Group 6
BIOSTAT 536
Final Paper

Summary

Pregnant women attending a prenatal clinic in South Africa were followed to determine if changes in maternal weight and/or fetal growth in the second trimester differ between those who do and do not have an adverse pregnancy outcome, and to consider whether these profiles are predictive of an adverse outcome. Seven hundred and fifty-five pregnant women with singleton pregnancies who were unable to afford private insurance were followed from enrollment to delivery, with an average time of follow-up of 22 weeks gestation. Each woman's weight and SFH were recorded at the time of enrollment and at each clinic visit. Parity, smoking status, the sex of the baby, the baby's birth weight and the gestational age (week) of delivery were also documented.

Based on a logistic regression analysis controlling for the mother's baseline characteristics and sex of the infant, we estimate that greater increases in SFH during weeks 20-30 are associated with smaller odds of an adverse pregnancy outcome (OR: 0.49, 95% CI: 0.29, 0.84). Similarly, we estimate that greater increases in weight during weeks 20-30 are associated with smaller odds of an adverse pregnancy outcome (OR: 0.71, 95% CI: 0.35, 1.44).. The association between SFH profile and adverse pregnancy outcome was found to be significant at the 0.025 significance level (P-value 0.005). The association between weight profile and adverse pregnancy outcome was not found to be significant at the 0.025 significance level (P-value 0.173).

Our analysis provides strong evidence of an association between smaller changes in SFH during weeks 20 to 30 of gestation and adverse pregnancy outcomes in the study population. However, the study population is different from other groups of young women in several key aspects. As a result, these results may not generalize to other populations of young pregnant women. We recommend further study to investigate the predictive ability of SFH profiles for early referral of at risk mothers to additional prenatal care.

Comment [a1]: Start with the overall goal

Comment [a2]: what weeks of gestation

Comment [a3]: how often were the visits during the interval of greatest interest

Comment [a4]: how did you actually measure this? It was actually rates

Comment [a5]: units?

Comment [a6]: units?

Comment [a7]: But what other populations are we interested in

Comment [a8]: Why do you recommend this? Is it based on the results of your analysis. I argue I have enough info in this dataset to tell me this is not worthwhile. So if you are just saying this by force of habit, we did not need you to report on this analysis. This is where we were before doing anything.

Background

Perinatal mortality continues to be a significant public health problem for many developing nations where access to prenatal care services is limited or not available. In 2005, the World Health Organization (WHO) reported that 20% of African women lose an infant in their lifetime while less than 1% of women from developed nations lose an infant. The second leading cause of

infant mortality, after congenital malformations, is due to medical problems related to a short gestational period and low birth weight.

It is well known and documented that adequate prenatal care received during pregnancy can prevent pre-term births and low birth weight babies. The overall goal of this study was to develop a low cost and low technology method to identify pregnant women at risk for delivering pre-term or underweight babies at an early stage, so that they may be referred for vital additional prenatal care. Factors such as maternal weight and fetal size, as measured by symphysis-fundal height (SFH), have been used to spot symptoms or indicators of an adverse pregnancy outcome. This study was designed to follow women treated at a prenatal clinic to determine whether maternal weight and fetal size were associated with, and potentially predictive of, an adverse pregnancy outcome.

Scientific Questions of Interest

1. Do weight profiles and/or SFH profiles during pregnancy differ between women who do and do not have adverse pregnancy outcomes?

2. Are weight profiles and/or SFH profiles predictive of adverse pregnancy outcomes?

Keeping in mind the end goal of developing a predictive model for adverse pregnancy outcomes, this report investigates the association between adverse outcomes and both SFH and maternal weight in the 20-30 week gestational age period. This period approximates the second trimester, and a strong association with data from this period could lead to prediction of adverse outcomes in time for clinical intervention in the third trimester. Because the relationship between second trimester maternal weight changes and SFH changes and adverse outcomes is unknown, we set out to make use of data from the full time period under investigation, and specifically examine how changes in maternal weight and SFH over the weeks of interest are associated with adverse outcome. Therefore, the primary question we have addressed in this report is: “Is change in maternal weight and/or SFH between 20 and 30 weeks gestation associated with any adverse pregnancy outcome, after controlling for known and suspected risk factors?”

Study Design, Source of Data and Variable Definition

A longitudinal cohort study was conducted in Western Cape, South Africa. The study sample consisted of 755 pregnant women with singleton pregnancies who were unable to afford private insurance. The women were followed from enrollment to delivery with an average of 22 weeks of

follow-up time. Each woman's weight and SFH were recorded at the time of enrollment and at each subsequent clinic visit. Other characteristics that were collected at baseline include parity and smoking status, and at delivery the sex of the baby and the baby's birth weight and gestational age (week) were recorded.

We examined missing data by evaluating the intensity of the follow-up data. We looked for differences in the in the number of clinical visits during the 20-30 week timeframe and compared to the entire study period (15-44 gestational weeks). We found that the number of clinical visits matched the number of records for each woman and that the amount of missing data was negligible (results reported in Table 2). Two visit records were missing estimated gestational age and were dropped form the dataset prior to analysis. No subject had multiple missing observations within our time period of interest. There were no identifiable patterns to missingness and we assume data is MCAR.

As with all observational studies, it is possible that there is confounding by both measured and unmeasured variables. Confounding by measured variables is assessed on our analyses, but the possibility of residual confounding remains. When analyzing adverse birth outcomes, it is important to consider the effect of known predictors, including maternal blood pressure, preexisting conditions like diabetes, and both chronic (TB, HIV, malaria) and acute (UTI) infections, as well as prior maternal history of adverse outcome. Unfortunately, none of these are included in the dataset.

Predictors of Interest

- *SFH* Δ*:* The SFH profile for women in the sample was estimated as the difference between the final and first SFH measurements between 20 and 30 weeks, divided by the observed change in gestational age between 20 and 30 weeks
    - *SFH:* The size of the fetus was estimated using the SFH, a measure of the distance (cm) from the symphysis of the pelvic bone to the top of the uterus. It is expected to increase during the course of pregnancy
- *Weight* Δ*:* The weight profile for women in the sample was estimated as the difference between the final and first weight measurements between 20 and 30 weeks, divided by the observed change in gestational age between 20 and 30 weeks
    - *Weight:* Each woman's weight (kg) weight was recorded at all visits

Comment [a9]: I presume you are only calling data missing if you have some missing observation on a recorded visit. Of course, subjects who did not show up for some visits will not have any record at all. Did you look at this?

Comment [a10]: I'll note that by virtue of the scope of our question, "unmeasured confounding" is indicative of other variables that might be useful in prediction, and "confounding among the available data" just means that our SFH and weight gain during pregnancy variables might not be adding much info over the baseline characteristics

Comment [a11]: very nice (and very important) to define these so explicitly

Comment [a12]: what did you do when there were fewer than two measurements? How often did that occur?

Outcome

- *Adverse outcome (ADV):* ADV is a binary variable defined as newborns born pre-term, low birth weight, or small for their gestational age
  - *Pre-term birth (PTB):* PTB is a binary variable defined as newborns born prior to 37 weeks of gestational age
  - *Low birth weight (LBW):* LBW is a binary variable defined as newborns whose weights are less than 2,500 grams at birth
  - *Small for gestational age (SGA):* SGA is a binary variable defined as newborns whose size or weight is below the 10th percentile for their estimated gestational age at birth

Covariates

- *Mother's age*: Mother's age is a categorical variable defined as <20, 20-24, 25-30, and 31+ years
- *Smoking status:* Smoking status is a binary variable defined as 1=smoker, 0=non-smoker
- *Sex of the infant:* The sex of the infant is a binary variable defined as 1=male, 0=female
- *Mother's height*: Mother's height is a categorical variable defined as <153cm, 153 - >160 cm, 161 - 167cm, and 168+ cm
- *Parity*: Parity is the number of prior deliveries and is categorized as 0, 1, 2, and 3+

Statistical Methods

Hypothesis and Conceptual Model

Our hypothesis is that maternal weight and SFH are associated with adverse pregnancy outcomes; with a smaller ratio of SFH change and maternal weight gain being positively associated with adverse birth outcomes after controlling for potential confounding. Figure 1 illustrates the theoretical relationships between the outcome, predictors of interest, and covariates in our conceptual model. Those who are underweight, with less than the expected weight gain for their pregnancy, are known to have worse pregnancy outcomes than those who are normal weight. Similarly, smaller fetal growth during pregnancy is likely to lead to smaller babies at birth, and so we believe that abnormally low SFH changes are more likely to have adverse pregnancy outcomes than those with larger SFH changes. Smoking can cause adverse pregnancy outcomes, but the effect of smoking on weight and SFH are not well understood. For this analysis, we assume that there is an association between smoking and maternal weight/SFH. Having more pregnancies (parity) is associated with fewer adverse pregnancy outcomes and with maternal weight gain

Comment [a13]: My comments on the categorization of these variables relates to the regression modeling. I do not think this a good thing to do with most of these variables. However, for descriptive purposes it can be useful.

Comment [a14]: Why did you categorize these? And why at these ages? There are some good scientific reasons why you might do this, but if this is just something you always do, that is not good.

Comment [a15]: And I cannot think of a reason that I would have categorized this variable

Comment [a16]: And I would probably not categorize this variable

Comment [a17]: You are correct that this is nearly a tautology when viewed over the entire pregnancy. But adverse fetal growth may not be linear. (In fact, my analysis suggests that the IUGR only starts showing up around 27 weeks EGA, but of course, I cannot put good confidence bounds on that estimate.)

because it becomes more difficult to lose weight after each pregnancy. We assume that as weight increases from multiple pregnancies SFH also changes with higher parity. Age is known to be associated with adverse pregnancy outcomes in both the highest and lowest age categories and with weight gain (as one gets older, the metabolism slows down and weight gain occurs). We assume that age is also associated with SFH. We are uncertain about the relationship between infant sex and the predictors of interests, but being born male is negatively associated with low birth weight. By including these potential confounders in our conceptual model and controlling for them in the analysis we are able to make comparisons of SFH and weight profiles within groups of similar pregnant women.

Comment [a18]: but this is a different issue than weight gain during a pregnancy. Perhaps it just shifts the baseline.

Comment [a19]: It may be associated with fetal growth, and SFH is a proxy for that. It

Comment [a20]: Differences between the sexes is most pronounced in the upper tails of the BW distribution.

Descriptive Statistics

In Table 1 we present descriptive statistics for all the subjects in aggregate and within subgroups defined by adverse outcome. This includes the number of observations, the average for continuous variables, the proportions for categorical variables, and minimum, median, and maximum observations when appropriate.

Table 2 shows the descriptive statistics of the intensity of follow-up and depicts issues with attrition (common in a longitudinal study) and missing data. With this table we can see variations in the number of clinical visits during the 20-30 week timeframe and compare them to the entire study period (15-44 gestational weeks). This information allows us to determine when women enter and drop out of prenatal care. To evaluate available data throughout this timeframe and to see how much missing information we have the number of records for gestational age, maternal weight and maternal SFH are displayed. We compared the number of clinical visits with the number of maternal weight records to see if there were more clinical visits than maternal weight records.

Comment [a21]: A very useful table would have been to give the descriptive statistics for SFH and maternal weight by EGA within outcome groups. You would have seen how the sample sizes differed, as well as seeing how the trends in SFH and maternal weight changed over time. There would only have been 11 lines in such a table, so

Comment [a22]: we do not expect uniform distribution of clinic visits.

Comment [a23]: I do not think I understand. Aren't you just looking at missing data, given that each recorded clinic visit is a line in the data file.

Table 3 shows descriptive statistics for adverse pregnancy outcome by SFH and weight quartiles. To assess the potential associations between our outcome and our predictors of interest, these descriptive statistics were computed both for the overall sample and within subgroups defined by quartiles of the two predictors of interest. Quartiles were chosen because there is no commonly used threshold or categories for appropriate weight gain in the population this sample is drawn from. The descriptive statistics presented are the number of observations, the number of missing observations, and the proportion of subjects who experienced any type of adverse outcome. Table 4 shows the makeup of our grouped adverse outcome variable by presenting descriptive statistics

for low birth weight (<2,500g), small for gestational age, and pre-term birth and the change in mean weight and mean SFH in the adverse outcome group.

Inferential Statistics

To assess the association between weight/SFH change between 20 and 30 weeks gestation and adverse pregnancy outcomes, we fit a logistic regression model to the data. Any adverse pregnancy event was used as the outcome and the predictors of interest used were SFH change and weight change. We estimated the crude odds ratio for the predictors of interest and an adjusted estimate controlling for variables that were presented in the conceptual model (Figure 1)

Robust sandwich standard errors and 95% confidence intervals were computed for each coefficient estimate. Because we have two predictors of interest, we performed hypothesis tests for the coefficients associated with these predictors. To account for multiple testing, we performed both tests at a Bonferroni corrected significance level of 0.025. For each predictor, we tested the hypothesis that the coefficient associated with the predictor of interest was greater than or equal to zero. Rejection of this hypothesis will be taken as evidence of a positive association between smaller values of the respective predictor of interest and adverse pregnancy outcome. Coefficient estimates, standard errors, 95% confidence intervals, and p-values from the fitted model are presented in Table 5. All analyses were conducted in STATA version 12 and R 3.0.2.

Comment [a24]: Because we are ultimately interested in prediction, and because estimates and CI become more difficult, I probably would not do adjustment for multiple comparisons and I would just remark on that fact.

Comment [a25]: I am betting you did not do adjusted CI (I would not either)

Results

From Table 1 you can see that women in this study differ in some important ways from study populations in other areas of the world. The majority of women in the sample were in their twenties (29.8% between 20-24 years, 33.3% between 25-30 years) with few women giving birth in their 30s and 40s. Women in this population are also remarkably short in stature, with 24% of women in the sample being less than 153 cm in height, and another 57% of women being between 153 and 163 cm. The average weight gain per week was 0.42 kg, with a standard deviation of 0.36kg and the average SFH gain per week was 1.02 cm, with a standard deviation of 0.41cm, ranging from -1.50cm to 3.00cm. The majority of women (70%) reported having 1 or fewer prior pregnancies. Thirty percent of women reported that they smoke, and 50% of the babies delivered were males.

Comment [a26]: Yes, that is why we are asking our question in the population we care about. The women living in a resource poor environment in SAfr.

There is a large amount of missingness in our predictors of interest, due to the requirement that each subject have at least two observations in our time period of interest in order to calculate

change in weight and SFH. Therefore, two dummy variables were created to evaluate whether adverse outcomes differ among women who are missing compared to those who are not missing for change in SFH and change in weight variables. No significant associations were found between adverse outcomes and the missing dummy variables.

Fewer than 1 in 5 women enrolled in the study experienced an adverse outcome (13.9%), and compared to women without an adverse outcome, more women who experienced an adverse outcome were smokers (43.3% vs. 28.7%). Women with adverse outcomes also tended to be younger, shorter, giving birth for the first time, giving birth to a girl, and gained less weight and had smaller SFH values than women without adverse outcomes.

Table 2 shows that the number of clinical visits and the number of maternal weight records match for the group without adverse outcomes, while the adverse outcome group is missing a few maternal variables. Both outcome groups attended an average of 3 clinic visits during the time frame under investigation, with women experiencing adverse outcomes having a higher maximum number of visits in this time. Women without adverse outcomes had more visits overall. .

Table 3 shows the distribution of adverse outcome in groups defined by predictor quartiles. While adverse outcomes are almost evenly distributed in maternal weight change quartiles, SFH change quartiles show a distinct trend, with the lower quartiles including the majority of adverse outcomes.

The breakdown of the adverse outcome variable is shown in Table 4. Almost half of the adverse outcome cases experience both low birth weight and SGA, with the other half of cases being split between SGA only and having all three adverse outcomes. Mean changes in SFH and weight were similar for low birth weight and SGA and SGA only cases, but cases with all three outcomes had both the smallest change in maternal weight and the largest change in SFH.

After exclusions for missing data, there were 645 subjects available for analysis in our logistic regression model.

Based on our regression analysis, we estimate that the odds ratio between women who differ in SFH difference by 1 unit is 0.49 (SE 0.13). Thus women with greater SFH difference are estimated to have lower odds of an adverse pregnancy outcome. A 95% confidence interval for this estimate

Comment [a27]: Nice to do. I would not rely too much on significance testing, because you cannot prove equality.

I do note that an argument can be made that we are trying to learn how to use the clinic data that we have on the women who come to clinic, so the women who do not come are not of as much of an issue. (Of course, if they are different and later start coming, our predictive model will not be good. But that is the issue with all predictive models.)

Comment [a28]: Good to present. And I will go even further. Note that everyone who is LBW is called SGA. This is not how it should be. I do not think they defined SGA very well. But for the focus of your analyses, that is not really an issue.

Comment [a29]: Aren't these adjusted analyses? Why did you not interpret them as an adjusted analysis?

Comment [a30]: How does this 1 unit compare to a reasonable range of data? I think you should use a lower comparison difference. And then tell us what the unit is in the real world.

is (0.29, 0.84). Based on a P-value of 0.005, we have sufficient evidence at the 0.025 significance level to reject the null hypothesis.

Based on our regression analysis, we estimate that the odds ratio between women who differ in weight difference by 1 unit is 0.71 (SE 0.26). Thus women with greater weight difference are estimated to have lower odds of an adverse pregnancy outcome. A 95% confidence interval for this estimate is (0.35, 1.44). Based on a P-value of 0.173, we lack sufficient evidence at the 0.025 significance level to reject the null hypothesis.

Comment [a31]: adjusted for what?

Estimated odds ratios for adverse outcome for both SFH change and weight change were very similar to crude estimates, suggesting that these measures are not confounded by the covariates included in the multivariate model. After adjusting for potential confounding four variables were found to be significantly associated with odds of adverse outcome: SFH change, maternal smoking, infant sex and being taller than 168 cm.

Comment [a32]: Did you drop some of the height categories? Are you reporting only selected parts of a dummy variable? If we were doing proper prediction and validation r

Discussion

These results come from an observational study from a small sample with limited data, and so should be interpreted with caution. We see in the results a highly significant association between larger SFH change between 20 and 30 weeks and lower odds of adverse outcome even after adjusting for covariates. Without more data we cannot be certain that residual confounding is not present, but this does suggest that clinicians may be able to track changes in an expectant woman's SFH during the second trimester to anticipate adverse birth outcomes. The significant associations with infant sex and maternal smoking are consistent with existing literature. If our analysis had not found these associations the data and any other results would be more suspect.

Comment [a33]: I disagree. We know that men and women have different average heights, but using height to predict sex is pretty bad.

Did you do any analysis to see how any threshold of SFH might separate the groups? I think you will find there is way too large an overlap between the groups to be useful predictions.

SFH is an appealing predictor because it should be less correlated to features of a woman's body which vary regionally (height, weight and pelvic width, for example) and so this measure may be useful in a wide range of populations around the world. But this strength of the predictor brings up an important weakness in the outcome variable; namely that birth weight and size also vary around the world, and using standard measures for adverse outcome developed in the United States and Europe may be misclassifying infants in this African study population. It would be worth continuing to follow women in this study and their infants to assess how accurate these adverse birth outcomes are in predicting childhood morbidity and mortality.

In addition to its potential unsuitability to the sample, our outcome measure is a grouped variable combining three related but not identical adverse outcomes. It may be that the relationships identified as significant or nonsignificant in our model would change if a more fine-grained outcome measure were chosen. Some predictors may be better at predicting a specific adverse outcome.

Comment [a34]: But our ultimate action is the same no matter which adverse outcome they have

The sample population may also limit the generalizability of these results. The women in the sample are generally quite short and quite young, and may have important unrecognized characteristics that affect the results of these analyses. Many of the women also lacked multiple visits during the time period of interest and could not be included in the analysis. The reason these women were unable to attend clinic visits during their second trimester could affect our results.

Finally, these results characterize the change in weight and SFH that occur over a ten-week period that approximates the second trimester, but a prediction based on a shorter or earlier time frame would be even more useful in identifying high-risk pregnancies for early intervention. A different time frame may lead to different results.

Comment [a35]: Good to note, especially because in practice, there may be a tendency for people to always use two measurements from successive visits, while you used visits that had maximal separation in our data.

The analyses we describe above do not directly address the secondary scientific question of interest: the utility of SFH change in predicting adverse pregnancy outcomes. The overlap in SFH change between women with and without adverse outcomes is substantial, and if this pattern is found in other populations even a strong association may not lead to a valuable predictive tool. However, the results do show that women with smaller changes in SFH between weeks 20 and 30 of their gestation are more likely to give birth to a baby with an adverse outcome, and this result is not confounded by any of the covariates in our multivariate analysis. This association, coming as it does from data primarily obtained in the second trimester, provides a reasonable foundation for additional study. With access to an enhanced dataset that includes additional maternal information, such as blood pressure and health status, we could more fully explore the strength of this association.

Comment [a36]: Okay, so now you comment on it. You could have quickly quantified how bad this overlap is.

Table and Figures

Table 1. Demographic and clinical characteristics of sample overall and by outcome

	N	Percent	Mean	SD	Min	Max
Overall Sample	**755**					
Maternal Age <20	131	17.4	17.92	1.20	14	19
20-24	225	29.8	21.60	1.01	20	23
25-30	251	33.3	26.27	1.65	24	29
31+	148	19.6	33.20	2.95	30	43
Missing	*0*					
Maternal Height (cm) <153	186	24.8	148.58	4.52	106	152
153 - <158	226	30.2	155.14	1.28	153	157
158 - <163	201	26.8	159.74	1.46	158	162
163+	136	18.2	165.82	2.82	163	176
Missing	*0*					
Avg. Maternal weight Δ (kg/wk.)	653	-	0.42	0.36	-1.50	3.00
Missing	*102*					
Avg. SFH Δ (cm/wk.)	655	-	1.02	0.41	-1.50	3.55
Missing	*100*					
Parity 0	293	38.8	n/a	0.49	0	0
1	240	31.8	n/a	0.47	1	1
2	133	17.6	n/a	0.38	2	2
3+	89	11.8	n/a	0.32	3	6
Missing	*0*					
Maternal Smoking = yes	231	30.8	n/a	0.46	1	1
Missing	*4*					
Infant Sex= male	383	51.0	n/a	0.50	1	1
Missing	*4*					
Adverse Outcome Group	105	13.9	n/a	0.35	1	1
Maternal Age <20	25	23.8	17.84	1.11	16	19
20-24	30	28.6	21.67	0.92	20	23
25-30	35	33.3	26.43	1.54	24	29
31+	15	14.3	32.20	1.61	30	35
Maternal Height (cm) <153	35	35.4	148.37	2.89	142	152
153-160	36	36.4	155.14	1.36	153	157
161-167	19	19.2	159.58	1.43	158	162
168+	9	9.1	165.67	2.60	163	172
Avg. Maternal weight Δ (kg/wk.)	91	-	0.38	0.34	-1.50	1.43
Avg. SFH Δ (cm/wk.)	93	-	0.91	0.45	-1.50	2.00

Table 1. Demographic and clinical characteristics of sample overall and by outcome [cont'd]

	N	Percent	Mean	SD	Min	Max
Parity 0	49	46.7	n/a	0.50	0	0
1	32	30.5	n/a	0.46	1	1
2	14	13.3	n/a	0.34	2	2
3+	10	9.5	n/a	0.29	3	6
Maternal Smoking = yes	45	43.3	n/a	0.50	1	1
Infant Sex= male	44	42.3	n/a	0.50	1	1
No Adverse Outcome Group	650	86.1	n/a	0.35	0	0
Maternal Age <20	106	16.3	17.94	1.23	14	19
20-24	195	30.0	21.58	1.02	20	23
25-30	216	33.2	26.25	1.66	24	29
31+	133	20.5	33.32	3.05	30	43
Maternal Height (cm) <153	151	23.2	148.62	4.83	106	152
153-160	190	29.2	155.14	1.27	153	157
161-167	182	28.0	159.76	1.47	158	162
168+	127	19.5	165.83	2.85	163	176
Avg. Maternal weight Δ (kg/wk.)	562	-	0.42	0.37	-1.00	3.00
Avg. SFH Δ (cm/wk.)	462	-	1.04	0.40	-1.40	3.55
Parity 0	244	37.5	n/a	0.48	0	0
1	208	32.0	n/a	0.47	1	1
2	119	18.3	n/a	0.39	2	2
3+	79	12.2	n/a	0.33	3	6
Maternal Smoking = yes	186	28.7	n/a	0.45	1	1
Infant Sex= male	339	52.4	n/a	0.50	1	1

Table 2. Intensity of follow-up of sample overall and by outcome

	20-30 Week Gestation						15-44 Weeks Gestation (Total)					
	N*	Sum	Mean	SD	Min	Max	N*	Sum	Mean	SD	Min	M
Overall												
# Clinical Visits	709	2186	3.08	1.06	1	8	755	5849	7.75	2.28	2	14
# Gestational Age Records	709	2186	3.08	1.06	1	8	755	5847	7.74	2.28	2	14
# Maternal Weight Records	709	2181	3.08	1.06	0	8	755	5836	7.73	2.29	1	14
# Maternal SFH Records	709	2181	3.08	1.06	1	8	755	5840	7.74	2.29	1	14
Adverse Outcome												
# Clinical Visits	103	321	3.12	1.14	1	8	105	747	7.13	2.67	2	13
# Gestational Age Records	103	321	3.12	1.14	1	8	105	747	7.11	2.68	2	13
# Maternal Weight Records	103	316	3.07	1.17	0	8	105	736	7.01	2.68	1	13
# Maternal SFH Records	103	316	3.07	1.16	1	8	105	740	7.05	2.73	1	13
No Adverse Outcome												
# Clinical Visits	606	1865	3.08	1.04	1	6	650	5100	7.85	2.20	2	14
# Gestational Age Records	606	1865	3.08	1.04	1	6	650	5100	7.85	2.20	2	14
# Maternal Weight Records	606	1865	3.08	1.04	1	6	650	5100	7.85	2.20	2	14
# Maternal SFH Records	606	1865	3.08	1.04	1	6	650	5100	7.85	2.20	2	14

***N refers to the number of subjects in the sample, and sum is the total number of visits**

Comment [a37]: This seems a rather complicated way to tell us about missing EGA and Wt. Why do we care about the sum? (We can compute it from N and the mean if we really had to have it)

Table 3. Distribution of the adverse outcome by predictor

	Overall N	Adverse outcome N	Missing	Prevalence of adverse outcome (%)
Overall	706	105	3	14.6
Weight Δ quartile 1	161	17	1	10.6
Weight Δ quartile 2	163	30	1	18.4
Weight Δ quartile 3	162	25	0	15.4
Weight Δ quartile 4	164	19	1	11.6
SFH Δ quartile 1	162	33	1	20.4
SFH Δ quartile 2	163	30	1	18.4
SFH Δ quartile 3	162	15	1	9.3
SFH Δ quartile 4	165	15	0	9.1

Comment [a38]: I am not a fan of using quartiles, but I can understand your argument that you did not have any scientific threshold to use.

That, however, does not justify your failure to tell us what the quartiles corresponded to. This is egregious.

Table 4. Breakdown of grouped outcome by specific adverse outcomes

	Count	%	Mean weight Δ	Mean SFH Δ
Low birth weight (<2500g) Only	0	0	---	---
Small for Gestational Age Only	27	26	0.37	0.92
Pre-term Birth Only	0	0	---	---
LBW & SGA Only	50	49	0.39	0.89
LBW & Preterm Only	0	0	---	---
SGA & Preterm Only	0	0	---	---
LBW & SGA & Preterm	24	23	0.24	1.2
Total		**100**		

Table 5. Crude and adjusted odds ratios of adverse outcome

	Estimate OR (crude)	SE	95% CI	P-value	Estimated OR (adjusted)*	SE	95% CI	P-value
SFH Δ	**0.48**	**0.42**	**(0.29, 0.80)**	**0.003**	**0.49**	**0.13**	**(0.29, 0.84)**	**0.005**
Weight Δ	0.74	0.64	(0.41, 1.34)	0.16	0.71	0.26	(0.35, 1.44)	0.172
Maternal Smoking^	**1.83**	**0.40**	**(1.2, 2.80)**	**0.006**	**1.80**	**0.45**	**(1.10, 2.93)**	**0.019**
Infant Sex	**0.67**	**0.15**	**(0.44, 1.03)**	**0.065**	**0.62**	**0.15**	**(0.38, 1.00)**	**0.0495**
Maternal Age <20^	1.70	0.49	(0.96, 3.00)	0.0695	1.46	0.50	(0.75, 2.85)	0.27
25-30	1.09	0.29	(0.65, 1.83)	0.759	1.30	0.44	(0.67, 2.52)	0.442
31+	0.78	0.28	(0.39, 1.57)	0.488	0.88	0.49	(0.30, 2.60)	0.813
Maternal Height (cm)^ <153	1.18	0.31	(0.70, 1.99)	0.5273	1.40	0.40	(0.79, 2.45)	0.246
161-167	0.54	0.16	(0.30, 0.98)	0.0424	0.59	0.20	(0.30, 1.15)	0.123
168+	**0.36**	**0.14**	**(0.17, 0.78)**	**0.010**	**0.38**	**0.17**	**(0.16, 0.90)**	
Parity^ 1	0.71	0.18	(0.43, 1.2)	0.168	0.71	0.23	(0.38, 1.33)	
2	0.57	0.19	(0.30, 1.1)	0.085	0.57	0.26	(0.23, 1.40)	
3+	0.63	0.23	(0.30, 1.3)	0.209	0.60	0.34	(0.20, 1.84)	
Intercept	---	---	---	---	0.46	0.19	(0.21, 1.02)	

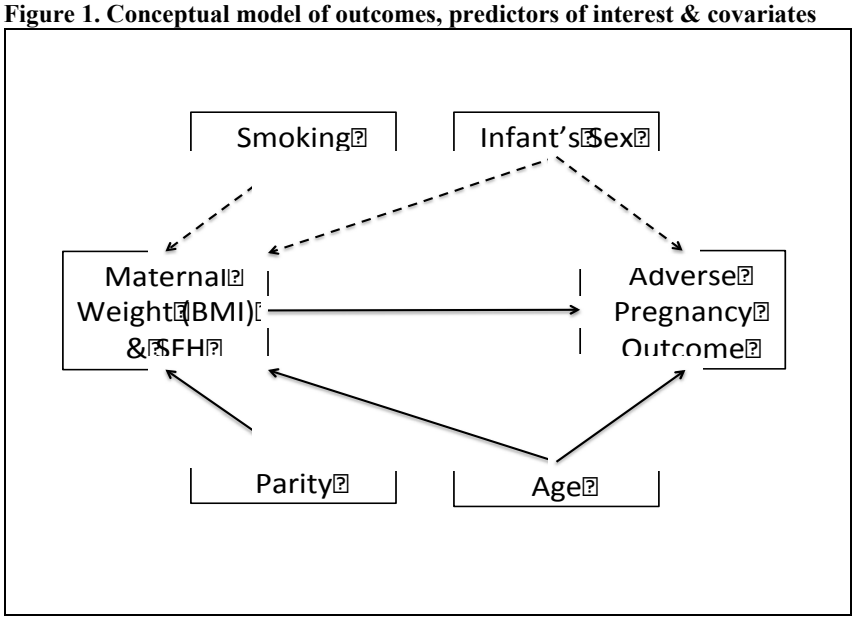
*Adjusted for parity, maternal age, maternal smoking, infant sex, maternal height

^ Referent categories are: non-smokers, female infants, maternal age 20-24, maternal height 154-160 cm, primipara.

Comment [a39]: This is a very risky thing to do. You have a single variable (height) and three coefficients. Do not highlight the inference associated with one of several dummy variables computed from the same variable unless that had been totally pre-specified.

Comment [a40]: Certainly there is an intercept in the unadjusted model, too

Figure 1. Conceptual model of outcomes, predictors of interest & covariates



Note: Solid lines depict the associations between variables. For variables in which the relationship is unknown, the relationships of what we might expect are depicted with the dotted lines.