431 Class 21

github.com/THOMASELOVE/2019-431

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Today's Agenda

Analysis of Variance adjusting for a covariate (intro to Part C)

- Fitting the model
- Interpreting the result
- Checking assumptions

On Contingency Tables (Chapter 29)

- Building a $J \times K$ Table
- χ^2 Tests of Independence
 - Cochran Conditions and Checking Assumptions
- Stratifying a Table by a Third Categorical Variable
 - The Cochran-Mantel-Haenszel Test for a Three-Way Table
 - The Woolf test to check assumptions

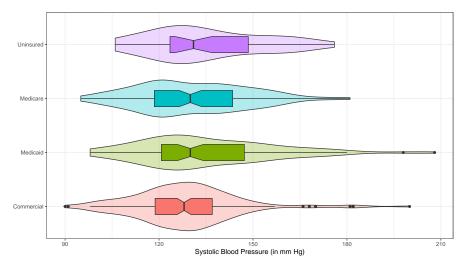
Today's Setup

```
library(vcd) # new today
library(here); library(magrittr); library(janitor)
library(patchwork); library(broom); library(tidyverse)
source(here("R", "Love-boost.R"))
dm431 <- readRDS(here("data", "dm431.Rds"))</pre>
```

Running a Regression Model to Compare Means

Returning to dm431 data

We want to compare systolic blood pressure levels for four groups, defined by insurance.



Analysis of Variance Table

```
model_1 \leftarrow lm(sbp \sim insurance, data = dm431)
anova(model 1)
Analysis of Variance Table
Response: sbp
           Df Sum Sq Mean Sq F value Pr(>F)
insurance 3 3403 1134.44 3.3619 0.01874 *
Residuals 427 144089 337.44
Signif. codes:
```

• Model 1
$$\eta^2 = \frac{3403}{3403+144089} = \frac{3403}{147492} = 0.023$$

0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Summary of Model One (edited to fit the screen)

```
Residuals: Min 1Q Median 3Q Max -38.421 -11.844 -2.421 9.579 72.970
```

Call: lm(formula = sbp ~ insurance, data = dm431)

```
      Coefficients:
      Estimate
      Std.
      Error t value
      Pr(>|t|)

      (Intercept)
      128.421
      1.434
      89.527
      < 2e-16 ***</td>

      insuranceMedicaid
      6.609
      2.331
      2.836
      0.00479 **

      insuranceMedicare
      2.238
      2.191
      1.021
      0.30769

      insuranceUninsured
      6.579
      3.119
      2.110
      0.03548 *
```

Sig. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 18.37 on 427 degrees of freedom Multiple R-squared: 0.02307, Adjusted R-squared: 0.01621 F-statistic: 3.362 on 3 and 427 DF, p-value: 0.01874

What if we adjusted for SBP two years ago?

```
model_2 <- lm(sbp ~ insurance + sbp_old, data = dm431)
anova(model_2)</pre>
```

Analysis of Variance Table

This ANOVA table runs tests sequentially

```
model_2rev <- lm(sbp ~ sbp_old + insurance, data = dm431)</pre>
anova(model 2rev)
Analysis of Variance Table
Response: sbp
          Df Sum Sq Mean Sq F value Pr(>F)
sbp old 1 14994 14993.8 49.0841 9.63e-12 ***
insurance 3 2367 789.1 2.5832 0.0529.
Residuals 426 130131 305.5
```

Signif. codes:

• Model 2
$$\eta^2 = \frac{14994 + 2367}{14994 + 2367 + 130131} = \frac{17361}{147492} = 0.118$$

Summary of Model Two (edited to fit the screen)

```
summary(model_2)
```

```
Call: lm(formula = sbp ~ insurance + sbp_old, data = dm431)
```

```
Residuals: Min 1Q Median 3Q Max -41.030 -11.737 -2.301 10.386 74.136
```

```
Coefficients: Estimate Std. Error t value Pr(>|t|) (Intercept) 86.9253 6.2886 13.823 < 2e-16 *** insuranceMedicaid 5.5800 2.2227 2.510 0.0124 * insuranceMedicare 1.7207 2.0861 0.825 0.4099 insuranceUninsured 5.3081 2.9733 1.785 0.0749 . sbp_old 0.3245 0.0480 6.760 4.57e-11 ***
```

Residual standard error: 17.48 on 426 degrees of freedom Multiple R-squared: 0.1177, Adjusted R-squared: 0.1094 F-statistic: 14.21 on 4 and 426 DF, p-value: 6.785e-11

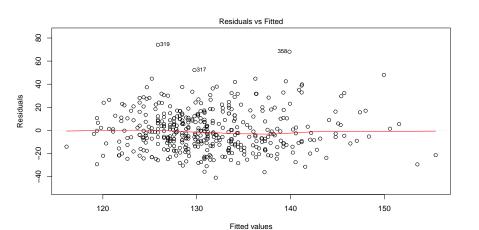
Comparing Model 1 to Model 2

model	r.squared	adjr2	sigma	df	anova_F	p.value	AIC
Model 1	0.023	0.016	18.37	4	3.36	0.019	3738.1
Model 2	0.118	0.109	17.48	5	14.21	0.000	3696.2

Model 2 Assumption Checking: Residual Plot 1

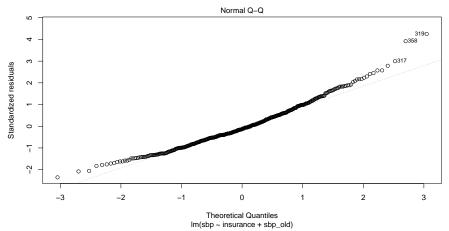
• Residuals vs. Fitted (predicted) values should show fuzzy football...

```
plot(model_2, which = 1)
```



Model 2 Assumption Checking: Residual Plots

• Normal Q-Q plot of Standardized Residuals. . .



New Topic: Larger Contingency Tables

A 2×3 contingency table

This table displays the count of patients who show *complete*, *partial*, or *no response* after treatment with either **active** medication or a **placebo** in our study of 100 patients...

Group	None	Partial	Complete
Active	8	24	20
Placebo	12	26	10

Is there a statistically detectable association here, at $\alpha = 0.10$?

- H_0 : Response Distribution is the same, regardless of Treatment.
- \bullet H_A : There is an association between Treatment and Response.

The Pearson Chi-Square Test

The Pearson χ^2 test assumes the null hypothesis is true (rows and columns are independent.) That is a model for our data. How does it work? Here's the table, with marginal totals added.

_	None	Partial	Complete	TOTAL
Active	8	24	20	52
Placebo	12	26	10	48
TOTAL	20	50	30	100

The test needs to estimate the expected frequency in each of the six cells under the assumption of independence. If the rows and columns are in fact independent of each other, then what is the expected number of subjects that will fall in the Active/None cell?

The Independence Model

The independence model means the overall rate of "Response = None" or "Partial" or "Complete" applies to both "Active" and "Placebo" subjects.

	None	Partial	Complete	TOTAL
Active	_	_	_	52
Placebo	_	_	_	48
TOTAL	20	50	30	100

If the rows and columns were independent, then:

- \bullet 20/100 or 20% of subjects would have the response "None"
 - That means 20% of the 52 Active, and 20% of the 48 Placebo subjects.
- 50% would have a "Partial" response in each exposure group, and
- 30% would have a "Complete" response in each group.

So, can we fill in the expected frequencies under our independence model?

Observed (Expected) Cell Counts

_	None	Partial	Complete	TOTAL
Active	8 (10.4)	24 (26.0)	20 (15.6)	52
Placebo	12 (9.6)	26 (24.0)	10 (14.4)	48
TOTAL	20	50	30	100

General Formula for Expected Frequencies under Independence

$$\mathsf{Expected} \ \mathsf{Frequency} = \frac{\mathsf{Row} \ \mathsf{total} \times \mathsf{Column} \ \mathsf{total}}{\mathsf{Grand} \ \mathsf{Total}}$$

This assumes that the independence model holds: the probability of being in a particular column is exactly the same in each row, and vice versa.

Chi-Square Assumptions

- Expected Frequencies: We assume that the expected frequency, under the null hypothesized model of independence, will be **at least 5** (and ideally at least 10) in each cell. If that is not the case, then the χ^2 test is likely to give unreliable results. The *Cochran conditions* require us to have no cells with zero and at least 80% of the cells in our table with expected counts of 5 or higher. That's what R uses to warn you of trouble.
- Don't meet the standards? Consider collapsing categories.

Observed (Expected) Cell Counts

	None	Partial	Complete	TOTAL
Active	8 (10.4)	24 (26.0)	20 (15.6)	52
Placebo	12 (9.6)	26 (24.0)	10 (14.4)	48
TOTAL	20	50	30	100

Getting the Table into R

We'll put the table into a matrix in R. Here's one approach...

```
None Partial Complete
Active 8 24 20
Placebo 12 26 10
```

Chi-Square Test Results in R

- H_0 : Response Distribution is the same, regardless of Treatment.
 - Rows and Columns of the table are independent
- H_A : There is an association between Treatment and Response.
 - Rows and Columns of the table are associated.

```
chisq.test(T1)
```

Pearson's Chi-squared test

data: T1 X-squared = 4.0598, df = 2, p-value = 0.1313

What is the conclusion?

Does Sample Size Affect The χ^2 Test?

- T1 results were: $\chi^2 = 4.0598$, df = 2, p = 0.1313
- What if we had the same pattern, but twice as much data?

```
T1_doubled <- T1*2
T1_doubled
```

```
None Partial Complete
Active 16 48 40
Placebo 24 52 20
chisq.test(T1_doubled)
```

Pearson's Chi-squared test

```
data: T1_doubled
X-squared = 8.1197, df = 2, p-value = 0.01725
```

Can we run Fisher's exact test instead?

Yes, but ... if the Pearson assumptions don't hold, then the Fisher's test is not generally an improvement.

```
fisher.test(T1)
```

Fisher's Exact Test for Count Data

```
data: T1
p-value = 0.1358
alternative hypothesis: two.sided
```

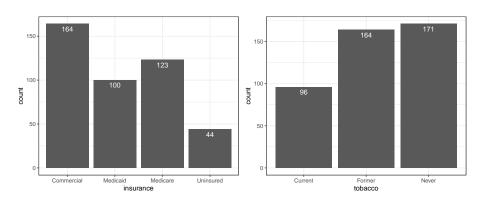
• It's also really meant more for square tables, with the same number of rows as columns, and relatively modest sample sizes.

OK. Back to dm431

What am I plotting here?

```
p1 <- ggplot(dm431, aes(x = insurance)) + geom_bar() +
    theme bw() +
    geom_text(aes(label = ..count..), stat = "count",
              vjust = 1.5, col = "white")
p2 \leftarrow ggplot(dm431, aes(x = tobacco)) + geom bar() +
    theme bw() +
    geom text(aes(label = ..count..), stat = "count",
              vjust = 1.5, col = "white")
p1 + p2 # requires patchwork package
```

dm431: Two Categorical Variables of interest



A 4×3 table with the dm431 data

17

11

96

```
dm431 %>%
    tabyl(insurance, tobacco) %>%
    adorn totals(where = c("row", "col"))
  insurance Current Former Never Total
Commercial
                 35
                        60
                              69
                                    164
  Medicaid
                 33
                        33
                                    100
```

58

164

13 20

34

48

171

123

44

431

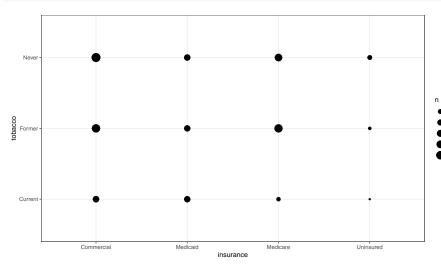
Medicare

Uninsured

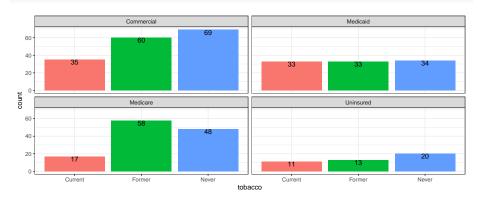
Total

Plotting a Cross-Tabulation?

```
ggplot(dm431, aes(x = insurance, y = tobacco)) +
   geom_count() + theme_bw()
```



Tobacco Bar Chart faceted by Insurance



Tobacco Status and Insurance in dm431

- H₀: Insurance type and Tobacco status are independent
- \bullet H_A : Insurance type and Tobacco status have a detectable association

Pearson χ^2 results?

```
dm431 %>% tabyl(insurance, tobacco) %>% chisq.test()
```

Pearson's Chi-squared test

```
data:
```

```
X-squared = 15.033, df = 6, p-value = 0.02
```

Can we check our expected frequencies?

Tobacco Status and Insurance in dm431

Checking Assumptions:

```
res <- dm431 %>% tabyl(insurance, tobacco) %>% chisq.test()
res$observed
```

```
insurance Current Former Never
Commercial
                35
                       60
                             69
  Medicaid
                33
                       33
                             34
                17
                       58
  Medicare
                             48
 Uninsured
                11
                       13
                             20
```

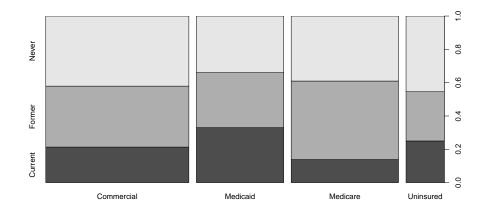
res\$expected

```
insurance Current Former Never
Commercial 36.529002 62.40371 65.06729
Medicaid 22.273782 38.05104 39.67517
Medicare 27.396752 46.80278 48.80046
Uninsured 9.800464 16.74246 17.45708
```

Mosaic Plot for Cross-Tabulation

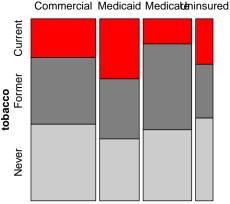
Each rectangle's area is proportional to the number of cases in that cell.

dm431 %\$% plot(insurance, tobacco, ylab = "", xlab = "")



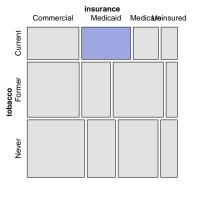
Mosaic Plot from the vcd package (highlighting)

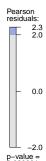
insurance



Mosaic Plot from the vcd package (with χ^2 shading)

mosaic(~ tobacco + insurance, data = dm431, shade = TRUE)





Working with Three-Way Tables (Cochran-Mantel-Haenszel Procedure) in the Treatment of Kidney Stones

Kidney Stone Treatment Example

Suppose we compare the success rates of two treatments for kidney stones.

- Treatment A (all open surgical procedures): 273/350 patients (78%) had a successful result.
- Treatment B (percutaneous nephrolithotomy less invasive): 289/350 were successful (83%).

Kidney Stones	Successful Outcome	Bad Outcome
A (open surgery) B (less invasive)	273 (78%) 289 (83%)	77 (22%) 61 (17%)

Which approach would you choose?

• Sources: Wikipedia and Charig CR et al. (1986) PMID 3083922.

Kidney Stones, twobytwo results

```
twobytwo(273, 77, 289, 61, "A", "B", "Success", "Bad")
2 by 2 table analysis:
Outcome : Success Comparing : A vs. B
 Success Bad P(Success) 95% conf. interval
                 0.7800 0.7336 0.8203
A 273 77
 289 61 0.8257 0.7823 0.8620
В
                            95% conf. interval
       Relative Risk: 0.9446 0.8776 1.0168
    Sample Odds Ratio: 0.7483 0.5146 1.0883
Probability difference: -0.0457 -0.1045 0.0133
Exact P-value: 0.154
                    Asymptotic P-value: 0.1292
```

Kidney Stones: A Third Variable

But this comparison may be misleading.

Some kidney stones are small, and some are large.

- Open Surgery (A) used in 87 small stones, and 263 large ones.
- Less Invasive (B) used in 270 small stones, and 80 large ones.

Could that bias our results?

• Should we account for this difference in "size mix"?

Kidney Stone results stratified by stone size

 For small stones, the odds ratio for a successful outcome comparing A to B is 2.08 (95% CI 0.84, 5.11)

Small Stones	Successful Outcome	Bad Outcome	
A (open surgery) B (less invasive)	81 (93%) 234 (87%)	6 (7%) 36 (13%)	

• For large stones, that odds ratio is 1.23 (95% CI 0.71, 2.12)

Large Stones	Successful Outcome	Bad Outcome	
A (open surgery) B (less invasive)	192 (73%) 55 (69%)	71 (27%) 25 (31%)	

Aggregated Data: % with Successful Outcome

78% of Treatment A subjects, 83% of Treatment B

What We Have Here is a Three-Way Table

- rows: which treatment was received (A or B)
- columns: was the outcome Successful or Bad?
- strata or layers: was the stone Small or Large?

Size	Treatment	Good	Bad	Total	% Good
${\tt Small}$	Α	81	6	87	93
${\tt Small}$	В	234	36	270	87
Large	Α	192	71	263	73
Large	В	55	25	80	69

We'll talk about three-way and larger contingency tables more in 432, but in 431, we focus on the situation where a 2x2 table is repeated over multiple strata (categories in a third variable.)

Cochran-Mantel-Haenszel Test

The Cochran-Mantel-Haenszel test is designed to test whether the rate of a successful (Good) outcome is the same across the two levels of the treatment (i.e. A or B.)

- We could do this by simply adding up the results across the stone sizes, but that wouldn't be wise, because the stone size is likely to be related to the outcome and the choice of procedure.
- But we can account for the differences between stone sizes to some extent by adjusting for stone size as a stratifying variable in a CMH test.
- The big assumption we'll have to make, though, is that the odds ratio
 for a good outcome for treatment A versus treatment B is the same for
 small stones and large stones. Is this reasonable here? We'll use a
 Woolf test to decide.

But first, let's get the data into a useful form.

Building the Three-Way Table

```
stone <- c(rep("Small", 4), rep("Large", 4))
treat <- c(rep(c("A", "A", "B", "B"), 2))
result <- c(rep(c("Good", "Bad"), 4))
counts <- c(81, 6, 234, 36, 192, 71, 55, 25)
kidney_dat <- tibble(stone, treat, result, counts)</pre>
```

What do we have so far?

kidney_dat

```
A tibble: 8 x 4
  stone treat result counts
  <chr> <chr> <chr>
                      <dbl>
1 Small A
         Good
                        81
2 Small A
             Bad
                         6
3 Small B
            Good
                       234
4 Small B
             Bad
                       36
                       192
5 Large A
         Good
6 Large A
             Bad
                        71
             Good
                        55
7 Large B
 Large B
              Bad
                         25
```

The Three-Way Table

```
big.tab <- xtabs(counts ~ treat + result + stone,
                data = kidney_dat)
big.tab
, , stone = Large
     result
treat Bad Good
    A 71 192
    B 25 55
  , stone = Small
     result
treat Bad Good
     6 81
```

36 234

Three-Way Table as a "Flat" Table

ftable(big.tab)

		stone	Large	Small
treat	result			
Α	Bad		71	6
	Good		192	81
В	Bad		25	36
	Good		55	234

Can we assume a Common Odds Ratio?

 Recall the sample odds ratio in small stones was 2.08 and in large stones was 1.23

The Woolf test checks a key assumption for the Cochran-Mantel-Haenszel test. The Woolf test assesses the null hypothesis of a common odds ratio across the two stone sizes.

```
woolf_test(big.tab)
```

Woolf-test on Homogeneity of Odds Ratios (no 3-Way assoc.)

```
data: big.tab
X-squared = 0.95353, df = 1, p-value = 0.3288
```

Our conclusion from the Woolf test is that we are able to retain the null hypothesis of homogeneous odds ratios. So it's not crazy to fit a test that requires that all of the odds ratios be the same in the population.

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Running the Cochran-Mantel-Haenszel test

So, we can use the Cochran-Mantel-Haenszel test to make inferences about the population odds ratio (for revascularization given niacin rather than placebo) accounting for the five studies. We'll use a 90% confidence interval, and the results appear on the next slide.

```
mantelhaen.test(big.tab, conf.level = .90)
```

Complete CMH output (Edited to fit on the screen)

```
mantelhaen.test(big.tab, conf.level = .90)
```

Mantel-Haenszel chi-squared test with continuity correction

data: big.tab

Mantel-Haenszel X-squared = 2.0913, df = 1, p-value = 0.1481

alt. hypothesis: true common odds ratio is not equal to 1

90 percent confidence interval: 0.4708539 1.0145392 sample estimates: common odds ratio 0.6911583

What can we conclude in this case?

OK. That's everything for Part B of the course, and that's everything that you need to complete Project Study A.

Bonus: The Niacin and Heart Disease Meta-Analysis

Duggal et al (2010) did a meta-analysis¹ of 5 placebo-controlled studies (AFREGS, ARBITER2, CLAS1, FATS and HATS) of niacin and heart disease, where the primary outcome was the need to do a coronary artery revascularization procedure.

For example, the FATS study had these results:

FATS	Revascularization	No Revasc.
Niacin	2	46
Placebo	11	41

FATS is just one of the five studies, and this table exists in each!

¹Duggal JK et al. 2010. Effect of niacin therapy on cardiovascular outcomes in patients with coronary artery disease. J Cardiovasc Pharmacology & Therapeutics 15: 158-166. My Source: http://www.biostathandbook.com/cmh.html

Exploring the FATS study

FATS	Revascularization	No Revasc.
Niacin	2	46
Placebo	11	41

- Pr(revascularization | Niacin) = $\frac{2}{2+46}$ = 0.042
- Odds(revascularization | Niacin) = $\frac{2}{46}$ = 0.043 Pr(revascularization | Placebo) = $\frac{11}{11+41}$ = 0.212
- Odds(revascularization | Placebo) = $\frac{11}{41}$ = 0.268

and so the Odds Ratio = $\frac{2*41}{11*46} = 0.16$.

But that is just the result for the FATS study.

Building the Meta-Analysis Table

```
study <- c(rep("FATS", 4), rep("AFREGS", 4),
           rep("ARBITER2", 4), rep("HATS", 4),
           rep("CLAS1", 4))
treat <- c(rep(c("Niacin", "Niacin",</pre>
                  "Placebo", "Placebo"),5))
outcome <- c(rep(c("Revasc.", "No Rev."), 10))
counts \leftarrow c(2, 46, 11, 41, 4, 67, 12, 60, 1, 86,
            4. 76. 1. 37. 6. 32. 2. 92. 1. 93)
meta <- data.frame(study, treat, outcome, counts) %>% tbl df
meta$treat <- fct relevel(meta$treat, "Niacin")</pre>
meta$outcome <- fct relevel(meta$outcome, "Revasc.")</pre>
meta.tab <- xtabs(counts ~ treat + outcome + study,
                   data = meta)
```

Five Studies in the Meta-Analysis

```
ftable(meta.tab)
               study AFREGS ARBITER2 CLAS1 FATS HATS
treat
       outcome
Niacin Revasc.
                                   1
                                         2
                                        92 46
                                                 37
       No Rev.
                         67
                                  86
                                        1 11
Placebo Revasc.
                         12
                                                 6
                                  76
       No Rev.
                         60
                                        93
                                            41
                                                 32
```

The three variables we are studying are:

- treat (2 levels: Niacin/Placebo),
- outcome (2 levels: Revascularization or No Revascularization) across
- study (5 levels: AFREGS, ARBITER2, CLAS1, FATS, HATS)

Cochran-Mantel-Haenszel Test

The Cochran-Mantel-Haenszel test is designed to test whether the rate of revascularization is the same across the two levels of the treatment (i.e. Niacin or Placebo).

- We could do this by simply adding up the results across the five studies, but that wouldn't be wise, because the studies used different populations and looked for revascularization after different lengths of time.
- But we can account for the differences between studies to some extent by adjusting for study as a stratifying variable in a CMH test.
- The big assumption we'll have to make, though, is that the odds ratio for revascularization given Niacin instead of Placebo does not change across the studies. Is this reasonable in our case?

Looking at the Study-Specific Odds Ratios

We'll calculate the odds ratios, comparing revascularization odds with niacin vs. placebo, within each separate study.

Study	Rev N	Rev P	NoRev N	NoRev P	Odds Ratio
AFREGS	4	67	12	60	$\frac{4*60}{67*12} = 0.3$
ARBITER2	1	86	4	76	0.22
CLAS1	2	92	1	93	2.02
FATS	2	46	11	41	0.16
HATS	1	37	6	32	0.14

The table shows patient counts for the categories in each of the respective two-by-two tables (Rev N = Revascularization and Niacin, NoRev P = No Revascularization and Placebo, etc.)

Can we assume a Common Odds Ratio?

The Woolf test checks a key assumption for the Cochran-Mantel-Haenszel test. The Woolf test assesses the null hypothesis of a common odds ratio across the five studies.

```
woolf_test(meta.tab)
```

```
Woolf-test on Homogeneity of Odds Ratios (no 3-Way assoc.)
```

```
data: meta.tab
X-squared = 3.4512, df = 4, p-value = 0.4853
```

Our conclusion from the Woolf test is that we are able to retain the null hypothesis of homogeneous odds ratios. So it's not crazy to fit a test that requires that all of the odds ratios be the same in the population.

Running the Cochran-Mantel-Haenszel test

So, we can use the Cochran-Mantel-Haenszel test to make inferences about the population odds ratio (for revascularization given niacin rather than placebo) accounting for the five studies. We'll use a 90% confidence interval, and the results appear on the next slide.

```
mantelhaen.test(meta.tab, conf.level = .90)
```

Complete CMH output

```
mantelhaen.test(meta.tab, conf.level = .90)
Mantel-Haenszel chi-squared test with continuity correction
data: meta.tab
Mantel-Haenszel
X-squared = 12.746, df = 1, p-value = 0.0003568
alt. hypothesis: true common odds ratio is not equal to 1
90 percent confidence interval: 0.1468942 0.4968686
sample estimates: common odds ratio 0.2701612
What can we conclude in this case?
```