BIOS 662, Fall 2018
Midterm Examination

Assigned: Tuesday, October 23

Due: 11:59 PM on Thursday, November 1

Instructions:

The midterm exam is a take-home exam. It is due just before midnight on Thursday, November 1. Please put your completed exam in the BIOS662 mailbox in the Department of Biostatistics. (I will collect the exams from the mailbox *very* early on the Friday.)

Do not discuss the exam with anyone. If you need clarification on any question you may contact me by email (david_couper@unc.edu). The graders will not answer questions about the exam but you may continue to ask them more general questions during their office hours.

Please sign your name on the exam indicating that you did not receive assistance from anyone. Note that obtaining help from anyone other than me is an Honor Code violation.

You may use software to perform calculations but make sure that you include enough information in your answers that I can see what you have done. For instance, include the SAS or R statements you used, not just the output. For all problems involving statistical testing, include a definition of the parameters to be tested, the null and alternative hypotheses, the test statistic to be employed and its distribution (when this is relevant), whether you reject the null, and *an interpretation of the results in a language suitable for investigators.* You may do tests either by determining whether the test statistic falls in the critical region or by obtaining a p-value (you don't have to use both approaches). For any method you use, be sure to state and check the required assumptions. All tests should be performed at the $\alpha = 0.05$ significance level.

Datasets and manuscripts referred to in the questions are available on the Sakai web site, in the folder "Midterm materials" under "Resources". All data are fictitious, even when based on real studies.

1. Write and sign a statement confirming you have not obtained assistance from anyone.

2. The gestational age (GA) of an embryo or newborn infant is approximately the time since the mother's last menstrual period. GA is used to determine whether the pregnancy has reached full term (40 weeks). An infant born prior to 37 weeks GA is regarded as being premature or preterm. There has been some epidemiologic evidence for an association between a pregnant woman having periodontal disease and giving birth prematurely or for the infant's birthweight to be below normal.

   The MOTOR Study was a randomized clinical trial to investigate whether treating periodontal disease in pregnant women reduces the risk of preterm delivery and/or increases average birthweight. (The manuscript by Offenbacher *et al.* assigned in homework 1 provides information about the study. It is not necessary to consult that manuscript in order to complete this exam.)

   In MOTOR about 1,800 pregnant women with periodontal disease were randomized into two treatment groups. The "prenatal treatment" group received periodontal therapy early in pregnancy. The "post-partum treatment" group received periodontal therapy a few weeks after delivery.

   Two measures of GA at birth were available. The more accurate one was made using an ultrasound examination early in the pregnancy. This is given in weeks, calculated from days. So, for instance, 38.1429 corresponds to a GA of 38 weeks and 1 day. The other measure of GA was an estimate made when the infant was born and is in whole weeks.

   Various periodontal measurements were made around each tooth at baseline (early in the pregnancy, before randomization) and were repeated shortly after giving birth. For each woman, the measurements on the teeth were averaged to give a summary score for each type of measurement. One such measurement is probing depth, in millimeters, with larger values indicating more periodontal disease.

   The file "Midterm_BWT.dat" and corresponding SAS and R datasets contain data from a subset of the live births in the trial. The columns in the file are, respectively, ID (participant identifier), group (treatment group; 1 = prenatal, 2 = post-partum), rand_month (month in which the woman was randomized, with 1=January, 2=February, etc.), birth_month (month in which the woman gave birth), GA_ultra (GA estimated by ultrasound), GA_est (GA estimated at birth), ppnum (number of previous pregnancies, as a character variable, with ≥ 3 denoted as "3+"), PD_pre (average pocket depth at the time of randomization), PD_post (average pocket depth after delivery).

   If you detect any apparently incorrect data values, make a note of these, explain why you believe the data are incorrect, and set the values to missing. Regard a

value as being incorrect only if it is clearly impossible. You may assume that there are no errors in the pocket depth variables. *Set incorrect values to missing.*

(a) Is the ultrasound version of GA approximately normally distributed?

(b) Do the means of the two gestational age variables differ?

(c) After taking into account any difference in the means (whether or not statistically significant), do the shapes of the distributions of the two gestational age variables differ?

(d) Classify both versions of gestational age into 3 intervals, $(0, 37)$, $[37, 40)$, and $[40, \infty)$. Determine how well the two versions agree and provide a 95% confidence interval for the true agreement.

(e) Is the number of women randomized in each month consistent with the number of days in each month?

(f) Without doing any additional tests, comment on how the distribution of the number of births each month compares with that of the number of women randomized each month.

For parts (g) and (h), dichotomize the ultrasound version of GA to define preterm delivery.

(g) Does the risk of preterm delivery vary monotonically with the number of previous pregnancies?

(h) Based on this study, is treating periodontal disease in pregnant women effective in terms of reducing the risk of prematurity?

The effect of the periodontal therapy on mean birthweight was smaller than the investigators had expected – there was not a statistically significant difference between the mean birthweights in the two treatment groups. One potential explanation for the lack of effect is that the periodontal therapy provided may not have been intensive enough to yield a substantial and sustained reduction in the amount of periodontal disease.

(i) Ignoring treatment group, is there a difference between the mean average pocket depth at randomization and the mean average pocket depth after delivery.?

(j) Did the mean change in average pocket depth differ between the two treatment groups?

(k) Based on the data on average pocket depth, discuss the effectiveness of the periodontal therapy and the consequences for the potential to affect birthweight.

3. The evidence on which the MOTOR Study was based includes data from case-control studies. The file "Midterm_CC.dat" contains data from one such study. Cases were defined as women who had given birth prematurely (< 37 weeks GA). Controls had full-term babies. The women had a periodontal examination soon after giving birth. Those who had moderate or severe periodontal disease (based on the investigators' criteria) were classified as "exposed" to periodontal disease and those who had no evidence of periodontal disease or just mild disease were classified as "unexposed". Age was considered to be a potential confounder of the association.

   The columns in the file are, respectively, ID (participant identifier), case (indicator of premature birth case status; 1 = case, 0 = control), exposed (indicator of periodontal disease status; 1 = moderate or severe periodontal disease, 0 = no more than mild periodontal disease), and age_group (the age group of the mother, with 1 representing the youngest age group and 3 the oldest). You may assume there are no errors in this dataset.

   First assume this was an unmatched case-control study.

   (a) Determine whether premature birth case status is associated with being exposed to periodontal disease.

   (b) Provide an estimate for a measure of the association between exposure and case status and give a 95% confidence interval for the true measure.

   (c) Repeat part (b) above, taking age group into account.

   (d) Does age group appear to be a confounder? Is the pooled estimate in part (c) a reasonable way to summarize the association here?

   The data were actually from an individually-matched case-control study, with one control per case, matching on age and number of previous pregnancies. The first 4 characters of the ID indicate the case-control pair (the case and the control in the pair have the same first 4 characters). The final character of the ID is 1 for the case in the pair and 0 for the control.

   (e) Repeat parts (a) and (b) above assuming an individually-matched case-control design.

   (f) Which of the estimates of the measure of association in (b), (c) and (e) is most appropriate? Justify your choice.

   (g) Discuss the strength of the evidence from this case-control study for an association between periodontal disease and preterm delivery.