2017 Qualifying Exam

Question 2

Part A:

Table 1 shows descriptive statistics for participants in a randomized trial of child obesity. Of the 204 participants, 103 were randomized to control and 101 were randomized to intervention. The mean age overall and in both groups is 9 years old. There is a slightly higher percentage of females in the intervention group (60/113, 53%), vs males (41/91, 45%), as compared to control group, and an overall slightly higher percentage of females in the study. There are slightly more African Americans in the intervention group (35 vs 33) and slightly more Caucasians in the control group (70 vs 66) but overall the races are balanced across control and intervention. Of all parents, 167 were obese, vs 37 who were not obese. Children of non-obese parents were not well randomized across treatment groups (30% in the control group and 70% in intervention). However, children of obese parents were split almost evenly across groups (55% in control and 45% in intervention). At baseline visit there were 71 non-obese children, split 55% in control and 45% in intervention, and 133 obese children split almost evenly with 48% in control and 52% in intervention. At follow-up there were 86 confirmed non-obese children, 80 confirmed obese children, and 38 children missing data at this time point. Of those missing data, 24 (63%) were in the control group and 14 (37%) were in the intervention group.

Table : Descriptive Statistics By Treatment Group and Overall

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **AGE** | | | | **SEX** | | | | **RACE** | | | |
| **Female** | | **Male** | | **African-Am** | | **Caucasian** | |
| **N** | **Mean** | **Median** | **Std** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** |
| **RX** | 103 | 9.02 | 9.00 | 0.92 | 53 | 46.90 | 50 | 54.95 | 33 | 48.53 | 70 | 51.47 |
| **Control** |
| **Intervention** | 101 | 9.08 | 9.00 | 1.03 | 60 | 53.10 | 41 | 45.05 | 35 | 51.47 | 66 | 48.53 |
| **All** | 204 | 9.05 | 9.00 | 0.97 | 113 | 100.00 | 91 | 100.00 | 68 | 100.00 | 136 | 100.00 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PARENT\_WT** | | | | **Y0** | | | | **Y1** | | | | | |
| **0** | | **1** | | **0** | | **1** | | **.** | | **0** | | **1** | |
| **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** |
| **RX** | 11 | 29.73 | 92 | 55.09 | 39 | 54.93 | 64 | 48.12 | 24 | 63.16 | 40 | 46.51 | 39 | 48.75 |
| **Control** |
| **Intervention** | 26 | 70.27 | 75 | 44.91 | 32 | 45.07 | 69 | 51.88 | 14 | 36.84 | 46 | 53.49 | 41 | 51.25 |
| **All** | 37 | 100.00 | 167 | 100.00 | 71 | 100.00 | 133 | 100.00 | 38 | 100.00 | 86 | 100.00 | 80 | 100.00 |

\*\* Note: Below is the table output using proc report – it is not in an ideal format, but still informative.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | **N** | **Mean** | **Std** |  | | | |
| **Treatment** | **Sex** | **Race** | **Age** | **Age** | **Age** | **Parent obesity status** | **Obesity status at baseline** | **Obesity status at follow-up** | **Missing data at follow-up** |
| Control | Female | African-American | 14.00 | 8.79 | 0.70 | 27% | 50% | 48% | 27% |
|  |  | Caucasian | 39.00 | 9.15 | 0.99 | 31% | 39% | 50% | 46% |
|  | Male | African-American | 19.00 | 8.84 | 0.90 | 37% | 51% | 49% | 32% |
|  |  | Caucasian | 31.00 | 9.06 | 0.93 | 30% | 50% | 51% | 48% |
| Intervention | Female | African-American | 23.00 | 9.04 | 0.82 | 49% | 49% | 51% | 29% |
|  |  | Caucasian | 37.00 | 8.95 | 1.08 | 43% | 47% | 51% | 31% |
|  | Male | African-American | 12.00 | 9.00 | 1.13 | 39% | 49% | 53% | 39% |
|  |  | Caucasian | 29.00 | 9.31 | 1.07 | 44% | 45% | 51% | 41% |
|  |  |  | 204.0 | 9.05 | 0.97 | 39% | 48% | 50% | 39% |

Part B:

Table 2 shows descriptive statistics for participants by group, where group is indicated by M1, an indicator variable for whether the follow-up outcome is missing. If M1=0 the outcome is not missing and if M1=1 the outcome is missing. There appears to be no association of missing status with age or sex. There appears to be some association of missing with sex, parent obesity status, race and baseline child obesity status. None of the children who were not obese at baseline had missing data at follow-up. Of particular interest is whether there is an association between intervention group and status of missing outcome at follow-up. In the control group, 79 (77%) vs 24 (23%) of children did not have missing data. In the intervention group, 87 (86%) vs 14 (14%) of children did not have missing data. The control group had a 9% higher missing rate compared to intervention. Knowing that there were no non-obese children with missing data, this indicates that drop out was only by children who were obese at baseline and also in the control group. Almost 30% of obese participants were lost to follow-up, 63% of whom were in the control group. This pattern of missing data may bias the results of the trial because we do not know whether these obese children remained obese, potentially indicating a significant effect of intervention, or did not remain obese, potentially indicating that there were factors other than intervention that may have led to change in obesity status.

Table : Descriptive Statistics by Loss to Follow-Up

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **AGE** | | | | **RX** | | | | **SEX** | | | |
| **Control** | | **Interven** | | **Female** | | **Male** | |
| **N** | **Mean** | **Median** | **Std** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** |
| **M1** | 166 | 8.98 | 9.00 | 0.94 | 79 | 76.70 | 87 | 86.14 | 95 | 84.07 | 71 | 78.02 |
| **0** |
| **1** | 38 | 9.34 | 10.00 | 1.07 | 24 | 23.30 | 14 | 13.86 | 18 | 15.93 | 20 | 21.98 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **RACE** | | | | **PARENT\_WT** | | | | **Y0** | | | |
| **African-** | | **Caucasia** | | **0** | | **1** | | **0** | | **1** | |
| **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** | **N** | **Percent** |
| **M1** | 61 | 89.71 | 105 | 77.21 | 34 | 91.89 | 132 | 79.04 | 71 | 100.00 | 95 | 71.43 |
| **0** |
| **1** | 7 | 10.29 | 31 | 22.79 | 3 | 8.11 | 35 | 20.96 | . | . | 38 | 28.57 |

Part C:

Using a complete-case analysis we use a logistic regression model (M1), adjusting for child’s baseline obesity status, age, sex, race and parents’ obesity status, to determine whether there is a significant treatment effect on the risk of obesity at follow-up.

M1: Logit(Y1) = Beta0 + Y0=1\*Beta1 + Age\*Beta2 + Sex=Female\*Beta3 + Race=AA\*Beta4 + Parent\_WT=1\*Beta5 + RX=intervention\*Beta6

Using M1 we estimate regression parameters for the treatment and for adjustment covariates in the model. We want to test the null hypothesis of no intervention effect, which translates in this model to a test of Beta6=0, vs the alternative hypothesis of Beta6≠0. We use a Wald-type test which follows a chi squared distribution with 1 degree of freedom. The test statistic is 3.58 with an associated p value of 0.0583. At a significance level of p<0.05, we do not reject the null hypothesis of no treatment effect. The parameter estimate for treatment in this model is -0.925. Using a logit link for model M1, this estimate translates to an estimated odds ratio of 0.397 (Table 3) and confidence intervals for that odds ratio of 0.152 to 1.033. Our model estimates that a child in the control group, adjusting for baseline obesity status, age, sex, race and parents’ obesity status, is approximately 0.4 times as likely to be obese as compared to a child in the intervention group who has the same baseline characteristics. This is only a complete-case analysis and we do not know if, after losing 38 subjects to follow-up, we are underpowered to detect a significant treatment effect at a p<0.05 level. We note, however, that a child who is obese at baseline is 60 times as likely as a non-obese child to be obese at follow-up, keeping all other covariates constant.

Table : Odds Ratio Estimates from Logistic Model M1

|  |  |  |  |
| --- | --- | --- | --- |
| **Odds Ratio Estimates** | | | |
| **Effect** | **Point Estimate** | **95% Wald Confidence Limits** | |
| **RX Intervention vs Control** | 0.397 | 0.152 | 1.033 |
| **AGE** | 0.986 | 0.622 | 1.564 |
| **SEX Female vs Male** | 0.449 | 0.174 | 1.158 |
| **RACE African- vs Caucasia** | 0.796 | 0.321 | 1.978 |
| **PARENT\_WT 1 vs 0** | 0.712 | 0.244 | 2.078 |
| **Y0 1 vs 0** | 59.552 | 19.039 | 186.272 |

Part D:

As we discovered in part B, there appears to be an association of loss to follow-up with several of the baseline variables. We will use multiple imputation to impute the child’s follow-up obesity status if the data are missing. Multiple imputation (MI) uses regression to predict values of variables based on other available data. In the first step, a regression model is used to impute the missing values for the follow-up outcome for the 38 children lost to follow-up. Since a regression method will deterministically impute values given certain covariates, random variability is introduced for each iteration of the first MI step. Once the deterministically calculated values are estimated using regression, a random sampling from the error distribution is performed, and this random value is added to the imputed value. The error distribution being sampled is the posterior distribution of the variable for which imputation is being performed. Twenty five imputed data sets are created using MI. The next step is to perform 25 independent regression analyses, one for each imputed data set created. This will result in 25 sets of regression parameters. In the last step, one final set of regression parameters is estimated using an unweighted average of the regression parameters derived from the 25 imputed data sets. Figure 1 shows the covariance of the parameter estimates. B (between-imputation variability) is a basic variance calculation, taking the adjusted (1/m-1 instead of 1/m) averaged sum of squared differences between the mean parameter and each instance of the parameter estimate. This is adjusted further (multiplied by (1+1/m)) and added to W (within-imputation variability), which is the inverse of the sum of covariance of all m parameter estimates. The total covariance is therefore the sum of the within- and between-imputation variability. For this data, m=25. The calculation of the confidence intervals of the parameter estimates follows trivially once the covariances for parameter estimates are calculated.



Figure : Calculation of parameter estimates and their estimated covariance using MI

By calculating imputed values, and thus regression parameters, by introducing variability associated with the data itself, we can calculate more realistic variance estimates for the regression parameters of interest. If we only used the deterministic values for imputed data, the variance estimates of the regression parameters in our logistic model M1 would be anti-conservative.

Table 4: Parameter Estimates using MI

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter Estimates (25 Imputations)** | | | | | | | | | | |
| **Parameter** | **Estimate** | **Std Error** | **95% Confidence Limits** | | **DF** | **Minimum** | **Maximum** | **Theta0** | **t for H0: Parameter=Theta0** | **Pr > |t|** |
| **intercept** | -1.551734 | 2.246687 | -5.96898 | 2.865516 | 386.75 | -3.079200 | 0.741395 | 0 | -0.69 | 0.4902 |
| **rx** | -0.928122 | 0.497075 | -1.90564 | 0.049395 | 362.1 | -1.356170 | -0.330250 | 0 | -1.87 | 0.0627 |
| **age** | 0.017614 | 0.236115 | -0.44677 | 0.481996 | 350.16 | -0.231871 | 0.181714 | 0 | 0.07 | 0.9406 |
| **sex** | -0.792801 | 0.486679 | -1.74948 | 0.163876 | 412.96 | -1.195631 | -0.385697 | 0 | -1.63 | 0.1041 |
| **race** | -0.132293 | 0.479745 | -1.07475 | 0.810164 | 524.63 | -0.511541 | 0.216517 | 0 | -0.28 | 0.7828 |
| **parent\_wt** | -0.371612 | 0.544640 | -1.43961 | 0.696385 | 2473.3 | -0.670093 | -0.038822 | 0 | -0.68 | 0.4951 |
| **y0** | 4.110984 | 0.578847 | 2.97588 | 5.246087 | 2354.7 | 3.833221 | 4.561768 | 0 | 7.10 | <.0001 |

Table 4 shows the unweighted averaged parameter estimate for treatment using MI is estimated to be -0.9281 with an associated standard error of 0.498. The 95% confidence interval is -1.91 to 0.0494. These values are not very different from the values calculated using complete case analysis. The p value for the null hypothesis of no treatment effect (beta6=0 from M1) is 0.0627. Using the imputed values for the children lost to follow-up, we do not reject the null hypothesis of no treatment effect. The p value using MI is slightly farther towards the null, but overall there is not much of a difference between the two regression analyses.

Part E:

If data are missing completely at random (MCAR) there should be no association between missing status (M1) and the values that would have been observed, given any of the observed outcome data (i.e., obesity status at baseline, Y0). To specify this mathematically,

Prob(Mi2=1|Yi1, Yi2, Xi) = Prob(Mi2=1|Xi)

where the subscript i indicates the subject, subscript 1 indicates baseline visit so Yi1 is the observed outcome at baseline for subject i, and subscript 2 indicates follow-up visit, so Yi2 is the observed outcome at follow-up. Mi2 is the indicator for missingness at follow-up. X is the matrix of covariates for subject i.

To determine whether data are MCAR, we test for an association between baseline obesity status and loss to follow-up. We use a chi square test (and confirm with a Fisher’s exact test, because not all of the cells have at least a count of 5) which follows a chi square distribution with one degree of freedom. The p values for both tests are <0.0001, indicating a strong statistical association between baseline obesity status and loss to follow-up. Therefore, we cannot conclude that the data are MCAR.

Table 5: MCAR Analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Table of Y0 by M1** | | | |
| **Y0** | **M1** | | |
| **0** | **1** | **Total** |
| **0** | 71 | 0 | 71 |
|  | 34.80 | 0.00 | 34.80 |
|  | 100.00 | 0.00 |  |
|  | 42.77 | 0.00 |  |
| **1** | 95 | 38 | 133 |
|  | 46.57 | 18.63 | 65.20 |
|  | 71.43 | 28.57 |  |
|  | 57.23 | 100.00 |  |
| **Total** | 166 | 38 | 204 |
|  | 81.37 | 18.63 | 100.00 |

If data are missing at random (MAR), missing status would be associated with other observed outcomes (i.e., obesity status at baseline) but conditionally independent of values that would have been observed for obesity status at follow-up given the other observed values (i.e., obesity status at baseline). To specify this mathematically,

Prob(Mi2=1|Yi1, Yi2, Xi) = Prob(Mi2=1|Yi1, Xi)

From examining the data, we know that obesity status at baseline is associated with missing status at follow-up. Because we do not observe the missing data for obesity status at follow-up we cannot confirm that this outcome would be conditionally independent of missingness. We can only assume that data are MAR, given that they are not MCAR. Our inferences on these data would only be accurate if the data are MAR, and not NMAR.

If missing data are not missing at random (NMAR), then missing status is associated with unobserved outcomes, and the extent of the bias inherent in our estimates and inference made using these data would be unknown. In other words, if all of the children who dropped out remained obese, or if all of the children who dropped out became non-obese, our parameter estimates in M1 would not be valid if we did not take into consideration these unobserved outcomes. To specify this mathematically,

Prob(Mi2=1|Yi1, Yi2, Xi) = Prob(Mi2=1|Yi1, Yi2, Xi)

We perform our analyses assuming the data are missing at random. The complete case analysis in part C would only be valid if the data are MCAR, where there would be no association between missing status and outcome. We could assume the population being analyzed would be a representative sample of the entire study population. The MI analysis in part D would be valid if data are MCAR or MAR. We assume the unobserved outcomes are conditionally independent given the baseline obesity status. Therefore we can assume that subjects missing data are representative populations given their baseline obesity status.

After performing a multiple imputation analysis on the data, with all 38 children lost to follow-up having been obese in the control group, the regression parameter estimate for treatment effect is not much different from that calculated using complete case analysis. We do, however, believe this estimate to be more valid than the complete case analysis. Although, using a Wald test, it was determined that the parameter estimate for treatment was not significantly different from 0 at a 0.05 significance threshold, the p value for both analysis methods was very close to 0.05. If this study population is representative of the larger population, we can conclude from this study that there is some chance that we would expect children using this intervention to be 2.5 times as likely as children with similar characteristics to become non-obese after a 6 month period. However, there is some chance that the effects in this population are due to random chance and would not be a realistic estimate for the population.

General Comments when working through this problem

I am not sure whether it is necessary to use a GEE method to account for correlation between baseline and follow-up obesity status. The problem and data are organized such that it would be difficult to include clustering effects because there is no column in the data for ID and one would need to be created.