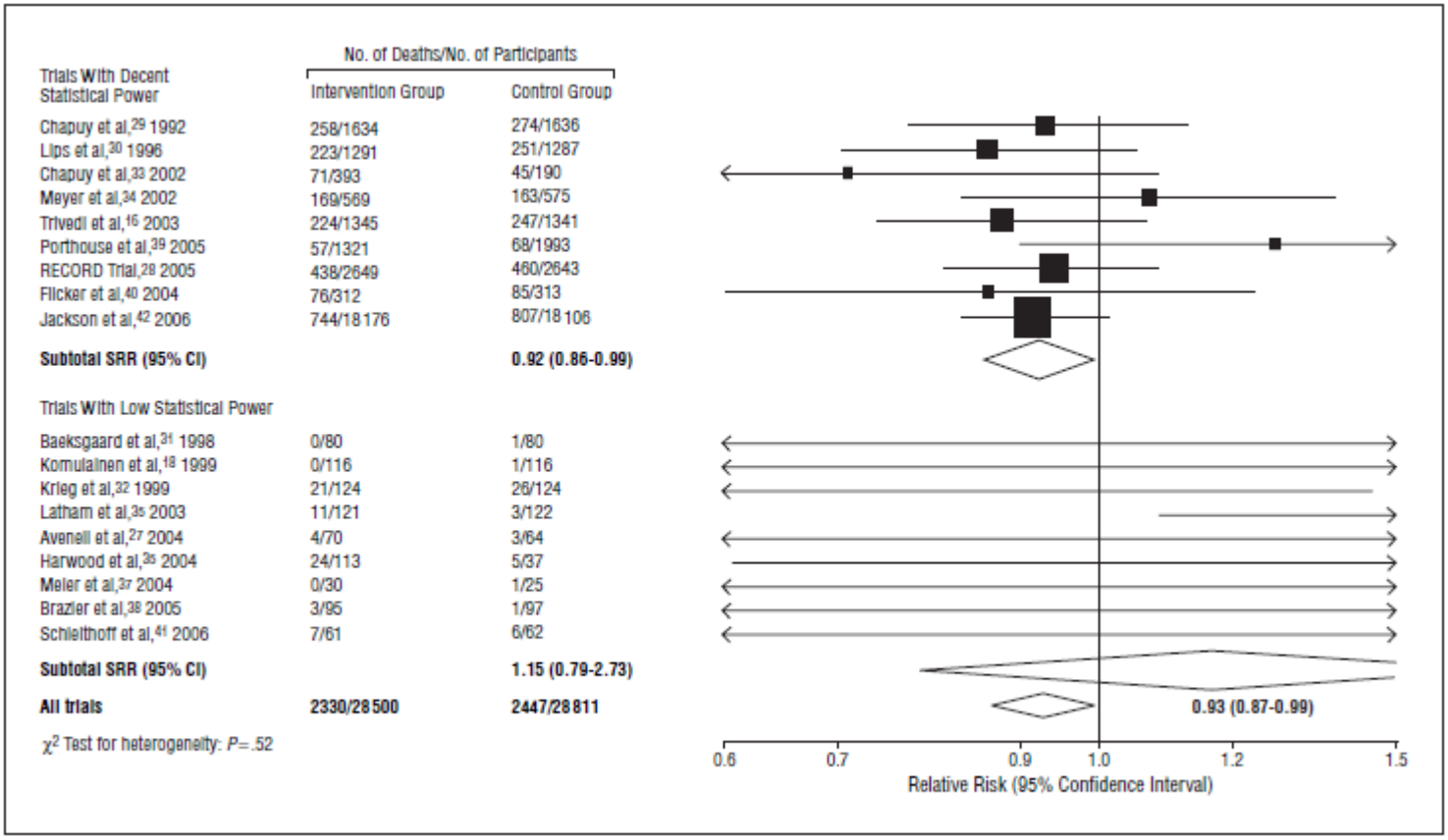


Figure. Meta-analysis of data on all-cause mortality in 18 randomized controlled trials with vitamin D. SRR indicates summary relative risk.

 Autier P. Arch Intern Med. 2007;167(16):1730-1737

Heterogeneous Distributions: What Now?

- Assume variability is random and fit a random effects model.
- Analyze excess between study (ES) variability
  - categorical variables with the analog to the one-way ANOVA / subgroup analyses
  - continuous variables and/or multiple variables
    - Meta-regression
    - Subgroup analyses

Exploring heterogeneity

- Test for covariates that you expect influence summary effect estimate
- Ideally pre-planned in protocol
  - Use expert advice
  - Be based on logical or scientific rationale
  - Be few where possible
  - List all proposed methods
    - Decision tool for level of statistical heterogeneity
    - Statistical techniques
      - Multiple meta-analyses on subgroups of trials with particular characteristics
      - Meta-regression
    - How will examine data to identify post-hoc covariates

Exploring Heterogeneity

- Subgroup analyses
  - Do separate meta-analyses on subgroups of studies (e.g., different intervention characteristics)
  - Compare means with analogue to the ANOVA
- Meta-regression
  - Same as standard regression
  - Outcome variable (pooled effect estimate) is predicted by one or more explanatory variables (covariates; e.g. dose or duration of intervention)
  - 10 trials per covariate

Analyzing Heterogeneous Distributions: The Analog to the ANOVA

Study	Grp	ES	w	w*ES	w*ES^2
1	1	-0.33	11.91	-3.93	1.30
2	1	0.32	28.57	9.14	2.93
3	1	0.39	58.82	22.94	8.95
4	1	0.31	29.41	9.12	2.83
5	1	0.17	13.89	2.36	0.40
6	1	0.64	8.55	5.47	3.50
			151.15	45.10	19.90
7	2	-0.33	9.80	-3.24	1.07
8	2	0.15	10.75	1.61	0.24
9	2	-0.02	83.33	-1.67	0.03
10	2	0.00	14.93	0.00	0.00
			118.82	-3.29	1.34

- Calculate the 3 sums for each subgroup of effect sizes.

A grouping variable (e.g., random vs. nonrandom)

Analyzing Heterogeneous Distributions: The Analog to the ANOVA

Calculate a separate Q for each group:

$$Q_{GROUP\_1} = 19.90 - \frac{45.10^2}{151.15} = 6.44$$

$$Q_{GROUP\_2} = 1.34 - \frac{-3.29^2}{118.82} = 1.25$$

Analyzing Heterogeneous Distributions: The Analog to the ANOVA

The sum of the individual group Qs = Q within:

$$Q_W = Q_{GROUP\_1} + Q_{GROUP\_2} = 6.44 + 1.25 = 7.69$$

$$df = k - j = 10 - 2 = 8$$

Where k is the number of effect sizes and j is the number of groups.

The difference between the Q total and the Q within is the Q between:

$$Q_B = Q_T - Q_W = 14.76 - 7.69 = 7.07$$

$$df = j - 1 = 2 - 1 = 1$$

Where j is the number of groups.

Analyzing Heterogeneous Distributions: The Analog to the ANOVA

All we did was partition the overall Q into two pieces, a within groups Q and a between groups Q.

$Q_B = 7.69$	$df_B = 1$	$Q_{CV\_.05}(1) = 3.84$	$p_B < .05$
$Q_W = 7.07$	$df_W = 8$	$Q_{CV\_.05}(8) = 15.51$	$p_W > .05$
$Q_T = 14.76$	$df_T = 9$	$Q_{CV\_.05}(9) = 16.92$	$p_T > .05$

The grouping variable accounts for significant variability in effect sizes.

Mean ES for each Group

The mean ES, standard error and confidence intervals can be calculated for each group:

$$ES_{GROUP\_1} = \frac{\sum(w \times ES)}{\sum w} = \frac{45.10}{151.15} = 0.30$$

$$ES_{GROUP\_2} = \frac{\sum(w \times ES)}{\sum w} = \frac{-3.29}{118.82} = -0.03$$

Analyzing Heterogeneous Distributions: Multiple Regression Analysis

- Analog to the ANOVA is restricted to a single categorical between studies variable.
- What if you are interested in a continuous variable or multiple between study variables?
- Weighted Multiple Regression Analysis (meta-regression)
  - as always, it is weighted analysis
  - CMA, STATA etc will run these

Meta-Regression Analysis

- Analysis is weighted.
- Q for the model indicates if the regression model explains a significant portion of the variability across effect sizes.
- Q for the residual indicates if the remaining variability across effect sizes is homogeneous. (eg. CMA)

Subgroup and Sensitivity analyses

Table 3. Vitamin D Supplements and All-Cause Mortality: Subgroup and Sensitivity Analysis

Variable	No. of Trials in the Meta-Analysis	SRR (95% CI)	I^2 Parameter, %[a]	χ^2 for Heterogeneity, *P* Value
Subgroup analysis				
Follow-up ≥3 y	6	0.92 (0.83-1.01)	0	.50
Follow-up <3 y	12	0.95 (0.83-1.10)	5	.40
Vitamin D, ≥800 IU/d	12	0.93 (0.85-1.03)	15	.30
Vitamin D, 300 to 799 IU/d	6	0.92 (0.82-1.03)	0	.70
Placebo-controlled trials only	12	0.92 (0.86-0.98)	0	.51
Open-label trials only[b]	6	1.10 (0.84-1.45)	0	.67
Intervention was vitamin D and calcium supplements	13	0.93 (0.86-1.01)	0	.69
Intervention was vitamin D supplements only	5	0.91 (0.78-1.06)	42	.14
Cholecalciferol (vitamin D_3) and not ergocalciferol (vitamin D_2)	16	0.93 (0.87-0.98)	0	.43
Sensitivity analysis				
Exclusion of Meyer et al,[34] 2002	17	0.92 (0.86-0.98)	0	.54
Inclusion of Law et al,[24] 2006	19	0.97 (0.89-1.06)	32	.09

Abbreviation: CI, confidence interval; SRR, summary relative risk.

[a] The I^2 parameter represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[46]

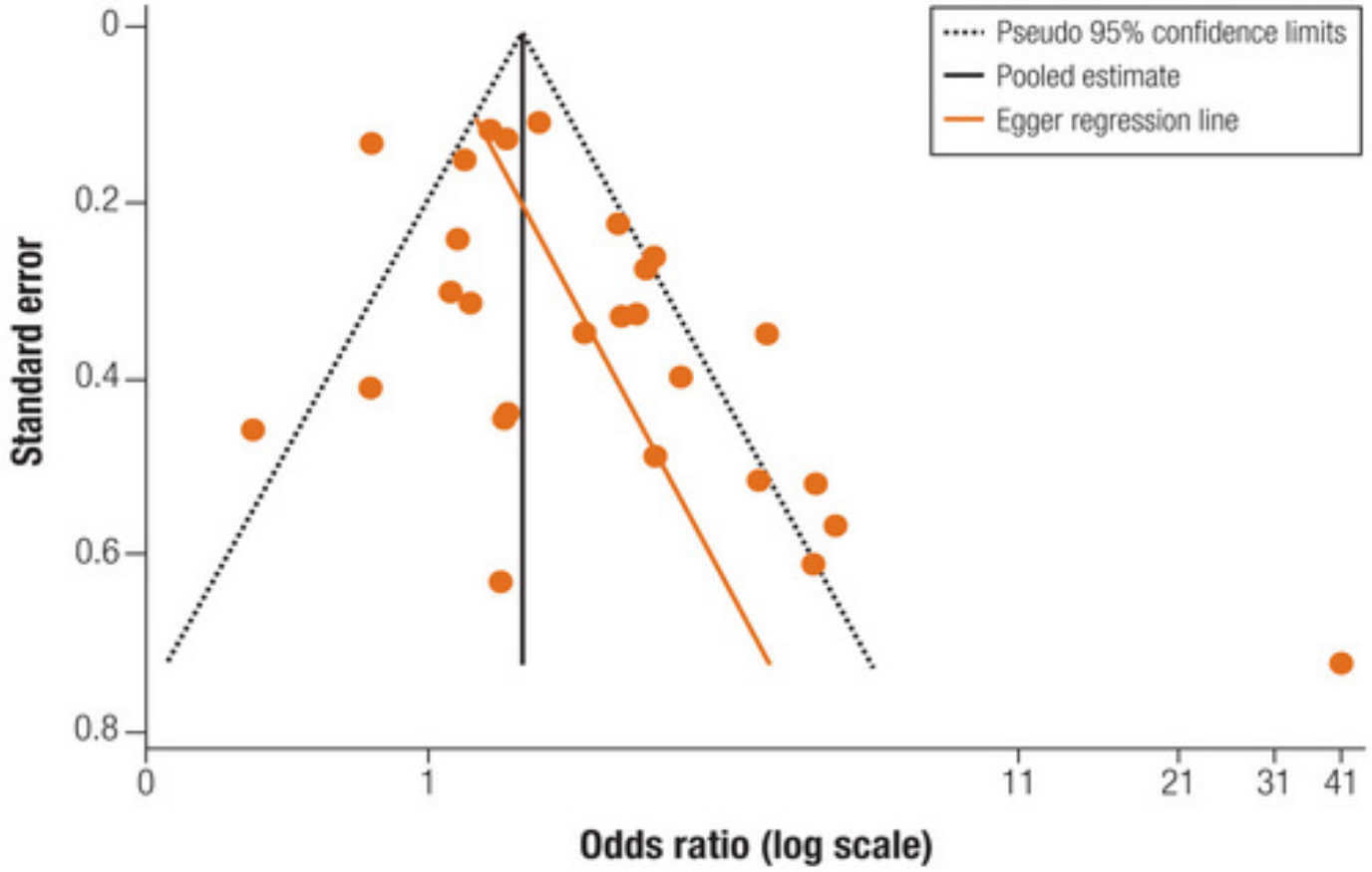
[b] No placebo for vitamin D in the control group.

Sensitivity analyses

- Tests the robustness of findings relative to decisions made in the review process
  - Excluding certain studies
    - Those of low quality (high in bias)
    - For those with imputed data (e.g., variances)
      - We may do this…some data may be missing
- Can do separate meta-analyses or meta-regression

Assessment of Publication Bias

- Publication bias = higher likelihood of published studies to have positive results
- Tested with a funnel plot (plot variance against effect measure)
  - Visually…funnel shape
  - Statistically; Egger's test, Begg's test
- Idea is…all things being equal
  - larger studies should more precisely estimate some "true" effect
  - Smaller studies will estimate the same "true" effect but do so less precisely
    - Should spread equally around the larger study estimates
    - If not, then studies are being published in a selective way



The funnel plot shows asymmetry (Fig. 2), with significant Begg's ($P = 0.027$) and Egger's tests ($P = 0.005$).

 Dherani M. et al. Bulletin of the World Health Organization 2008;86:390–398.

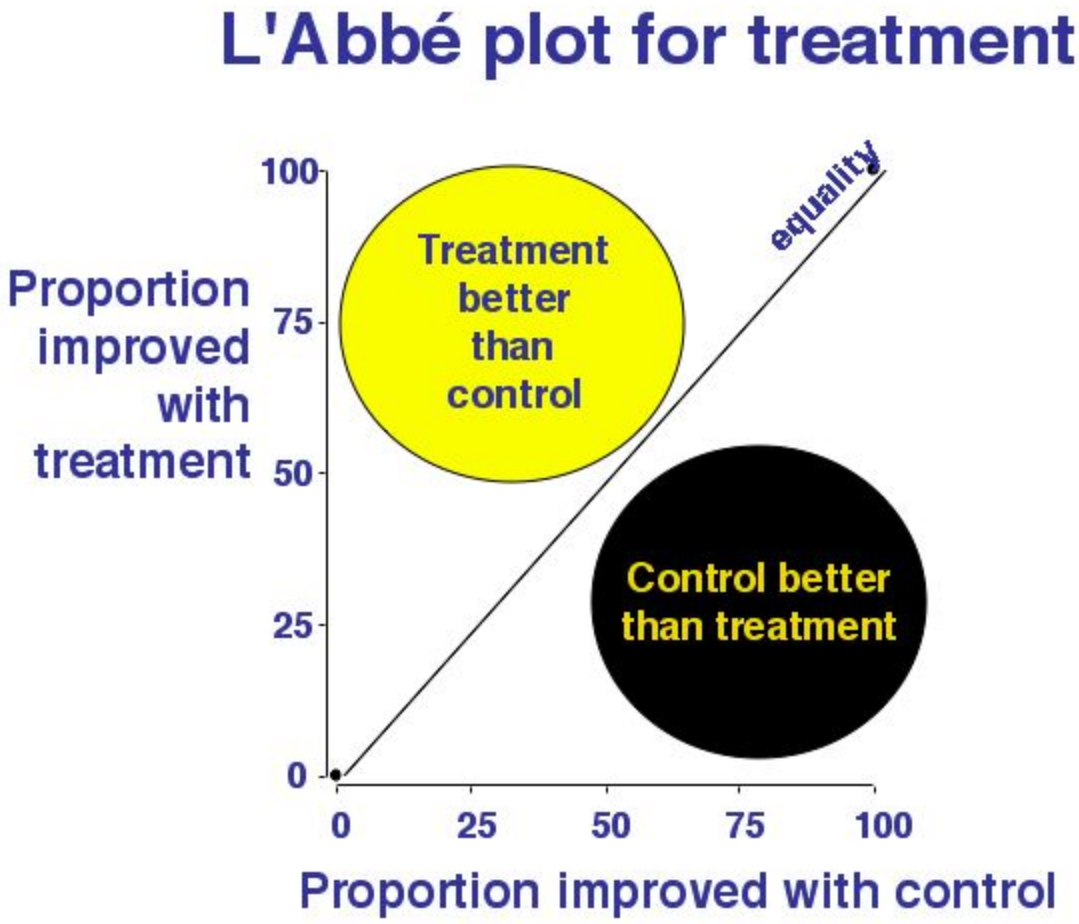
Statistical tests for funnel plot asymmetry

- Egger test:
  - Linear regression of the intervention estimate against is SE, weighted by the inverse variance of the intervention effect estimate
- Begg test:
  - Rank correlation between standardized intervention effect and is SE
- Both have low power, require 10+ studies, should be interpreted with caution
- Thus, should use visual data as well

Funnel Plots

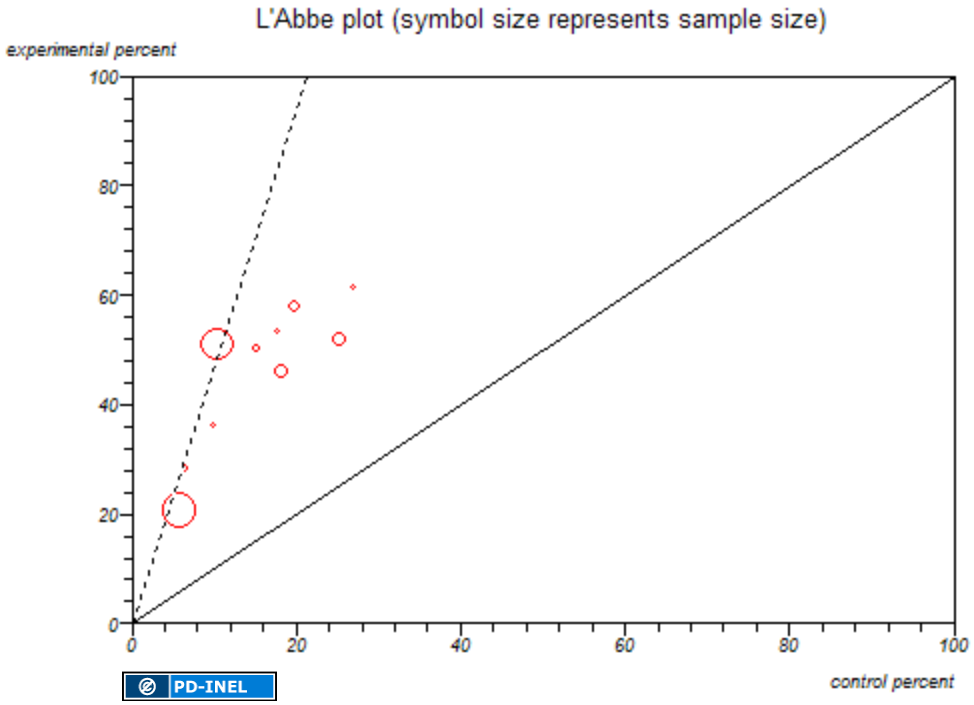
- Reasons for funnel plot asymmetry (small studies effects)
  - Lack of publication of small studies = publication bias
  - Inflated results of small studies from poor methods
  - True heterogeneity (e.g., smaller studies had more intensely administered intervention..personalized ACL prevention program) others??
  - Chance

L'Abbe Plot



This plots the event rate in the experimental (intervention) group against the event rate in the control group, as an aid to exploring the heterogeneity of effect estimates within a meta-analysis (Song, 1999; L'Abbé et al. 1987).

L'Abbe Plot



This plots the event rate in the experimental (intervention) group against the event rate in the control group, as an aid to exploring the heterogeneity of effect estimates within a meta-analysis (Song, 1999; L'Abbé et al. 1987).

Computer Lab!!

SPH II Classroom A