Problems to Turn In

6. Ear Infections (Based on Rosner 13.66):

In this problem we assess the impact of two different antibiotics on the chances a child will be cured of an ear infection after adjusting for age and whether one or both ears were infected. The variables are **clear** which indicates whether or not the infection has been cleared from both ears after 14 days of treatment, **antibiotic** which indicates which medication the child was given (1 = Ceftriaxone, 0 = Amoxicillin), **numears** which says how many ears were infected (either 1 or 2), and age which is divided into three categories: under 2 years old, 2-5 years old and 6 years or older. This variable is provided in two forms in the data set: first as **agegroup** with 1 = under two years old, 2 = two to five years old and 3 = six years or older; and second as a set of indicator variables for the three categories, **undertwo**, **twotofive** and **sixplus**.

(a) MLE Basics: Our reference point in logistic regression (as indeed in any regression!) is a model with no predictor variables:

$$\ln\left(\frac{p}{1-p}\right) = \beta_0$$

(i) Explain briefly what the interpretation of this model is and in particular what the maximum likelihood estimates of p and β_0 ought to be intuitively for this data set. (Note: It may help to get the frequency table for the **clear** variable.)

The interpretation of this model is that the log odds of the infection being cleared from both ears after 14 days of treatment with probability p is equal to β_0 . In other words, β_0 is the log odds of the probability of clearing the infection, and p is the probability of clearing an infection. Intuitively, the maximum likelihood estimates of p and β_0 ought to be $\hat{p} = 0.488$ and $\hat{\beta}_0 = \ln\left(\frac{\hat{p}}{1-\hat{p}}\right) = -0.0480$.

The FREQ Procedure

clear							
clear	Frequency	Percent	Cumulative Frequency	Cumulative Percent			
0	104	51.23	104	51.23			
1	99	48.77	203	100.00			
Frequency Missing = 797							

(ii) Fit the model with no predictors in STATA or SAS and check that the estimated value of β_0 matches your prediction from part (i).

After fitting the model with no predictors in SAS (by using a dummy variable as a predictor), we see that the estimated value of β_0 is $\hat{\beta_0} = -0.0493$, which is close to my prediction in part (i).

Note: The following parameters have been set to 0, since the variables are a linear combination of other variables as shown.

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	
Intercept	1	-0.0493	0.1404	0.1231	0.7257	
dummy	0	0				

(iii) (Optional Bonus) Write down the general expression for the likelihood corresponding to this model and evaluate it for the value of p that you suggested as the MLE in (i). (You can get even more credit for actually deriving the MLE by using calculus to perform the relevant maximization!) Then check that the likelihood matches the value on the STATA or SAS printout from part (ii).

Let the data be represented by X with data points $x_1, ..., x_n$. Then,

$$p(Y=1|X=x) = \prod_{i=1}^{n} n$$

Note: Parts (b)-(d) focus on a simple comparison of the clearance rates in the two medication groups without adjusting for age or severity of infection.

(b) Test of Proportions: Use a two-sample test of proportions to compare the rate of infection clearance for the two medication groups. Carefully state the null and alternative hypotheses mathematically and in words, use STATA or SAS to get the sample proportions for each group, obtain the test statistic and p-value, and explain your real-world conclusions. Show by hand how you can obtain the odds ratio for comparing children who were on Ceftriaxone to those on Amoxicillin from the sample proportions.

Letting the subscript C represent children on Ceftriaxone and subscript A represent children on Amoxicillin, and the proportions p representing proportion of children that had cleared infections, we write the hypotheses as follows:

$$H_0: p_C = p_A$$
$$H_A: p_C \neq p_A$$

The null hypothesis states that there is no statistical difference observed in the rate of infection clearance between the Ceftriaxone and Amoxicillin groups. The alternative hypothesis states that there is a statistically significant difference observed in the rate of infection clearance between the two medication groups.

We use a two-sided test since we are looking to observe any statistical difference between the two groups, so we also want to report a two-sided p-value. We get that $p_C = 40/97 = 0.4124$ and $p_A = 59/106 = 0.5566$. The test statistic for the two-sample test of proportions gives us Z = -2.054 and a two sided p-value of p = 0.04. Since the p-value is below the significance level of $\alpha = 0.05$, we reject H_0 and conclude that there is a statistically significant difference in the proportions of cleared infections between the Ceftriaxone and Amoxicillin groups.

To calculate the odds ratio for comparing children who were on Ceftriaxone to those on Amoxicillin using the sample proportions, we do the following:

$$OR_{C \ vs \ A} = \frac{\frac{p_C}{1-p_C}}{\frac{p_A}{1-p_A}}$$

$$= \frac{\frac{0.4124}{1-0.4124}}{\frac{0.5566}{1-0.5566}}$$

$$= 0.559$$

Confidence Limits for the Risk Difference
Risk Difference = -0.1440

Type 95% Confidence Limits

Wald -0.2800 -0.0081

Column 1 (antibiotic = .)

Risk Difference Test				
H0: P1 - P2 = 0 Wa	ald Method			
Risk Difference	-0.1440			
ASE (H0)	0.0701			
Z	-2.0536			
One-sided Pr < Z	0.0200			
Two-sided Pr > Z 0.0400				
Column 1 (antibiotic = .)				

(c) Contingency Table Approach: Now use a contingency table (chi-squared) test to perform the same test in STATA or SAS. Confirm that your chi-squared test statistic is just the square of the Z statistic in part (b) and that your p-values match. (If you are feeling really brave you can compute the chi-squared statistic by hand too and derive the fact that the Z test and the chi-squared test are equivalent!)

Looking at the output from the chi-squared test in SAS, we see that the Chi-Square test statistic value is 4.2173 and the p-value is p = 0.04. 4.2173 is exactly the square of Z = -2.0536, so we confirm that the chi-squared test statistic is equivalent to the square of the Z statistic and that the p-values do match in both scenarios.

Statistics for Table of clear by antibiotic

Statistic	DF	Value	Prob
Chi-Square	1	4.2173	0.0400
Likelihood Ratio Chi-Square	1	4.2331	0.0396
Continuity Adj. Chi-Square	1	3.6598	0.0557
Mantel-Haenszel Chi-Square	1	4.1965	0.0405
Phi Coefficient		-0.1441	
Contingency Coefficient		0.1427	
Cramer's V		-0.1441	

Fisher's Exact Test					
Cell (1,1) Frequency (F)	47				
Left-sided Pr <= F	0.0277				
Right-sided Pr >= F	0.9860				
Table Probability (P)	0.0137				
Two-sided Pr <= P	0.0492				

(d) Now suppose that the researcher analyzes the data with a logistic regression model with Y being whether or not the ear infection cleared (Y=1 for yes and Y=0 for no) and X being the indicator for the antibiotic with which the child was treated (X=1 for Ceftriaxone and X=0 for Amoxicillin). Figure out what the estimated regression coefficients, $\hat{\beta}_0$ and $\hat{\beta}_1$ must be by hand based on the various values you computed in part (b) and verify your results by fitting the logistic model in STATA or SAS.

$$\hat{\beta}_1 = \log(OR_{C \ vs \ A}) = \log(0.559)$$

$$= -0.581$$

$$\hat{\beta}_0 = \log(\frac{p}{1-p}) - \hat{\beta}_1 * X$$

$$= \log(\frac{0.5566}{1 - 0.5566}) - (-0.581) * 0$$

$$= 0.227$$

Testing Global Null Hypothesis: BETA=0						
Test	Chi-Square	DF	Pr > ChiSq			
Likelihood Ratio	4.2331	1	0.0396			
Score	4.2173	1	0.0400			
Wald	4.1874	1	0.0407			

Analysis of Maximum Likelihood Estimates						
_			Standard	Wald		
Parameter	DF	Estimate	Error	Chi-Square	Pr > ChiSq	
Intercept	1	0.2274	0.1955	1.3527	0.2448	
antibiotic	1	-0.5816	0.2842	4.1874	0.0407	

Note: For the remainder of the problem we focus on the model involving all of the predictors.

(e) Fit the model with all of the predictors in STATA or SAS, obtaining the estimates on both the logit scale and the odds ratio scale. Overall do these variables help explain how likely a child is to have their ear

infections cleared in 14 days? Carefully write the null and alternative hypotheses mathematically and in words, obtain the test statistic and p-value and give your real-world conclusions using $\alpha = .05$. Verify the test statistic given in the printout for the likelihood-ratio chi-squared test by calculating it by hand from the log-likelihoods for the null model (fit in part (a)) and the full model (fit here).

$$H_0: \beta_1 = \beta_2 = \beta_3 = \beta_4 = \beta_5 = 0$$

 $H_A: At least 1 of the \beta_i \neq 0$

The null hypothesis states that there is no statistically significant relationship between any of the predictors with the response variable of infection clearance. The alternative hypothesis states that there is a statistically significant relationship between at least one of the predictors with the response variable of infection clearance.

0.1018 Max-rescaled R-Square 0.1357

R-Square

Testing Global Null Hypothesis: BETA=0					
Test	Chi-Square	DF	Pr > ChiSq		
Likelihood Ratio	21.7887	4	0.0002		
Score	20.8702	4	0.0003		
Wald	10 1931	Δ	0.0007		

Note: The following parameters have been set to 0, since the variables are a linear combination of other variables as shown.

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq		
Intercept	1	0.9117	0.5423	2.8263	0.0927		
antibiotic	1	-0.6693	0.3008	4.9499	0.0261		
numears	1	0.0440	0.3219	0.0186	0.8914		
undertwo	1	-1.6596	0.4422	14.0892	0.0002		
twotofive	1	-0.5109	0.3707	1.8995	0.1681		
sixplus	0	0					

(f) Do these variables explain a lot of the "variability" in how likely an ear infection is to clear? Explain briefly. What are the practical implications of this statement for treating ear infections in small children with antibiotics?

These variables do not explain a lot of the "variability" in how likely an ear infection is to clear, as the requested R-Square and Max-rescaled R-square from the model output are both 0.1018 and 0.1347 respectively, meaning that these variables only explain around 10.2% (13.5%, if using max-rescaled R-square) of the variability in how likely an ear infection is to clear. This statement has practical implications that indicate there might be little clinical difference in the likeliness of infection clearance despite any relationship observed between the independent predictors and the response. It may also indicate there are other variables that could better explain the likeliness of ear infection clearance that are not included in this dataset.

(g) Give a brief interpretation of the odds ratio for the **antibiotic** variable and its confidence interval and show how you would compute these values from the parameter estimates table (i.e. the output on the logit scale.) After adjusting for age and number of infected ears does it seem that the type of antibiotic matters and if so which one is superior? Explain briefly.

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The odds ratio for antibiotic is e^{-0.6693} = 0.512, and the 95% confidence interval for the odds ratio is \left[e^{-0.6693} \pm z_{0.975} * 0.3008\right] = \left[e^{-1.2589}, e^{-0.0797}\right] = \left[0.2840, 0.9234\right]
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After adjusting for age and number of infected ears, it seems like the type of antibiotic does matter since the 95% confidence interval does not include 1, and we can see that antibiotic 0 - Amoxicillin is superior since the parameter estimate is negative, indicating that there is a difference of -0.6693 in the log odds if antibiotic 1 - Ceftriaxone is assigned instead of antibiotic 0 - Amoxicillin.

Odds Ratio Estimates							
95% Wald Effect Point Estimate Confidence Limits							
antibiotic	0.512	0.284	0.923				
numears	1.045	0.556	1.964				
undertwo	0.190	0.080	0.452				
twotofive	0.600	0.290	1.241				

(h) Does our model show whether either antibiotic helps cure ear infections? Explain briefly.

Our model shows that the amoxicillin antibiotic helps cure ear infections better since the parameter estimate is negative, indicating a decrease in the log odds by -0.6693 if ceftriaxone was the assigned anithiotic. This predictor for antibiotic is significant at the $\alpha = 0.05$ significance level (p = 0.0261).

(i) After adjusting for the other factors, does age impact the likelihood of an infection clearing within 14 days? Perform an appropriate test, writing out the null and alternative hypotheses mathematically and in words, obtain the likelihood ratio chi-squared statistic and give your real-world conclusions using $\alpha = .05$. (Note: There are several different ways to do this. If you use the indicator versions of the age group variables, picking one as the reference, you can either fit the models with and without the indicators and manually compute the likelihood ratio test statistic or else you can do the test as a follow-up contrast to the full model fit from part (e). If you use **agegroup** and specify it as a class variable you will get the test for free as part of your output. You only need to show one of the versions but make sure you understand how to do each of them!)

$$H_0: \beta_4 = \beta_5 = \beta_6 = 0$$

 $H_A: At \ least \ 1 \ of \ the \ \beta_4, \beta_5, \beta_6 \neq 0$

The null hypothesis states that age does not explain anything about the likelihood of an infection clearing within 14 days beyond what is explained by the other variables (antibiotic and numears). The alternative hypothesis states that age contributes significant predictive power to the model and explains beyond what is already explained by the other variables.

Conducting a likelihood ratio test by doing both a follow-up contrast using the indicator full model, and by fitting the class variable full model, the likelihood ratio chi-squared test statistic is $\chi^2 = 15.2158$ with a p-value of p = 0.0005. Since the p-value falls below the significance level of $\alpha = 0.05$, we reject H_0 and conclude that age contributes significant predictive power to the model after adjusting for other factors. Another interpretation is that at least one age group has a statistically significant relationship with the likelihood of infection clearance in children.

Contrast Test Results						
Wald						
Contrast	DF	Chi-Square	Pr > ChiSq			
age	2	15.2158	0.0005			

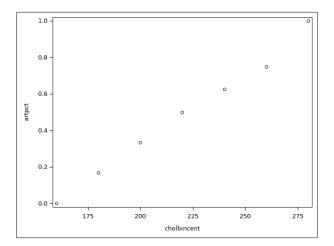
Type 3 Analysis of Effects						
Wald						
Effect	DF	Chi-Square	Pr > ChiSq			
antibiotic	1	4.9499	0.0261			
numears	1	0.0186	0.8914			
agegroup	2	15.2158	0.0005			

7. Arteriostatistics?:

A cardiologist at my favorite school, the University of Calculationally Literate Adults, is interested in the factors that lead to arteriosclerosis (hardening or blockage of the arteries, often due to the build-up of fatty plaques on the artery walls.) She is also studying medications for lowering cholesterol levels since high cholesterol is a risk factor for this disease. Her response variable is whether or not a person has arteriosclerosis (Y = 1 for yes and Y = 0 for no). Her possible predictor variables are age (in years), weight (in pounds), blood cholesterol level (measured in mg/dL) and whether the person has a family history of coronary artery disease (1 = yes, 0=no).

(a) First the investigator wants to look at the relationship between cholesterol level and arteriosclerosis. To help her visualize the relationship, bin the cholesterol variable by intervals of length 20 (i.e. 150-170 mg/dL, 179-190 mg/dL, etc.), find the proportion of subjects in each bin with arteriosclerosis, and plot your results. (Note that I have calculated the bin percentages for you in the data set but the commands are shown below in case you are interested in how I got them from the raw data. You can do the plot by hand or on the computer, whichever you prefer.) Based on your plot does it appear that there is a significant relationship in the expected direction?

Based on my plot, it does appear that there is a significant relationship in the expected direction (we expect that number of subjects with arteriosclerosis would be higher in bins representing the higher intervals of cholesterol level).



(b) Formally check your conclusions from part (a) by fitting a logistic regression of disease status on cholesterol level and performing an appropriate test. Write the null and alternative hypotheses mathematically and in words and give your real-world conclusions using $\alpha = .05$. Note that you can get two different test statistics from your printout-the likelihood ratio chi-squared statistic and the Wald test Z statistic. In general the Wald test is somewhat less stable (and tends to be more conservative) than the likelihood ratio test. Is that the case here and does it make any practical difference to your conclusions? (Note: To get an adequate number of decimal places on the p-values to check this you may need to use a distribution calculator-see the command instructions below.)

 $H_0: \beta_1 = 0$

 $H_A:\beta_1\neq 0$

The null hypothesis states that cholesterol does not have a statistically significant relationship with arteriosclerosis

disease status. The alternative hypothesis states that cholesterol has a statistically significant relationship with arteriosclerosis disease status.

The likelihood ratio chi-squared test statistic is $\chi^2 = 20.067$ with a p-value of p < 0.0001. The Wald test Z test statistic is Z = 12.278 with a p-value of p = 0.0005. Since in both test statistics the p-value falls below the significance level of $\alpha = 0.05$, we reject H_0 and conclude that cholesterol level has a statistically significant relationship with arteriosclerosis. The p-values here do indicate that the Wald test is more conservative than the likelihood ratio test, but it makes no practical difference to our conclusions here since both are well below the significance level threshold.

R-Square	0.3306	Max-rescaled R-Square	0.4429

Testing Global Null Hypothesis: BETA=0								
Test Chi-Square DF Pr > ChiSq								
Likelihood Ratio	20.0667	1	<.0001					
Score	17.2741	1	<.0001					
Wald	12.2773	1	0.0005					

Analysis of Maximum Likelihood Estimates							
Standard Wald Parameter DF Estimate Error Chi-Square Pr > ChiSq							
Intercept	1	-10.1767	2.8890	12.4090	0.0004		
cholesterol	1	0.0454	0.0130	12.2773	0.0005		

(c) Now fit the full model including age, weight, cholesterol level and family history. Does cholesterol remain a significant predictor? Explain what you think has happened and confirm your suspicions by (i) obtaining the correlations among the various predictors and (ii) refitting the model without the potential confounder. Note: For the remainder of the problem use the second model from part (c) with the confounder variable removed!

In this full model including age, weight, cholesterol level, and family history, cholesterol does not remain a significant predictor (p=0.11). This is possibly due to the inclusion of a confounder variable that is highly correlated with the cholesterol variable. Looking at the correlation coefficients for the predictors, there is a significant correlation between **cholesterol** and **weight** that may be confounding our analysis with a coefficient of 0.834 (p < .0001). When we exclude this potential confounder of **weight** from our model, we restore the significance of the parameter estimate of **cholesterol** which is similar to our results in the original simple logistic regression model.

R-Square 0.4322 Max-rescaled R-Square 0.5791

Testing Global Null Hypothesis: BETA=0								
Test Chi-Square DF Pr > ChiSq								
Likelihood Ratio	28.2984	4	<.0001					
Score	22.7636	4	0.0001					
Wald	13.5048	4	0.0091					

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq			
Intercept	1	-9.0790	4.0307	5.0735	0.0243			
cholesterol	1	0.0728	0.0457	2.5382	0.1111			
age	1	-0.0624	0.0441	2.0006	0.1572			
weight	1	-0.0334	0.0473	0.4985	0.4801			
familyhistory	1	0.8795	1.6516	0.2835	0.5944			

Pearson Correlation Coefficients, N = 50 Prob > r under H0: Rho=0									
	cholesterol age weight familyhistory								
cholesterol cholesterol	1.00000	-0.00052 0.9972	0.83557 <.0001	0.45295 0.0010					
age	-0.00052	1.00000	-0.01981	0.08321					
age	0.9972		0.8914	0.5656					
weight	0.83557	-0.01981	1.00000	-0.03078					
weight	<.0001	0.8914		0.8320					
familyhistory	0.45295	0.08321	-0.03078	1.00000					
familyhistory	0.0010	0.5656	0.8320						

R-Square 0.4264 Max-rescaled R-Square 0.5713

Testing Global Null Hypothesis: BETA=0								
Test Chi-Square DF Pr > ChiSq								
Likelihood Ratio	27.7881	3	<.0001					
Score	22.5183	3	<.0001					
Wald	13.1265	3	0.0044					

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq			
Intercept	1	-8.0047	3.6324	4.8563	0.0275			
cholesterol	1	0.0431	0.0153	7.9386	0.0048			
age	1	-0.0621	0.0429	2.0974	0.1475			
familyhistory	1	1.9274	0.8200	5.5251	0.0187			

(d) Find the probability that a 50 year old with a cholesterol level of 250 and no family history of coronary artery disease would have arteriosclerosis. You may do this either using the computer package or by hand. You only need to include one method with your homework but make sure you know how to do it both ways!

The probability that a 50 year old with a cholesterol level of 250 and no family history of coronary artery disease would have arteriosclerosis is approximately 0.418, or around 41.8%.

By hand:

$$p = \frac{\exp(\beta_0 + \beta_{age} * 50 + \beta_{cholesterol} * 250)}{1 + \exp(\beta_0 + \beta_{age} * 50 + \beta_{cholesterol} * 250)}$$

Contrast Estimation and Testing Results by Row									
Standard Wald Contrast Type Row Estimate Error Alpha Confidence Limits Chi-Square Pr > ChiSq									
age50chol250	71							0.1637	0.6857

(e) Give a brief interpretation of the confidence interval for the odds ratio of the age variable. What does this interval tell you about the usefulness of the age variable in this model?

The 95% confidence interval for the odds ratio of the age variable is [0.864, 1.022]. This means that an odds ratio for age of 0.940 with a confidence interval of 0.864 to 1.022 suggests that there is a 95% probability that the true odds ratio for age would fall in the range of 0.864 and 1.022 assuming there is no confounding or bias. This interval suggests that the calculated odds ratio for age may not be statistically significant in the model, as it contains values both above and below 1. Thus, we are uncertain on whether age would increase or decrease the odds of arteriosclerosis happening with the specified level of 95% confidence.

Odds Ratio Estimates								
95% Wald Effect Point Estimate Confidence Limits								
cholesterol	1.044	1.013	1.076					
age	0.940	0.864	1.022					
familyhistory	6.872	1.377	34.279					

(f) Give your best estimate of and a 95% confidence interval for the odds ratio comparing the likelihood of arteriosclerosis for a person with high cholesterol (250 $\rm mg/dL$) to an otherwise equivalent person with normal cholesterol (200 $\rm mg/dL$). Show your work.

$$OR_{250\ vs\ 200mg/dL} = e^{\beta_{cholesterol}*50} = (e^{\beta_{cholesterol}})^{50}$$

$$= (OR_{1mg/dL})^{50}$$

$$= 1.044^{50}$$

$$= 8.610$$
 $CI\ for\ OR_{250\ vs\ 200mg/dL} = [1.013^{50}, 1.076^{50}] = [1.908, 38.960]$

(g) Suppose a medication could lower your cholesterol by 50 mg/dL. The manufacturer would like to claim that this would cut your odds of arteriosclerosis in half. Based on your answer to (f) is this a reasonable claim? If not, what is the strongest claim they could make with 95% (really 97.5%) confidence?

Based on my answer to (f), this is not a reasonable claim. The lower bound of the CI is 1.908, indicating that the odds of arteriosclerosis are 90.8% higher for a 50 mg/dL increase cholesterol level. This also means that the odds of arteriosclerosis decrease by 1/1.908, or 52.4% lower in individuals for a 50 mg/dL drop in cholesterol level. However, the upper bound of the CI is 38.960, indicating that the odds of arteriosclerosis are 3796% higher for a 50 mg/dL

increase in cholesterol level, and also that the odds of arteriosclerosis decrease by 1/38.960, or 2.57% lower for a 50 mg/dL drop in cholesterol level. That means the strongest claim they could make at that specified confidence is that the odds of arteriosclerosis will decrease by 2.57%.

(h) Optional Bonus: In ordinary least squares regression, the estimated change in Y associated with a 1 unit change in X is constant (this is what it means for the relationship to be linear). Similarly, if you have an indicator variable for a characteristic, the difference between people who do and do not have the characteristic is constant, regardless of the levels of the other variables (at least as long as there are no interactions!) However this is not the case for the predicted probabilities in a logistic regression. To illustrate this point use the code provided in the commands section below to create predicted probabilities of arteriosclerosis as a function of cholesterol for people who do and do not have a family history of the disease, assuming age is fixed at 50 years old, and plot these predicted probabilities on a common graph. Give a brief clinical description based on your graph of how these variables jointly affect the predicted probability of the disease.

Assuming age is fixed at 50 years old, the plot of predicted probabilities of arteriosclerosis as a function of cholesterol for people with and without family history shows that the effect of family history (difference between the two predicted probability curves) is largest in individuals with a cholesterol range of around 210-260 mg/dL and is less impactful (smaller difference between the two predicted probability functions) at the lower and upper bounds of the cholesterol levels recorded. While cholesterol level will increase the predicted probability of arteriosclerosis, the presence of family history will accelerate the logistic function and increase the predicted probabilities quite significantly in that range of 210-260 mg/dL.

