EMBLEM
High Quality, High Impact Research

Cancer Research Methods Workshop

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Mwanza, Tanzania

September 18-19, 2012

Yale SCHOOL OF PUBLIC HEALTH

Interaction (Effect Modification)

Interaction (effect modification)

- The terms "interaction" and "effect modification" are usually used synonymously
- The situation where independent variables *interact* with one other, such that the *effect* of one on the outcome is *modified* (or moderated) by another
- Heterogeneity (vs. homogeneity) of effect: the association between exposure and outcome varies by the level (or across the strata) of another variable

Multiplicative interaction

We're asking the question:

- Does the association between exposure and outcome (i.e., does the effect in terms of a ratio measure like OR or RR) differ by the level of a third variable?

We can evaluate this using two different but complementary approaches:

- Are the stratum-specific ORs (RRs) heterogeneous?
- Does the observed joint effect of the exposure and the potential effect modifier differ from the expected joint effect?

Hypothetical cohort study:
Is smoking an effect modifier of the association between alcohol use and oral cancer? (multiplicative interaction?)

Among non-smokers: RR=3.0

	Oral Ca -	Oral Ca +	Total
Alc -	98	2	100
Alc +	94	6	100

Among smokers: RR=3.0

	Oral Ca -	Oral Ca +	Total
Alc -	90	10	100
Alc +	70	30	100

Smk	Alc	Risk
No	No	2%
No	Yes	6%
Yes	No	10%
Yes	Yes	30%

RRs	Alc -	Alc +
Smk -	Ref = 1.0	3.0
Smk +	5.0	***15.0***

Observed joint effect = Expected joint effect

Hypothetical cohort study:
Is smoking an effect modifier of the association between alcohol use and oral cancer? (multiplicative interaction?)

Among non-smokers: RR=3.0

	Oral Ca -	Oral Ca +	Total
Alc -	98	2	100
Alc +	94	6	100

Among smokers: RR=6.0

	Oral Ca -	Oral Ca +	Total
Alc -	90	10	100
Alc +	40	60	100

Smk	Alc	Risk
No	No	2%
No	Yes	6%
Yes	No	10%
Yes	Yes	60%

RRs	Alc -	Alc +
Smk -	Ref = 1.0	3.0
Smk +	5.0	***30.0***

Observed joint effect ≠ Expected joint effect

Confounding vs. effect modification

- Technically, a third variable that is not in the causal pathway can be a confounder, an effect modifier (moderator), both, or neither
- However, if there is effect modification, it trumps confounding, since it would be inappropriate and misleading to calculate an adjusted OR or RR when the stratum-specific values are heterogeneous

Gender and thrombolytic therapy example

Is there a gender difference (1=female, 0=male) in the use of thrombolytic therapy (1=yes, 0=no) in the first 24 hours after myocardial infarction?

Gender and thrombolytic therapy example
Unadjusted association.

FEMALE TT24GIV (TT within 24h: 0 = NO; 1 = Yes)

Frequency	0	1	Total
0	461 66.52	232 33.48	693
1	396 76.30	123 23.70	519
Total	857	355	1212

Unadjusted OR = 0.62, p < 0.001

	TT +	TT -
F	123	396
M	232	461

Gender and thrombolytic therapy example (cont.)

Using stratified analysis, assess whether age (0=<65, 1=65-74, 2=75-84, 3=85+) is a confounder or an effect modifier of the association between gender and use of thrombolytic therapy

Gender and thrombolytic therapy example
Age-stratified results

TABLE 1 OF FEMALE BY TT24GIV

CONTROLLING FOR AGE4CAT = 0 <65

FEMALE TT24GIV (TT within 24h: 0 = No; 1 = Yes)

Frequency	0	1	Total
0	154 55.00	126 45.00	280
1	69 59.48	47 40.52	116
Total	223	173	396

OR = 0.83, p = 0.413

Gender and thrombolytic therapy example
Age-stratified results

TABLE 2 OF FEMALE BY TT24GIV

CONTROLLING FOR AGE4CAT = 1 65-74

FEMALE TT24GIV (TT within 24h: 0 = No; 1 = Yes)

Frequency	0	1	Total
0	143 66.51	72 33.49	215
1	108 75.00	36 25.00	144
Total	251	108	359

OR = 0.66, p = 0.086

Gender and thrombolytic therapy example

Age-stratified results

TABLE 3 OF FEMALE BY TT24GIV

CONTROLLING FOR AGE4CAT = 2 ← 75-84

FEMAL TT24GIV (TT within 24h: 0 = No; 1 = Yes)

Frequency	0	1	Total
0	128 80.50	31 19.50	159
1	134 79.76	34 20.24	168
Total	262	65	327

OR = 1.05, p = 0.867

Gender and thrombolytic therapy example

Age-stratified results

TABLE 4 OF FEMALE BY TT24GIV

CONTROLLING FOR AGE4CAT = 3 ← 85+

FEMAL TT24GIV (TT within 24h: 0 = No; 1 = Yes)

Frequency	0	1	Total
0	36 92.31	3 7.69	39
1	85 93.41	6 6.59	91
Total	121	9	130

OR = 0.85, p = 0.821

Gender and thrombolytic therapy example

Summary

So what did we find…

Unadjusted OR = 0.62, p < 0.001

Stratum-specific ORs

<65	0.83, p = 0.413	**Breslow-Day test for homogeneity of the ORs: p = 0.664**
65-74	0.66, p = 0.086	
75-84	1.05, p = 0.867	
85+	0.85, p = 0.821	

Adjusted OR = 0.82, p = NS

Gender and thrombolytic therapy example

Summary

- Mantel-Haenszel summary estimate and statistical test
  - are adjusted for the stratification variable
  - key assumption is that estimates are homogenous across strata
- Breslow-Day test
  - tests the null hypothesis that estimates are homogenous across strata
  - tests for interaction between predictor (gender) and stratification variable (age) on outcome (use of thrombolytic therapy)

Gender and thrombolytic therapy example

Summary

In the above example, age acts as a <u>confounder</u> of the association between gender and use of thrombolytic therapy. After adjusting for age, the association between gender and thrombolytic therapy is <u>much less strong</u> and is no longer statistically significant.

The Breslow-Day test indicates that there is no interaction effect (stratum-specific ORs are homogenous); therefore, the Mantel-Haenszel summary estimate and test are appropriate.

Diabetes and mortality example

Is having diabetes (1=yes, 0=no) a risk factor for 30-day mortality (1=dead, 0=alive) following myocardial infarction?

Diabetes and mortality example
Unadjusted association

DIABETES MORT30D

Frequency	0	1	Total
0	7690 81.70	1722 18.30	9412
1	2717 79.26	711 20.74	3428
Total	10407	2433	12840

Unadjusted OR = 1.17, p = 0.002

Diabetes and mortality example (cont.)

Using stratified analysis, assess whether age (1=65-74, 2=75-84, 3=85+) is a confounder or an effect modifier of the association between diabetes and 30-day post-MI mortality

Diabetes and mortality example
Age-stratified results

TABLE 1 OF DIABETES BY MORT30D

CONTROLLING FOR AGEGP = 1 ← 65-74

DIABETES MORT30D

Frequency	0	1	Total
0	3711 89.36	442 10.64	4153
1	1462 84.51	268 15.49	1730
Total	5173	710	5883

OR = 1.54, p < 0.001

Diabetes and mortality example
Age-stratified results

TABLE 2 OF DIABETES BY MORT30D

CONTROLLING FOR AGEGP = 2 ← 75-84

DIABETES MORT30D

Frequency	0	1	Total
0	3010 78.90	805 21.10	3815
1	1014 75.62	327 24.38	1341
Total	4024	1132	5156

OR = 1.21, p = 0.012

Diabetes and mortality example
Age-stratified results

TABLE 3 OF DIABETES BY MORT30D

CONTROLLING FOR AGEGP = 3 ← 85+

DIABETES MORT30D

Frequency	0	1	Total
0	969 67.11	475 32.89	1444
1	241 67.51	116 32.49	357
Total	1210	591	1801

OR = 0.98, p = 0.885

Diabetes and mortality example
Summary

So what did we find…

Unadjusted OR = 1.17, p = 0.002

Stratum-specific ORs

65-74	1.54, p < 0.001	**Breslow-Day test for homogeneity of the ORs:**
75-84	1.21, p = 0.012	
85+	0.98, p = 0.885	**p = 0.007**

Adjusted OR = 1.27, p < 0.001

Diabetes and mortality example

Summary

In the above example, age acts as an effect modifier of the association between diabetes and 30-day mortality following MI. The ORs differ markedly across strata: the younger the age, the stronger the effect of diabetes.

The Breslow-Day test indicates that there is an interaction effect (stratum-specific ORs are not homogenous); therefore, the Mantel-Haenszel summary estimate and test are not appropriate. Must report stratum-specific results.

Social support and glycemic control example

In this example, we're going to examine whether the relationship between a measure of social support and glycemic control differs by gender in a sample of older persons with diabetes (data from NHANES III)

Social support measure:

How often do you get together with friends or relatives?

(dichotomized as 1=at least once a day, 0=less than daily)

Glycemic control measure:

HbA_{1c} level

(dichotomized as 1="poor" control and 0="adequate" control, based on HbA_{1c} > 8% cutoff)

Social support and glycemic control example

Unadjusted association

GE_DAILY HBA1CGT8

Frequency	0	1	Total
0	369 68.33	171 31.67	540
1	76 62.81	45 37.19	121
Total	445	216	661

Unadjusted OR = 1.28, p = NS

Social support and glycemic control example

Gender-stratified results

TABLE 1 OF GE_DAILY BY HBA1CGT8

CONTROLLING FOR SEX = 1 ← Men

GE_DAILY HBA1CGT8

Frequency	0	1	Total
0	174 70.45	73 29.55	247
1	22 46.81	25 53.19	47
Total	196	98	294

OR = 2.71, p < 0.05

Social support and glycemic control example

Gender-stratified results

TABLE 2 OF GE_DAILY BY HBA1CGT8

CONTROLLING FOR SEX = 2 ← Women

GE_DAILY HBA1CGT8

Frequency	0	1	Total
0	195 66.55	98 33.45	293
1	54 72.97	20 27.03	74
Total	249	118	367

OR = 0.74, p = NS

Social support and glycemic control example

Summary

So what did we find…

Unadjusted OR = 1.28, p = NS

Stratum-specific ORs

Men 2.71, p < 0.05

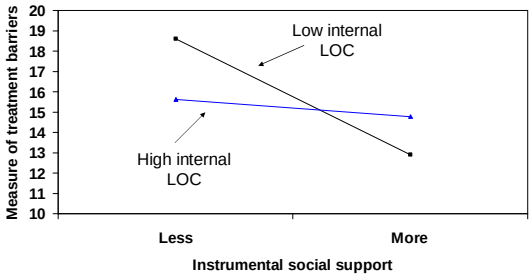
Women 0.74, p = NS

Breslow-Day test for homogeneity of the ORs:

p = 0.002

Adjusted OR = 1.28, p = NS

Locus of control significantly modifies the relationship between level of social support and perceived treatment barriers among elderly patients with depression



(Voils et al. Am J Geriatr Psychiatry, 2005)

Summary of confounding and effect modification

Confounding	Effect modification
• Must be avoided, controlled	• Interesting, need to report
• Not assessable by significance testing	• Assessable by significance testing
• Stratification: removes confounding (OK to calculate adjusted OR)	• Stratification: reveals effect modification (not OK to calculate adjusted OR)
• Restriction: eliminates confounding	• Restriction: doesn't eliminate EM, but rather the ability to evaluate it
• Matching: can't evaluate the independent effect of the matched variable	• Matching: can still evaluate whether the matched variable is an effect modifier
• Reciprocity: no – if A confounds B, it doesn't imply that B confounds A, and vice versa	• Reciprocity: yes – if A modifies the effect of B, B modifies the effect of A