Interaction: assessing Homogeneity

Some examples:

- **controlled trial: compare active with placebo groups**
- **observational study: compare exposed with non-exposed**

Use a *t*-test, χ^2 test, etc.

gives a single effect, mean difference, mean relative risk:

average over all patients in study

Perhaps effects different for different types of patients

Comparing Subgroups

Two problems:

1. **Correct method for assessing differences**
2. **How are the groups chosen?**

Doesn't only apply to subgroups

Effect of one variable differs depending on level of other variable.

Called interaction or effect modification

Only two binary variables considered, to simplify exposition only

Example

Trial of antenatal vitamin D supplementation for prevention of neonatal hypocalcaemia (BMJ 1980 Cockburn et al. 281, 11-14)

Mothers randomised to placebo or supplementation

Outcome is serum Ca in baby at 1 week (mmol/l)

Separate analyses of treatment effect in breast-fed and in bottle-fed babies

Breast-fed P=0.44

Bottle-fed P=0.0002

Does NOT establish a difference between feeding groups

P = 0.44 means no evidence of difference ≠ evidence of no difference

Summary of trial

	Breast-fed		Bottle-fed	
	Supplement	Placebo	Supplement	Placebo
Treatment Mean	2.445	2.408	2.300	2.195
n	64	102	169	285
SE	0.0365	0.0311	0.0211	0.0189
Treatment Effect	0.037		0.105	
SE	0.0480		0.0283	
P-value	0.44		0.0002	

To get P=0.44, *treatment effect =* 2.445 - 2.408 = 0.037 mmol/l

Standard error of difference = $\sqrt{(0.0365^2 + 0.0311^2)} = 0.0480$

P value found from 0.037/0.0480 = 0.771

Assessing Difference in Treatment Effects

Assessing *differences* in treatment effects is same as assessing treatments

Define treatment effect as difference in treatment means

Assess difference in treatment effects directly

Effect in breast-fed group	**=**	**0.037**
Effect in bottle-fed group	**=**	**0.105**
Difference in effects	**=**	**0.105 - 0.037 = 0.068**
SE this difference	**=**	$\sqrt{(0.0480^2 + 0.0238^2)} = 0.0557$

P-value found from 0.068/0.0557 = 1.22 , P=0.22

So no evidence of difference in treatment effects

Another Example

Antenatal steroid or placebo for neonatal RDS
(*American Journal of Obstetrics and Gynecology*, 141, 276-287

Treatment effect in boys and girls

mothers with and without pre-eclampsia

Outcome is binary, methods same once SEs found.

Summary of Results

Percentages with RDS

	Steroid group		Placebo group		P-value
Sex of Baby					
Boys	14.9%	24/161	14.1%	24/170	0.96
Girls	4.8%	7/146	18.8%	24/128	<0.001
Pre-eclampsia groups					
with pre-eclampsia	21.2%	7/33	27.3%	9/33	0.57
without pre-eclampsia	7.9%	21/267	14.1%	37/262	0.021

Treatment Effect (difference in percentage with RDS)

Boys -0.8% (P=0.96) **Girls 14% (P<0.001)**

No pre-eclampsia 6.3% (P=0.021) **pre-eclampsia 6.1% (P=0.57)**

Strong evidence of interaction for sex effect (P=0.007)
no evidence for interaction for pre-eclampsia (P=0.99)

Selection of Groups

Ten variables - 45 two-way interactions

Some will come up significant data dredging

Pre-specification helps

Unanticipated findings need cautious interpretation

(sex difference in antenatal steroid trial not sustained in other studies)