Biost 518: Applied Biostatistics II
Emerson, Winter 2006

Homework #5 Key
March 10, 2006

Written problems due at the beginning of class, Wednesday, February 22, 2006.

1. Problem 1 relates to the data set from the clinical trial of DFMO. For each of the following models, provide inference (P values, and where appropriate, 95% confidence intervals with scientific interpretation of the parameters) regarding the effect of DFMO on the mucosal spermidine levels after 12 months of treatment. Also provide a table of predicted values for each of these models.

Ans: I chose to compare the distribution of spermidine levels across the dose groups using the geometric means. Hence, I log transformed the response measurements and performed linear regressions. In doing so, I had to consider the single measurement that was 0.00 for one individual. As the next lowest measurement was 0.295, I chose to substitute 0.15 for this individual level that was below the lowest detectable limit. The annotated Stata log file accompanying this key contains the code I used to solve this problem. For parameter interpretations, I generally back transformed (i.e., exponentiated) the parameter estimates using Excel.

Because I was using geometric means for inference, I also included the geometric means in my descriptive statistics.

Table 1: Descriptive statistics for spermidine levels after 12 months of treatment by dose.

Dose	N	Mean	SD	Min	25th%	Mdn	75th%	Max	Geom Mn
0.000	28	3.256	1.314	1.013	2.262	2.816	4.273	5.910	3.008
0.075	26	2.920	0.994	1.352	2.127	2.859	3.635	4.923	2.750
0.200	21	2.712	1.395	0.293	1.757	2.509	3.777	6.454	2.325
0.400	20	1.950	0.799	0.000	1.475	1.929	2.456	3.417	1.713

The following table contains the fitted values from each of the six models. I note that the fitted geometric means from the dummy variables (Model B) and the cubic polynomial (Model G) each correspond exactly to the sample geometric means for each dose group. This correspondence between the cubic polynomial and the dummy variables is due to the fact that there were only four levels of dose sampled (and three is one less than four). The estimates from Model C would lie exactly on a straight line. The estimates from Model D would very nearly lie on a straight line, because the sample geometric means from each group are very nearly linear. In Model E, the estimated geometric means are the same for all dose groups above 0, and the dose 0 group estimate corresponds exactly to the sample geometric mean for that group. In Model F, the estimated geometric means for dose groups higher than 0 lie exactly on a straight line, and the dose 0 group estimate corresponds exactly to the sample geometric mean for that group.

Table 2: Fitted geometric means from the six models.

Dose	Model B	Model C	Model D	Model E	Model F	Model G
0.000	3.008	3.038	3.009	3.008	3.008	3.008
0.075	2.750	2.733	2.748	2.265	2.763	2.750
0.200	2.325	2.292	2.326	2.265	2.302	2.325
0.400	1.713	1.729	1.713	2.265	1.720	1.713

a. Provide descriptive statistics for spermidine levels after 12 months of treatment by dose group.

Ans: See Table 1 above.

b. Model dose as dummy variables.

Ans: An analysis of variance of the log transformed spermidine levels finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0079). The placebo group is estimated to have a geometric mean spermidine level of 3.01 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.58 to 3.51 µmol / mg protein). The dose 0.075 group is estimated to have a geometric mean only 0.91 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 0.74 to 1.13 times as large), the dose 0.200 group is estimated to have a geometric mean only 0.77 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 0.56 to 1.06 times as large), and the dose 0.400 group is estimated to have a geometric mean only 0.57 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 0.41 to 0.79 times as large).

c. Model dose continuously as a linear predictor.

Ans: An analysis performed by regressing the log transformed spermidine levels on a linear dose variable estimates that the geometric mean tends to decrease 76% (95% CI: decreases 46% to 89%) for each 1.00 difference in dose (or decrease 13% (95% CI: decreases 6% to 20%) for each 0.10 difference in dose). Such a difference is beyond that which might be reasonably expected to be observed when there is no true effect of DFMO on mucosal spermidine levels (P= .0006). The placebo group is estimated to have a geometric mean spermidine level of 3.04 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.69 to 3.43 µmol / mg protein).

d. Model dose as two variables: a continuous linear predictor along with a quadratic term (so an additional predictor equal to the square of dose).

Ans: An analysis performed by regressing the log transformed spermidine levels on a quadratic polynomial in dose finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0079). (Interpreting the slope parameters is difficult here, though we can interpret the intercept: The placebo group is estimated to have

a geometric mean spermidine level of 3.01 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.60 to 3.48 µmol / mg protein).) *(We could, of course, obtained predicted geometric means and 95% CI for the dose groups.)*

e. Model dose as a binary variable indicating whether dose was greater than 0.

Ans: An analysis comparing the placebo group to the combined groups receiving some dose of DFMO finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0082). (Interpreting the slope parameters is difficult here, because there is no good scientific reason to estimate the effect of DFMO across combined dose groups. We can interpret the intercept: The placebo group is estimated to have a geometric mean spermidine level of 3.01 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.58 to 3.51 µmol / mg protein). *(Had we obtained predicted geometric means and 95% CI for the dose groups, they would have been the same for all doses higher than 0.)*

f. Model dose as two variables: a binary variable indicating whether dose was greater than 0 and a continuous linear term.

Ans: Analysis finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0026). From the modeling of dose as a linear continuous predictor and a threshold effect at dose 0, we do not have sufficient evidence to reject the hypothesis of a linear relationship among log geometric means across all dose levels (P= .850). The estimated linear trend across dose groups suggests the geometric mean tends to decrease 77% (95% CI unadjusted for multiple comparisons: decreases 36% to 92%) for each 1.00 difference in dose when comparing doses above 0 (or decrease 14% (95% CI: decreases 4% to 22%) for each 0.10 difference in dose). The placebo group is estimated to have a geometric mean spermidine level of 3.01 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.58 to 3.51 µmol / mg protein.

g. Model dose as three variables: a continuous linear predictor, a quadratic term, and a cubic term.

Ans: An analysis performed by regressing the log transformed spermidine levels on a cubic polynomial in dose finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0079). (Interpreting the slope parameters is difficult here, though we can interpret the intercept: The placebo group is estimated to have a geometric mean spermidine level of 3.01 µmol / mg protein (95% confidence interval unadjusted for multiple comparisons: 2.58 to 3.51 µmol / mg protein). Note that a test can be performed to assess evidence against a true linear relationship among the log geometric means across dose groups. Such a test is not significant: P= 0.98.)

2. Repeat the analyses in problem 1 adjusting for the baseline mucosal spermidine levels. Note that the Stata functions "test" and "testparm" can be used to perform Wald tests of multiple

parameters adjusted for other covariates. You do not need to consider the descriptive statistics or the fitted values for this problem.

Ans: Again I chose to compare the distribution of spermidine levels across the dose groups using the geometric means. Hence, I also log transformed the baseline mucosal spermidine measurements for adjusted linear regressions. In all problems, interpretation of the intercept is not generally of scientific interest, as there were no subjects with a baseline spermidine measurement of 0. Interpretation of the parameters modeling dose will generally have the same interpretation as in problem 1, except we will now note that comparisons are adjusted for baseline measurements.

a. Model dose as dummy variables.

Ans: An analysis of covariance of the log transformed spermidine levels adjusted for the baseline spermidine measurements finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0071). Treatment with dose 0.075 is estimated to have a geometric mean only 0.91 times as large as a placebo group with similar baseline values (95% CI unadjusted for multiple comparisons: 0.75 to 1.11 times as large), the dose 0.200 group is estimated to have a geometric mean only 0.77 times as large as a placebo group with similar baseline values (95% CI unadjusted for multiple comparisons: 0.56 to 1.05 times as large), and the dose 0.400 group is estimated to have a geometric mean only 0.56 times as large as a placebo group with similar baseline values (95% CI unadjusted for multiple comparisons: 0.40 to 0.79 times as large).

b. Model dose continuously as a linear predictor.

Ans: An analysis performed by regressing the log transformed spermidine levels on a linear dose variable and adjusting for baseline provides estimates that the geometric mean tends to decrease 76% (95% CI: decreases 47% to 89%) for each 1.00 difference in dose (or decrease 13% (95% CI: decreases 6% to 20%) for each 0.10 difference in dose). Such a difference is beyond that which might be reasonably expected to be observed when there is no true effect of DFMO on mucosal spermidine levels (P= .0006).

c. Model dose as two variables: a continuous linear predictor along with a quadratic term (so an additional predictor equal to the square of dose).

Ans: An analysis performed by regressing the log transformed spermidine levels on a quadratic polynomial in dose and adjusting for baseline finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0023).

d. Model dose as a binary variable indicating whether dose was greater than 0.

Ans: An analysis adjusted for baseline and comparing the placebo group to the combined groups receiving some dose of DFMO finds that the observed differences

between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .005).

e. Model dose as two variables: a binary variable indicating whether dose was greater than 0 and a continuous linear term.

Ans: Analysis finds that after adjusting for baseline, the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0024). From the modeling of dose as a linear continuous predictor and a threshold effect at dose 0, we do not have sufficient evidence to reject the hypothesis of a linear relationship among log geometric means across all dose levels (P= .844). The estimated linear trend across dose groups suggests the geometric mean tends to decrease 77% (95% CI unadjusted for multiple comparisons: decreases 37% to 92%) for each 1.00 difference in dose when comparing doses above 0 among patients with similar baseline values (or decrease 14% (95% CI: decreases 5% to 22%) for each 0.10 difference in dose).

f. Model dose as three variables: a continuous linear predictor, a quadratic term, and a cubic term.

Ans: An analysis performed by regressing the log transformed spermidine levels on a cubic polynomial in dose and adjusting for baseline spermidine finds that the observed differences between the dose groups geometric means is greater than what might reasonably be expected when DFMO had no true effect (P = .0071).

3. For each of the following models, provide inference (P values, and where appropriate, 95% confidence intervals with scientific interpretation of the parameters) regarding the effect of DFMO on the odds of decreased spermidine levels after 12 months of treatment (i.e., a lower spermidine level at 12 months than at baseline). Also provide a table of predicted values for the odds of decreased spermidine as well as the probability of decreased spermidine for each of these models.

The following tables contain the fitted values for probabilities (Table 3), odds (Table 4), and log odds (Table 5) from each of the six models, as well as from sample descriptive statistics (I used Excel to convert the probabilities to odds and log odds). I note that the fitted proportions/odds from the dummy variables (Model B) and the cubic polynomial (Model G) each correspond exactly to the sample proportions/odds for each dose group. This correspondence between the cubic polynomial and the dummy variables is due to the fact that there were only four levels of dose sampled (and three is one less than four). The estimates of the log odds from Model C would lie exactly on a straight line. The estimates from Model D would very nearly lie on a straight line, because the sample log odds departures from a straight line are not particularly better fit by a quadratic. In Model E, the estimated proportions/odds are the same for all dose groups above 0, and the dose 0 group estimate corresponds exactly to the sample proportions/odds for that group. In Model F, the estimated log odds for dose groups higher than 0 lie exactly on a straight line, and the dose 0 group estimate corresponds exactly to the sample proportions/odds for that group.

Table 3: Fitted probabilities from the six models.

Dose	Sample Probs	Model B	Model C	Model D	Model E	Model F	Model G
0.000	0.464	0.464	0.493	0.491	0.464	0.464	0.464
0.075	0.615	0.615	0.557	0.559	0.672	0.590	0.615
0.200	0.619	0.619	0.659	0.662	0.672	0.670	0.619
0.400	0.800	0.800	0.793	0.791	0.672	0.779	0.800

Table 4: Fitted odds from the six models.

Dose	Sample Probs	Model B	Model C	Model D	Model E	Model F	Model G
0.000	0.317	0.317	0.330	0.329	0.317	0.317	0.317
0.075	0.381	0.381	0.358	0.358	0.402	0.371	0.381
0.200	0.382	0.382	0.397	0.398	0.402	0.401	0.382
0.400	0.444	0.444	0.442	0.442	0.402	0.438	0.444

Table 5: Fitted log odds from the six models.

Dose	Sample Probs	Model B	Model C	Model D	Model E	Model F	Model G
0.000	-0.499	-0.499	-0.481	-0.482	-0.499	-0.499	-0.499
0.075	-0.419	-0.419	-0.446	-0.446	-0.396	-0.431	-0.419
0.200	-0.418	-0.418	-0.401	-0.400	-0.396	-0.397	-0.418
0.400	-0.352	-0.352	-0.354	-0.355	-0.396	-0.359	-0.352

a. Provide descriptive statistics for the probability and odds of decreased spermidine levels after 12 months of treatment by dose group.

Ans: See Tables 3 and 4 above.

b. Model dose as dummy variables.

Ans: The observed differences between the dose groups with respect to the odds of decreased spermidine levels is not greater than what might reasonably be expected when DFMO had no true effect (P = .1594). The dose 0.075 group is estimated to have odds of decreased spermidine 1.85 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 0.62 to 5.49 times as large), the dose 0.200 group is estimated to have odds of decreased spermidine 1.88 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 0.59 to 5.97 times as large), and the dose 0.400 group is estimated to have odds of decreased spermidine 4.62 times as large as the placebo group (95% CI unadjusted for multiple comparisons: 1.22 to 17.5 times as large). *(Note that the "logistic" command in Stata does not display an estimate of the intercept from the logistic regression model. I did not provide an interpretation of an intercept therefore. Note also that the dose 0.4 group had a statistically significantly increased odds of decreased spermidine when we do not*

consider the multiple comparisons, but overall we could not declare sufficient evidence for an effect of DFMO.)

c. Model dose continuously as a linear predictor.

Ans: An analysis using a linear dose variable estimates that the odds of decreased spermidine tends to be 30.9 times higher (95% CI: 1.40 to 682.0 times higher) for each 1.00 difference in dose (or $30.9^{0.1}$= 1.41 times higher (95% CI: $1.40^{0.1}$=1.03 to $682^{0.1}$=1.92 times higher) for each 0.10 difference in dose). Such a difference is beyond that which might be reasonably expected to be observed when there is no true effect of DFMO on mucosal spermidine levels (P= .0299). (*Note the much lower P value obtained when the analysis borrows strength across the ordered dose groups compared to the dummy variable model.)*

d. Model dose as two variables: a continuous linear predictor along with a quadratic term (so an additional predictor equal to the square of dose).

Ans: A logistic regression analysis performed using a quadratic polynomial in dose finds that the observed differences between the doses with respect to the odds of decreased spermidine is not greater than what might reasonably be expected when DFMO had no true effect (P = .0931). (Interpreting the slope parameters is difficult here.) *(We could, of course, obtain predicted proportions/odds and 95% CI for the dose groups. Note that the fitted values for this model and for the model in part c are nearly identical, but that we do not have statistical significance here. This is because we are having to test two parameters here without any particular gain in the statistical precision. This leads to a loss of precision, thereby illustrating the advantages of "parsimony": using as few predictors as possible to model the true relationship. But we do not, of course, know the true relationship, so we have to make tradeoffs when we fere there might be nonlinearities.)*

e. Model dose as a binary variable indicating whether dose was greater than 0.

Ans: An analysis comparing the placebo group to the combined groups receiving some dose of DFMO finds that the observed differences between the dose groups odds of decreased spermidine is not greater than what might reasonably be expected when DFMO had no true effect (P = .0631). (Interpreting the slope parameters is difficult here, because there is no good scientific reason to estimate the effect of DFMO across combined dose groups. *(Had we obtained predicted odds ratios and 95% CI for the dose groups, they would have been the same for all doses higher than 0, with an estimated odds ratio of 2.36.)*

f. Model dose as two variables: a binary variable indicating whether dose was greater than 0 and a continuous linear term.

Ans: Analysis finds that the observed differences between the dose groups' odds of decreased spermidine is not greater than what might reasonably be expected when DFMO had no true effect (P = .0765). From the modeling of dose as a linear continuous predictor and a threshold effect at dose 0, we do not have sufficient evidence to reject the hypothesis of a linear relationship among log odds of

decreased spermidine across all dose levels (P= .623). The estimated linear trend across dose groups suggests the odds of decreased spermidine tends to be 15.9 times higher (95% CI unadjusted for multiple comparisons: 0.301 times as high to 833 times higher) for each 1.00 difference in dose when comparing doses above 0 (or 1.32 times higher (95% CI: 0.887 times as high to 1.96 times higher) for each 0.10 difference in dose fwhen comparing doses above 0). *(Note that the fitted values for this model differed more from those in part c than did the quadratic model, even though both used two predictors to model dose. This model borrowed data less distantly to estimate the linear trend (the linear trend did not use the dose 0 group in its estimate), hence we would expect less power.)*

g. Model dose as three variables: a continuous linear predictor, a quadratic term, and a cubic term.

Ans: As noted in the answers to problem 1, this is of course the exact same model as the dummy variable model in part b, so the tests of statistical significance will be the exact same. This parameterization is much more difficult to interpret.

4. Which of the above analyses would you prefer *a priori* to test for an effect of beta-carotene supplementation on plasma levels of beta-carotene?

Ans: I would generally prefer using the continuous spermidine levels, as there is no compelling scientific threshold, and the continuous measurements provide greater statistical power than would dichotomized data. I would also prefer adjusting for baseline, as that will tend to provide greater precision. I also tend to prefer the model in part f of problem 1, as that allows some flexibility in fitting dose response while maintaining some interpretability of parameters: In addition to testing for an effect by DFMO, I can assess evidence against linear relationships as well as whether there is any advantage in giving a dose above the lowest positive dose tested. In this analysis, I would conclude that the data are relatively well fit by a straight line relationship, and thus higher doses tend to provide greater suppression of polyamines.