# Meta-analysis of Genome-wide Association Studies

# Effect size

- Encodes relationship of interest into a common index
- Must be:
  - comparable across studies
  - independent of sample size
  - have a computable standard error
- Many different effect size indices
- Multiple methods of computing each
- Most common:
  - Correlation coefficient ($r$)
  - Standard mean difference ($d$)
  - Odds ratio (OR)
  - Risk ratio (RR)

# Computing effect sizes

- Effect size can be computed from provided information:
  - from other statistics like t-test, p-value, descriptive statistics, etc.
  - from manipulation of data such as collasing across subgroups.
- Some studies simply do not provide necessary information.

# Standardized mean difference

$$ES_{sm} = \frac{\bar{x}_1 - \bar{x}_2}{s_{pooled}} \tag{1}$$

- Example: meta-analysis of the effectiveness of therapy in reducing high blood pressure.

$$ES_{sm} = t\sqrt{\frac{n_1 + n_2}{n_1 n_2}} \tag{2}$$

- inferred from t-test.

$$ES_{sm} = \frac{2r}{\sqrt{1 - r^2}} \tag{3}$$

- based on a correlation

$$ES_{sm} = \ln(\frac{ad}{bc})\frac{\sqrt{3}}{\pi} \tag{4}$$

- Based on 2-by-2 contingency table (dichotomous outcome; logit method)

# Odds ratio (OR)

- Dichotomous outcome
- Data can be represented in a $2 \times 2$ contingency table:

| | $g_A$ | $g_B$ |
|---|---|---|
| Case | $a$ | $b$ |
| Control | $c$ | $d$ |

- OR can be computed as:

$$ES_{OR} = \frac{ad}{bc} \tag{5}$$

# Basics of meta-analysis

- Goals:
  - Describe the distribution, including its mean
  - Establish a confidence interval around the mean
  - TEst that the mean differs from zero.
  - Test whether studies are homogeneous.
  - Explore the relationship between study features and effect size.

# Determining the mean effect size

- **Problem**: some effect sizes are more accurate than others
- What we need is a measure of **precision**
- **Standard error** is a direct measure of precision.
- Hedges and Olkin solution:
  - Weighted by the inverse variance
  - Provides a statistical basis for (1) standard error of the mean effect size; (2) confidence intervals; (3) Homogeneity testing

# Some preliminary transformations

- Small sample size bias correction on standardized mean difference:

$$ES'_{sm} = (1 - \frac{3}{4N - 9})ES_{sm} \quad (6)$$

- Fisher's $Z_r$-transform of correlations ($ES_r$)

$$ES_{Zr} = \frac{1}{2}\log(\frac{1+r}{1-r}) \quad (7)$$

- Log-transform of OR:

$$ES_{\ln(OR)} = \log(OR) \quad (8)$$

# Inverse variance weights

- Standard mean difference $ES_{sm}$:

$$se_{sm} = \sqrt{\frac{n_1 + n_2}{n_1 n_2} + \frac{ES_{sm}^2}{2(n_1 + n_2)}} \tag{9}$$

- Correlation $ES_r$ (the Fisher's $Z$):

$$se_r = \frac{1}{\sqrt{n-3}} \tag{10}$$

- Odds ratio

$$se_{OR} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \tag{11}$$

- Inverse variance weight $w$:

$$w = \frac{1}{se^2} \tag{12}$$

# Now the data is ready...

- At this point, we have for each study:
  - An effect size
  - An inverse variance weight
- **Problem**: statistical models assume independence
- Only include one effect size per study (or independent sample)
- Multiple analyses for different subsets of independent effects:
  - Different outcome constructs
  - Different time periods

# Summary effect size

The meta-analysis mean effect size can be computed as the inverse-variance weighted mean effect size:

$$\overline{ES} = \frac{\sum w_i ES_i}{\sum w_i} \tag{13}$$

where $ES_i$ is the effect size for study $i$ and $w_i$ is the inverse variance weight. Standard error of the mean effect size is:

$$se_{\overline{ES}} = \frac{1}{\sum w_i} \tag{14}$$

# Some basic inferential statistics

- Confidnece intervals of the mean effect size:

$$\overline{ES}_{lower} = \overline{ES} - se_{\overline{ES}} \times 1.96 \quad (15)$$

$$\overline{ES}_{upper} = \overline{ES} + se_{\overline{ES}} \times 1.96 \quad (16)$$

- A $z$-test can be performed as:

$$z = \frac{\overline{ES}}{se_{\overline{ES}}} \quad (17)$$

# Forest plot

# Funnel plot

# Homogeneity testing

- Homogeneity analysis tests whether the assumption that all of the effect size are estimating the same population mean is a reasonable assumption.
- If homogeneity is rejected, the distribution of effect sizes is assumed to be heterogeneous.
  - A single mean *ES* is not a good descriptor of the distribution.
  - There are real between-study difference.
  - Three options:
    - model between-study difference
    - fit a random-effect model (REM)
    - do both

# Computation of the homogeneity $Q$ statistic

- $Q$ is simply a weighted sums-of-squares:

$$Q = \sum w_i (ES_i - \overline{ES})^2 \tag{18}$$

- An equivalent formulae:

$$Q = \sum w_i ES_i^2 - \frac{(\sum w_i ES_i)^2}{\sum w_i} \tag{19}$$

- $Q \sim \chi^2_{k-1}$, where $k$ is the number of effect sizes.

# Alternative to $Q$

- $Q$ is statistically under-powered when the number of studies is low and when the sample size within the studies is low

$$I^2 = 100\% \times \frac{Q - df}{Q} \tag{20}$$

- Larger values of $I^2$, the more heterogeneity
  - 75%: large heterogeneity
  - 50%: moderate heterogeneity
  - 25%: low heterogeneity

# Random vs. fixed effects models

- Fixed effect model (FEM) assumes:
  - There is one true population effect that all studies are estimating.
  - all of the variability between effect sizes is due to sampling error.
- Random effects model (REM) assumes:
  - There are multiple (i.e. a distribution) of population effects that the studies are estimating
  - variability between effect sizes is due to sampling error + variability in the population of effects
- Known versus unknown influences of true effects
- Mixture (mixed) models
- Current advise: assume random effects model a priori

# Random effects model

- FEM: **weights are a function of sampling error**.
- REM: **weights are a function of sampling error + study-level variability**
- Thus, a new set of weights should be used for REM
- You need to compute the **random effects variance component** $\tau^2$:

$$\tau^2 = \frac{Q - df_Q}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \tag{21}$$

- Then you can re-compute the **inverse variance weights** $w_i$:

$$w_i = \frac{1}{se^2 + \tau^2} \tag{22}$$

- Now use the new weights to re-compute the meta- analysis results.

# FEM vs REM: How to choose?

- REMs become FEMs when distributions are homogeneous
- Assumptions of FEMs are usually unreasonable, which will lead to under-estimated standard error and too narrow CI.
- General advise within meta-analysis literature: use random effects models
- Area of active debate among statisticians.

# Publication bias

- Statistically significant effects are more likely to be published than non-significant effects.
- Threat to the validity of meta-analysis (and any other method of systematic review)
- The solution is to find and include unpublished studies that meet eligibility criteria, but this is not practical under most of the conditions.
- Examine difference between published and unpublished studies.
- Statistical approaches to assessing publication bias:
  - Funnel plot: scatterplot of effect size against standard error of effect size
  - Trim-and-fill method

# Questions