Meta Analysis

- reference: "Meta-Analysis: Formulating, Evaluating, Combining and Reporting", Normand, S.T. *Statistics in Medicine*, 18, 321-359, 1999.
- meta analysis is the quantitative review and synthesis of the results of related but independent studies
- by combining studies, we get more power to detect a treatment effect
- choice of studies is crucial. For example, some researchers might include only randomized controlled trials.
- in compiling studies, beware of *publication bias*, the tendency to publish only statistically significant results.
  A funnel plot (http://en.wikipedia.org/wiki/Funnel_plot) is useful to assess publication bias.

- we need to choose a summary measure common to all studies
  - this could be risk difference, relative risk or odds ratio for binary outcome
  - for continuous studies it could be the average difference, or *effect size*,

$$\frac{\bar{Y}_T - \bar{Y}_C}{s_p}$$

  - we assume the summary measure for the i'th study, Y_i, is normally distributed with standard error σ_i

With a fixed effects model:

- we can make inferences only for populations which have been sampled
- we can generalize only to studies having identical characteristics and effects
- we assume that the only source of uncertainty results from sampling of subjects into studies
- we believe all studies are estimating a common parameter

- assume $Y_i = \theta + \epsilon_i$, where ϵ_i has zero mean and standard deviation σ_i

- uses weighted average of the study summary measures for the combined estimate
$$\hat{\theta} = \frac{\sum W_i Y_i}{\sum W_i}$$
where $W_i = 1/s_i^2$, with s_i^2 the sample variance from the i'th study.

- note that weights account for the different sample sizes and other differences in variation in the studies

- the estimate $\hat{\theta}$ is normally distributed with variance $1/\sum W_i$, and so a composite confidence interval can be calculated or a test performed. Specifically,

$$\hat{\theta} \pm Z_{\alpha/2} \sqrt{1/\sum_i W_i}$$

- The composite confidence interval is often plotted below the individual study confidence intervals, forming a so-called forest plot http://en.wikipedia.org/wiki/Forest_plot
- it is also possible to test for homogeneity, that is whether the studies *are* estimating the same quantity. This is typically done before making the composite confidence interval, but we won't consider the details.

An example

6 randomized controlled trials were run in which prophylactic lidocaine was given to patients with acute myocardial infarction. The question of interest is whether there is a detrimental effect of lidocaine. The studies were conducted to compare rates of arrhythmias following MI. The sample sizes were too small for the studies to individually show an effect on mortality.

Source	Number randomized		Number dead	
	Lidocaine	Control	Lidocaine	Control
1.	39	43	2	1
2.	44	44	4	4
3.	107	110	6	4
4.	103	100	7	5
5.	110	106	7	3
6.	154	146	11	4
Total	557	549	37	21

- the study-specific risk differences, variances, sample sizes and weights are shown below, where

$$d_i = \hat{p}_{Ti} - \hat{p}_{Ci}$$

$$s^2_{d_i} = \frac{p_{Ti}(1 - p_{Ti})}{n_{Ti}} + \frac{p_{Ci}(1 - p_{Ci})}{n_{Ci}}$$

Source	d_i	s_i^2	n_i	W_i	$\frac{W_i d_i}{\sum W_i}$
1.	.028	.001778	82	563.1	.002695
2.	.000	.003757	88	266.2	.000000
3.	.020	.00813	217	1229.7	.004139
4.	.018	.001090	203	917.5	.002814
5.	.035	.000801	216	1248.2	.007532
6.	.044	.000613	300	1630.7	.01226
Total			1106	5855.5	$\bar{d}_W = .02944$

- For example,

$$d_1 = (2/39) - (1/43) = .028$$

$$s_1^2 = \frac{(2/39)(1-2/39)}{39} + \frac{(1/43)(1-1/43)}{43} = .00177$$

$$W_1 = 1/.00177 = 563.1$$

- the estimated variance of the combined estimate is $var(\bar{d}_W) = 1/5855.5 = .000171$
- an approximate 95% confidence interval is $.02944 \pm 1.96\sqrt{.000171}$, or $.02944 \pm .0256$, or $(.004,\ .055)$
- this does not include zero, and so we can conclude that there is a significant difference in mortality due to lidocaine

Random effects meta analysis

this won't be covered on assignments or tests

- we want to generalize to a population in which studies are permitted to have different effects and characteristics
- the rationale is that there are many different approaches to conducting a study, and small changes in the study design will lead to small changes in the treatment effect
- we believe each study is associated with a different but related parameter

The random effects meta analysis:

- assumes $Y_i = \theta + \gamma_i + \epsilon_i$, where γ_i is a study specific treatment effect
- this effect is assumed to be normal with zero mean and variance τ^2, and to be independent of ϵ_i