Meta-Analysis based upon the Meta-Likelihood: a unifying approach for dealing with covariates, heterogeneity, publication bias and study quality

Dankmar Böhning
Aim of the talk

- To demonstrate the potential usefulness of MA using the right tools at hand of a recent controversial example
- To enlighten the impact of ignorance and consequences for medical practice
Overview

- Introduction
- MA: HRT and Breast Cancer
- Outcome Measure
- Meta-Likelihood
- Modelling with the Meta-Likelihood
  - Heterogeneity
  - Covariates
  - Publication Bias
  - Study Quality
  - MA: HRT and Breast Cancer
Introduction

• Meta-Analysis: numerous good reasons for it (base tool for EBM)
  – Type II error and conflicting findings
  – Sample size problem
  – Generalizability
  – Potential for deeper understanding

• Critics: Guidelines for GMAP
HRT and Breast Cancer

Die Tagesthemen[1]

Das CCTV-News bei Channel One unter dem Thema "Hormone" wurde von der ARD erstmals ausgestrahlt. Der Public German Television Channel One has typically led the news segment.

Neue Zweifel an Hormontherapie


Über die Risiken der Hormontherapie sprach Anne Will mit Martina Dören, Professorin für Frauengesundheit am Berliner Universitätsklinikum "Benjamin Franklin" und Mitglied der Deutschen Menopause Gesellschaft.
HRT and Breast Cancer

- OR of 1.26 provided in the WHI-trial (Rossouw et al. 2002 JAMA)
- Implication: in a population with one million women and baseline risk of 1 in 100 one can expect 2600 cases through treatment.

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**Risk and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women**

Principal Results From the Women’s Health Initiative Randomized Controlled Trial

**Writing Group for the Women’s Health Initiative Investigators**

**THE WOMEN’S HEALTH INITIATIVE (WHI)** focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161,809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States. This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2003, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential cardioprotection was based on generally

**Context** Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

**Objective** To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

**Design** Estrogen plus progestin component of the Women’s Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

**Interventions** Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

**Main Outcomes Measures** The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

**Results** On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.89) with 212 cases; PE, 2.13 (1.39-3.29) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEIs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10,000 person-years.

**Conclusions** Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:373-383 www.jama.com

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For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.
Medikamenten-Studie an Frauen: Gefährdet ein Arzt seine Patienten?

Hormontherapie kann Brustkrebs auslösen, dennoch will FU-Professor weiter forschen

VON INGO BACH


Die Ergebnisse der US-Kollegen lassen auch Dieter Felsenberg nicht unbeteiligt: „Vor diesem Hintergrund hätte ich es mir noch einmal sehr genau überlegt, ob ich diese Untersuchung machen soll.“


Wolfgang Becker-Brüser, Geschäftsführer des „Arznei-Telegramms“, das den Ruf als seines Fachblatt genießt, widerspricht: „Bei einer theoretisch möglichen Marktwirtschaft von vier Millionen Frauen, die in der Bundesrepublik Hormonpräparate erhalten, wären die 150 Fälle immerhin rund 3200 durch das Medikament ausgelöst. Brustkrebsfälle.“ Und eine durch die Studie erkrankte Patientin sei die statistische Wahrscheinlichkeit belanglos. „Für sie zählt nur, dass sie Krebs hat."

DER TAGESSPIEGL

MORGEN IN DER BEILAGE

ROLLS ROYCE

MIT DEM PHANTOM WIEDER AN DER SPITZE

Studie erhalten. Er setzt deshalb seine For- schung fort, „Ihre klinischen der Praparat-Hersteller damit werben kann, dass die Frauen durch eine geringere Hautbekom- men oder schöneres Haar.“

150 Frauen sollen dafür ein Jahr lang das Medikament testen. Er habe die Teilneh- rinnen über die Resultate aus den USA unterrichtet und sie vor die Wahl gestellt, den Ver- such abzubrechen. Keine sei zurückgetreten, sagt Felsenberg.

ETHIKKOMMISSION UND PATIENTENSCHUTZ

Jede Pharma-Untersuchung muss von einer Ethikkommission begutachtet werden. Allerdings ist ihr Votum nicht bindend. Der Arzt, der die Studie leitet, hat immer das letzte Wort und kann seine Versuchsreihe auch gegen das Urteil der Kommission fortdienen. Das aber wird er im Normalfall nicht tun, sagt Joachim W. Dudenhausen, Dekan der Charité. Nähmen die Pa- tienten im Laufe einer solchen Studie Scha- den, hätte der Arzt im Falle eines Un-


Trotz möglicher gesundheitlicher Risiken für die Teilnehmer könnten auf Studien-
Revisit of existing MA

Obstetrics & Gynecology 1992

MENOPAUSAL HORMONE
REPLACEMENT THERAPY AND
BREAST CANCER: A META-ANALYSIS

María Sillero-Arenas, MD,
Miguel Delgado-Rodríguez, MD, MPH,
Rafael Rodíguez-Canteras, MD,
Aurora Bueno-Cavallillas, MD,
and Ramón Galve-Vargas, MD

A meta-analysis was performed to determine whether the scientific literature provides enough evidence that hormone replacement therapy after menopause increases the risk of breast cancer. Studies were located by MEDLINE, supplemented by a hand search of all the references in the articles located. The papers were graded as to quality. Those considered unbiased were combined using Woolf's method. Thirty-seven original studies were found: 23 case-control, 13 cohort, and one clinical trial. Overall, a small but statisti-
cally significant relative risk (RR) figure of 1.06 was calculated. Women who experienced natural menopause seemed to be at increased risk (RR = 1.13). A significant weighted RR was observed in current hormone replacement therapy users, especially in those who had natural menopause (RR = 1.63). A nonsignificant increasing trend was found between duration of hormone replacement therapy and breast cancer risk, although the opposite was seen when the association was analyzed by time since last use. These results imply that hormone replacement therapy could promote breast cancer. (Obstet Gynecol 1992;79:286–94)

Breast cancer is the most common cancer in women in developed countries. Epidemiologic evidence of the relationship between hormone replacement therapy and breast cancer remains controversial. Because the proportion of postmenopausal women receiving hormone supplements is increasing, we performed a meta-analysis of published studies to see whether the available information is enough to establish an association between hormone replacement therapy in the menopause and breast cancer.

Methods
We located potential studies for analysis using the following methods: 1) searching the MEDLINE data
Reanalysis of MA by Sillero - Arenas

What are the results using appropriate methods?
Reanalysis of MA by Sillero - Arenas

• MA by SA: 23 Case-Control and 13 cohort
• Effect measure (OR) 95% CI
• Sample size
• Date of data collection
• Study type
• Number of covariates adjusted for
Outcome Measures

• Binary (prevalence or incidence study)
• Effect based upon binary outcome
  – Relative Risk
  – Risk Difference
  – Odds ratio
• Effect based upon quantitative outcome
  – Standardized Difference
  – Correlation Coefficient
Meta-Likelihood

There are $k$ studies for the MA available.

It is assumed that the effect measure $\hat{\lambda}_i$ for the $i$-th study is following (at least approximately) a normal distribution with density of $\hat{\lambda}_i$:

$$\frac{1}{\sqrt{2\pi\sigma_i^2}} \exp\left\{ - \frac{1}{2} \left( \frac{\hat{\lambda}_i - \lambda_i}{\sigma_i} \right)^2 \right\}$$

where $\lambda_i$ is the unknown effect measure in study $i$ and $\sigma_i^2$ is the known study variance.

Difference to conventional analysis: each datum has difference variance parameter!
Meta-Likelihood

• Minimal Information: effect measure and its variance

Table 1: Extracted Data from Meta-Analysis by Sillero-Arenas et al. (1992)

<table>
<thead>
<tr>
<th>Study*</th>
<th>OR</th>
<th>95% CI</th>
<th>Study-Type*</th>
<th>Date of Data Coll.*</th>
<th>Adjusted for Co-variates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.11</td>
<td>0.38</td>
<td>1.19</td>
<td>1</td>
<td>72.0</td>
</tr>
<tr>
<td>2</td>
<td>0.97</td>
<td>0.49</td>
<td>1.92</td>
<td>1</td>
<td>68.0</td>
</tr>
<tr>
<td>3</td>
<td>2.15</td>
<td>0.71</td>
<td>6.49</td>
<td>1</td>
<td>71.0</td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>0.60</td>
<td>1.20</td>
<td>1</td>
<td>71.5</td>
</tr>
<tr>
<td>5</td>
<td>0.90</td>
<td>0.66</td>
<td>1.22</td>
<td>1</td>
<td>72.0</td>
</tr>
<tr>
<td>6</td>
<td>0.89</td>
<td>0.60</td>
<td>1.32</td>
<td>1</td>
<td>73.0</td>
</tr>
<tr>
<td>7</td>
<td>1.10</td>
<td>0.80</td>
<td>1.90</td>
<td>1</td>
<td>74.0</td>
</tr>
<tr>
<td>8</td>
<td>1.30</td>
<td>1.00</td>
<td>1.70</td>
<td>1</td>
<td>72.0</td>
</tr>
</tbody>
</table>

Table to be continued
Meta-Likelihood

- Computation of SE: \( SE = \frac{U - L}{1.96 \times 2} \), where \( U, L = \log(OR) \pm 1.96 \ SE \)

Table 2: Log-Odds Ratios with Associated Standard Errors from Meta-Analysis by Sillero-Arenas *et al.* (1992)

<table>
<thead>
<tr>
<th>Study(^*)</th>
<th>log OR</th>
<th>Standard Error</th>
<th>Study-Type(^*)</th>
<th>Date of Data Coll.(^y)</th>
<th>Adjusted for Covariates(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.11</td>
<td>0.29</td>
<td>1</td>
<td>72.0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.97</td>
<td>0.35</td>
<td>1</td>
<td>68.0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2.15</td>
<td>0.56</td>
<td>1</td>
<td>71.0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>0.18</td>
<td>1</td>
<td>71.5</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0.90</td>
<td>0.16</td>
<td>1</td>
<td>72.0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.89</td>
<td>0.20</td>
<td>1</td>
<td>73.0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1.10</td>
<td>0.22</td>
<td>1</td>
<td>74.0</td>
<td>*</td>
</tr>
<tr>
<td>8</td>
<td>1.30</td>
<td>0.14</td>
<td>1</td>
<td>72.0</td>
<td>*</td>
</tr>
</tbody>
</table>

Table to be continued
Meta-Likelihood

Having \( k \) independent studies available this leads to the \textit{meta-likelihood}

\[
\prod_{i=1}^{k} \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp\left\{ -\frac{1}{2} \frac{(\lambda_i - \hat{\lambda}_i)^2}{\sigma_i^2} \right\}
\]

which will be the basis for all inferential conclusions.
Meta-Likelihood

Now different models for $\lambda_i$ can be considered:

**Homogeneity:** $\lambda_1=\lambda_2=\ldots=\lambda_k = \lambda$

and maximizing the meta-likelihood leads to the weighted mean

$$\hat{\lambda}_+ = w_1\hat{\lambda}_1 + \ldots + w_k\hat{\lambda}_k / (w_1 + \ldots + w_k)$$

of the effect measures of the $k$ studies with $w_i = 1/\sigma_i^2$. This is also called the *pooled* or *fixed* effect estimate.

the variance of this estimate is readily available as $1/(w_1 + \ldots + w_k)$. 
Meta-Likelihood

**Heterogeneity.** Effect-heterogeneity implies that for some studies a certain value for the effect is valid, whereas for others a different value is correct.

How can such a situation now validly captured by means of a model?
Meta-Likelihood for Unobserved Heterogeneity

$k$ observable effects

$k$ study estimates

$\hat{\lambda}_1, \hat{\lambda}_2, \ldots, \hat{\lambda}_k$

$m$ subpopulations
Meta-Likelihood: Heterogeneity

**meta-likelihood for heterogeneity**

\[
\prod_{i=1}^{k} \sum_{j=1}^{m} p_j \frac{1}{\sqrt{2\pi}\sigma_i^2} \exp\left\{ - \frac{1}{2} \left( \hat{\lambda}_i - \lambda_j \right)^2 / \sigma_i^2 \right\} \text{ in }
\]

the parameters \( \lambda_1, \ldots, \lambda_m, p_1, \ldots, p_m \).

Maximum Likelihood Estimation of the 2m-1 parameters can be readily accomplished with C.A.MAN, a software tool freely available from the author’s homepage. Details on the approach can be found in Böhning (2000).
Applied to MA of SA

Measures to evaluate the meta-likelihood of various models: good models should have large BIC-value

\[
\text{BIC} = 2 \log\text{-likelihood} - \# \text{ parameters} \log(\#\text{studies})
\]

<table>
<thead>
<tr>
<th>Model</th>
<th>log-likelihood</th>
<th>Number of Parameters</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>homogeneity</td>
<td>-34.4630</td>
<td>1</td>
<td>-72.5095</td>
</tr>
<tr>
<td>mixture 2-components</td>
<td>-21.9740</td>
<td>3</td>
<td>-54.6986</td>
</tr>
<tr>
<td>mixture 3-components</td>
<td>-17.1960</td>
<td>5</td>
<td>-52.3096</td>
</tr>
<tr>
<td>mixture 4-components (NPMLE)</td>
<td>-16.1373</td>
<td>7</td>
<td>-57.3592</td>
</tr>
</tbody>
</table>
Meta-Likelihood: Covariates

Including covariates to explain heterogeneity. Having identified considerable heterogeneity the questions arises whether any observed variables can be associated with this latent form of heterogeneity.

To put it in other words, one knows that there is heterogeneity, but it is yet unclear what it stands for. Having observed further covariates, $x_1, x_2, ..., x_p$, say, one can formulate a regression model to include these into the meta-likelihood.
Meta-Likelihood: Covariates

Meta-likelihood to include covariates:

\[
\prod_{i=1}^{k} \frac{1}{\sqrt{2\pi \sigma_i^2}} \exp\left\{ - \frac{1}{2} \left( \hat{\lambda}_i - \lambda_i \right)^2 / \sigma_i^2 \right\}
\]

where now \( \lambda_i = \beta_i x_{1i} + \beta_i x_{2i} + \ldots + \beta_i x_{pi} = \mathbf{x}_i^T \beta \)

is provided by the regression model.
Meta-Likelihood: Covariates

\[ \hat{\beta} = (X^T W X)^{-1} X^T W Y, \]

where

\[ W = \begin{pmatrix} w_1 & 0 & 0 & \ldots & 0 \\ 0 & w_2 & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & 0 & w_k \end{pmatrix} \]

contain on the diagonal the inverse study variances \( w_i = \frac{1}{\sigma_i^2} \),

\[ Y = \begin{pmatrix} \hat{\lambda}_1 \\ \hat{\lambda}_2 \\ \vdots \\ \hat{\lambda}_k \end{pmatrix}^T \]

and \( X \) is the design matrix

\[
\begin{pmatrix}
  x_{11} & x_{12} & \ldots & x_{1p} \\
  x_{21} & x_{22} & \ldots & x_{2p} \\
  \vdots & \vdots & \ddots & \vdots \\
  x_{k1} & x_{k2} & \ldots & x_{kp}
\end{pmatrix}
\]

containing the study data of the \( p \) predictors in the \( k \) studies.

Finding the maximum likelihood estimate according to the meta-likelihood leads to the weighted regression estimator (which is provided for compactness in vector notation):

This powerful tool is readily available by means of any statistical package which can do weighted regression. Here, the package MINITAB (Minitab 2000) was used.
MA of SA: Covariates

Number of Covariates Adjusted For vs. logOR
MA of SA: Covariates

It can be expected (presence of unobserved heterogeneity) that covariates are to be found to explain the residual heterogeneity.

When we include the covariates one at a time, none of them is significant, though Case-Control and Number-of-Covariates are borderline.

When we include these two simultaneously the latter becomes significant.
## MA of SA: Covariates

**Table 3:** Regression Output for Weighted Regression of Log-Odds-Ratio on Study Type (*Case-control*) and Covariate Adjustment (*number of covariates adjusted for*)

The regression equation is

\[
\text{logOR} = 0.145 - 0.147 \text{ cas_control}
\]

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef</th>
<th>StDev</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.14545</td>
<td>0.06601</td>
<td>2.20</td>
<td>0.034</td>
</tr>
<tr>
<td>cas_cont</td>
<td>-0.14699</td>
<td>0.08664</td>
<td>-1.70</td>
<td>0.099</td>
</tr>
</tbody>
</table>

The regression equation is

\[
\text{logOR} = -0.229 + 0.356 \text{ number of covariates} - 0.104 \text{ cas_control}
\]

31 cases used 5 cases contain missing values or had zero weight

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef</th>
<th>StDev</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.2288</td>
<td>0.1810</td>
<td>-1.26</td>
<td>0.217</td>
</tr>
<tr>
<td>number o</td>
<td>0.3564</td>
<td>0.1738</td>
<td>2.05</td>
<td>0.050</td>
</tr>
<tr>
<td>case_cont</td>
<td>-0.10384</td>
<td>0.09389</td>
<td>-1.11</td>
<td>0.278</td>
</tr>
</tbody>
</table>
MA of SA: Covariates

This also corresponds to a considerable amount of increase in the log-likelihood. If now the BIC-value of regression model is compared with the BIC-model of the heterogeneity model, it is seen that the regression model provides the better BIC-value. Thus, it can be argued that most of the heterogeneity is explained.

<table>
<thead>
<tr>
<th>Model</th>
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<th>Number of Parameters</th>
<th>BIC</th>
</tr>
</thead>
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</tr>
<tr>
<td>mixture 4-components</td>
<td>-16.1373</td>
<td>7</td>
<td>-57.3592</td>
</tr>
<tr>
<td>covariates</td>
<td>-19.2900</td>
<td>3</td>
<td>-49.3306</td>
</tr>
</tbody>
</table>
MA of SA: OR adjusted for covariates

**Estimated Adjusted Relative Risk.** The estimated relative risk adjusted for study type and confounding variables can be found using the equation

\[
\log \text{OR} = -0.229 + 0.356 \text{ number of covariates} - 0.104 \text{ case_control}
\]

which leads to a log-odds ratio of 0.128 with 95% C.I. of (0.002-0.255) when *number of covariates* takes on the value 1 and *case_control* the value 0. This corresponds to an OR of 1.137 with 95% CI of (1.002-1.291).
Modelling with the Meta-Likelihood: Publication Bias

To avoid drawing unbiased conclusions from a meta-analysis it is important that all relevant primary studies need to be identified on a given subject. It has been long accepted that research with statistically significant results is potentially more likely to be submitted, published or published more rapidly than work with null or non-significant results, leading to incorrect, usually effect over-estimating conclusions. This problem is known as *publication bias*. Methods are available for the diagnosis of publication bias including graphical methods such as the *funnel plot* and statistical methods such as the rank correlation test or regression techniques.
Identification of Publication Bias

Idea: measure of effect estimate has with increasing sample size smaller variation

more precisely: standard error of estimate of effect is proportional $1/\sqrt{n}$

therefore:
Graph of $\hat{\lambda}_i$ vs $n_i$ should have pattern of a Funnel! (if sample size is not reported, one replaces $n$ by inverse variance or inverse standard error of study estimate)
The Idea of the Funnel Plot

Identification of Publication Bias

Sample Size

- ▼ All Studies
- ▲ Published

Effect Measure

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Effect Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
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<td>0.5</td>
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<td>10</td>
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<td>11</td>
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<td>12</td>
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<td>17</td>
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</table>
Identification of Publication Bias

If there is a *publication bias*, e.g. *significant* studies have a larger chance for publication than *non-significant* ones, studies with large effect or those with larger sample size have higher chances for publication than others: there occurs a *whole* in the funnel, in the graph in the lower left corner

alternatively, one could say, the symmetry of the funnel is disturbed

idea of funnel plot goes back to Light und Pillemer (1984)
The Lower Left Hole In the Funnel Plot

Published
MA of SA: Publication Bias?
Modelling Publication Bias

The basic idea of most of the techniques are based on the assumption that if there is *no* publication bias effect, then the effect measure should be unrelated to the sample size. If the sample size of the study is not available one uses as surrogate $1/\text{SE}$, since one knows that the standard error is inversely related to the sample size.
Modelling Publication Bias

In the approach here, we focus on regression methods since this is allowing a unifying treatment of the subject. We follow the ideas suggest in Macaskill et al. (2001) in which the effect measure is regressed on \( w_i = 1/\sigma_i^2 \) using weights \( w_i \). If there is no publication bias, then the regression to the inverse variance should show no effect. The benefit of this approach is that it can be simultaneously included in the previously mentioned regression approach for the covariates.
Table: Identifying Publication Bias: Weighted Regression of \( \log OR \) on \( \text{Weight} \)

The regression equation is
\[
\log OR = 0.0199 + 0.000285 \text{ weight}
\]

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef</th>
<th>StDev</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
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<td>weight</td>
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<td>0.0004288</td>
<td>0.67</td>
<td>0.511</td>
</tr>
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</table>

No correction for Publication Bias needed!
Modelling Study Quality

• Assumptions: SQ can be assessed and quantified
• Option 1: SQ is expressed in a simple score
  – Cohort study: 1 point; Case-Control: 0 points
  – Careful exposure assessment 1 point, 0 otherwise
  – Samples likely to be representative 1 point, 0 otherwise
  – ....
• Option 2: SQ is expressed in terms of several factors like
  – study type,
  – sample design,
  – confounder adjustment,
  – observer bias,
  – ....
Modelling Study Quality

regression modelling

this idea can be extended further by regressing the estimate of the effect measure onto the quality score ($\hat{\lambda}_i$ on $QS_i$):

find best regression line

$$\hat{\lambda}_i = \alpha + \beta QS_i \text{ for } i=1,...,k$$

note: use weighted regression with weights according to inverse variance
Hypothetical Example

Regression Analysis: log-or versus QS

Weighted analysis using weights in 1/var

The regression equation is

\[ \text{log-or} = -0.603 + 0.142 \times QS \]

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef</th>
<th>SE Coef</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
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Summary: a general framework

Unobserved Heterogeneity

Effect Measure

- use mixture analysis
- use weighted regression

observed covariates
publication bias
study quality