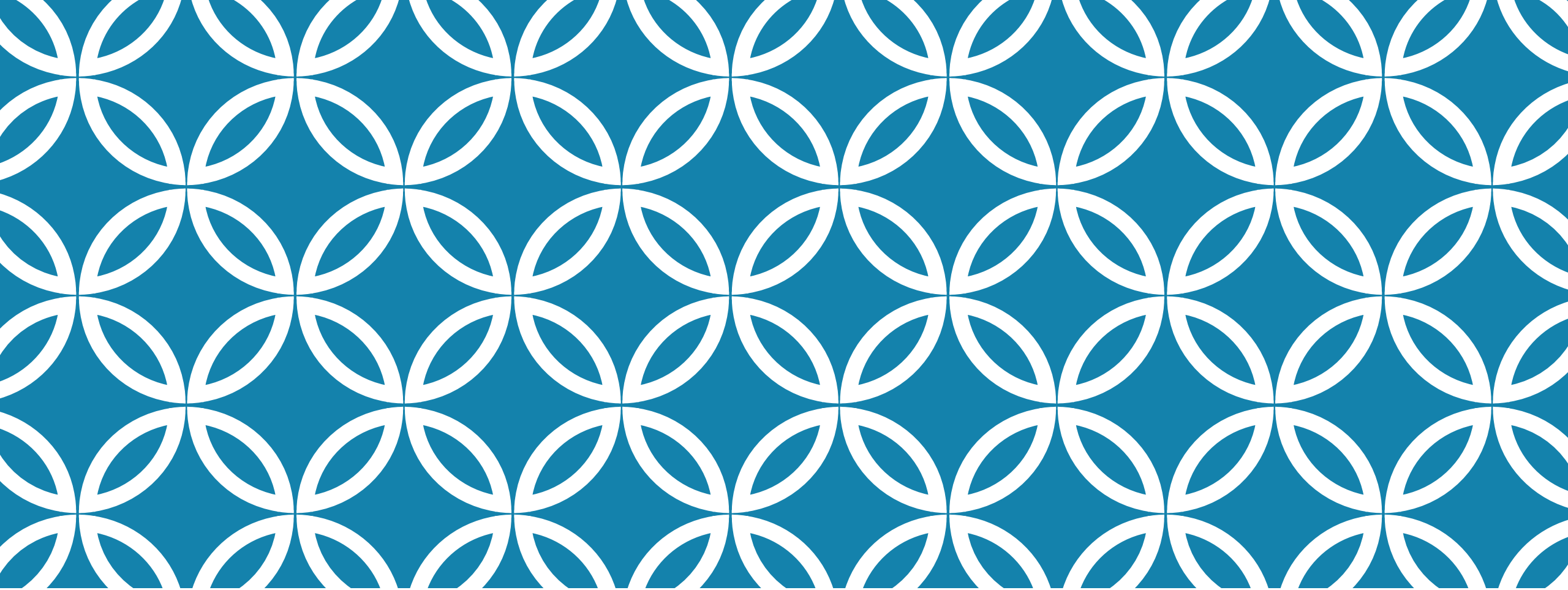

META-ANALYSIS

STAT3622

Data Visualization

META-ANALYSIS | INTRODUCTION

- A meta-analysis *combines* the results of *multiple* scientific studies *addressing the same question*, with each individual study reporting measurements that are expected to have some degree of error.
  - Included studies: evaluate the same endpoint (e.g., all-cause mortality) for the same problem (e.g., treatment A vs B for disease C)
  - Goal: Obtain pooled (summary) estimates from individual studies; evaluate heterogeneity among individual studies
  - Benefit: aggregated information leads to higher statistical power and more robust point estimate than that from each individual study
- An Individual study collects data from each subject (subjects are data points)

A meta-analysis collects data from individual studies (studies are data points)

META-ANALYSIS | PROCEDURE

1. Define the research question of interest (Population, Intervention, Comparison, Outcome)
2. Define inclusion/exclusion criteria for individual studies screened
3. Search literature (determine search strategies and databases to search)
4. Select eligible studies
5. Collect data (study characteristics, demographic and clinical characteristics of patients, endpoints of interest)
6. Aggregate findings across studies and obtain pooled estimates of effect size
7. Evaluate heterogeneity of included studies
8. Conduct sensitivity and subgroup analyses

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→ Statistical Analysis and Data Visualization

META-ANALYSIS | STATISTICAL MODELS

- Pool effect sizes (of individual studies) into one overall effect
- Two types of statistical models to combine data

  Fixed effects model vs Random effects model

- Frequentist framework vs Bayesian framework

META-ANALYSIS | FREQUENTIST FRAMEWORK

- Observations: the effect sizes $\{\hat{\theta}_i, i = 1, \dots, n\}$ and variances $\{\hat{V}_i, i = 1, \dots, n\}$ for each study, where n is the number of included studies.
- Goal: find appropriate weights $\{\omega_i, i = 1, \dots, n\}$, and calculate a weighted average from results of individual studies as the pooled estimate,

$$\hat{\theta} = \frac{\Sigma_{i=1}^{n} \omega_i \hat{\theta}_i}{\Sigma_{i=1}^{n} \omega_i},$$

with the corresponding variance $\hat{V} = \frac{\Sigma_{i=1}^{n} \omega_i^2 \hat{V}_i}{(\Sigma_{i=1}^{n} \omega_i)^2}$.

- The $100(1-\alpha)\%$ confidence interval for the combined effect:

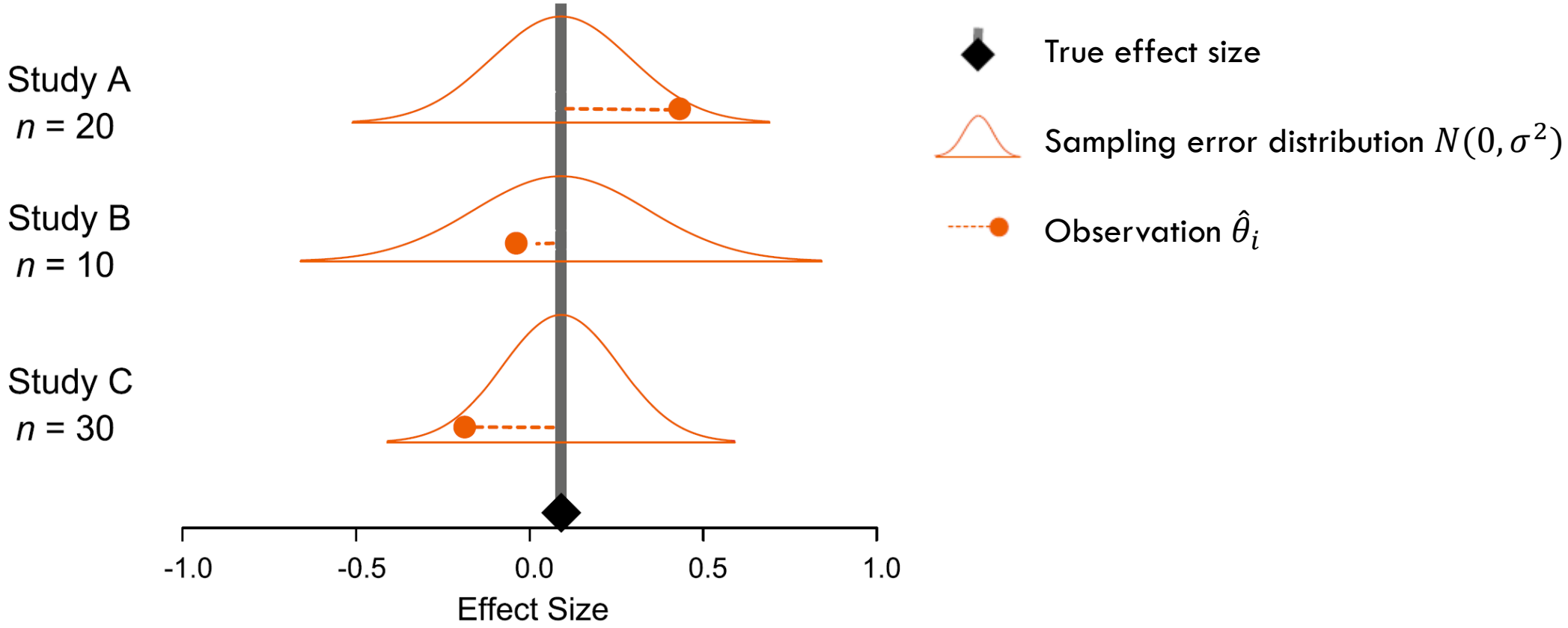
$$\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\hat{V}},$$

where α is the significance level, z_q is the q-th quantile of the standard normal distribution.

META-ANALYSIS | FIXED EFFECTS MODEL

- The fixed effects model assumes that the observed effects are sampled from a normal distribution with true effect θ and variance σ^2, i.e.,

$$\hat{\theta}_i = \theta + \epsilon_i, \qquad \epsilon_i \sim N(0, \sigma^2)$$



META-ANALYSIS | FIXED EFFECTS MODEL

- Higher weights on studies with greater precision (smaller variance)
- For the fixed effects model, we can use the inverse variance weighting,

$$\omega_i = \frac{1}{\hat{V}_i},$$

$$\hat{\theta} = \frac{\Sigma_{i=1}^{n} \hat{\theta}_i / \hat{V}_i}{\Sigma_{i=1}^{n} 1/\hat{V}_i},$$

$$\hat{V} = \frac{1}{\Sigma_{i=1}^{n} 1/\hat{V}_i}.$$

- The inverse-variance weighted average has the least variance among all weighted averages.

META-ANALYSIS | RANDOM EFFECTS MODEL

- Fixed effects model: all included studies come from the same population
- This assumption may be implausible in real cases
- Random effects model: there is a distribution of true effect sizes

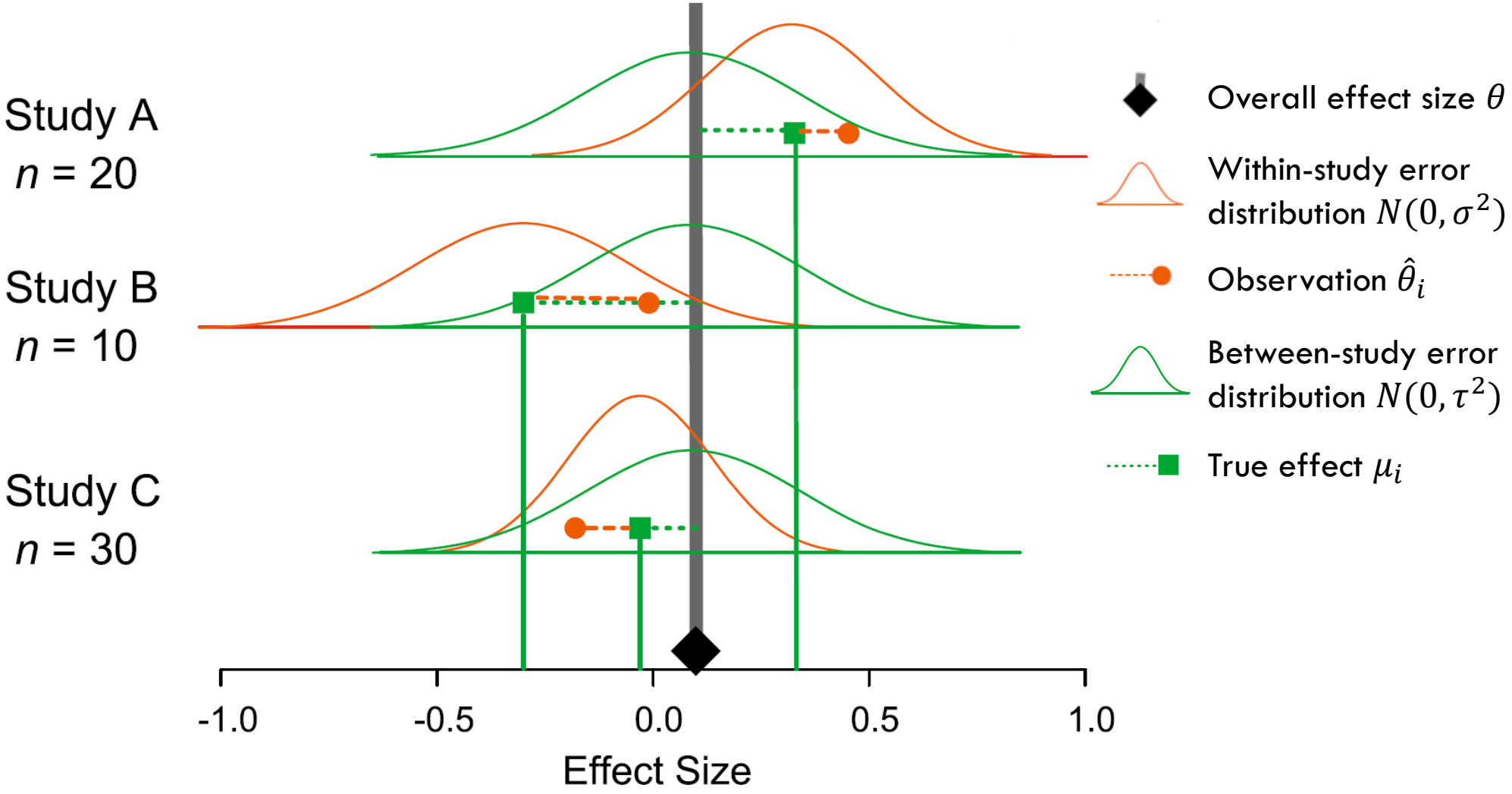
META-ANALYSIS | RANDOM EFFECTS MODEL

- $$\hat{\theta}_i = \mu_i + \epsilon_i,$$
$$\mu_i = \theta + \eta_i,$$
$$\hat{\theta}_i = \theta + \eta_i + \epsilon_i.$$

- The observed effect $\hat{\theta}_i$ in study i is determined by the true effect μ_i plus the *within-study* error $\epsilon_i \sim N(0, \sigma^2)$.

- The true effect μ_i is sampled from a normal distribution with mean θ and variance τ^2. $\eta_i \sim N(0, \tau^2)$ is called the *between-study* error.

META-ANALYSIS | RANDOM EFFECTS MODEL



META-ANALYSIS | RANDOM EFFECTS MODEL

- For random effects model, we also use inverse variance weighting to assign weights
- While the variance includes the original variance $\hat{V}_i$ plus the between-study variance τ^2

$$\omega_i^* = \frac{1}{V_i^*},$$

$$V_i^* = \hat{V}_i + \tau^2,$$

$$\hat{\theta}^* = \frac{\Sigma_{i=1}^n \hat{\theta}_i / V_i^*}{\Sigma_{i=1}^n 1/V_i^*},$$

$$\hat{V} = \frac{1}{\Sigma_{i=1}^n 1/V_i^*}$$

META-ANALYSIS | DECOMPOSING VARIANCE

- For random effects model, the observed variance should be decomposed into two parts, within-study and between-study variances
- We have to estimate the between-study variance τ^2 for the calculation of pooled estimates
- There exist several approaches to estimate τ^2, for example, *DerSimonian-Laird*, *maximum likelihood*, *profile likelihood*, *restricted maximum likelihood*, *empirical Bayes* estimators
- In medical and psychological research, the by far most often used estimator is the *DerSimonian-Laird* estimator

META-ANALYSIS | BINARY CASES

- We have introduced the inverse variance weighting for continuous data
- In binary cases, several different approaches (Mantel-Haenszel method, inverse variance weighting, Peto method, sample size weighting) are used for pooling individual estimates.
- Mantel-Haenszel method is the most commonly used approach.

META-ANALYSIS | MANTEL-HAENSZEL METHOD

Table. Binary observations for the i-th study

	Event	Non-event
Intervention	a_i	b_i
Control	c_i	d_i

$$n_i = a_i + b_i + c_i + d_i$$

$$\hat{\theta}_{MH} = \frac{\Sigma_{i=1}^{n} \omega_i \hat{\theta}_i}{\Sigma_{i=1}^{n} \omega_i}$$

Fixed effects model:

- Odds ratio (OR)

$$\omega_i = \frac{b_i c_i}{n_i}$$

- Risk ratio (RR)

$$\omega_i = \frac{(a_i + b_i)c_i}{n_i}$$

- Risk difference (RD)

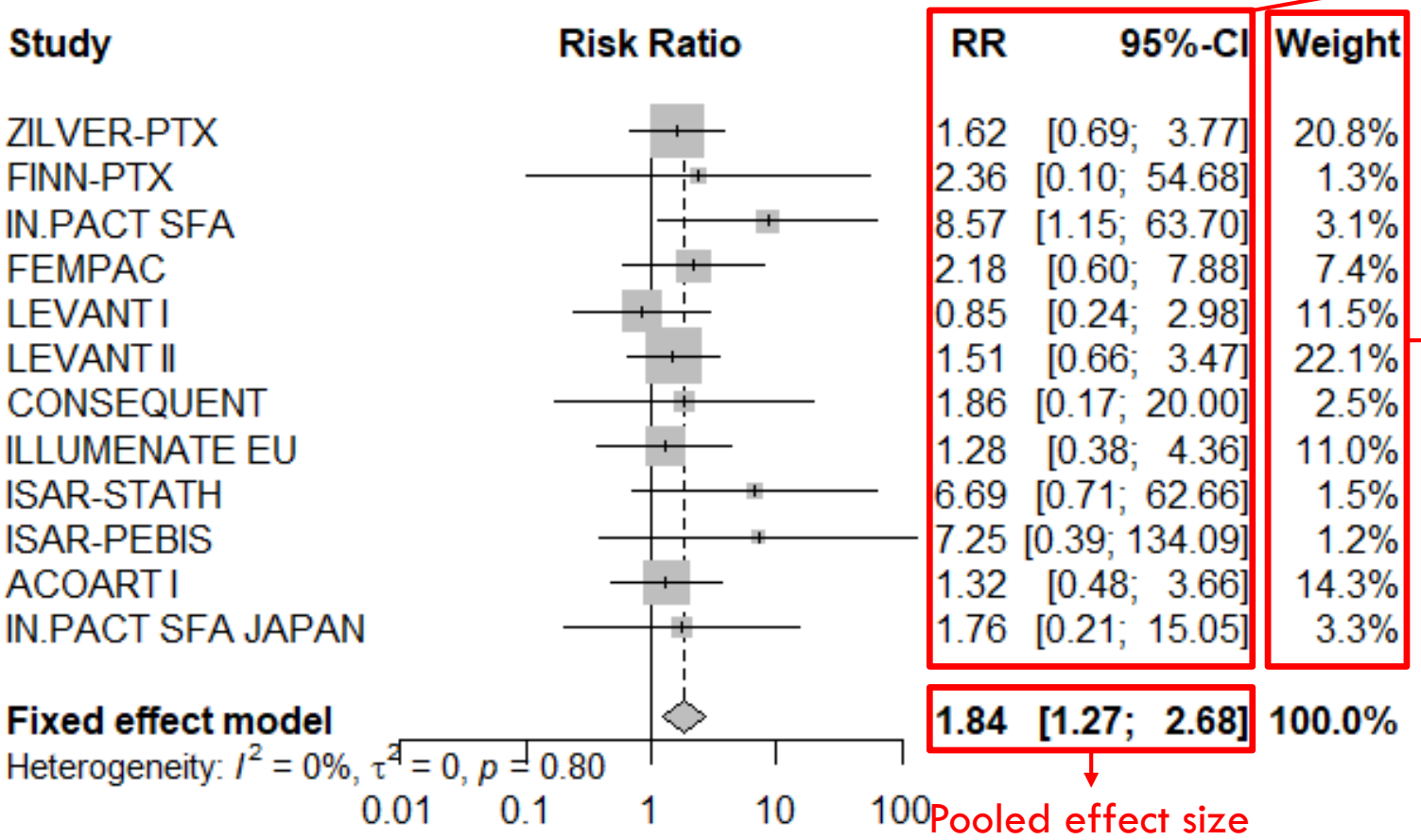
$$\omega_i = \frac{(a_i + b_i)(c_i + d_i)}{n_i}$$

Random effects model:

Most of statistical software treat transformed effect size (e.g., log(OR), log(RR)) as normal (variance calculated by the delta method) and use Mantel-Haenszel estimator for the calculation of Cochran's Q.

META-ANALYSIS | FOREST PLOT

- Forest plot (blobbogram): graphical display of estimated results from *a number of individual* studies addressing the same question along with the *pooled* result.



Individual effect sizes

Weights ω_i

Pooled effect size

META-ANALYSIS | FIXED OR RANDOM?

- Which model should be used in the meta-analysis? Fixed effects or random effects?
- The fixed effects model can be used when
  1. All included studies come from the same population
  2. Goal is to compute the common effect size for the identified population, and not to generalize to other populations
- The fixed effects model is a special case of random effects model when the *between-study variance* τ^2 equals to 0. The fixed effects model is not appropriate when *statistical heterogeneity* (τ^2) is present
- Two types of heterogeneity measures are commonly used to test and assess the degree of heterogeneity.

META-ANALYSIS | HETEROGENEITY

- ***Cochran's Q***:

  squared, weighted and summed difference between the observed effect sizes and the fixed-effect model estimate of the effect size

$$Q = \sum_{i=1}^{n} \omega_i \left(\hat{\theta}_i - \frac{\Sigma_{j=1}^{n} \omega_j \hat{\theta}_j}{\Sigma_{j=1}^{n} \omega_j} \right)^2, \qquad \omega_i = \frac{1}{\hat{V}_i}$$

- Under the null hypothesis (no heterogeneity), $Q \sim \chi^2_{n-1}$, the chi-squared distribution with $n - 1$ degree of freedom

- For significance level α, the critical region is

$$Q > \chi^2_{n-1}(1 - \alpha)$$

META-ANALYSIS | HETEROGENEITY

- ***Higgin's & Thompson's I^2***:

  the percentage of variability in the effect sizes that is not caused by sampling error (derived from Q)

$$I^2 = \max\left\{0, \frac{Q-(n-1)}{Q}\right\}$$

- Interpret I^2 *(Higgins et al. 2013)*
  - $I^2 = 0\%$*:* no heterogeneity
  - $I^2 = 25\%$*:* low heterogeneity
  - $I^2 = 50\%$: moderate heterogeneity
  - $I^2 = 75\%$: high heterogeneity

META-ANALYSIS | HETEROGENEITY

- Problems of Cochran's Q test
  - The Cochran's Q test has low power (may fail to detect heterogeneity as statistically significant when it exists), especially when the number of included studies is low
  - Using a cut-off of 10% for significance can ameliorate this problem but increases the risk of drawing a false positive conclusion (type I error)
  - We should therefore not just rely on Cochran's Q when assessing heterogeneity.

META-ANALYSIS | HETEROGENEITY

- Advantages of I^2
  - I^2 can be calculated and compared across meta-analyses of different sizes, of different types of study, and of different types of outcome data
  - I^2 describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error
  - I^2 can be accompanied by an uncertainty interval

META-ANALYSIS | HETEROGENEITY

- However, the thresholds of I^2 for evaluating degree of heterogeneity are roughly made without statistical proof
- I^2 heavily depends on the precision of the included studies (Rücker et al. 2008)
- When the sample size of individual studies increases, the sampling error tends to zero and I^2 would tend to 100%.
- Therefore, I^2 and Cochran's Q should be considered jointly to assess the heterogeneity

META-ANALYSIS | PUBLICATION BIAS

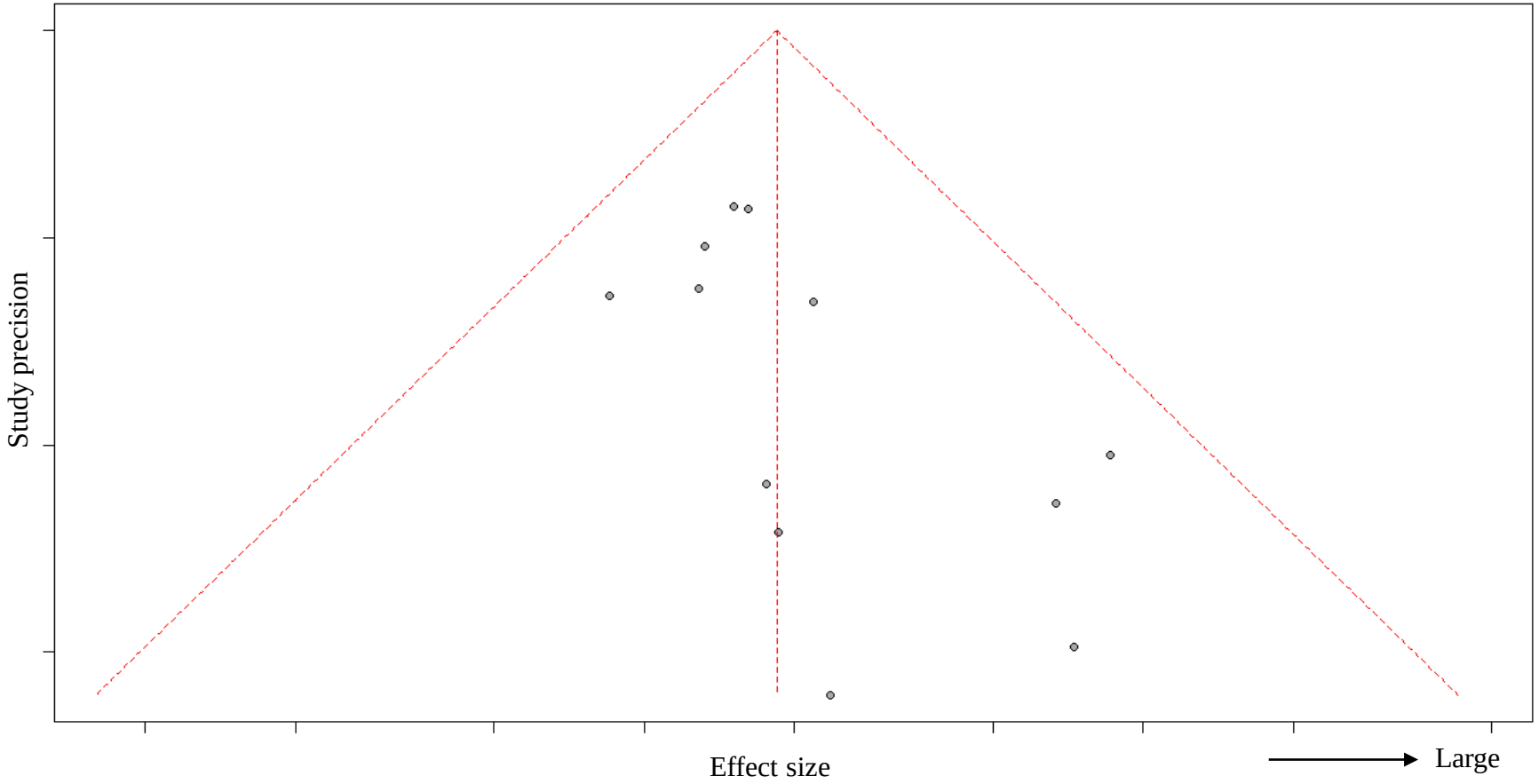
- In most meta-analyses, we usually include eligible **published** works.
- *"Publication bias occurs when the publication of research results depends not just on the* ***quality*** *of the research but also on the hypothesis tested, and the* ***significance*** *and* ***direction*** *of effects detected"*
- Studies with **high** effect sizes / **large** sample sizes / **significant** results are **more likely** to be published than studies with **low** effect sizes / **small** sample sizes / **insignificant** results.
- The *pooled* effect might be **higher** than the *true* effect size because we did not consider the missing studies with lower effects due to the simple fact that they were never published.

META-ANALYSIS | PUBLICATION BIAS

- Assumptions for small sample bias methods:
  - Large studies are likely to get published, whether the results are significant or not
  - Moderately sized studies are at greater risk of not being published but are more likely to become significant, which means that only some studies will be missing.
  - Small studies are at greatest risk for being non-significant, and thus being missing.
- Evaluate potential publication bias: whether small studies with small effect sizes are missing

META-ANALYSIS | FUNNEL PLOT

- Funnel plots: check for the existence of publication bias



X-axis: effect size

Y-axis: study precision (e.g., sample size, standard error)

Grey dots: individual studies

Red vertical line: pooled effect size

In the absence of publication bias, it assumes that studies with high precision will be plotted near the average, and studies with low precision will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution.

META-ANALYSIS | FUNNEL PLOT

- Without publication bias, all studies would lie **symmetrically around the pooled effect size** within the form of the funnel
- An **asymmetric** funnel indicates a relationship between treatment effect estimate and study precision => possibility of publication bias
- Small studies without a significant, large effect would be missing => **sparsity at the left-bottom corner** of a funnel plot
- The standard error is recommended for measuring study precision (as the y-axis)

META-ANALYSIS | EGGER'S TEST

- Egger et al. (1997) proposed a test for asymmetry of the funnel plot.
- They tested 'intercept=0' from a linear regression model of normalized effect sizes (effect size divided by the corresponding standard error) against reciprocal of the standard error of the effect size,

$$\frac{\hat{\theta}_i}{\sqrt{\hat{V}_i}} = a + b \times \frac{1}{\sqrt{\hat{V}_i}}$$

$$H_0 : a = 0$$

META-ANALYSIS | R IMPLEMENTATIONS

- ‘**meta**’ package
- What the package can do?
  - Fixed effect and random effects model for continuous outcome data, binary outcome data, incidence rates, single arm data.
  - Plots for meta-analysis, e.g., forest plot, funnel plot, Galbraith plot / radial plot.
  - Statistical test for meta-analysis
  - Meta-regression
  - …

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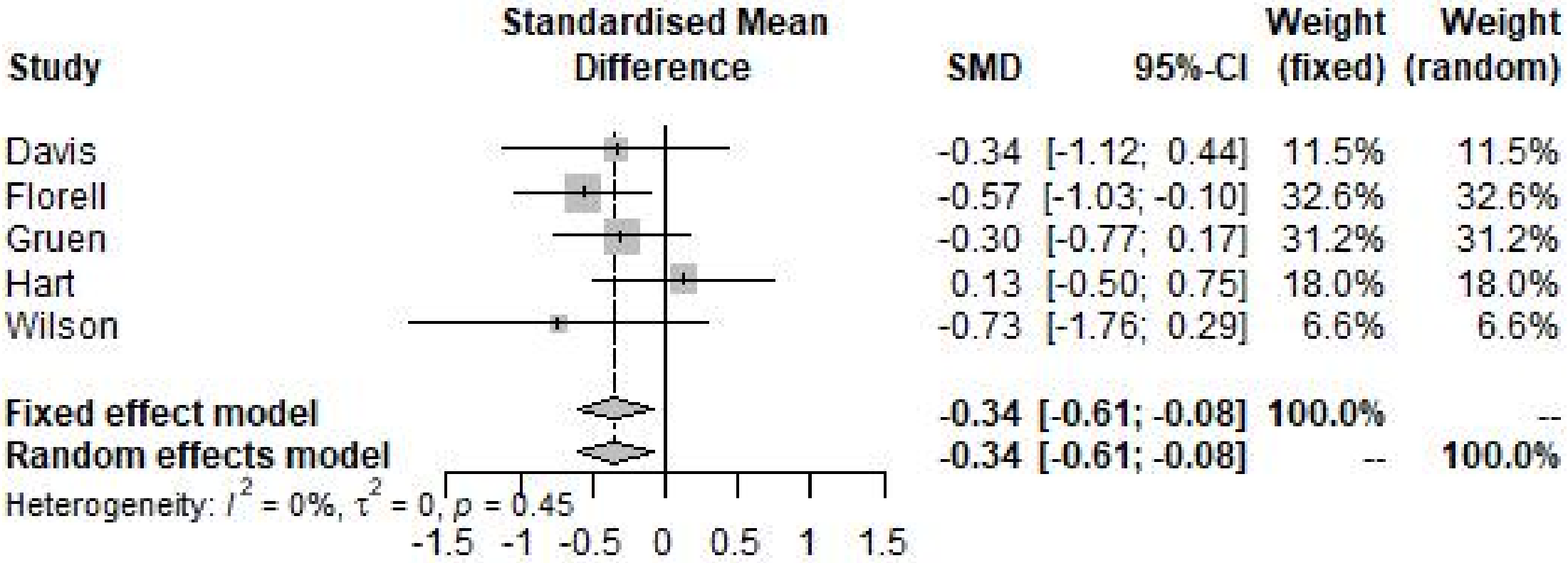

- According to the pooled results of meta-analysis, both fixed and random effects models yield a significant benefit of the intervention group against the control group (for the days of hospital stay, the lower, the better).
- Based on $I^2 = 0$, estimated between-study variance $\tau^2 = 0$, p-value =0.45 for the Cochran's Q test, there was no heterogeneity.