To: Scott Emerson, MD PhD

From: Group 9

Date: December 15, 2013

Subject: Identifying problem pregnancies in the developing world

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Below is the preliminary analysis of the predictions of the problem pregnancy dataset. We have listed assumptions which went into the analysis in the Background and Description sections. Please let us know which, if any, of these assumptions are incorrect or not appropriate for this population. We look forward to answering any questions you may have. It has been a pleasure working with you and this data.

Summary

A total of 755 pregnant women attending prenatal care in Western Cape, South Africa, were followed through delivery to determine risk factors for adverse birth outcomes (preterm birth, low birth weight, and small for gestational age). Only women with singleton pregnancies were enrolled. Maternal weight and symphysis fundal height (SFH) were measured at each prenatal visit.

From week 20 to 30 of gestation, women with an increase in SFH, measured using either the minimum ratio of SFH to Estimated Gestational Age (EGA) or the slope of SFH over all week 20–30 prenatal visits, were less likely to have adverse birth outcomes (OR:0.0014, 95% CI 0.00036–0.55 & OR:0.49, 95% CI 0.30-0.82). The association between SFH slope and adverse birth outcome remained after adjusting for age, BMI, parity, height, smoking status, and number of prenatal visits (OR:0.51, 95% CI 0.30–0.87). The association did not hold for SFH ratio after adjustment. Change in mother's weight between visits as measured by either the weight difference between two consecutive visits or the slope of weight over prenatal visits between weeks 20 and 30 was not significantly associated with any adverse birth outcomes.

Comment [a1]: Lead off with a statement of the overall goal.

Comment [a2]: low income

Comment [a3]: how many women were available for these analyses

Comment [a4]: These OR are so low, because your unit of comparison (1 cm/week difference in rate) is a rather large difference for your data. It would have been better to choose a value that was maybe 1 or 2 SD difference.

Comment [a5]: What was the value of these measures for predicting high risk?

Background

Proper prenatal care can improve birth outcomes, and identifying pregnancies at a higher risk of an adverse birth outcome is an important step in ensuring women and newborns receive the levels of care they need. Prenatal clinics in limited resource settings do not provide standard diagnostic services such as ultrasound to every mother. Instead, these resources are reserved for women who are at higher risk for preterm, low birth weight (LBW), or small for gestational age (SGA) infants. In these cases, low-cost measures to distinguish lower and higher risk pregnancies are needed to ensure that women at higher risk for adverse outcomes are properly referred to specialty clinics. Of greatest interest are measurements taken between 20 and 30 weeks of gestation since this time period is far enough along in the pregnancy to predict adverse birth outcomes yet early enough to take corrective action. Two common values measured at prenatal clinic visits are the mother's weight and the symphysis fundal height (SFH).

Questions of Interest

1. Is there evidence that weight profiles and/or SFH profiles over pregnancy differ between women who do and do not deliver preterm, LBW, and SGA babies? Of greatest interest would be the association between

measurements made between 20–30 weeks EGA and the three adverse pregnancy outcomes, in order to be able to refer high-risk women to more intense prenatal care.

2. Is it possible, using measurements taken prior to week 30 of pregnancy, to develop a model which accurately distinguishes between women who will and will not have growth retarded babies?

Description of the Data

The study followed 755 pregnant women who attended at least one prenatal care visit prior to delivery. At enrollment, information on each woman's age (years), height (cm), smoking status (yes/no), and number of prior deliveries (parity) was collected. During prenatal visits, estimated gestational age (weeks) along with maternal weight (kg) and SFH (cm) were measured. At delivery, the infant's sex, birth weight (grams), and gestational age (weeks) was recorded, and whether the infant is small for gestational age or not was determined (SGA: yes/no).

Not available in this dataset are any pre-existing health conditions of the mother which may also affect birth outcome. Infection such as HIV, tuberculosis, syphilis, and malaria, as well as chronic conditions such as diabetes and high blood pressure can increase the risk of adverse birth outcomes. Additional factors such as nutrient deficiencies of the mother and intimate partner violence may also play a role.

Useful information not available in this dataset:
1. Blood pressure measurements during prenatal visits
2. History of adverse outcomes from previous pregnancies
3. Maternal pre-pregnancy weight to determine pre-pregnancy obesity
4. Chronic and acute health conditions discussed above

Statistical Methods

Data analysis was conducted using Stata 12.1. Characteristics of pregnant women were summarized in aggregate (Table 1) and by pregnancy outcome (Table 2). P values, when reported, were two-tailed using a 5% significance level.

Data definitions and cleaning

In other studies, maternal age and BMI each have had u-shaped relationships with adverse birth outcome, hence quadratic forms of these variables were included in the models. We expect the risk of adverse birth outcome to be higher when a woman is very young or older than the ideal age range for pregnancy and when she is either under or over the normal BMI range (18.5–24.9). Because there is no pre-pregnancy weight measurement in the dataset, the mother's weight at her first prenatal visit was used as a baseline for pre-pregnancy weight. Body Mass Index (BMI) was calculated as the weight (kg) at first visit divided by height (m) squared and was used as a baseline for pre-pregnancy obesity.

Infants weighing less than 2500 g at birth were classified as having low birth weight (LBW). Those born with fewer than 37 weeks of gestation were classified as preterm infants (preterm). The small for gestational age (SGA) variable was determined prior to analysis and defined as infants whose size or birth weight was below the 10th percentile for their gestational age. The outcomes low birth weight, preterm delivery, and small for gestational age were collapsed into a composite outcome called adverse birth outcome.

The smoked variable classified women as either smokers or nonsmokers. Smoking status, parity, number of visits, and mother's height attended were included in the models because they could confound the association

Comment [a6]: In this problem, the role of "confounders" is really more related to the fact that we want to know what new information is provided during pregnancy visits. This distinction is only an issue because of what causal diagrams we might consider in assessing confounding would not matter to us as we are trying to do predictions.

between SFH and weight measurements with adverse birth outcomes. Specifically, height could serve as a surrogate for nutritional deficiency and height-related pregnancy complications such as cephalopelvic disproportion. Parity and number of prenatal visits attended were modeled as continuous variables.

Comment [a7]: I will note that I also worry about genetics here, though it could be that the San's shorter stature is more nutritionally related than genetic (and I don't have proof that any of the women were San—that is just a presumption on my part)

Missing data was treated as missing completely at random. Subjects with missing data in any variable were omitted from models using that variable. Therefore models varied in the number of observations used. The SFH ratio predictor has fewer missing data compared to the slope and weight difference predictors because it could be determined after only one prenatal visit while weight difference and the weight and SFH slopes required at least two prenatal visits to calculate.

Comment [a8]: Did you examine whether this was reasonable? (We can sometimes detect that data is not MCAR, but we can never prove that it is MCAR.

Predictors of interest

To determine whether SFH or maternal weight profiles between weeks 20 and 30 differ for women who did and did not deliver LBW, preterm, or SGA infants, we derived four variables (two for SFH and two for maternal weight) and assessed the associations of these variables and adverse birth outcome.

For each prenatal visit between weeks 20 and 30, the SFH measurement was divided by the estimated gestational age to determine the ratio of SFH to EGA. Because SFH measured in centimeters is thought to approximate week of gestation starting at 20 weeks, the ratio of SFH to EGA for each clinic visit serves as an indicator of fetal growth. If the ratio of SFH to EGA is near one, we would expect the fetus to be growing at the right pace. Ratios excessively lower or higher than one may suggest problems with the pregnancy. The minimum ratio of SFH to EGA (min SFH ratio) was used as a predictor.

For each woman with more than one prenatal visit between weeks 20 and 30, we calculated the change in weight between each consecutive visit. The minimum of these differences (weight change) was used as a predictor.

The least squares slope that summarizes the trend in SFH and weight measurements during prenatal visits over weeks 20 to 30 was determined for each pregnant woman with available data. This slope is a straight line that best fits the distributions of SFH and weight measurements over weeks 20 to 30. The formulas for the least squares slope for SFH (SFH slope) and weight (weight slope) are shown in Figure 1.

Analysis

Logistic regression was performed to assess the association between SFH and adverse birth outcome using the predictor variables SFH ratio and SFH slope. The relationship of predictor to outcome was first assessed individually and then adjusted for smoking status, a quadratic association with age (age and age squared), a quadratic association with BMI (BMI and BMI squared), parity, height, and number of prenatal visits attended.

Logistic regression was performed in the same manner to assess the associations between weight and adverse birth outcome using the predictor variables weight change and weight slope. Unadjusted and adjusted logistic regressions were performed.

Finally, logistic regression models were used for exploratory analysis on the three outcomes (preterm birth, low birth weight, and SGA) separately. Since the goal is to determine which variables will predict adverse outcomes, multiple comparison issues are not as important as when determining an association between predictor and outcome. However, multiple comparisons are present and may result in an overstatement of a variable's significance.

Data issues

There are several issues which may affect the analysis results:
1. Errors in measurement. For example, Several women have higher SFH measurements during early prenatal visits and lower SFH measurements during later visits. These measurements may reflect a true decrease in SFH or may be measurement or recording errors.

2. Estimation of gestational age. Different methods were used to determine gestational age prior to and after birth, therefore gestational age in weeks and gestational age at delivery estimates may not agree. Also, gestational age during pregnancy is difficult to estimate and is known to have high variability.

3. Missed visits. Several women had only one visit between weeks 20 and 30, therefore measures using differences between visits could not be determined for these women.

Results

Descriptive statistics

Among the 755 women in the dataset, 708 (93.8%) attended at least one prenatal visit between weeks 20 to 30 while 658 (87.1%) attended at least two visits. This was the first delivery for 293 (39%) women. Table 1 presents additional descriptive statistics. Among the participants, there were 105 (14%) adverse birth outcomes with 24 (3%) of the infants preterm births, 75 (10%) less than 2500 grams, and 105 (14%) small for gestational age.

Comment [a9]: What were the patterns of overlap. FWIW: I find it surprising that all LBW were also called SGA in this dataset. Premature infants will likely be LBW, but will not always be SGA, so I am personally concerned about how this variable was defined.

Characteristics of participants were similar across the outcomes low birth weight, preterm birth, SGA, and no adverse event (Table 2). One exception is smoking which was less prevalent among mothers with preterm and no adverse outcomes (each 29%) than among mothers with low birth weight and SGA infants (44%, 43%). Birth weight by definition was lower in the low birth weight group with a mean of 2071 g. Birth weight was also lower in the preterm (mean 1787 g) and SGA (mean 2231 g) groups than the healthy group (mean 3246 g). The three adverse birth outcome categories overlap and are not mutually exclusive. The SGA group includes all women with preterm and LBW infants and is identical to the any adverse event group.

Models

SFH

From logistic regression using min SFH ratio as the predictor, the odds ratio for any adverse birth outcome was 0.014 (95% CI 0.00036–0.55, p=0.023). The odds ratio adjusted for age, age^2, BMI, BMI^2, height, smoking status, parity and number of prenatal visits was 0.036 (95% CI 0.00058–2.26, p=0.115) (Table 3). In the exploratory analysis, SFH ratio is associated with both preterm delivery and low birth weight in the unadjusted and adjusted models (Table 4).

Comment [a10]: What is the interpretation of the OR. What groups are you comparing? Do they make scientific sense?

Using SFH slope as the predictor, the odds ratio for any adverse birth outcome was 0.49 (95% CI 0.30-0.82, p=0.007). Adjusting for the confounders listed above, the odds ratio was 0.51 (95% CI 0.30–0.87, p=0.012). In the exploratory analysis, SFH slope was associated with low birth weight but not preterm delivery in both unadjusted and adjusted analyses.

Weight

Weight was not associated with any adverse outcome using either weight change or weight slope as predictors (Table 3).

Comment [a11]: Provide full inference even when not significant. (Some might say especially when not significant.)

Out of the 658 women whose change in weight could be calculated, 155 had a negative change in weight and weighed more at an earlier visit than a subsequent one. Another 51 women had a weight change of zero. Decreases in weight over pregnancy could be intentional if a woman is overweight prior to pregnancy or unintentional as a result of underfeeding.

In exploratory analysis looking at the outcomes low birth weight and preterm birth, weight change was not associated with low birth weight or preterm birth in either adjusted or unadjusted analyses (Table 4).

Discussion

The goal of this analysis was to determine whether differences in either weight change or SFH change over pregnancy were associated with adverse birth outcomes and to evaluate whether these associations could potentially be used to predict whether a women would have a growth retarded baby.

Weight change

Weight change, defined as either the minimum change between two visits or the least squares slope of change over weeks 20–30, was not associated with adverse birth events in any of the models developed.

It is possible in this setting that a woman's actual weight may be a more important predictor of adverse outcome than change in weight (Figure 2). Women with adverse outcomes had consistently lower weights throughout pregnancy compared to women with no adverse outcomes. However, change in weight over time among the two groups was relatively constant.

This dataset did not have the weight of the mother before pregnancy, nor did it have blood pressure measurements of the mother. We believe that these are two variables that would have improved the predictive models for the birth outcomes addressed and may help future analysis.

SFH change

For prediction, it would be ideal if one visit could provide a clinician with enough information to make a referral, and the SFH ratio variable uses information from just one visit. While SFH ratio was a significant predictor of any adverse birth outcome on its own, it was no longer significant after adjusting for the chosen confounders. However, in the exploratory analysis, SFH ratio was a significant predictor of either low birth weight or preterm delivery in the adjusted models.

The fact that SFH ratio was associated with preterm delivery and low birth weight but not associated with small for gestational age infants could indicate that, in this population, a proportion of infants are small but healthy, possibly related to smaller-stature mothers. SFH increase over weeks of pregnancy was similar for women both with and without adverse birth outcomes, which directly mirrors infants small for gestational age (Figure 3). Among small for gestational age infants who were neither preterm nor low birth weight, 66% had mothers below the median height of 156 cm. Information on infants classified as small for gestational age should be re-examined to see if they were also in need of additional prenatal or post-natal care. The SGA variable may not be a reliable indicator of adverse birth event in this population.

A large source of error in the SFH ratio variable is the estimation of the gestational age. When gestational age is overestimated women may be considered for referral who are proceeding in a normal pregnancy while when the gestational age is underestimated a pregnancy may look normal when it is at higher risk for adverse events.

Comment [a12]: But as you note, the clinic will have to go with that best guess.

From these data there is evidence that SFH profiles over weeks 20-30 of pregnancy differ between women who deliver preterm and low birth weight infants, but less so for small for gestational age infants. An SFH measurement taken during a single prenatal visit, the SFH to EGA ratio, can be used to develop a model to distinguish women who have preterm or low birth weight infants and women who will not.

Comment [a13]: Will such a model do very well at predicting? There is enough info in this data to suggest that it willnot.

Table 1: Characteristics of study participants (n = 755)

	Missing	Freq (%)	Mean (SD)	(Min, Max)	Median (IQR)
Age (years)	0		24.8 (5.4)	(14, 43)	24 (21, 28)
Height (cm)	6		156.7 (6.5)	(106, 176)	156 (153, 161)
BMI at enrollment (kg/m^2)	6		25.5 (4.6)	(15.9, 49.1)	24.5 (22.1, 28.0)
Number of prior deliveries	0		1.1 (1.2)	(0, 6)	1 (0, 2)
Smoked	4	231 (31%)			
Pregnancy outcomes					
Birth weight (g)	4		3105.6 (534.5)	(1035, 4730)	3140 (2810, 3440)
Gestational age at delivery (wk)	5		39.2 (1.5)	(30, 44)	39 (38, 40)
Male infant	4	383 (51%)			
Low birth weight (LBW)	4	75 (10%)			
Pre-term delivery (pre-term)	5	24 (3%)			
Small for gestational age (SGA)	3	105 (14%)			
Adverse birth outcome (LBW, pre-term, or SGA)	3	105 (14%)			
Prenatal visits					
Number of visits	0		7.7 (2.2)	(2, 14)	8 (6, 9)
Gestational age at enrollment (wk)	0		22.5 (4.0)	(15, 39)	22 (20, 25)
SFH change, wk 20–30					
Minimum ratio of SFH to EGA	47		0.93 (0.61)	(0.6, 1.12)	0.93 (0.89, 0.96)
SFH slope	97		1.01 (0.41)	(-1.5, 3.55)	1.01 (0.83, 1.21)
Maternal weight change, wk 20–30					
Minimum consecutive slope	97		0.16 (0.45)	(-2.5, 3.00)	0.15 (0, 0.38)
Weight slope	97		0.42 (0.36)	(-1.50, 3.00)	0.39 (0.22, 0.57)

BMI = body mass index, SFH = symphysis fundal height, EGA = estimated gestational age, SGA = small for gestational age

Table 2: Characteristics of study participants by birth outcome

Comment [a14]: There is overlap among these groups. You ought to make that clear.

I think you would have found it informative to consider the mean SFH and weight by EGA week in each of these groups.

	Low Birth Weight (n=75) Mean (SD) or Frequency (%)	Preterm Birth (n=24) Mean (SD) or Frequency (%)	Small for Gestational Age (n=99) Mean (SD) or Frequency (%)	No Adverse Outcome (n=647) Mean (SD) or Frequency (%)
Age (years)	23.9 (4.8)	23.9 (4.8)	23.8 (4.9)	24.9 (5.4)
Height (cm)	153.6 (5.8)	156.2 (4.8)	154.5 (5.9)	157.0 (6.5)
BMI at enrollment (kg/m^2)	23.8 (4.1)	23.8 (3.9)	23.5 (4.8)	25.7 (4.6)
Number of prior deliveries	0.9 (1.2)	1.1 (1.1)	0.9 (1.1)	1.1 (1.2)
Smoked	35 (45%)	7 (29%)	44 (44%)	186 (29%)
Pregnancy outcomes				
Birth weight (g)	2071.2 (351.1)	1787.2 (236.2)	2216.8 (417.9)	3246.2 (402.1)
Gestational age at delivery (wk)	37.2 (2.1)	34.8 (1.6)	37.9 (2.2)	39.4 (1.2)
Male infant	30 (41%)	10 (36%)	41 (41%)	339 (52%)
Prenatal visits				
Number of visits	6.8 (2.7)	5.3 (2.4)	7.1 (2.7)	7.8 (2.2)
Gestational age at enrollment (wk)	21.6 (3.1)	21.4 (3.1)	21.9 (3.4)	22.6 (4.1)
SFH change, wk 20-30				
Minimum SFH to EGA ratio	0.91 (0.06)	0.90 (0.05)	0.91 (0.07)	0.93 (0.06)
SFH slope	0.90 (0.46)	0.97 (0.45)	0.91 (0.45)	1.03 (0.40)
Maternal weight change, wk 20-30				
Minimum weight change	0.15 (0.43)	0.19 (0.50)	0.15 (0.42)	0.17 (0.46)
Weight slope	0.38 (0.35)	0.36 (0.51)	0.39 (0.34)	0.42 (0.37)

BMI = body mass index, SFH = symphysis fundal height, EGA = estimated gestational age, SGA = small for gestational age

Table 3: Estimated proportionate change in odds of any adverse birth outcome

	Unadjusted Analysis				Adjusted Analysis*			
	n	Odds ratio	P value	95% CI	n	Odds ratio	P value	95% CI
SFH change								
Min SFH to EGA ratio	705	0.014	0.023	0.00036, 0.55	699	0.036	0.115	0.00058, 2.26
SFH slope	655	0.49	0.007	0.30, 0.82	649	0.50	0.011	0.30, 0.85
Maternal weight change								
Min weight change	655	0.85	0.476	0.55, 1.32	649	0.76	0.272	0.47, 1.23
Weight slope	655	0.77	0.389	0.43, 1.39	649	0.79	0.387	0.45, 1.36

* adjusted for age, age^2, BMI, BMI^2, height, smoking status, parity and number of prenatal visits
SFH = symphysis fundal height, EGA = estimated gestational age

Table 4: Estimated proportionate change in odds of each adverse birth outcome

	Unadjusted Analysis				Adjusted Analysis*			
	n	**Odds ratio**	**P value**	**95% CI**	**n**	**Odds ratio**	**P value**	**95% CI**
Low birth weight								
SFH change								
Min SFH to EGA ratio	704	0.0058	0.011	0.00011, 0.31	699	0.0088	0.038	0.00010, 0.77
SFH slope	654	0.49	0.011	0.28, 0.85	649	0.48	0.01	0.28, 0.84
Maternal weight change								
Min weight change	654	0.94	0.80	0.56, 1.57	649	0.80	0.42	0.46, 1.38
Weight slope	654	0.76	0.441	0.38, 1.53	649	0.90	0.713	0.51, 1.59
Preterm delivery								
SFH change								
Min SFH to EGA ratio	703	0.0016	0.002	0.000026, 0.069	698	0.001	0.006	$7.68x10^{-6}$, 0.14
SFH slope	653	0.75	0.594	0.26, 2.16	648	0.75	0.635	0.23, 2.44
Maternal Weight								
Min weight change	653	1.13	0.816	0.39, 3.26	648	0.90	0.792	0.43, 1.91
Weight slope	653	0.64	0.618	0.11, 3.77	648	1.05	0.893	0.53, 2.08
Small for gestational age								
SFH change								
Min SFH to EGA ratio	703	0.014	0.027	0.00033, 0.56	699	0.036	0.115	0.00058, 2.26
SFH slope	658	0.50	0.007	0.30, 0.83	649	0.51	0.012	0.30, 0.87
Maternal weight change								
Min weight change	653	0.91	0.67	0.58, 1.42	649	0.76	0.272	0.47, 1.23
Weight slope	658	0.79	0.388	0.44, 1.44	649	0.79	0.387	0.45, 1.36

* adjusted for age, age^2, BMI, BMI^2, height, smoking status, parity and number of prenatal visits
SFH = symphysis fundal height, EGA = estimated gestational age

Figure 1: Least squares slope calculation

Comment [a15]: This does not look correct to me.

1a. Least squares slope for symphysis fundal height (SFH)

$$slope\ SFH = \frac{\frac{(\sum week)(\sum SFH)}{n}}{\sum week^2 - \frac{(\sum week)^2}{n}}$$

1b. Least squares slope for weight

$$slope\ weight = \frac{\frac{(\sum week)(\sum weight)}{n}}{\sum week^2 - \frac{(\sum week)^2}{n}}$$

Figure 2: Least squares lines of SFH versus EGA by adverse outcome

Comment [a16]: Lowess curves would have been far better than these predicted lines. Had you done lowess, you might have seen coincident lines up to about 27 weeks EGA

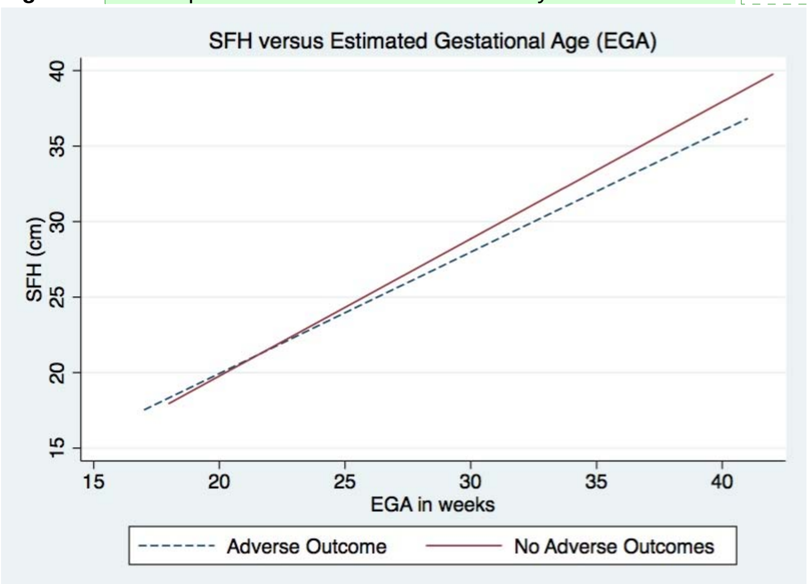
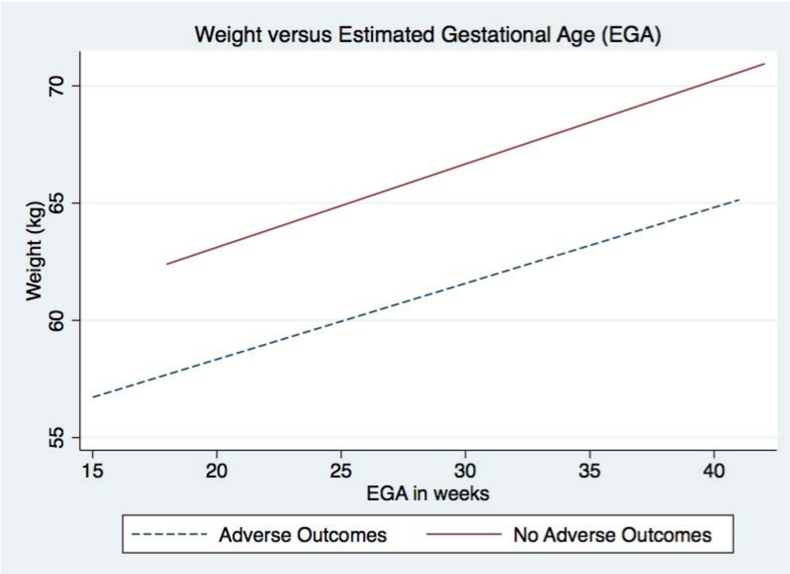


Figure 3: Least squares lines for weight during pregnancy versus estimated gestational age (EGA) by adverse



outcome