Public Health Sciences 310
Epidemiologic Methods

Meta-Analysis

February 20, 2024

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Systematic Reviews and Meta- Analysis

ex) Point estimates, RR, OR

- The unit/subject of the study is not individuals but studies
- Goal: Obtain comprehensive and unbiased assessment of the best current information, assembled in a manner that minimizes biases and provides a solid basis for decisions
- Systematic review steps intended to minimize biases
- Approach is *well-defined, systematic, reproducible*
- Aims to identify *all relevant* studies on a *well-defined research question*
- If appropriate, summarizes numerical estimate of overall effect (*meta-analysis*)

Meta-analysis vs systematic review

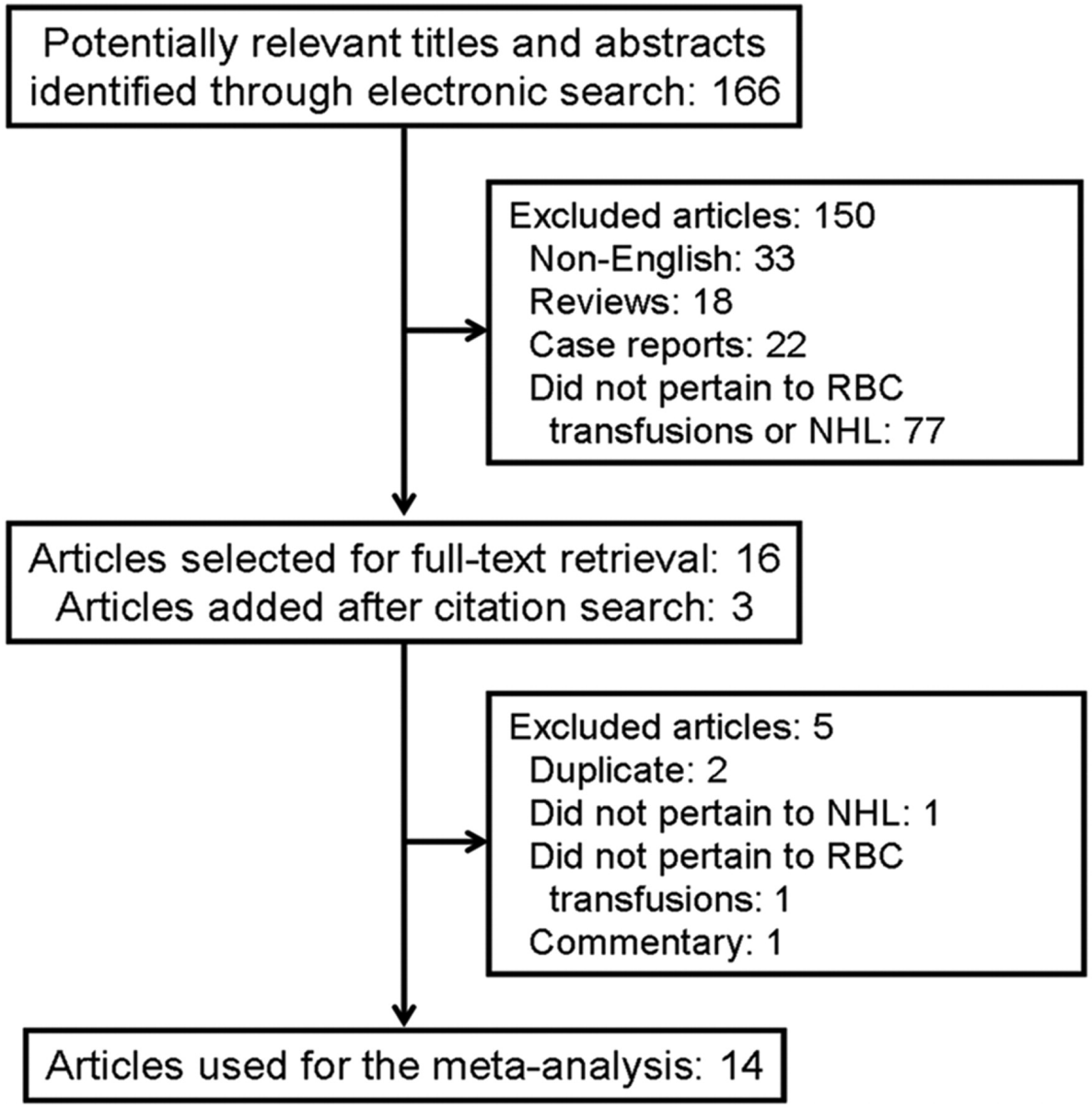
- Meta-analysis is the statistical calculation of an overall effect size from the individual studies
- Systematic reviews may or may not contain a meta-analysis
- Meta-analysis may or may not be part of a systematic review
- Good systematic review will conduct a meta-analysis *if appropriate*
- Typically MA will be a suitably weighted average of individual effects to obtain a summary result

Elements of Good Systematic Reviews & Meta-Analysis

- Systematic Reviews:
  - A written protocol
  - Clear research question
  - Comprehensive, unbiased identification of completed studies
  - Prespecified inclusion and exclusion criteria for studies
  - Uniform, unbiased extraction of study characteristics & findings
  - Uniform, clear presentation of individual study results
  - Quality assessment
- Meta-Analysis:
  - Summary estimate of effect and CI based on eligible studies *when appropriate*
  - Assessment of heterogeneity of findings of individual studies
  - Assessment of potential for publication bias
  - Subgroup and sensitivity analyses

Source: Hulley

Example: Search results



Jorge J. Castillo et al. Blood 2010;116:2897-2907

Quality Assessment

- The validity of a systematic review ultimately depends on the scientific method of the retrieved studies and the reporting of data
  - GRADE (Grading of Recommendations Assessment, Development and Evaluation)

    Guyatt et al., BMJ. 2008;336(7651):995-8.
  - NOS: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis (high quality NOS>6)

Data Synthesis

Once the data have been extracted and their quality and validity assessed, the outcomes of individual studies within a systematic review may be pooled and presented as summary outcome or effect

META-ANALYSIS

Summary estimates of effects & Heterogeneity

- Summary effects obtained as weighted averages
- Calculations for relative risks and odds ratio done on transformed scale, then untransformed to original
- Weights reflect relative sample sizes
- Random effects vs fixed effects models
- Formal tests of heterogeneity
  - often use p>0.1 as guideline

Solid vertical line: set at the null value

Square black boxes and corresponding horizontal lines: point estimates and their 95% CI

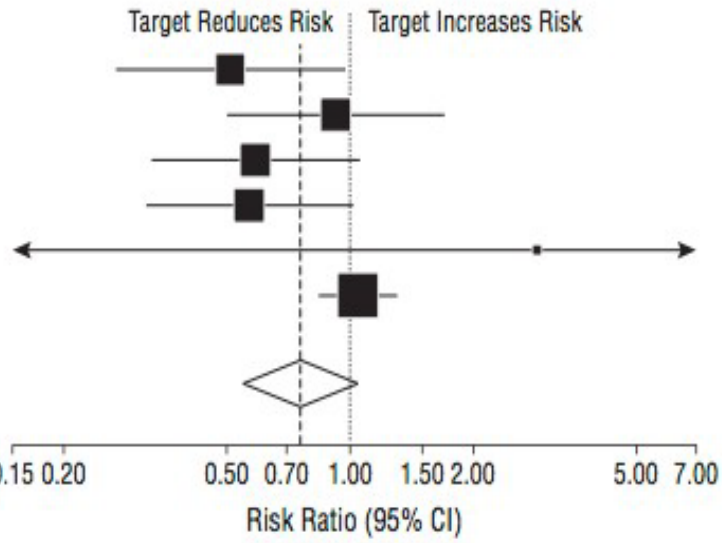
Area of each black box: shows the point estimate is proportional to the precision of the estimate

Diamond: represents the summary measure of the meta association

A Outcome: Mortality

Trial	Events		Risk Ratio (95% CI)	Weight, %
	Intensive	Standard		
ABCD-H	13/237	25/233	0.51 (0.27-0.97)	15.26
ABCD-N	18/237	20/243	0.92 (0.50-1.70)	16.29
HOT-80/85	17/499	29/501	0.59 (0.33-1.06)	17.11
HOT-80/90	17/499	30/501	0.57 (0.32-1.02)	17.23
ABCD-2V	1/66	0/63	2.87 (0.12-69.06)	1.00
ACCORD-BP	150/2362	144/2371	1.05 (0.84-1.30)	33.11
Overall (I^2=47.8%, P=.9)	216/3900	248/3912	0.76 (0.55-1.05)	100.00

NOTE: Weights are from random-effects analysis



McBrien et al., Arch Intern Med 2012

Statistical Models: Fixed vs Random Effects

- *Fixed effects (or Mantel-Haenzel) model:*
  - Assume the underlying true exposure effect in each study is the same
  - Combined effect is an estimate of this common effect size

$$\hat{\beta}_s = \beta + \varepsilon_s,\ s = 1,\ldots,S \text{ studies}$$

β = true common log relative risk

ε_s = random within – study (sampling var iability)

$\hat{\beta}_s$ = estimated log relative risk in study s

$E(\varepsilon_s) = 0,\ s = 1,\ldots,S$

$Var(\varepsilon_s) = Var(\hat{\beta}_s)$

$$\text{Pooled } \hat{\beta} = \frac{\sum_{s=1}^{S} w_s \hat{\beta}_s}{\sum_{s=1}^{S} w_s},\ w_s = [\hat{Var}(\hat{\beta}_s)]^{-1}$$

$$\hat{Var}(\hat{\beta}) == \left(\sum_{s=1}^{S} [\hat{Var}(\hat{\beta}_s)]^{-1}\right)^{-1} = [\sum_{s=1}^{S} w_s]^{-1}$$

- min imum var iance weights

- *Random* effects (or DerSimonian-Laird) model:
  - Assumes that each study has its own (true) exposure effect and that there is a random distribution of these true exposure effects around a central effect
  - Incorporates variation between studies
  - Combined effect is an estimate of the mean effect in the distribution of effects

$$\hat{\beta}_s = \beta + b_s + \varepsilon_s,\ s = 1,\ldots,S \text{ studies}$$

β = true common log relative risk

b_s = random between – studies var iability

ε_s = random within – study (sampling var iability

$\hat{\beta}_s$ = estimated log relative risk in study s

$E(\varepsilon_s) = E(b_s) = 0,\ s = 1,\ldots,S$

$Var(\varepsilon_s) = Var(\hat{\beta}_s),\ s = 1,\ldots,S$

$Var(b_s) = \sigma_B^2,\ s = 1,\ldots,S$

$$\text{Pooled } \hat{\beta} = \frac{\sum_{s=1}^{S} w_s \hat{\beta}_s}{\sum_{s=1}^{S} w_s},\ w_s = [\hat{Var}(\hat{\beta}_s) + \hat{\sigma}_B^2]^{-1}$$

$$Var(\hat{\beta}) = \left(\sum_{s=1}^{S} [\hat{Var}(\hat{\beta}_s) + \hat{\sigma}_B^2]^{-1}\right)^{-1} = \left(\sum_{s=1}^{S} w_s\right)^{-1}$$

- min imum var iance weights

Differences

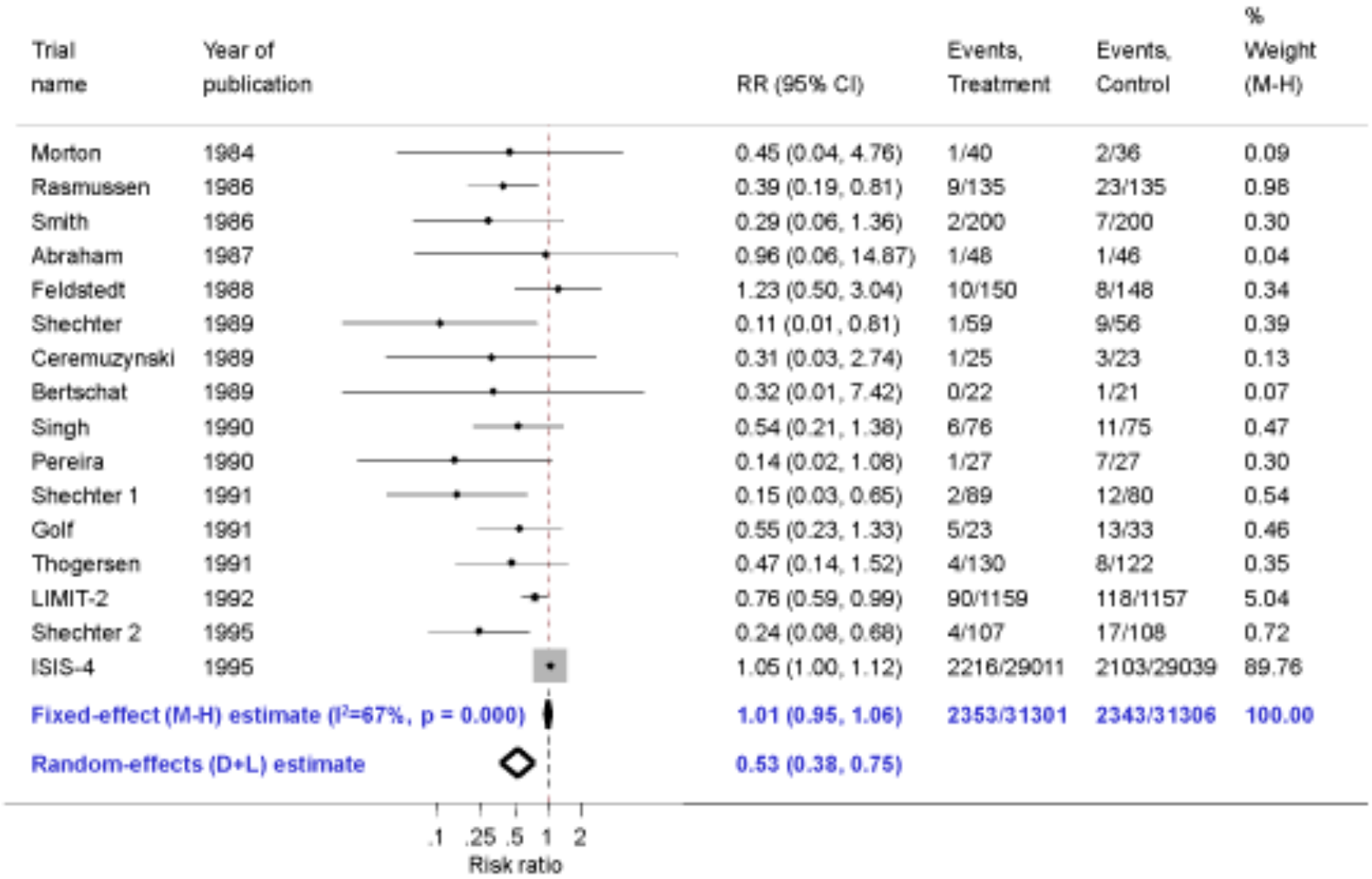
- Weighting of individual studies
  - Large studies have a greater impact in fixed effect model than in random effects model.
  - Weighting is generally by a study's inverse variance rather than sample size (though both are closely related.)

- Confidence intervals for summary effect wider under the random effects model than under the fixed effect model (random effect model more conservative as it accounts not only the within-study variance but also the variance between studies).

Choice of Model

- Fixed Effect – 2 Conditions:
  - All studies in analysis are functionally identical.
  - Want to calculate common effect size for the identified population, rather than generalizing to other populations.
- Random Effects Model – 2 Conditions
  - Subjects and interventions differ among studies in ways that would impact the results
  - Interested in generalizing to different populations.
- Run both models. If test of heterogeneity is significant, go for random effects model (Weight decreases for larger studies compared to the fixed effects model)
- Pooling in the presence of heterogeneity may be seriously misleading

Comparison of fixed- and random-effects meta-analytic estimates of the effect of intravenous magnesium on mortality following myocardial infarction



Sources of Between Study Heterogeneity

- Different study designs
- Different length of follow-up
- Different distributions of effect modifiers
- Different statistical methods/models used
- Different sources of bias
- Study quality
- Etc.

Examining Heterogeneity

- Statistical tests
  - Cochrane Q statistic:
    - Calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method.
    - A p value decided a priori (e.g., $p<0.1$) defines the presence of significant heterogeneity.
  - I^2 statistic:
    - Describes the percentage of variation across studies that is due to heterogeneity rather than chance.
    - >50%: represent substantial heterogeneity
- Visual inspection/graphical approach
  - Forest plot
  - Galbraith plot

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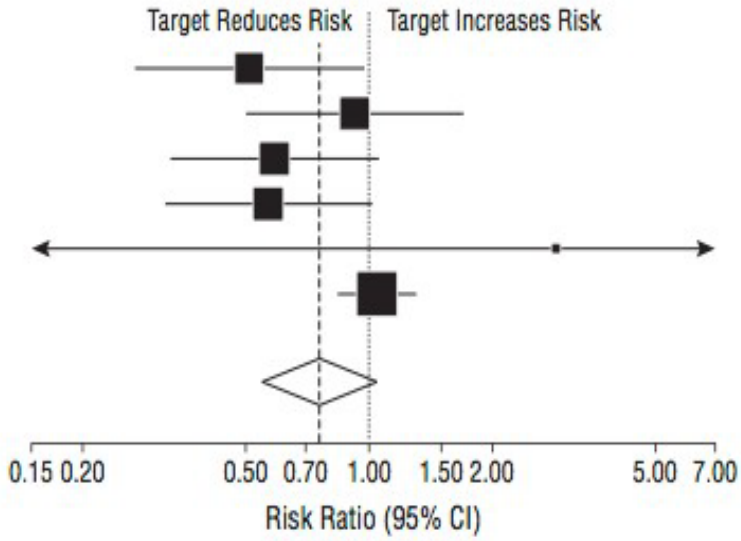
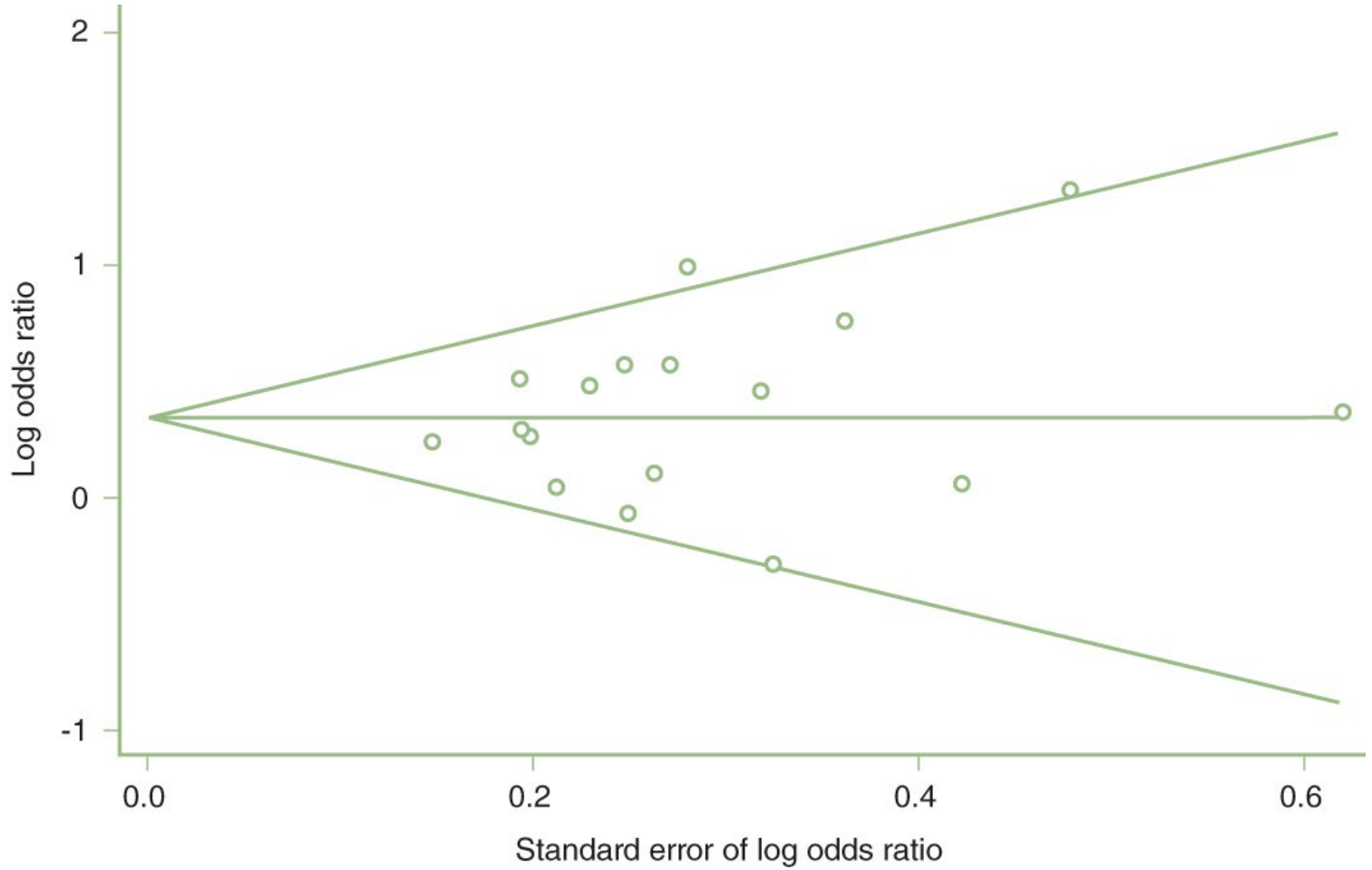


McBrien et al., Arch Intern Med 2012

Publication Bias

- “Negative” studies are less likely to be submitted or published
- Can bias the results of a meta-analysis toward a positive finding
- Assessing publication bias:
  - Funnel plots (representing effect by sample size)
  - Statistical analysis:
    - Trim-and-fill method (estimates and adjusts for the potential effect that nonpublished studies might have on the measured outcome)
    - Macaskill’s approach, Egger’s test, Begg’s test, etc.

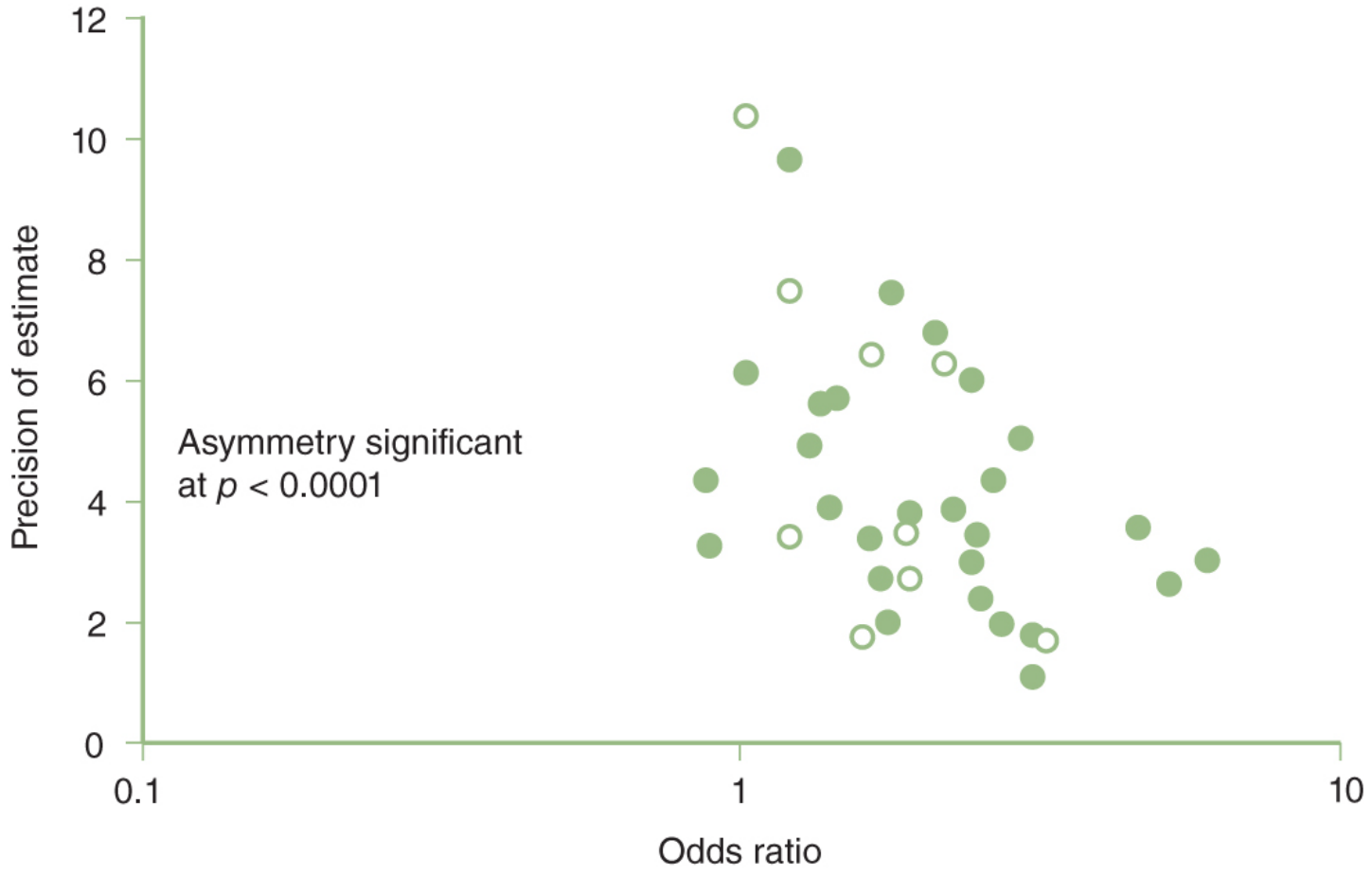
Assessing Publication Bias – Funnel Plot



Funnel plot for assessing publication bias in relation to gluthatione *S*-transfer as M1 (GSTM1) null status and bladder cancer risk. The horizontal line corresponds to the meta-analysis pooled odds ratio estimate.

Source: Szklo and Nieto, Ch 10

Assessing Publication Bias



Funnel plot of odds ratio (OR) of family history of stroke as a risk factor for stroke vs precision (i.e., inverse of the standard error of the OR) in case-control (full circles) and cohort studies (empty circles). Note the asymmetry of the plot due to lack of estimates when OR < 1 (i.e., small negative studies).

Source: Szklo and Nieto, Ch 10

Subgroup and sensitivity analyses

- Looking at effects in more homogeneous subgroups helpful
- Account for heterogeneity
- Sensitivity: repeat analysis under different design choices

Meta-analysis of observational studies

- These are often highly problematic
- Why? Apples-to-apples comparison hard to achieve
- No common research design
- Bias, treatment of confounding, etc.
- Diversity of study population
- Selection bias or ascertainment bias in one study can taint MA
- MOOSE (Meta-analysis of observational studies in epidemiology) guidelines: useful checklist in general

Meta-analysis vs. Pooled analysis

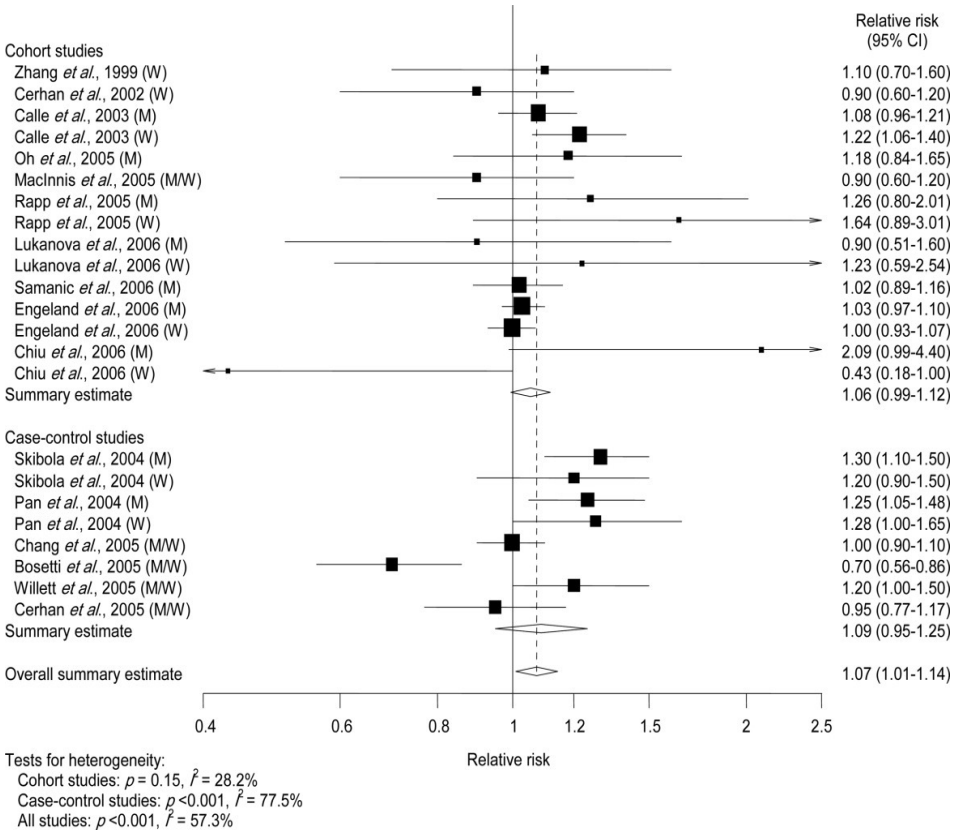
Int. J. Cancer: **121,** 1564–1570 (2007)

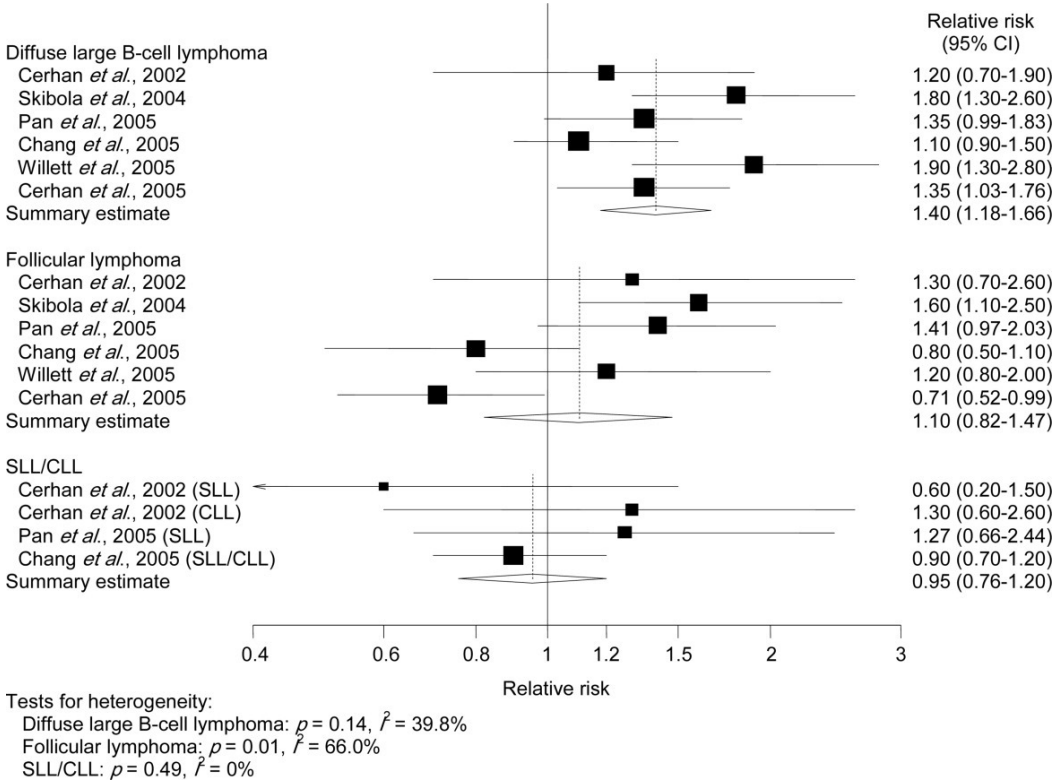
Obesity and risk of non-Hodgkin's lymphoma: A meta-analysis

Susanna C. Larsson* and Alicja Wolk

Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

to non-Hodgkin's lymphoma have been inconsistent. We conducted a meta-analysis to summarize the epidemiologic evidence on the association between excess body weight and risk of non-Hodgkin's lymphoma. Relevant studies were identified by searching MEDLINE (1966 to February 2007) and the reference lists of retrieved publications. We included cohort and case–control studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) for the association of body mass index (BMI) with non-Hodgkin's lymphoma incidence or mortality. A random-effects model was used to combine results from individual studies. Sixteen studies (10 cohorts and 6 case–control studies), with 21,720 cases, met the inclusion criteria. Compared to individuals





Meta-analysis vs. Pooled analysis

Medical History, Lifestyle, Family History, and Occupational Risk Factors for Follicular Lymphoma: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

Martha S. Linet, Claire M. Vajdic, Lindsay M. Morton, Anneclaire J. de Roos, Christine F. Skibola, Paolo Boffetta, James R. Cerhan, Christopher R. Flowers, Silvia de Sanjosé, Alain Monnereau, Pierluigi Cocco, Jennifer L. Kelly, Alexandra G. Smith, Dennis D. Weisenburger, Christina A. Clarke, Aaron Blair, Leslie Bernstein, Tongzhang Zheng, Lucia Miligi, Jacqueline Clavel, Yolanda Benavente, Brian C. H. Chiu

Methods We assessed associations of medical, hormonal, family history, lifestyle, and occupational factors with FL risk in 3530 cases and 22 639 controls from 19 case–control studies in the InterLymph consortium. Age-, race/ethnicity-, sex- and study-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression.

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
BMI, weight, and height				
BMI as a young adult, kg/m^2				
15–<18.5	382 (2.5)	66 (2.5)	0.90 (0.67 to 1.19)	
18.5–<22.5	2800 (18.1)	464 (17.8)	1.00 (referent)	.001
22.5–<25	1391 (9.0)	201 (7.7)	1.03 (0.85 to 1.24)	
25–<30	838 (5.4)	164 (6.3)	1.49 (1.21 to 1.83)	
30–50	172 (1.1)	34 (1.3)	1.46 (0.98 to 2.17)	
Continuous (5 kg/m^2 increase in BMI)	5583	929	1.21 (1.09 to 1.35)	<.001
Usual adult BMI, kg/m^2				
15–<18.5	267 (1.6)	25 (0.9)	0.67 (0.44 to 1.03)	
18.5–<22.5	3481 (20.3)	538 (19.4)	1.00 (referent)	.143
22.5–<25	4276 (25.0)	706 (25.5)	1.09 (0.96 to 1.23)	
25–<30	6112 (35.7)	959 (34.6)	1.01 (0.89 to 1.14)	
30–<35	1760 (10.3)	325 (11.7)	1.07 (0.91 to 1.25)	
35–50	608 (3.6)	109 (3.9)	0.93 (0.73 to 1.17)	
Continuous (5 kg/m^2 increase in BMI)	16 504	2662	0.99 (0.95 to 1.04)	.735

J Natl Cancer Inst Monogr 2014;48:26–40

Resources

- Higgins J and Thomas S (editors). *Cochrane Handbook for Systematic Reviews of Interventions. Version 6.2. The Cochrane Training, 2021. Available from* https://training.cochrane.org/handbook/current

- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA 2000; 283(15): 2041.*

- Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. JAMA Surg 2021;156:787-788.

- Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group. Analysing data and undertaking meta-analysis. https://training.cochrane.org/handbook/current/chapter-10