ASSESSING EVIDENCE ON SAFETY AND EFFICACY:

THE ROLE OF META-ANALYSIS

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- What is a meta-analysis?
- What types of studies should be included?
- What outcomes should be combined?
- Is it appropriate to examine subgroups?
- How robust are conclusions?

What is a Meta-Analysis?

- **Observational** study of "studies"
  - Combining information across related but independent studies
- Why useful?
  - Increase power to detect a safety or efficacy signal
  - Estimation of degree of benefit or risk associated with a particular study
  - Identify study characteristic associated with a particularly effective (or unsafe) treatment.
- Key features:
  - Data are often summary statistics, not identically distributed, and hierarchical in structure.

Examples: Assessing safety	
Risk of **suicidality** with anticonvulsants in bipolar patients	New York Times Feb. 1, 2008
Risk of **suicidality** with antidepressants in adolescents	FDA Briefing overview for Dec. 13, 2006 PDAC
Risk of **heart attack and death** from rosiglitazone (versus other drug regimens) in diabetic patients	Nissen and Wolski, NEJM 2007, 356(24):2457-2471
Risk of **stent thrombosis** from drug eluting stents (versus bare metal stents) in patients with CAD	Mauri et al. NEJM 2007, 356(10):1020-1029
Risk of **heart attack and stroke** from COX-2 inhibitors and selective NSAIDS versus placebo or other NSAIDS	Kearney et al., BMJ 2006;332(3 June):1302-1308

What Types of Studies Should Be Included?

DESIGN	COMMENTS
Randomized	**QUOROM** statement (Lancet 1999;354:1896-1900)
Observational	**MOOSE** statement (JAMA 2000;283(15):2008-2012)
Mixture of the two	No guidelines □Need to **adjust** for type of study
UNIT OF OBSERVATION	**COMMENTS**
Individual versus study summary data	Individual data preferred (ecological bias) (Lancet 1993;341:418-412)

Ecological Fallacy

- Regression of mean patient characteristics across studies on study-specific efficacy estimates.
- Ecological regression yields
  - "Studies with younger subjects show worse efficacy"
- And **NOT**
  - "Younger subjects have worse results."

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What Types of Outcomes Should Be Combined?

- **Multiple outcomes:**
  - Two strategies often adopted:
    - (pool and analyze) **versus** (analyze separately).
  - Guidelines on composite measures exist (pooling).
- **Unit of Observation:**
  - Patient-level data: pooling rules include "and" or "or" rules; separate regressions.
    - Problems with both strategies.
  - Study-level summary data: same problem but now the correlation between outcomes of the same subject is not accounted for in the analysis.

Problems not unique to meta-analysis.

What Type of Treatments Should Be Combined?

- Some trials are placebo-controlled, some are active-controlled.
- Many active treatments available for a single disease.
- Interest may involve assessing efficacy/safety of a new treatment with current standard treatment
- **Network meta-analysis** used to assess the relative effectiveness of two treatments when they may not have been directly compared in an RCT.
  - Want relative treatment effect of A versus B and have:
    - Direct information (A versus B).
    - Indirect information (A versus C) and (B versus C) studies.

Examining Subgroups.

Meta-analysis is an **observational** study.

- Subgroup analyses are appropriate to the extent that differences in outcomes between the treatment groups are not **confounded** by unobserved factors.
- Difficult to ensure balance between treatment groups with study-level data.
  - How much overlap between treatment groups?
- Sensitivity analyses should be conducted to determine how sensitive conclusions are to unmeasured confounder.

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Sources of Variation

- Within-Study: variability in the number of subjects.
- Safety or efficacy may vary across subgroups defined by study design covariates (delivery mechanism).
- Between-study: effectiveness may vary across studies due to differences in conducting each study.
- Between-study variation: how much artifactual study-specific factors contribute to unpredictable deviations within subgroups.

Sources of variation are not mutually exclusive.

Fixed versus Random Effects

Fixed Effects

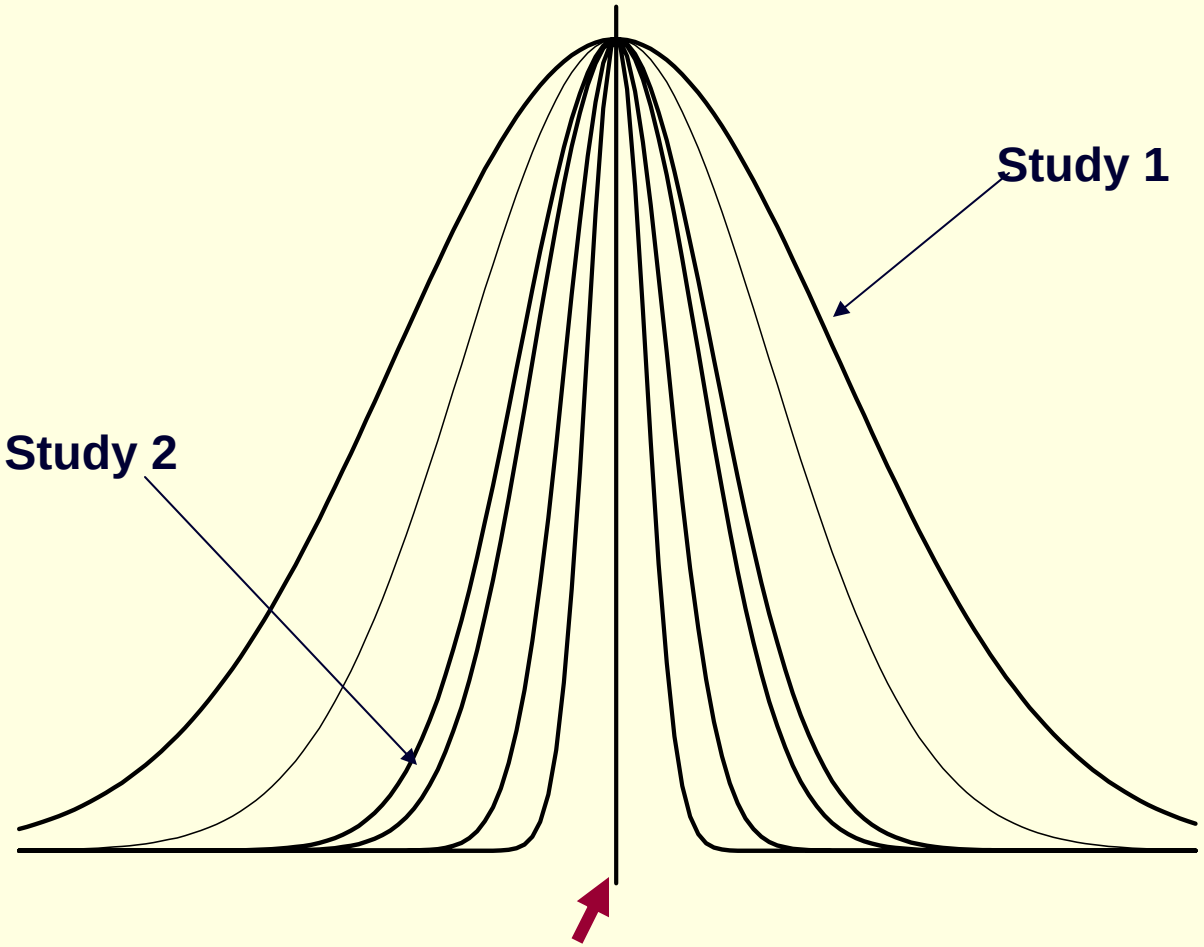
- Each study provides an estimate of the true risk difference.
- Uncertainty in true risk difference is due to sample size in primary studies.
- Between-study variance = zero (strong assumption)

Random Effects

- Each study effect is sampled from a super-population of effects.
- Super-population of effects is centered about the true (average) risk difference.
- Uncertainty in true risk difference is due to (1) sample size in primary studies and (2) between-study variation.

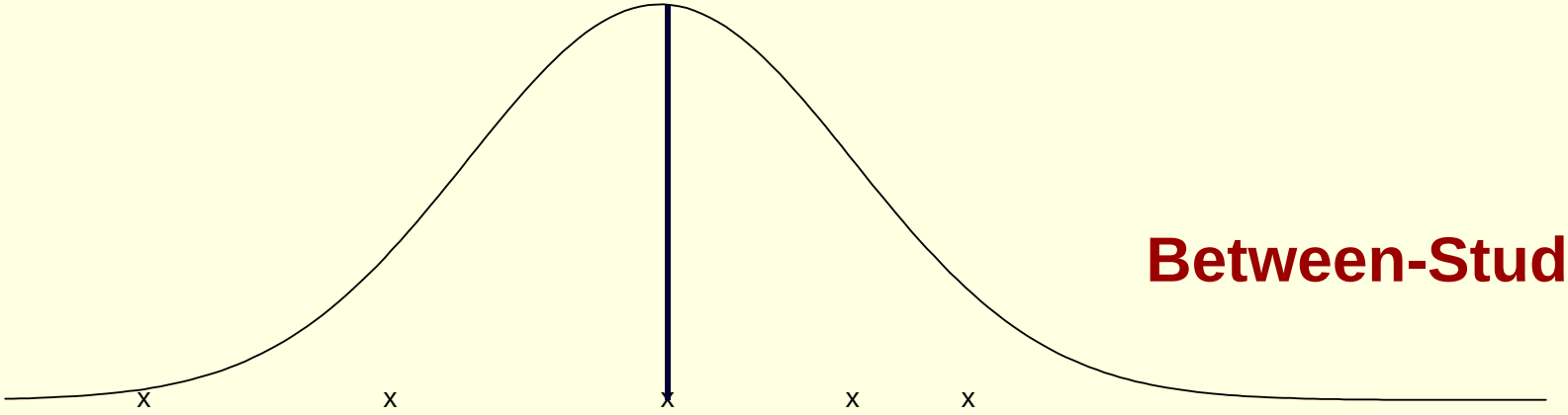
FIXED EFFECTS MODEL

Only variability is due to differences in number of patients in each study.



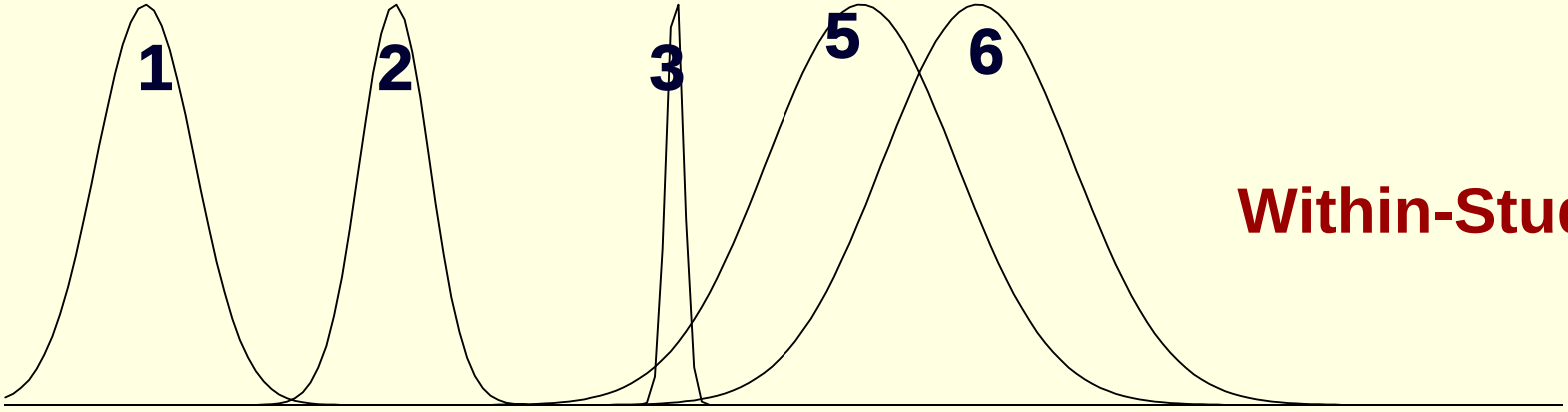
Distribution of True Risk Differences

RANDOM EFFECTS MODEL



Between-Studies

Distribution of True Study-Specific Risk Differences



Within-Studies

Estimated Study-Specific Risk Differences

How Robust are Conclusions?

Key Assumptions:

- Variation: common to assume within study variation is known – often this is too strong of an assumption.
- Distributional assumptions: of test statistics, of individual data, of variance components.
- Independence assumptions: multiple outcomes within a study, outcomes between studies.
- Missing data

Types of Missing Data.

- Entire studies are missing: publication bias.
- Data for study-specific summaries are missing, e.g., sample size. [Rothstein, Sutton, Borenstein (2005) Wiley book]
- Data from patients within a study are missing, e.g., attrition. [Yuan and Little, Applied Statistics (2007)]
  - Fixed Effects: imprecise if low response rates; biased if probability of response depends on observed value.
  - Random Effects: more precise than fixed effects if low response rates but even if data are MAR within study, need to fix estimate because it is still biased.

Concluding Remarks

- Meta-analysis is a **valid** and **powerful** tool to detect safety signals.
- Meta-analysis is an observational study – suffers all the problems of observational studies.
- More emphasis needs to be placed on assessing the sensitivity of results to plausible departures from assumptions.