Statistics 305/605: Introduction to Biostatistical Methods for Health Sciences

Chapter 16: Multiple 2×2 Contingency Tables

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Associations and extraneous variables

- Want to study the association between two dichotomous variables: an exposure variable and a disease outcome.
- However, a third, extraneous variable with g different values (levels) is also present
  - Does ignoring it lead to incorrect conclusions?
- When associating the disease outcome and the exposure variable, need to account for the possibility that the extraneous variable is either
  1. an **effect modifier** or
  2. a **confounder**.

Example: Aortic Stenosis (AS) Study

- What is the association between AS and smoking? How does sex affect this association?
  - AS: disease outcome
  - smoking: exposure variable
  - sex: extraneous variable with $g = 2$ levels.
- First few lines of the data:

```
##   smoke AS sex
## 1     1  1   1
## 2     1  1   1
## 3     1  1   1
## 4     1  1   1
## 5     1  1   1
## 6     1  1   1
```

- When associating AS and smoking, we should account for the possibility that sex is either
  1. an **effect modifier** or
  2. a **confounder**.

Effect Modification

Effect Modification

- When the ORs for different strata of the extraneous variable are different, the extraneous variable is an **effect modifier**.
- Inference (estimates, CIs, tests) of these different ORs must then be based on the stratified tables.
- That is, we estimate the ORs, perform tests, and construct CIs with each stratum-specific table, separately.

Testing for Effect Modification

- When the ORs for different strata of the extraneous variable are the same, they are said to be **homogeneous**.
- Can test for this with.
  - H_0: homogeneity of ORs, versus
  - H_a: effect modification.
- If we reject H_0, declare the extraneous variable to be an effect modifier.

Test of Homogeneity (Text, Section 16.2.1)

- Suppose the extraneous variable has g levels or **strata**
- Let $\widehat{OR}_i$ be the estimated OR between the exposure and the disease outcome in the ith stratum of the extraneous variable.
- Let $y_i = \log_e \widehat{OR}_i$, with variance estimated by

$$se^2(\log_e \widehat{OR}_i) = 1/a + 1/b + 1/c + 1/d.$$

- Let $w_i = 1/se^2(\log_e \widehat{OR}_i)$.
  - The larger the $se(\log_e \widehat{OR}_i)$, the smaller the weight w_i accorded to stratum i of the extraneous variable.
- A weighted average of the y_i's that diminishes the contribution of values with high standard errors is:

$$Y = \sum_{i=1}^{g} \left(\frac{w_i}{\sum_{j=1}^{g} w_j} \right) y_i = \frac{\sum_{i=1}^{g} w_i y_i}{\sum_{j=1}^{g} w_j}.$$

- The test statistic tallies up the deviations of the estimated log-ORs from this average:

$$X^2 = \sum_{i=1}^{g} w_i (y_i - Y)^2$$

  Large deviations suggest heterogeneous ORs.
- Under H_0: homogeneous ORs, the statistic X^2 has a chi-square distribution with $g - 1$ df.

Test of Homogeneity in the AS Example

- In the AS example, the gender-specific tables are:

```
## , , sex = 0
##
##    smoke
## AS   0  1
##   0 47 19
##   1 29 14
##
## , , sex = 1
##
##    smoke
## AS   0  1
##   0 20 24
##   1 25 37
```

- We test for homogeneity of the ORs for AS across the strata defined by sex at level 5%.
- We get (see R demo):

```
## $X2
## [1] 0.003072521
##
## $pval
## [1] 0.9557956
```

- Retain the null hypothesis of homogeneous ORs at 5% level. Insufficient evidence that sex modifies the effect of smoking on AS.
  - See text, section 16.2.1 for another example.
- Next question (and topic): Sex doesn't appear to be an effect modifier but is it a confounder?

Confounding

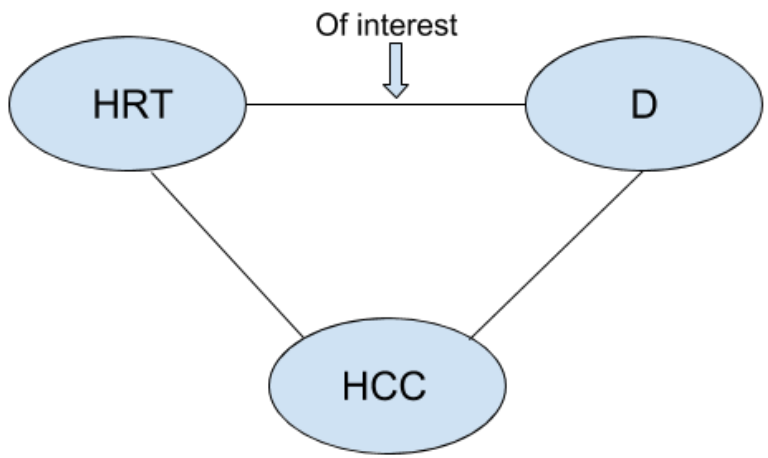
What is a Confounder?

- A confounding variable is an extraneous variable that is associated with both the disease outcome and the exposure of interest.
- Why is this important?
- Ignoring a confounder leads to biased inference of the effect of the exposure on the disease outcome (i.e., incorrect estimate, test and CI) and potentially **wrong conclusions**.
- Confounding is thus a **big concern** in any observational study.

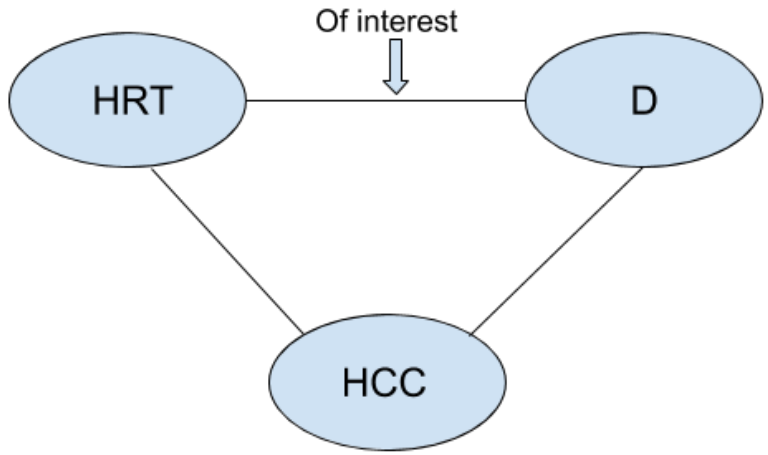
WHI Example

- Observational studies leading up to the WHI (a clinical trial) suggested that postmenopausal women on hormone-replacement therapy (HRT) had better disease outcomes.
- Drug companies were actively promoting synthetic hormones in their marketing targetted to the large demographic group of postmenopausal women.
  - Doctors were prescribing HRT for their postmenopausal patients.
- What everyone missed was the potential confounding by health-care coverage (in the US).
- Women with better health-care coverage tend to have better disease outcomes and also to have better access to HRT. Hence HRT seemed to be associated with better disease outcomes.

- In the diagram below, let D be disease outcome, HRT be hormone replace therapy (the exposure of interest) and HCC be health-care coverage.
  - Associations between variables are indicated by lines
  - HCC is associated with better disease outcomes (i.e. with D).
  - HCC is also associated with access to HRT.



Confounding of association between HRT and D by HCC



Confounding of association between HRT and D by HCC

- To properly understand the effect of *HRT* on *D*, it is important to control/adjust for the potential confounding effect of *HCC*.
- The WHI was a randomized, controlled, clinical trial of *HRT*.
  - The WHI investigators used treatment randomization to control/adjust for the potential confounding effects of *HCC*.
  - The randomization of *HRT* to women regardless of their *HCC* breaks the association between *HRT* and *HCC*.
- The trial established the harmful effects of *HRT*. Doctor's stopped prescribing and companies stopped marketing it.

Simpson's Paradox

- Confounding explains "Simpson's paradox":
  - When the effect of an exposure on the odds of the disease outcome differs in the stratified and pooled analyses.
- In the AS example, the estimated ORs summarizing the association between AS and smoking, stratified by sex, are about the same: 1.19 for females and 1.23 for males.
  - These results suggest that, for both females and males, smoking *slightly* increases the odds of AS.
- However, the estimated OR from the pooled table across genders is 1.47.
  - This result suggests a *stronger* effect of smoking than we obtain from the stratified tables!

Effect Modifier vs. Confounder

- When considering the OR summarizing the association between the disease outcome and the exposure variable, the extraneous variable is:
  1. an *effect modifier* if the ORs for different strata of the extraneous variable are **different**.
  2. a *confounder* if the ORs for different strata of the extraneous variable are the **same** but different from the OR that we get when we ignore the extraneous variable altogether.

The Mantel-Haenszel (MH) estimator

- To understand the effect of the exposure on disease outcome, we need to adjust the OR for the effects of a confounding variable.
- We can adjust the OR by using the Mantel-Haenszel (MH) estimator.
- The MH estimator of the OR adjusts for a confounding variable when
  - the disease outcome and exposure variable are dichotomous (i.e. have 2 categories) and
  - the confounding variable is categorical with 2 or more categories.

MH Summary OR

- The MH summary estimator is a weighted average of the stratum-specific OR estimators
  - The MH estimator was developed over 50 years ago, is common practice in Epidemiology, and has good statistical properties.
  - Hence it is worth knowing.
- The MH estimate of the OR is

$$\widehat{OR} = \frac{\sum_{i=1}^{g} a_i d_i / T_i}{\sum_{i=1}^{g} b_i c_i / T_i}$$

  where a_i, b_i, c_i, d_i are from the table for the ith stratum of the extraneous variable, and T_i is the table total for this ith table.
- See the text, page 381 for a worked example of this calculation.

The MH Test

- Once we have the MH estimate of the common OR across the strata of the confounding variable, we may test the null hypothesis that this common OR is one.
  - i.e., that there is no association between the disease outcome and the exposure variable after adjusting for the confounding variable.
- The text, section 16.2.3, goes into the details of the derivation, if you are interested.
- Instead, we'll use R to apply this test (see R demo).

MH Test on AS Example

```
##
##  Mantel-Haenszel chi-squared test without continuity correction
##
## data:  smoke and AS and sex
## Mantel-Haenszel X-squared = 0.44568, df = 1, p-value = 0.5044
## alternative hypothesis: true common odds ratio is not equal to 1
## 95 percent confidence interval:
##  0.6877312 2.1460496
## sample estimates:
## common odds ratio
##          1.214868
```

- Referring to the p-value of 0.5044 reported in the output, we see no statistical evidence that smoking affects the odds at the 5% level, once we adjust for sex.
- The MH estimate of the OR adjusted for sex is about 1.21.

  "We estimate that smoking is associated with a 1.21-fold increase in the odds of developing AS, **after adjusting for** *the effects of sex."*

CI for the Common OR

- The MH output from R returns a 95% CI of about $(0.69, 2.1)$.

  "With 95% confidence, we estimate that smoking is associated with between a 0.69- to 2.1-fold increase in the odds of developing AS, **after adjusting for** *the effects of sex."*

- Notes

  1. The association between smoking and AS is not significant at level 5%.
  2. Therefore, the 95% CI covers 1
  3. The lower limit of the CI corresponds to an estimated 0.69-fold "increase" in the odds of AS from smoking.
     - Re-express as a $1/0.69 = 1.45$-fold **decrease** in the odds of AS.
  4. Seems strange that smoking would decrease the odds of AS.
     - But remember that the CI is an interval estimate of the population OR that is subject to sampling variability.

Calculating CIs

- Though not discussed, can extend the MH test to arbitrary values of the common OR.
  - We only covered the special case where the value hypothesized is 1; i.e. $H_0 : OR = 1$ (unassociated) vs. $H_a : OR \neq 1$ (associated).
- The 95% CI is obtained by finding the set of all OR values that would be retained in a test at the 5% level.
  - E.G., With the AS data, if we were to test $H_0 : OR = 0.69$ vs. $H_a : OR \neq 0.69$, we'd retain H_0 at 5% level.
  - Similarly, if we were to test $H_0 : OR = 2.1$ vs. $H_a : OR \neq 2.1$, we'd retain H_0 at 5% level.
  - And the same for all values in between.
  - Any values smaller than 0.69 or larger than 2.1 for H_0 would lead to rejection with these data.
- Thus the 95% CI obtained from the AS data is (0.69, 2.1).
  - This is called "inverting the test" and is how R gets the CI (but not how the text gets it, which we'll skip).

Summary

- Inference of an association between an exposure variable and disease outcome should consider extraneous variables that could be effect modifiers or confounders.
- We first look for effect modification by testing for homogeneous ORs across the strata of the extraneous variable.
- If an extraneous variable is not an effect modifier, we may adjust for it as a potential confounder by applying the MH estimator of the common OR.
  - The MH estimator automatically adjusts for the extraneous variable (but is only valid if there is no effect modification).
  - In this class, we'll omit the material on the approximate CI for the common OR given in section 16.2.2 of the text and instead use the output from R which "inverts" the hypothesis test as described on the previous page.