1.3 Review of epidemiological tables

RR, OR, confounding, stratification, trend

Risk

The simplest measure of risk (probability) is estimated from the proportion that is observed

Example:

If in a cohort of 11034 people, there were 189 who had an MI

Risk of MI =189/11034=.0171 =1.7%

Can calculate risk from cohort or cross-sectional study

but not from case-control study (traditional wisdom!)

Comparing Proportions (Chi-square test)

For **any size table**, the Chi-square test answers the question:
”is there an association between the two factors

How?

By calculating the ”expected table” if no association
and comparing to actual observed table

If the ”discrepency” is large, conclude there is an association

How large? depends on size of table

Example of two-by-two table

		Marrow Cell Dose (10^8 cells/kg)		
		<3.0	**X3.0**	**Total**
Graft	**Yes**	17	4	21
Rejection	**No**	19	28	47
	Total	36	32	68

Column Totals

Grand Total

Question: Is there evidence that marrow dose is associated with GVHD?

i.e. is the above Table what we would expect even if there is no association?

Overall GVHD rate=21/68

- so *if no association*, we would expect:
- 21/68 of 36 in <3.0 group to get GVHD
- and 21/68 of 32 in the other group

i.e. we expect

$\frac{21}{68} \times 36$	$\frac{21}{68} \times 32$

Expected table

11.1	9.9	21
24.9	22.1	47
36	32	

similarly, 1-21/68 = 47/68 no GVHD
so we expect

$\frac{47}{68} \times 36$	$\frac{47}{68} \times 32$

Compare:

	Observed		Expected (if no association)	
	<3.0	X3.0	<3.0	X3.0
Yes	17	4	11.1	9.9
No	19	28	24.9	22.1

$$\text{Discrepency} = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

$$= \frac{(17-11.1)^2}{11.1} + \frac{(4-9.9)^2}{9.9} + \frac{(19-24.9)^2}{24.9} + \frac{(28-22.1)^2}{22.1}$$

$$= 9.64$$

Is this large or small?

Tests of discrepancy

If no association, discrepency has a Chi-Squared distribution with 1 degree of freedom, $\chi^2_{(1)}$ (square of standard normal!)

	0.05	0.01	0.001
$\chi^2_{(1)}$	3.841	6.635	10.828

⇒ our result has p-value < .01, so is unlikely to be simply due to randomness

⇒ we conclude that there **is** a difference in the two groups

This is called "***Pearson's Chi square test***"

For any size table (R rows, C columns), can also construct an observed and expected table, but under null hypothesis, distribution of discrepency now $\chi^2_{(R-1\ X\ C-1)}$

For 2-by-2 table, can also compare proportions using Relative Risk (Risk Ratio)

N Eng. Jour. Med. 1988 (262-264) Physicians Health Study: randomised trial of regular use of aspirin and 5-year MI rate

	Yes	No	Total
Placebo	189	10,845	11,034
Aspirin	104	10,933	11,037

Risk of MI for placebo =189/11034=.0171

Risk of MI for aspirin = 104/11037=.0094

$\Rightarrow$ RR=1.82

To assess significance: confidence interval (or Chi-square test)

Can also compare Odds (Odds Ratio)

Odds

"the ratio of successes to failures"

Example: Dental Analgesic Trial

	Relief	
	Y	N
Active	24	6
Placebo	3	17

Odds of relief in Active = 24/6

Odds of relief in Placebo=3/17

Odds Ratio of relief in Active compared to Placebo :

24/6 ÷ 3/17 = 22.7 ($p < .0001$)!

OR = 1 $\Rightarrow$ no association (like RR=1)

OR > 1 $\Rightarrow$ + association treatment & relief

OR < 1 $\Rightarrow$ - association treatment and pain

Reverse the Question

Compute OR of being on active treatment for those with pain relief compared to those with no pain relief

Example: Dental Analgesic Trial

	Relief	
	Y	N
Active	24	6
Placebo	3	17

same!

i.e. we can calculate and interpret OR from case-control studies

Traditional wisdom:

Only the OR is valid from case-control study

Relationship between OR and RR

Text book wisdom: if disease is rare then OR ≅ RR

(as in placebo vs. aspirin example)

Crude and stratified OR
(example from Zang and Wynder*)

	Overall			Smoker			Non-smoker		
	Lung Cancer			Lung Cancer			Lung Cancer		
	Yes	No		Yes	No		Yes	No	
Heavy Drinker	1057	1949	3006	786	665	1451	271	1248	1555
Light Drinker	1896	6220	8116	702	591	1293	1194	5629	6823
	2953	8169	11122	1488	1256	2744	1463	6913	8378
	OR = 1.78			OR = 1.0			OR = 1.0		

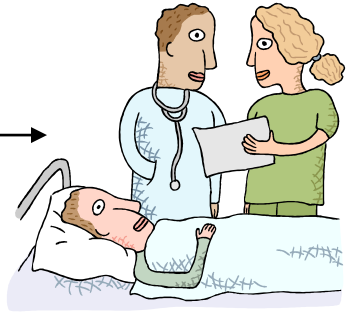
Illustration of confounding

**Zang E and Wynder E. Preventive Med 3, 359-370,2001*

Smoking is a potential “confounder”:

EXPOSURE

(drinking)



OUTCOME

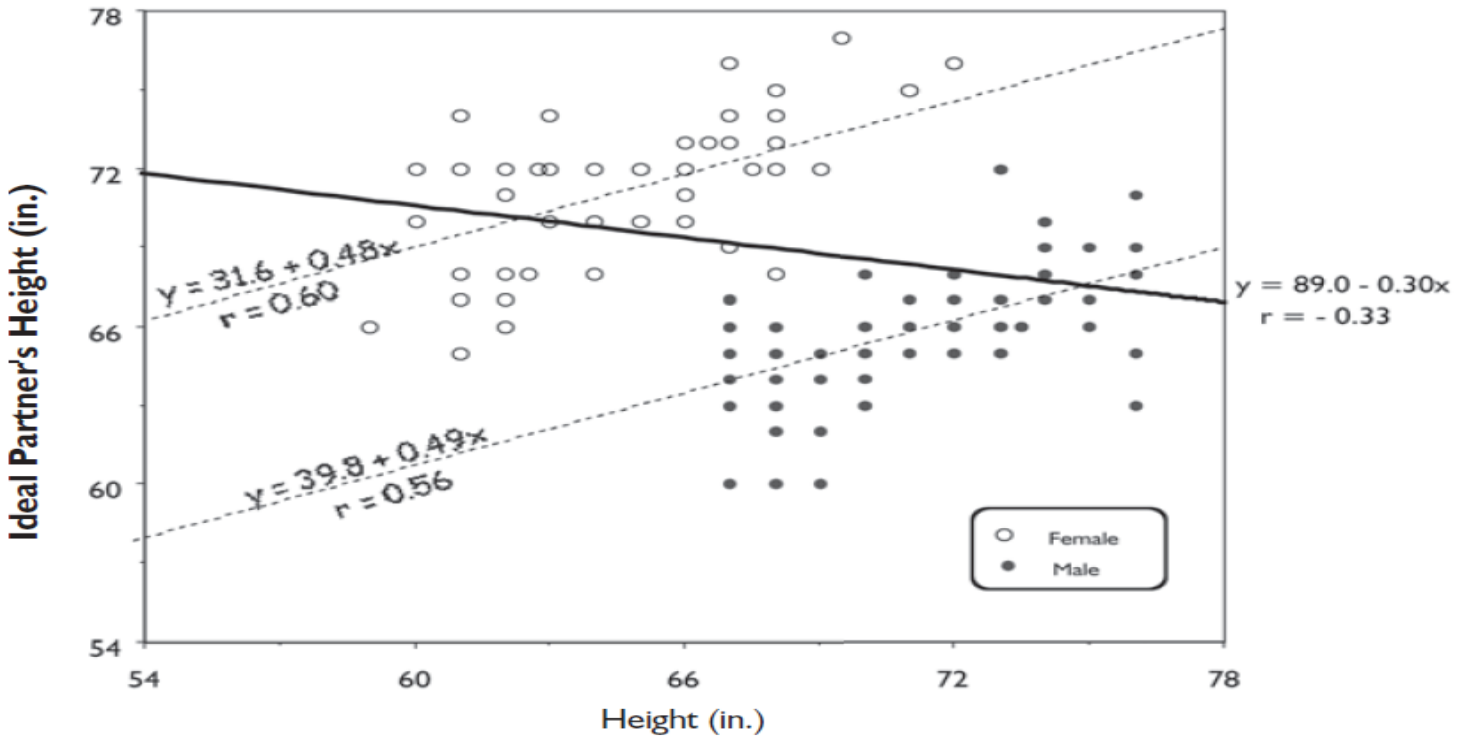
(lung cancer)

CONFOUNDNG VARIABLE

(cigarette - smoking)

Example for continuous variables

Where a ‘‘predictor’’ X is presumed to be associated causally with outcome, Y, but there is an additional variable, Z, that is associated with both X and Y



Wainer et al. Giving the Finger to Dating Services. CHANCE, 21:3, 59-61.

Examples of potential confounders

Studied association	Confounder?
Birth weight and adult heart disease	maternal smoking adult BMI/weight
Vitamin D and Mycardial infarction	fast food consumption sun exposure?
Prenatal tobacco and own tobacco use	Parental smoking in childhood, gestational age?

Mantel-Haenszel OR (common OR) for binary outcome and exposure

Karolinska Institutet

Stratum 1

	Disease: Yes	Disease: No
Exposed	a_1	b_1
Unexposed	c_1	d_1

n_1

Stratum 2

	Disease: Yes	Disease: No
Exposed	a_2	b_2
Unexposed	c_2	d_2

n_2

$$\widehat{OR}_{MH} = \frac{\frac{a_1 d_1}{n_1} + \frac{a_2 d_2}{n_2}}{\frac{b_1 c_1}{n_1} + \frac{b_2 c_2}{n_2}}$$

← Main diagonals

← Off diagonals

$$\widehat{OR}_{MH} = \frac{\frac{786 \times 591}{2744} + \frac{271 \times 5629}{8378}}{\frac{665 \times 702}{2744} + \frac{1248 \times 1194}{8378}}$$

$$= 351.367/347.988$$

$$= 1.0097$$

Can have any number of strata

The MH-OR estimates the *common* OR

So before computing OR_{MH}, we need to test whether it is reasonable to assume a common OR

"Tests of homogeneity"

- All are similar in spirit to the simple Chi-squared test of association
- **compare the observed data in each stratum to what would be expected if there was a common OR (i.e. the overall OR)**
- compare the total "discrepancy" to Chi-square distribution

Provided in statistical calculators (**Openepi.com**) and software

Example: Framingham data

Prevalent CHD	Diabetes: Yes	Diabetes: No	
Yes	12	175	187
No	104	3214	3318
	116	3389	3505

Crude OR = 2.12

Ages 42–51

CHD	Diabetes: Yes	Diabetes: No	
Yes	1	32	33
No	28	1553	1581
	29	1585	1614

OR = 1.73

Ages 52–61

CHD	Diabetes: Yes	Diabetes: No	
Yes	4	74	78
No	47	1221	1268
	51	1295	1346

OR = 1.40

Ages 62–71

CHD	Diabetes: Yes	Diabetes: No	
Yes	7	69	76
No	29	440	469
	36	509	545

OR = 1.54

Test of homogeneity χ^2=.04, p=.98

Mantel Haenszel OR = 1.5

Example: Framingham data (cont…)

		Diabetes: Yes	Diabetes: No	
Prevalent CHD	Yes	12	175	187
	No	104	3214	3318
		116	3389	3505

Crude OR = 2.12

Mantel Haenszel OR = 1.5

Conclude:

Confounding by age (adjusted differs by > 10% from crude)

Control of Confounding

Removing spurious associations from related variables can be done at the **design stage**, and/or the **analysis stage**.

confounding is due to "imbalance", so idea is to

"balance" the design

Control of confounding at design stage

Restriction

- Confounding cannot occur if the factor *does not vary*.
  For example if the study is limited to non-smoking women,
  then smoking and gender cannot be confounding variables.

- Restriction also limits the participants/ interpretation of the study.
  Often partial restriction is used.

Matching

Later lecture

Control of confounding at analysis stage

- Stratification (as shown for age groups earlier)
- Calculate adjusted OR (Mantel-Haenszel)
- Use “logistic regression” (more later) in a statistical package

Effect modification (also called interaction)

When the effect of exposure is **different** in different strata

(test of homogeneity provides evidence **against** a common OR),

We say:

the effect is “modified” by the stratum

there is an ”interaction”

Now a “common” OR not meaningful!!

If only a few strata, report the OR in each

Example: Framingham data

Prev. Hypertension	Diabetes: Yes	Diabetes: No	
Yes	67	1237	1304
No	49	2152	2201
	116	3389	3505

Crude OR = 2.38

Males

Prev. Hypertension	Diabetes: Yes	Diabetes: No	
Yes	25	520	545
No	32	951	983
	57	1471	1528

OR = 1.43

Females

Prev. Hypertension	Diabetes: Yes	Diabetes: No	
Yes	42	717	759
No	17	1201	1218
	59	1918	1977

OR = 4.14

Test of homogeneity χ^2=7.13, p=.008

Dose-response: test of trend

When the exposure is more than two levels and categories are ordered (e.g. age groups),

may be a steady increase/ decrease in the risk with the ‘dose’ of exposure.

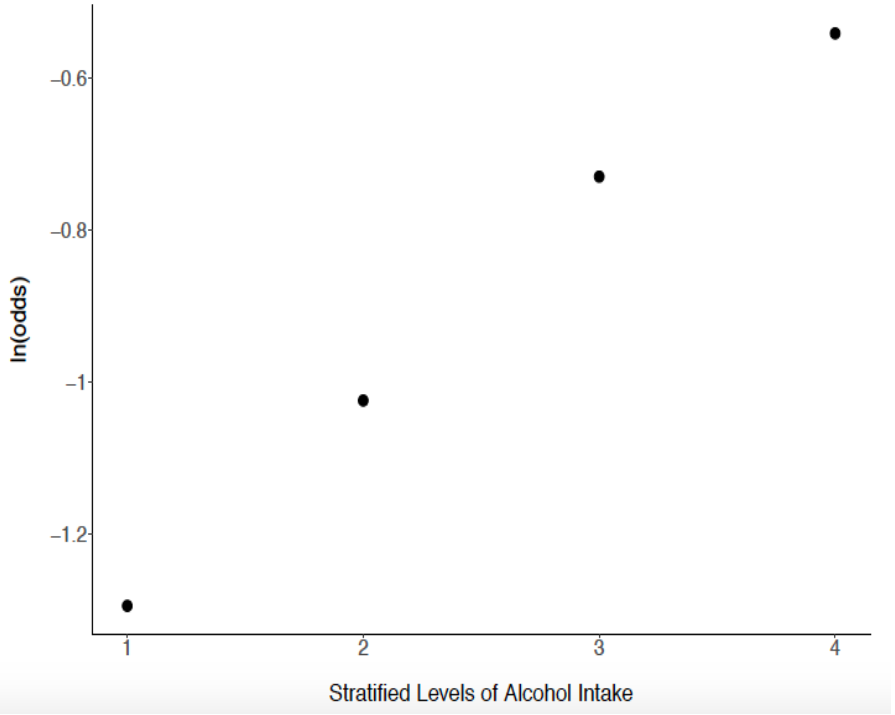
Important evidence: one of the Bradford-Hill criteria for causation

Return to alcohol and lung cancer (and smoking)example:

		Lung Cancer		
		Yes	No	Odds
Alcohol Intake	<1	1090	3976	.274
	1-3.9	806	2244	.359
	4-6.9	378	783	.482
	≥ 7	679	1166	.582
		2953	8169	

Dose-response: test of trend

	Lung Cancer		
	Yes	No	Odds
<1	1090	3976	.274
1-3.9	806	2244	.359
4-6.9	378	783	.482
≥ 7	679	1166	.582
	2953	8169	



Test of (any) association

χ^2=186.8, p-value < .000001 (from χ^2 with 3 d.o.f.)

χ^2 for trend (generally more powerful)

$$\frac{\left[\sum_{i=1}^{k} a_i x_i - A\bar{x}\right]^2}{p(1-p)N\left[\sum_{i=1}^{k} \frac{n_i x_i^2}{N} - \bar{x}^2\right]}$$

Where a_i= cases in each stratum

x_i = scores in the strata

N= total number of subjects (cases + controls)

A = total number of cases

p= overall proportion cases

Expression in [] in numerator=
Total score for cases – (no. of cases) (average score overall)

Expression in [] in denominator = variance of score
(avg. of square – square of avg.)

Under Null Hypothesis (no trend) this has Chi-squared distribution with 1 degree of freedom

Test for trend (cont.)

Note we need to use scores: common to use midpoints.

For equally spaced strata, 1,2,3…give the same result

If no natural scores, can simply use 1,2,3…..

Chi-squared test not sensitive to the choice.

What if the exposure is continuous?
(e.g. age, blood pressure, biomarker levels…)

Summary

- The effect of a risk factor on disease risk is usually measured by comparing prevalence, incidence, cumulative incidence or odds

- Comparisons in risk are most often based on relative difference, so by comparing the risk/odds of disease among exposed with the risk/odds among unexposed, e.g. RR or OR

- When comparing proportions across groups Chi-square tests are often used as a first test

  → However, only gives p-values and no measure of association

Summary (cont.)

- We looked at association between binary outcome and a single binary explanatory variable of interest

- Then we considered one explanatory variable and a confounder or stratum variable
  → Test of homogeneity
  → adjusted/common OR where appropriate

- Dose-reponse (test for trend)

- In practice we are often interested in a number of explanatory variables (independent risk factors, confounders, effect modifiers). So, after examining one-by-one ("univariate" analysis), we need to model their joint effect:

  Logistic regression (later lecture)