Biost 518: Applied Biostatistics II

Emerson, Winter 2006

Homework #1 Key

January 24, 2006

A separate file containing the Stata commands used to solve problem 3 is posted on the web pages.

Written problems: To be handed in at the beginning of class on Wednesday, January 11, 2006.

Suppose you are reading a scientific article in a journal with inadequate statistical review. The scientific question addressed by the article is the association between liver enlargement (hepatomegaly) and serum levels of albumin and bilirubin and quality of life in patients with primary biliary cirrhosis (PBC). The authors were also interested in the role of race/ethnicity (as categorized by Caucasian and Noncaucasian) in the relationship between hepatomegaly and the serum measurements.

The authors reported gathering data on 511 subjects: 438 Caucasians, 73 Noncaucasians. The data analysis presented in the manuscript is limited to the means and standard errors of the serum measures within subgroups as given in the following table.

Table 1. Means (standard errors) of serum albumin and bilirubin according to race/ethnicity and presence or absence of hepatomegaly.

	Caucasians		Noncaucasians	
	No hepatomegaly	**Hepatomegaly**	**No hepatomegaly**	**Hepatomegaly**
Albumin (g/dl)	4.019 (0.0235)	3.879 (0.0423)	3.783 (0.0699)	3.637 (0.1009)
Bilirubin (mg/dl)	0.840 (0.0429)	1.071 (0.1555)	1.364 (0.2223)	3.733 (0.8831)

1. You desire to do a more careful evaluation of the evidence at hand for albumin. You therefore desire to compute estimates, 95% confidence intervals, and P values to address questions of associations within subgroups, associations adjusted for race/ethnicity, and effect modification. In addressing the following questions, provide a sentence that interprets your inferential statistics in a manner suitable for inclusion in a scientific journal article. Avoid statistical jargon. (You note that without the sample sizes by hepatomegaly status, you will not be able to use the exact statistical methods (i.e., t tests) that you would have, but you will be able to perform analyses based on large sample approximations and the fact that sample means are approximately normally distributed.)
    a. Are mean albumin levels associated with hepatomegaly in Caucasians? (Recall that the standard error of two independent statistics, is the square root of the sum of the squares of the individual standard errors. Thus calculate the standard error for the difference in mean albumin using the standard errors for the hepatomegaly and nonhepatomegaly groups.)

<u>Ans:</u> **Mean albumin levels were found to be 0.14 g/dl lower in Caucasians with hepatomegaly than in Caucasisans without hepatomegaly. Such a difference was found sufficiently extreme to be able to rule out a null hypothesis of no difference in mean albumin across groups defined by the presence or absence of hepatomegaly (P = .0038). Based on a 95% confidence interval, we find that the observed difference in mean albumin is not atypical of settings in which the true difference in mean albumin were such that Caucasians with hepatomegaly had mean albumin 0.235 g/dl lower to 0.045 g/dl lower than Caucasians without hepatomegaly.**

<u>Calculations:</u>

- Estimate of effect: The difference in sample means

  3.879 – 4.019 = -0.140

- Estimate of standard error for comparison:

$$se(\overline{Y}_{hep} - \overline{Y}_{nohep}) = \sqrt{se^2(\overline{Y}_{hep}) + se^2(\overline{Y}_{nohep})} = \sqrt{0.0423^2 + 0.0235^2} = 0.0484$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{(\overline{Y}_{hep} - \overline{Y}_{nohep}) - 0}{se(\overline{Y}_{hep} - \overline{Y}_{nohep})} = \frac{-0.140}{0.0484} = -2.893$$

- Computation of two-sided P value from Stata using commands

  `"display 2 * norm(-2.893)"`

- Computation of 95% confidence interval

$$(\overline{Y}_{hep} - \overline{Y}_{nohep}) \pm 1.96 \times se(\overline{Y}_{hep} - \overline{Y}_{nohep}) = -0.140 \pm 1.96 \times 0.0484 = (-0.235, -0.0451)$$

b. Are mean albumin levels associated with hepatomegaly in Noncaucasians?

<u>Ans:</u> **Mean albumin levels were found to be .146 g/dl lower in Nonaucasians with hepatomegaly than in Noncaucasisans without hepatomegaly. Such a difference was not found sufficiently extreme to be able to rule out a null hypothesis of no difference in mean albumin across groups defined by the presence or absence of hepatomegaly (P = .234). Based on a 95% confidence interval, we find that the observed difference in mean albumin is not atypical of settings in which the true difference in mean albumin were such that Noncaucasians with hepatomegaly had mean albumin 0.386 g/dl lower to 0.0945 g/dl higher than Nonaucasians without hepatomegaly.**

<u>Calculations:</u>

- Estimate of effect: The difference in sample means

  3.637 – 3.783 = -0.146

- Estimate of standard error for comparison:

$$se(\overline{Y}_{hep} - \overline{Y}_{nohep}) = \sqrt{se^2(\overline{Y}_{hep}) + se^2(\overline{Y}_{nohep})} = \sqrt{0.0699^2 + 0.1009^2} = 0.1227$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) - 0}{se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right)} = \frac{-0.146}{0.1227} = -1.190$$

- Computation of two-sided P value from Stata using commands
  `"display 2 * norm(-1.190)"`
- Computation of 95% confidence interval

$$\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) \pm 1.96 \times se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) = -0.146 \pm 1.96 \times 0.1227 = \left(-0.386, 0.0945\right)$$

c. Are mean albumin levels associated with hepatomegaly after adjustment for race/ethnicity? (One method of adjustment is to find a weighted average of the measures of effect in each race/ethnicity group. Hence, you might use a weighted average of the estimates Δ_C and Δ_N you derived in parts a and b, respectively. A common approach is to weight each group according to its relative frequency. Because 14.29% of the subjects are noncaucasian, it would thus be reasonable to let the adjusted estimate be defined according to $\Delta_{adj} = 0.8571 \times \Delta_C + 0.1429 \times \Delta_N$. In order to find the standard error of this adjusted statistic, we have to use the properties of variances: Recall that when multiplying a random variable by a constant, $\text{Var}(cX) = c^2 \text{ Var}(X)$. Hence, you can find the standard error of the adjusted estimate can be found by

$$se\left(\Delta_{adj}\right) = \sqrt{0.8571^2 \times se^2\left(\Delta_C\right) + 0.1429^2 \times se^2\left(\Delta_N\right)}$$

<u>**Ans:**</u> **After adjustment for race/ethnicity, mean albumin levels were found to be .141 g/dl lower in patients with hepatomegaly than in patients of the same race without hepatomegaly. Such a difference was found sufficiently extreme to be able to rule out a null hypothesis of no difference in mean albumin across groups defined by the presence or absence of hepatomegaly (P = .0017). Based on a 95% confidence interval, we find that the observed difference in mean albumin is not atypical of settings in which the true difference in mean albumin were such that patients with hepatomegaly had mean albumin 0.229 g/dl lower to 0.053 g/dl lower than patients of the same race without hepatomegaly.**

<u>Calculations:</u>

- Estimate of effect: The weighted average of the difference in sample means

  $0.8571 \times (-0.140) + 0.1429 \times (-0.146) = -0.1409$

- Estimate of standard error for the weighted average:

$$se\left(\hat{\Delta}_{adj}\right) = \sqrt{0.8571^2 \times se^2\left(\hat{\Delta}_C\right) + 0.1429^2 \times se^2\left(\hat{\Delta}_N\right)}$$
$$= \sqrt{0.8571^2 \times 0.0484^2 + 0.1429^2 \times 0.1227^2} = 0.0450$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{\hat{\Delta}_{adj} - 0}{se(\hat{\Delta}_{adj})} = \frac{-0.1409}{0.0450} = -3.131$$

- Computation of two-sided P value from Stata using commands

  "`display 2 * norm(-3.131)`"

- Computation of 95% confidence interval

$$\hat{\Delta}_{adj} \pm 1.96 \times se(\hat{\Delta}_{adj}) = -0.1409 \pm 1.96 \times 0.0450 = (-0.229, -0.0527)$$

d. Does race/ethnicity modify the association between mean albumin level and hepatomegaly?

Ans: **The difference in mean albumin across groups defined by hepatomegaly was found to be .006 lower in Noncaucasians than in Caucasians. Such a difference was not found sufficiently extreme to be able to rule out a null hypothesis of no effect modification by race in the association between albumin level and hepatomegaly (P = .964). Based on a 95% confidence interval, we find that the observed difference in the association between albumin and hepatomegaly across the race groups not atypical of settings in which the true difference in effect were such that Noncaucasians had mean difference in albumin across hepatomegaly groups 0.265 g/dl lower to 0.253 g/dl higher than that in Caucasians.**

Calculations:

- Estimate of effect: Difference of the differences in sample means

  (-0.146) - (-0.140) = -0.006

- Estimate of standard error for estimated interaction contrast:

$$se(\hat{\Delta}_{EM}) = \sqrt{se^2(\hat{\Delta}_C) + se^2(\hat{\Delta}_N)}$$
$$= \sqrt{0.0484^2 + 0.1227^2} = 0.1319$$

- Computation of Z score to test the null hypothesis of no effect modification:

$$Z = \frac{\hat{\Delta}_{EM} - 0}{se(\hat{\Delta}_{EM})} = \frac{-0.006}{0.1319} = -0.0455$$

- Computation of two-sided P value from Stata using commands

  "`display 2 * norm(-0.0455)`"

- Computation of 95% confidence interval

$$\hat{\Delta}_{EM} \pm 1.96 \times se(\hat{\Delta}_{EM}) = -0.006 \pm 1.96 \times 0.1319 = (-0.265, 0.253)$$

2. You also desire to do a more careful evaluation of the evidence at hand for bilirubin. You therefore answer the questions of problem 1 using the statistics for bilirubin.

   a. Are mean bilirubin levels associated with hepatomegaly in Caucasians

Ans: Mean bilirubin levels were found to be .231 mg/dl higher in Caucasians with hepatomegaly than in Caucasisans without hepatomegaly. Such a difference was not sufficiently extreme to be able to rule out a null hypothesis of no difference in mean albumin across groups defined by the presence or absence of hepatomegaly (P = .152). Based on a 95% confidence interval, we find that the observed difference in mean bilirubin is not atypical of settings in which the true difference in mean bilirubin were such that Caucasians with hepatomegaly had mean bilirubin 0.085 mg/dl lower to 0.547 mg/dl higher than Caucasians without hepatomegaly.

Calculations:

- Estimate of effect: The difference in sample means

  1.071 – 0.840 = 0.231

- Estimate of standard error for comparison:

$$se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) = \sqrt{se^2\left(\overline{Y}_{hep}\right) + se^2\left(\overline{Y}_{nohep}\right)} = \sqrt{0.1555^2 + 0.0429^2} = 0.1613$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) - 0}{se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right)} = \frac{0.231}{0.1613} = 1.432$$

- Computation of two-sided P value from Stata using commands

  `"display 2 * norm(-1.432)"`

- Computation of 95% confidence interval

$$\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) \pm 1.96 \times se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) = 0.231 \pm 1.96 \times 0.1613 = (-0.0851, 0.547)$$

b. Are mean bilirubin levels associated with hepatomegaly in Noncaucasians?

Ans: Mean bilirubin levels were found to be 2.369 mg/dl higher in Noncaucasians with hepatomegaly than in Noncaucasisans without hepatomegaly. Such a difference was sufficiently extreme to be able to rule out with high confidence the possibility that it was due to chance in the presence of no true difference in mean bilirubin across groups defined by the presence or absence of hepatomegaly (P = .0093). Based on a 95% confidence interval, we find that the observed difference in mean bilirubin is not atypical of settings in which the true difference in mean bilirubin were such that Noncaucasians with hepatomegaly had mean bilirubin 0.584 mg/dl higher to 4.15 mg/dl higher than Noncaucasians without hepatomegaly.

Calculations:

- Estimate of effect: The difference in sample means

  3.733 – 1.364 = 2.369

- Estimate of standard error for comparison:

$$se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) = \sqrt{se^2\left(\overline{Y}_{hep}\right) + se^2\left(\overline{Y}_{nohep}\right)} = \sqrt{0.8831^2 + 0.2223^2} = 0.9106$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) - 0}{se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right)} = \frac{2.369}{0.9106} = 2.602$$

- Computation of two-sided P value from Stata using commands

  “display 2 * norm(-2.602)”

- Computation of 95% confidence interval

$$\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) \pm 1.96 \times se\left(\overline{Y}_{hep} - \overline{Y}_{nohep}\right) = 2.369 \pm 1.96 \times 0.9106 = (0.584,\ 4.15)$$

c. Are mean bilirubinin levels associated with hepatomegaly after adjustment for race/ethnicity?

Ans: After adjustment for race/ethnicity, mean bilirubin levels were found to be .537 mg/dl higher in patients with hepatomegaly than in patients of the same race without hepatomegaly. Such a difference was sufficiently extreme to be able to rule out a null hypothesis of no difference in mean bilirubin across groups defined by the presence or absence of hepatomegaly (P = .0047). Based on a 95% confidence interval, we find that the observed difference in mean bilirubin is not atypical of settings in which the true difference in mean bilirubin were such that patients with hepatomegaly had mean bilirubin 0.164 mg/dl higher to 0.909 mg/dl higher than patients of the same race without hepatomegaly.

Calculations:

- Estimate of effect: The weighted average of the difference in sample means

  0.8571 × (0.231) + 0.1429 × (2.369) = 0.5365

- Estimate of standard error for the weighted average:

$$se\left(\hat{\Delta}_{adj}\right) = \sqrt{0.8571^2 \times se^2\left(\hat{\Delta}_C\right) + 0.1429^2 \times se^2\left(\hat{\Delta}_N\right)}$$
$$= \sqrt{0.8571^2 \times 0.1613^2 + 0.1429^2 \times 0.9106^2} = 0.1899$$

- Computation of Z score to test the null hypothesis of no difference:

$$Z = \frac{\hat{\Delta}_{adj} - 0}{se\left(\hat{\Delta}_{adj}\right)} = \frac{0.5365}{0.1899} = 2.825$$

- Computation of two-sided P value from Stata using commands

  “display 2 * norm(-2.825)”

- Computation of 95% confidence interval

$$\hat{\Delta}_{adj} \pm 1.96 \times se\left(\hat{\Delta}_{adj}\right) = 0.5365 \pm 1.96 \times 0.1899 = (0.164,\ 0.909)$$

d. Does race/ethnicity modify the association between mean bilirubin level and hepatomegaly?

<u>Ans:</u> The difference in mean bilirubin across groups defined by hepatomegaly was found to be 2.138 mg/dl higher in Noncaucasians than in Caucasians. Such a difference was sufficiently extreme to be able to rule out with high confidence a null hypothesis of no effect modification by race in the association between bilirubin level and hepatomegaly (P = .021). Based on a 95% confidence interval, we find that the observed difference in the association between bilirubin and hepatomegaly across the race groups not atypical of settings in which the true difference in effect were such that Noncaucasians had mean difference in bilirubin across hepatomegaly groups 0.325 mg/dl higher to 3.95 mg/dl higher than that in Caucasians.

<u>Calculations:</u>

- Estimate of effect: Difference of the differences in sample means

  (2.369) - (0.231) = 2.138

- Estimate of standard error for estimated interaction contrast:

$$se\left(\hat{\Delta}_{EM}\right) = \sqrt{se^2\left(\hat{\Delta}_C\right) + se^2\left(\hat{\Delta}_N\right)}$$
$$= \sqrt{0.1613^2 + 0.9106^2} = 0.9248$$

- Computation of Z score to test the null hypothesis of no effect modification:

$$Z = \frac{\hat{\Delta}_{EM} - 0}{se\left(\hat{\Delta}_{EM}\right)} = \frac{2.138}{0.9248} = 2.312$$

- Computation of two-sided P value from Stata using commands

  `"display 2 * norm(-2.312)"`

- Computation of 95% confidence interval

$$\hat{\Delta}_{EM} \pm 1.96 \times se\left(\hat{\Delta}_{EM}\right) = 2.138 \pm 1.96 \times 0.9248 = (0.325, 3.95)$$

3. Suppose we are interested in the association between being a full professor and sex. We want to use the University salary data set (on the class web pages) to compute the odds ratio measuring the association between rank (full professor versus nonfull) and sex in the year 1995, and we also want to consider the role of field in that association. You should compute estimates, 95% confidence intervals, and P values to address all questions of associations. For effect modification, provide estimates indicative of the effect modification along with a P value (confidence intervals can be omitted here: Because there are three levels of field, there is not a single scientific estimate of effect modification, and we would have to consider multiple comparison issues.) In addressing the following questions, provide a sentence that interprets your inferential statistics in a manner suitable for inclusion in a scientific journal article. Avoid statistical jargon. (Use the Stata command "cc" to answer this question, as it provides the best output for the purpose of this problem. The by() command is used to produce stratified statistics.)

   a. In 1995, is there an association between being a full professor and being female?

Ans: The odds of a female being full professor in 1995 was only 0.290 as high as the odds of a male being full professor. Such an observation was found to be highly unusual in the absence of a true association between sex and rank (P < .0001). Based on a 95% confidence interval, we find that the observed data is not atypical of settings in which the true odds ratio is between 0.227 and 0.372.

b. In 1995, is there an association between being a full professor and being female within each field?

Ans: The odds of a female in Fine Arts being full professor in 1995 was only 0.538 as high as the odds of a male in that same field being full professor. Such an observation was found to be unusual in the absence of a true association between sex and rank (P = .0313). Based on a 95% confidence interval, we find that the observed data is not atypical of settings in which the true odds ratio is between 0.293 and 0.984.

The odds of a female in Professional fields being full professor in 1995 was only 0.343 as high as the odds of a male in that same field being full professor. Such an observation was found to be unusual in the absence of a true association between sex and rank (P = .0013). Based on a 95% confidence interval, we find that the observed data is not atypical of settings in which the true odds ratio is between 0.164 and 0.705.

The odds of a female in Other fields being full professor in 1995 was only 0.254 as high as the odds of a male in that same field being full professor. Such an observation was found to be unusual in the absence of a true association between sex and rank (P < .0001). Based on a 95% confidence interval, we find that the observed data is not atypical of settings in which the true odds ratio is between 0.187 and 0.344.

c. In 1995, is there an association between being a full professor and being female after adjustment for field? Use the Mantel-Haenszel estimate of the odds ratio to answer this question. (Mantel and Haenszel described a way to weight individual strata in order to come up with an adjusted estimate. Verify to yourself that this statistic is just a weighted average of the stratum specific odds ratios by weighting each stratum's odds ratio by proportion of the total weight represented by the stratum weight. That is, divide each stratum's weight by the sum of all the weights across strata, and compute a weighted average of the odds ratio.)

Ans: After adjustment for field, the odds of a female being full professor in 1995 was only 0.303 as high as the odds of a male in the same field being full professor. Such an observation was found to be highly unusual in the absence of a true association between sex and rank (P < .0001). Based on a 95% confidence interval, we find that the observed data is not atypical of settings in which the true adjusted odds ratio is between 0.238 and 0.386.

d. In 1995, is there evidence that the association between being a full professor and being female is modified by field? (This is a question about whether the odds ratio are homogeneous (equal) across strata. A P value testing the null hypothesis of homogeneity is provided by the Stata "cc" command.)

Ans: **Based on a Mantel-Haenszel test for homogeneity of odds ratios across field strata, we do not have enough evidence to be able to state with high confidence that field modifies the association between sex and being a full professor (P = 0.0648).**