Identifying High Risk Pregnancies in the Developing World

Group 3
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Summary

In this document we provide information regarding whether prenatal care biometric measurements on symphasis-fundal height (SFH) and other anthropometric values in pregnant women in developing countries might allow construction of a model of potential low birth weight, small for gestational age, or preterm birth outcomes. The data used for this analysis come from a cohort study of 755 pregnant women in Western Cape, South Africa. Because not every mother necessarily will come to prenatal care more than once, two models were tested: one that uses only minimum SFH:gestational age ratio as a predictor of interest, with covariate measures of age, parity, height, and smoking status, and another that adds mean SFH change as a second predictor of interest. SFH measurements were taken between 20 and 30 weeks, to ensure early detection of potential adverse outcomes. Model 1 shows an adjusted odds ratio of 0.017 for minimum SFH to gestational age ratio, with a 95% confidence interval of <0.001 to 0.934, and a p value of 0.046. Model 2 shows an adjusted odds ratio of 0.007 for minimum SFH to gestational age ratio, with a 95% confidence interval of <0.001 to 0.501, and a p value of 0.023. Though the model results are significant, we encourage caution, as mean values of the primary predictor of interest (minimum SFH to gestational age ratio) are very close across adverse and regular pregnancies, and test results may be very subject to measurement error.

Comment [A1]: There are not that many, list them

Comment [A2]: for what purposes—this matters in selection of models We need to know that we are focusing on 20-30 weeks

Comment [A3]: low income

Comment [A4]: How many relevant measurments did we have on each woman

Comment [A5]: What does this mean in real life? What are your units?

Comment [A6]: Provide more interpretation than this.

Background

Preterm delivery (delivery prior to 37 weeks of gestation), small for gestational age (birth size/weight <10th percentile for gestational age) and low birth weight (birth weight <2500g) are known causes of infant mortality especially in developing countries. Approximately 1 out of every 5 African women loses a baby compared to 1 out of 125 women in wealthier countries (WHO report, 2005). Prenatal care is a critical determinant in healthy pregnancies and deliveries, and has repeatedly been shown to improve pregnancy outcomes including term delivery and normal birth weight babies. Unfortunately, pregnant women in developing countries do not have access to the same quality and quantity of prenatal care that women in developed countries enjoy, resulting in many high risk pregnancies that go unidentified until delivery. One major challenge specific to developing countries is to develop risk assessment methods that are cost effective, not overly technical, and that can be easily disseminated to all types of care centers.

Questions of Interest

The ultimate goal of this project is to develop an approach to identify pregnancies during the second trimester (20-30 weeks) at high risk of adverse pregnancy outcomes such as low birth weight (LBW),

preterm delivery, and small-for-gestational age (SGA) in the developing world. Such a method would enable high-risk mothers to be referred to clinics capable of providing a higher level of care than they would otherwise receive in their standard community clinic, and decrease the risk of these adverse pregnancy outcomes. In order to identify pregnant women at high risk, we first will determine whether standard biometric measurements commonly obtained during prenatal care visits are associated with the above outcomes. Second, we will discuss potential measurements that can be considered in future predictive models.

Primary Specific Aim:

The aim of this study is to determine whether measurements on symphysis fundal height (SFH) taken between week 20 and week 30 of gestation can assist in the identification of women at high risk for an adverse pregnancy outcome (birth weight < 2500gms or gestational weeks < 38 or SGA).

Comment [A7]: Why did you eliminate weight from consideration?

Description of Data

A cohort study of 755 pregnant women in a peri-urban area of Western Cape, South Africa was undertaken in order to provide the data for this study. The sample population was limited to pregnant women with singleton pregnancies. Each woman was followed from enrollment at approximately 22 weeks gestation through delivery. Given that known risk factors for poor pregnancy outcomes include smoking, pre-eclampsia, maternal poor nutrition, and parity, study measurements at enrollment included participant smoking status, height, age, and parity. At every prenatal clinic visit following enrollment, each women's weight and SFH were obtained. Outcome measures taken at delivery included infant birth weight, infant sex, gestational age at delivery, and an indicator for small for gestational age (SGA).

Comment [A8]: How often did they occur? (This is a convenience sample, so just note that they followed clinical care guidelines in advising visits, and women came when they did.

Study Inclusion and Exclusion Criteria:

- Women able to provide written informed consent
- Women with viable singleton pregnancy with no known fetal abnormalities at the time of enrollment
- Women willing to be followed from the time of enrollment through delivery
- Women normotensive with no known signs or symptoms of pre-eclampsia/eclampsia at the time of enrollment

Statistical methods

Potential covariates of interest obtained at enrollment and throughout the study period included smoking, parity, age, SFH, height, and weight. Smoking was captured as a dichotomous outcome (0=non-smoker; 1=smoker). Parity was recorded as a discrete variable and subsequently transformed

into a binary variable (0=no prior delivery; 1=prior delivery) for analysis. Age was documented as a continuous variable in years. SFH in cm was obtained at each prenatal visit and for the analyses was converted into a minimum SFH:gestational age ratio, as well as evaluated as a mean SFH change over the study period. Height was measured at enrollment and recorded in cm. Weight was measured at enrollment and at each subsequent prenatal visit, and recorded in kg. Number of prenatal visits was also noted. Baby's sex, birth weight, and gestational age were all captured at the time of delivery.

Comment [A9]: Why?

Comment [A10]: Presumably for the 20-30 week period

Comment [A11]: Certainly the number of prior visits would be known at each visit, though we could not know the number of future visits.

Our primary outcome measure was a binary indicator of any adverse birth outcome: low birth weight (<2500gr), pre-term delivery (prior to the 38^{h} week of gestation) or SGA (below the 10th percentile of birth weight for the gestational age at which birth occurs).

Our predictors of interest were the minimum SFH:gestational age ratio and the mean change in the slope coefficient between successive measurements of SFH, for each woman from 20 to 30 weeks gestation.

Univariate analyses were performed for each predictor of interest and all covariates hypothesized to be associated with our primary outcome of interest. Descriptive statistics for study participants grouped by the primary outcome measure of any adverse birth outcome were reported.

In addition to these descriptive statistics, the results of bivariate statistic tests (Chi-Square for categorical, T-test for continuous variables) to identify which variables were associated with adverse birth outcomes, were described. Missing data were reported for each covariate of interest.

Our primary statistical inferential hypothesis was that the odds of an adverse birth outcome will be higher among women with smaller minimum SFH:gestational age ratios and smaller average weekly SFH changes, when considering measurements made between week 20 and week 30 of gestation. We tested this hypothesis using a total of two logistic regression models with our constructed binary adverse pregnancy variable as the outcome and minimum SFH:gestational age ratio as the predictor of interest in the first analysis. Mean change in SFH was added as the predictor of interest in the second analysis. This two modeling approach was hypothesized to allow the option of risk assessment with one visit, and potentially more accurate risk assessment on subsequent visits. Mother's weight was excluded from all analyses due to the imprecision of the measurement. In addition, baby's sex was excluded from all analyses based on our prior knowledge that the central tendencies of the distributions of weight and size for male and female are similar. Furthermore, the number of prenatal visits was excluded from all models due to an inability to operationalize it given that the ultimate predictive model's purpose is to determine a threshold for referral to high risk centers.

Comment [A12]: Imprecision? How? (There were indeed some data errors, but you need to describe)

Comment [A13]: central tendencies being equal does not mean it would have no predictive value

Comment [A14]: Actually, there are even more major scientific reasons to exclude this variable—it is conditioning on the future.

The final models were specified as follows:

Model 1: logit (adverse pregnancy outcome) = B0 + B1(minimum SFH:gestational age ratio) + B2(age) + B3(age^2) + B4(parity) + B5(height) + B6(smoking status)

Comment [A15]: what does this mean?

Model 2: logit (adverse pregnancy outcome) = B0 + B1(mean SFH change) + B2(minimum SFH:gestational age ratio) + B3(age) + B4(age^2) + B5(parity) + B6(height) + B7(smoking status)

Given that we anticipated a u-shaped curve where younger and older women might be more at risk than women in their 20s and 30s, we included both linear and quadratic terms for maternal age. An odds ratio with the associated 95% confidence interval was reported for each model and statistical significance was defined at an alpha level of 0.05.

Plots of fitted versus predicted values, AIC/BIC, and dfbetas were utilized to assess model adequacy. Stata 12 SE was used for all statistical analyses.

Results

Descriptive statistics

As can be seen in table 1 displaying participant characteristics grouped by adverse vs. non-adverse pregnancy, there are statistically significant differences between groups in the measures of minimum SFH:gestational age ratio and weekly change in SFH (p values of 0.023 and 0.008 respectively). However, the mean values for SFH:gestational age ratio are very similar, only differing by 0.02 centimeters.

Comment [A16]: I can agree with the use of your composite outcome measure. But we would still be interested in each of the three outcomes descriptively, at least to the extent of knowing which predominated.

Comment [A17]: per week?

The measure of overall weekly weight change was determined not to be significant. Additionally, height and weight were found to be significantly different between groups (with non-adverse pregnancies possessing the larger means). A significantly higher mean age was seen in non-adverse pregnancies, as well as a significantly lower percentage of smokers. There was no significant difference in baby's sex or parity.

In the disposition table (table 2), showing trends in gestational age and visits by adverse or non-adverse, it can be seen that gestational age at enrolment, visits between weeks 20 and 30 weeks, and 2+ visits between weeks 20 and 30 are all not statistically different across groups. This is encouraging for an analysis that uses these measures taken during this period as predictors of interest. It should be noted that the total visits were significantly less for adverse pregnancy, but this may not be surprising given that adverse pregnancies were shorter. It is important to note that 97 participants across the two groups (nine in the adverse group) had fewer than 2 visits.

Comment [A18]: very good to check and note

Figure 1 stratifies individual pregnancies by adverse vs. non-adverse outcome, and shows gestational week versus either overall weight gain or SFH. It can be seen from the lowess smoother lines that overall weight change appears to be parallel across groups, but SFH clearly shows a trend of lower SFH in the adverse group over the 20 to 30 week period. This shows visual evidence of the respectively insignificant and significant associations with these variables noted from table 1.

Comment [A19]: You need to comment more on this and what it means relative to your question. The parallel lines suggest risks that are more associated with baseline factors than with pregnancy factors. The differing slopes (and I would use that word explicitly) suggests something happening around week 25 or later. This may argue that only the latest values are really of interest, and we may not have too many of them. (I view the SFH graph as having coincident lines that diverge at later times. Had you produced a table of SFH measurement by EGA, you would see this as well.)

Model analysis

Table 3 shows the results of our two models, both in unadjusted form, and adjusted for minimum SFH:gestational age ratio, parity, age, age^2, height, and smoking. In model 1, as might be expected from the above-noted descriptive statistics, there were significant trends for the potential confounders age, height, and smoking, but not parity. Most significantly, the minimum SFH:gestational age ratio

Comment [A20]: so you fit four, not two, logistic regression models

showed an odds ratio of 0.014, with a 95% confidence interval of <0.001 to 0.548 before correction (p=0.023). After correction, the same odds ratio rises slightly to 0.017, with a 95% confidence interval of <0.001 to 0.934 – still a significant value (p=0.046). Model 2, adding weekly change in SFH to the model, does not show a significant trend for weekly change, but the resultant odds ratio for minimum SFH:gestational age ratio in the adjusted model with weekly change incorporated as well is a smaller, more significant value than in model 1 (OR=0.007; 95% CI <0.001 to 0.501; p=0.023).

Comment [A21]: what groups are you comparing? This is an amazingly low odds ratio (but not amazingly low given the physiologic impossible groups you are comparing)

Comment [A22]: What about results that pertain to its predictive capability.

Discussion

In comparing the performance of our two models, in Figure 2, we plotted the minimum SFH:gestational age ratio versus the fitted probability values of an adverse pregnancy predicted by each model. The resultant probabilities of adverse outcomes were higher for model 2, suggesting better model performance. Additionally, the AIC and BIC values determined for model 1 were AIC = 0.7744 and BIC = -4005.048 and the same values for model 2 were AIC = 0.7680, BIC = -3668.318, also suggesting higher performance for model 2. We performed an analysis that iteratively adds and removes variables from a model to optimize its AIC and BIC values, and the results were very close to our *a priori* selected models - 0.770 and -4016.892 for model 1 and 0.765 and -3679.166 for model 2 respectively. This suggests that our choices were good as regards fitting the data. We also graphed ROC curves for both models in Figure 3. The resultant areas under the curve for each model again show higher performance of model 2 (0.7037 vs. 0.6807). We compared these values versus the AUCs for the iteratively optimized models with lower AIC/BIC values, and determined that, while our *a priori* models didn't match the optimized models for AIC/BIC, they actually outperformed the optimized models in their ROC curves. The comparative area under the curve for our model 1 versus the optimized model 1 is 0.6807 vs. 0.6801, and the area under the curve for our model 2 versus the optimized model 2 is 0.7037 versus 0.7016. This gives further support for our model 2 in particular performing well.

Comment [A23]: I don't buy this. It could be that the second model was wrong.

Comment [A24]: What does any of this mean? If you can't explain it, don't put it in.

Comment [A25]: I don't think this says that at all.

Comment [A26]: You never told us about ROC curves in the methods. What are they, anyway? What do they tell you?

Comment [A27]: None of this tells us a thing about how the model is addressing our question of interest. What we would want to know is how well it predicts who is at high risk and whether it can be operationalized.

However, it is important to keep in mind that the minimum SFH:gestational age ratio in model 1 shows a wide 95% confidence interval for its odds ratio, so determining an acceptable diagnostic cut-point in using this model would likely be a challenge, and this model will be the only one available to women who attend prenatal care only once. Additionally, because the mean values for SFH:gestational age ratio only differ by 0.02 centimeters, it may be that measurement error could have a significant effect on the performance of both models.

To investigate the effect of influential points on model performance, Figure 4 shows DFbeta plots of minimum SFH:gestational age ratio, age, height, and weekly change in SFH. It can be seen that there is more influence in the extremes of minimum SFH:gestational age ratio, in lower maternal ages, and in low maternal heights. The data were reanalyzed twice with removal of influential points. The first reanalysis removed the single greatest outlier in height, and resulted in an a change in the estimated OR for minimum SFH:gestational age ratio from 0.017 to 0.015, with a narrower 95% confidence interval (from <0.001 to 0.934, to <0.001 to 0.851) and a more significant p value (0.046 down to 0.041). An additional analysis was done also removing the two influential points that produce a DFbeta close to 0.1.

Comment [A28]: What are DFbeta plots? You never told us about them, either.

Comment [A29]: Why would you do this? What does it tell you.

This also resulted in desirable changes in model 2: the adjusted estimated OR for the minimum SFH:gestational age ratio rose from 0.007 to 0.008, but the 95% confidence interval narrowed substantially (<0.001 to 0.501 vs. <0.001 to 0.256) and the p value became more significant (0.006 dropping to <0.001). In summary, much precision was gained by removing this influential points, and care should be used to ensure that all collected values are accurate if these models were to be used for prediction. It also appeared that three of the mothers may have had miscoded variables on SFH (mothers 50896496, 51405108, 52869468). However, these values were left in.

One further not about missing values: 46 women did not have measurement between week 20 and week 30, however, only 2 of those 46 experienced adverse outcomes. Therefore, it appears that those women who do not appear during this period may generally be healthier than average.

In summary, it may be that these models could serve as predictive models, but caution should be used due to the small differences in SFH measurements across groups, and the effect that influential values can have. We suggest checking these models on a large validation data set before making any final judgments on their predictive use.

Comment [A30]: These are "desirable" changes only if they got us closer to the truth. Did they? How could you possible know?

Comment [A31]: I strongly urge you to not interpret analysis of influential points this way in the future for any problem. But it is even more egregious to do such things when prediction is the ultimate goal.

Comment [A32]: This would have been important to put in the results.

Comment [A33]: This should have gone in the methods and in the results

Comment [A34]: How well would this model do predictively? Who would it have told us to send to high risk clinics?

Tables/Figures

Table 1: Participant Characteristics

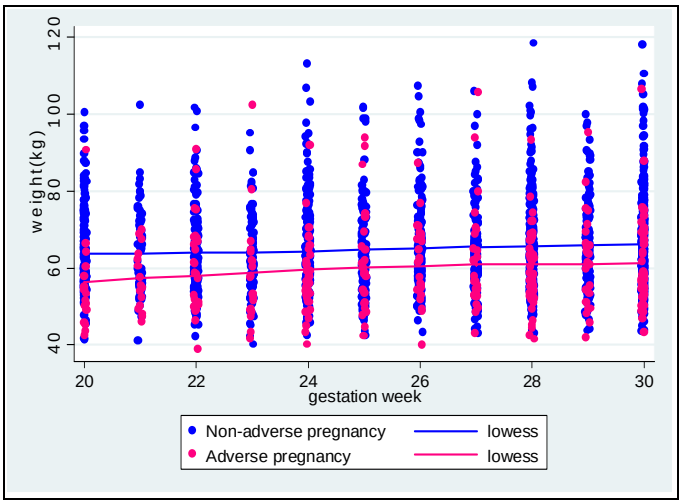
	Adverse pregnancy (n=105)					Non-adverse pregnancy (n=647)					
Variable	n (missing)	%	Mean	Std Dev	Min, Max	n (missing)	%	Mean	Std Dev	Min, Max	P value
Minimum SFH/GA ratio	102 (3)		0.91	0.07	0.76, 1.12	603 (44)		0.93	0.06	0.6, 1.10	0.023
Weekly change in SFH (cm)	96 (9)		0.91	0.44	-1.50, 2.00	559 (88)		1.04	0.4	-1.40, 3.55	0.008
Weekly change in weight (Kg)	96 (9)		0.39	0.33	-1.50, 1.42	559 (88)		0.42	0.37	-1.00, 3.00	0.327
Height (cm)	99 (6)		154.6	5.9	142.0, 172.0	647 (0)		157	6.5	106.0, 176.0	<0.001
Weight at enrollment (Kg)	105 (0)		57.9	10.7	38.6, 100.0	647 (0)		63.4	11.9	40.5, 119.0	<0.001
Age (yrs)	105 (0)		23.8	4.9	16, 35	647 (0)		24.9	5.4	14, 43	0.044
Smoke	45 (1)	43%				186 (0)	29%				0.003
Female baby	60 (1)	58%				308 (0)	48%				0.056
Parity >0	56 (0)	53%				404 (0)	62%				0.076

Table 2: Disposition Table

	Adverse pregnancy (n=105)					Non-adverse pregnancy (n=647)					
Variable	n (missing)	Percent	Mean	Std Dev	Min, Max	n (missing)	Percent	Mean	Std Dev	Min, Max	P value
GA at enrollment (weeks)	105 (0)		21.9	3.4	18, 39	647 (0)		22.6	4.1	15, 36	0.062
Total visits (n)	105 (0)		7.1	2.7	2, 14	647 (0)		7.8	2.2	2, 13	0.009
Visits between GA 20 and 30 weeks (n)	105 (0)		3.1	1.2	0, 6	647 (0)		2.9	1.3	0, 8	0.133
2+ visits between GA 20 and 30 weeks	96 (0)	91%				559 (0)	86%				0.154

Figure 1: Graphical descriptive characteristics of POI measures from week 20 to week 30

Comment [A35]: more jittering would make this plot way better



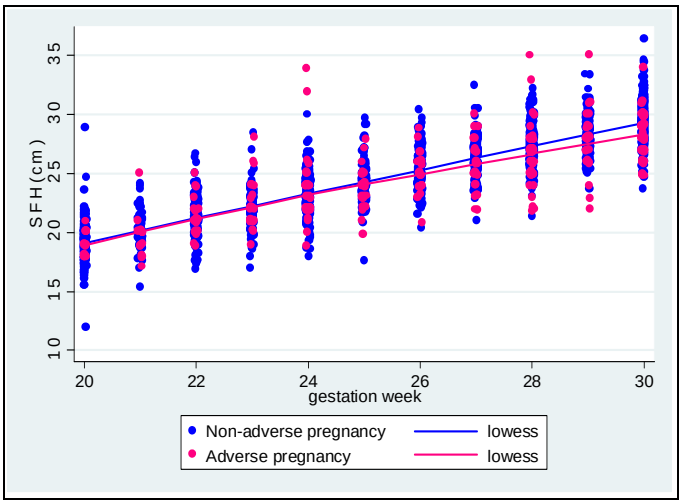


Table 3: Statistical inference

Model 1 – Any adverse pregnancy regressed on min SFH/GA ratio

	Unadjusted				Adjusted*			
Variable	n	OR	95% CI	P value	n	OR	95% CI	P value
Minimum SFH/GA ratio	705	0.014	(<0.001, 0.548)	0.023	699	0.017	(<0.001, 0.934)	0.046
Parity >0	752	0.69	(0.45, 1.04)	0.077	699	0.72	(0.40, 1.29)	0.264
Age (yrs)	752	0.96	(0.92, 1.00)	0.051	699	1.07	(0.73, 1.55)	0.739
Age (yrs^2)	752	1.00	(1.00, 1.00)	0.044	699	1.00	(0.99, 1.00)	0.595
Height (cm)	746	0.95	(0.91, 0.98)	0.002	699	0.95	(0.91, 0.98)	0.003
Smoker	751	1.89	(1.24, 2.89)	0.003	699	1.98	(1.26, 3.11)	0.003

* adjusted for minimum SFH/GA ratio, parity, age, age^2, height, and smoking. AIC = 0.7744, BIC = -4005.048

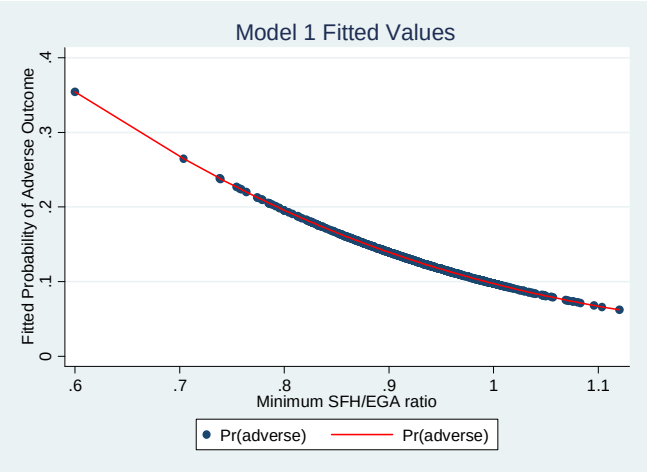
Model 2 – Any adverse pregnancy regressed on min SFH/GA ratio & weekly change in SFH

	Unadjusted				Adjusted*			
Variable	n	OR	95% CI	P value	n	OR	95% CI	P value
Minimum SFH/GA ratio	705	0.014	(<0.001, 0.548)	0.023	649	0.007	(<0.001, 0.501)	0.023
Weekly change in SFH (cm)	655	0.48	(0.29, 0.79)	0.004	649	0.48	(0.29, 0.81)	0.006
Parity >0	752	0.69	(0.45, 1.04)	0.077	649	0.64	(0.36, 1.15)	0.138
Age (yrs)	752	0.96	(0.92, 1.00)	0.051	649	1.18	(0.79, 1.77)	0.408
Age (yrs^2)	752	1.00	(1.00, 1.00)	0.044	649	1.00	(0.99, 1.00)	0.315
Height (cm)	746	0.95	(0.91, 0.98)	0.002	649	0.94	(0.91, 0.98)	0.002
Smoker	751	1.89	(1.24, 2.89)	0.003	649	1.91	(1.19, 3.05)	0.007

* adjusted for minimum SFH/GA ratio, weekly change in SFH, parity, age, age^2, height, and smoking. AIC = 0.7680, BIC = -3668.318

Figure 2: fitted values

Comment [A36]: These graphs provide little info to me.



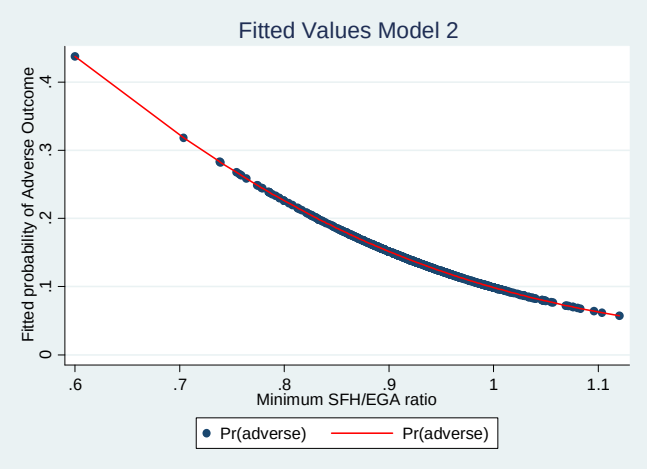
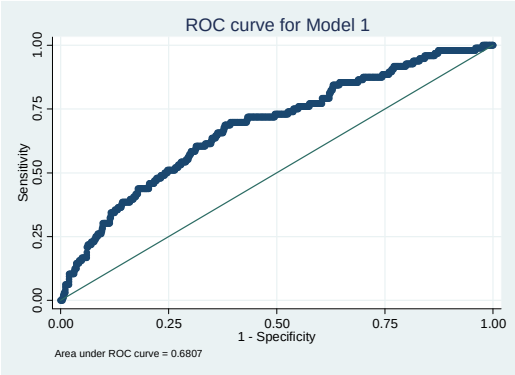
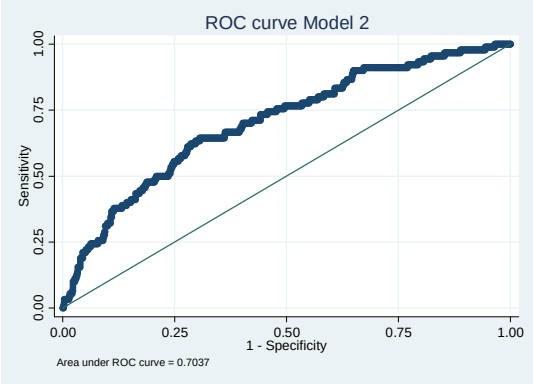


Figure 3: ROC curves for both models

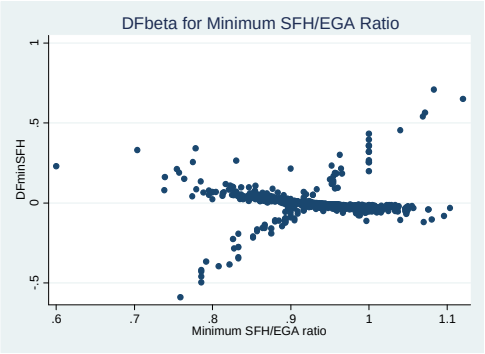


AUC = 0.6807



AUC = 0.7037

Figure 4: influential point diagnosis


DFbeta for Minimum SFH/EGA Ratio
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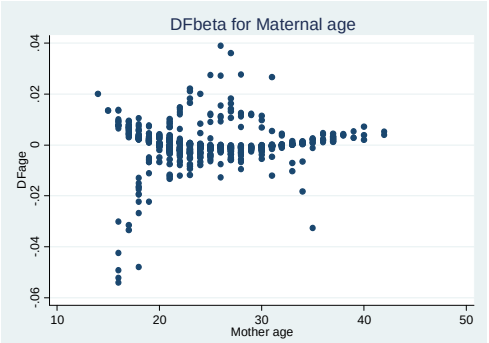
.6
.7
.8
.9
1
1.1
Minimum SFH/EGA ratio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30
40
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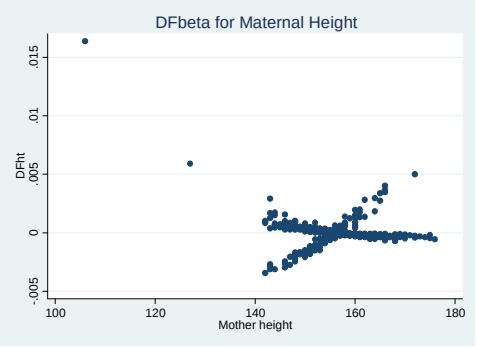
Mother age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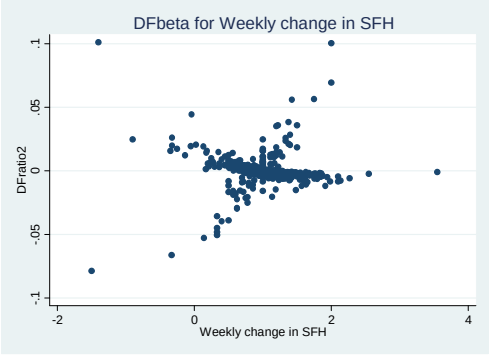
.005
0
-.005
100
120
140
160
180
Mother height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4
Weekly change in SFH