RESEARCH ARTICLE

REVISED Small for gestational age babies and depressive symptoms of mothers during pregnancy: Results from a birth cohort in India [version 2; peer review: 1 approved, 1 approved with reservations, 1 not approved]

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Abstract

Background: Annually, more than a million Low birthweight (LBW) are born in India, often afflicting disadvantaged families. Several studies have undertaken association of poverty, nutritional status, and obstetric factors with LBW. Through our study, we aimed to examine the possibility of any relation between Edinburgh Postnatal Depression Scale (EPDS) score measured during pregnancy with incidence of babies born Small for Gestational Age (SGA). Moreover, we explored if there is any utility for identifying a cut-off point of EPDS for predicting SGA.

Methods: Pregnant women attending the antenatal clinic at a public hospital between 14 to 32 weeks were recruited from April 2016 to Oct 2017. The EPDS was administered to assess depression through face-to-face interviews. Newborn anthropometry was performed post-delivery. For analysis, birth weight <10 percentile was classified as SGA and >90th percentile as Large for Gestational Age (LGA).

Results: Prevalence of depressive symptoms (EPDS score >11) was 16.5% (n=108/654) in antenatal mothers. These women delivered a higher proportion of SGA babies (21.3 v/s 15.8) and LGA (9.3 v/s 3.3) compared to women with no symptoms. The odds of women giving birth to a child with SGA were twice as high for women with EPDS scores >11 (adjusted OR = 2.03; 95% CI = 1.12 – 3.70) compared to the women with EPDS scores of ≤11. In terms of Area under curve (AUC), EPDS 11 cut off (AUC: 0.757, CI 0.707- 0.806) was same as EPDS 12 cut-off (AUC: 0.757, CI 0.708- 0.807), which was slightly lower than

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EPDS 13 cut off (AUC: 0.759 CI 0.709- 0.809).
Conclusions: We found a strong association of antenatal depressive symptoms during pregnancy with SGA measured by EPDS. Thus, we recommend implementation of timely and effective screening, diagnostic services, and evidence-based antenatal mental health services in order to combat SGA, and further associated-metabolic syndromes.

Keywords
Small for Gestational age, low birth weight, Prenatal depression, Screening, Pregnancy, birth cohort, public hospital, Low and Middle Income Country,

Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 1**

Due to an error in the coding of the variable (EPDS score cut-off 11, 12, 13), re-coding of the entire dataset was done. On thorough checking and analysis, the resulting AOR values changed gradually from one cut-off category to another. Additionally even the area under the ROC curves, obtained from the predicted probabilities of each model have changed and are now above the null value; Figure 2 has been updated. Moreover, we also ran separate models including interaction effect, with the respondent's education, occupation, and income that showed an increase in the predictability of the model.

The dataset has been updated with few new variables. We have updated Figure 1 to now list the numbers of twins and stillbirths that were excluded. Additionally, Supplementary File 1 includes the analysis of the relation between EPDS score as a continuous variable and proportion of women delivered with SGA represented graphically.

We are including two new authors in this version. Anjaly Krishnan has been added as a biostatistician in our team. She has been able to address the comments of two reviewers and has improved the manuscript. She has recoded and redone the significant portion of the analysis after correcting coding errors that had occurred previously, she has also created additional tables and graphs to answer several of the reviewer comments. Eunice Lobo is the other author who has joined our research team and she has significantly contributed to rewriting the discussion and abstract of the manuscript based on the new results and has also done language edits in the manuscript.

See referee reports

Introduction

Low birthweight (LBW; <2500 g), a marker of poor intrauterine growth, leads to the double burden of stunting in childhood and predisposes to obesity in adolescence[1,2]. The pathways triggered by LBW lead to perpetuating, independent cycles of ill health[3,4]. More than one million babies are born with LBW in India every year. LBW often afflicts disadvantaged families, accentuating the risk of child mortality and morbidity[5]. Despite the high prevalence of LBW, its causes are poorly recognized. Infants with LBW comprises of preterm babies (<37 weeks gestation) or Small for Gestational Age (SGA) or both[6]. SGA is defined as birth weight below the population-specific 10th percentile for the gestational age. Children, who are born SGA, have several short and long-term adverse outcomes[7–9].

Apart from the increased risk of mortality, infants with SGA might have a broad spectrum of adverse growth, morbidity, and developmental outcomes[10]. Due to poor nutritional status, a range of problems from malabsorption to growth retardation can affect the growing children[11]. The 'thrifty phenotype' hypothesis describes that adaptive mechanisms due to child undernutrition are on the rise and result in type 2 diabetes mellitus (T2DM), which is epidemic in low- and middle-income countries (LMICs). Confronted with undernutrition as a fetus and child, the compensatory adaptive mechanism stores excess energy as fat[12]. As a result, LBW in babies accentuates the risk of obesity, insulin resistance, cardiovascular diseases and T2DM[13].

Over the past several decades, program interventions to reduce LBW have mostly focused on addressing poverty, maternal nutritional status, and obstetric factors in India. However, the proportion of children with LBW has remained stagnant or reduced only minimally over this period in LMICs, such as India. The role of antepartum depression is often neglected as a determinant of SGA, despite evidence indicating that women with antepartum depression have an increased risk of having a preterm birth and LBW babies[14]. Meta-analyses also indicate that the magnitude of this association varies with how depression is measured, country of residence and socioeconomic status[14,15]. Almost all the evidence on the impact of antepartum depression on LBW is from developed countries. As an exception, a study from Bangladesh has suggested an association of high Edinburgh Postnatal Depression Scale (EPDS) score in pregnant women may be associated with LBW[16]. Also, the role of EPDS as screening criteria for antepartum depression is under explored in most LMICs, and studies have used different cut offs for different samples[17].

The aim of this study is to examine if the relation between Edinburgh Postnatal Depression Scale (EPDS) score and SGA. Further, we also explored if there is any utility for identifying a cut-off point of EPDS for predicting SGA.

Despite the high prevalence of SGA in LMICs such as India, the awareness of mental health problems is low. Antenatal depression in pregnancy is not routinely screened in LMICs, including whether it can be a risk factor for poor intrauterine growth. This is specifically relevant in metropolitan cities like Bangalore, which has relatively better socio-economic standards in communities compared to several other regions, but continues to experience persistently high proportions of children born with SGA.

Methods

Study setting

Maternal antecedents of adiposity and studying the transgenerational role of hyperglycemia and insulin (MAASTHI) is a birth cohort established to prospectively identify risk factors in pregnancy associated with adverse infant outcomes, especially in predicting the possible risk markers of later chronic diseases[18]. The detailed protocol of the study has been published elsewhere[18]. Briefly, pregnant women with gestational age (GA) between 14 to 32 weeks were recruited. GA was determined by ultrasonography record and if not available the last menstrual period was noted. In the 1557 women enrolled, 654 women who had completed follow up after delivery comprise the study sample for the present study, still birth and twins were excluded from the data analysis. (Figure 1).

Data collection

Data was collected from April 2016 to October 2017 at a secondary level public hospital. Data at baseline (second and third trimester of pregnancy) included socioeconomic conditions that included religion, education, occupation and the women's reproductive history, social support, depressive symptoms and consumption of tobacco and alcohol. EPDS tool was translated into local language (Kannada) and then back translated to English

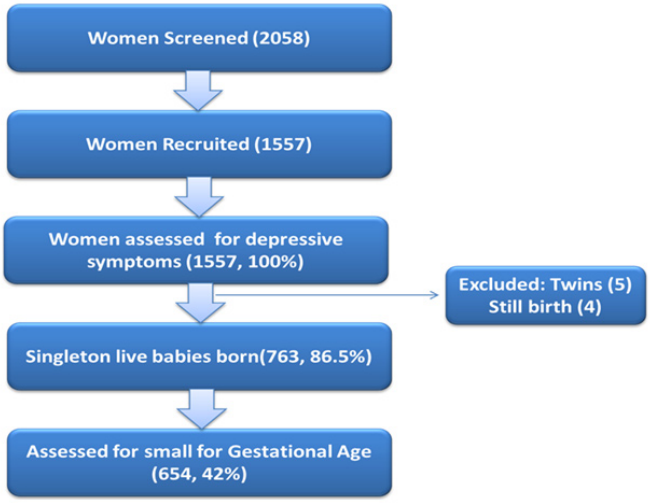

Figure 1. Flow diagram depicting the composition of the present study sample (n=654) from the MAASTHI birth cohort. See 18 for further details of the MAASTHI cohort.

for accuracy. Through this, efforts were made to ensure a clear and conceptually accurate translation that was easily understood by local population. The Questionnaire was then administered to the respondents by trained research assistants who would interview without altering the actual meaning. The response score is quantified by asking frequency of occurrence of depressive symptoms for number of days. The respondent's weight, height, Mid-upper arm circumference (MUAC), head circumference, biceps, triceps and subscapular skinfold thickness were recorded. Birth data were collected through structured interviews and anthropometric assessment by trained female research staff in the hospital. The data collection for pregnant women regarding depressive symptoms was done during the second and third trimester and the anthropometry of the newborn was recorded between 2 to 48 hours following delivery. Several birth outcomes were assessed including the length of pregnancy, mode and place of delivery, complications during labour, live or stillbirth, birth weight, length, head, chest, waist, hip and MUAC of the newborn. Skinfold thickness was measured using Holtain calipers at biceps, triceps and subscapular sites.

Measurements

Assessment of antepartum depressive symptoms. The Edinburgh Postnatal Depression Scale (EPDS) is a widely used self-reporting questionnaire developed specifically to screen for symptoms of perinatal depression[19,20]. EPDS has been validated by Fernandes *et al*. for prenatal depression in South India at a cut-off of ≥13 (sensitivity = 100%, specificity = 84.90%, and AUC = 0.95)[21]. Depressive symptoms are assessed by a 10-item scale, which determines the psychosocial stress level of pregnant women in the last seven days. Social support was measured using a questionnaire developed at St. John's Research Institute to evaluate a broad range of social support (i.e., emotional, instrumental, informational, and appraisal)[22]. This questionnaire has total 12 items and each item is scored between 0 (definitely not enough) to 3 (definitely enough). The highest score being 36 means excellent social support and 0 meaning low social support. The scale reported an excellent value of internal consistency, as determined by Cronbach's alpha of 0.935 all variables showing a high level of consistency. Trained Research Assistants using an Android tablet administered the questionnaire; the system is programmed to generate a EPDS score in real time, and in case the woman scored >13 she was referred to the psychiatrist at the hospital. The correlates of EPDS have internal consistency exceeding 0.8. Pregnant women were classified into two groups based on their EPDS score: 0–11, without depressive symptoms; 11+ with depressive symptoms. This 10-item scale has been translated into many different languages and validated in many countries including India[23]. The cutoff values of EPDS as a screening tool for antenatal depression in primary health care settings is dependent on cultural settings. For example, a cut-off EPDS score for the Spanish version of the EPDS is 8/9 and the Chinese version is 9/10[24]. A cutoff score of 11/12 was found to detect perinatal depression with acceptable sensitivity and specificity in Goa, India[25]. In concurrence with this evidence, we aimed to assess the exact EPDS score cut-off value (11, 12 or 13) as a better predictor of association between antenatal depression and SGA.

Other risk factors. Possible risk factors for SGA were assessed by a standardized questionnaire seeking information on women's medical and obstetric history (parity, abortion), socio-economic and demographic characteristics (age, education, and occupation), smoking habits and alcohol consumption. The research staff measured women's height, weight, MUAC. Skinfold thickness was measured using Holtain calipers at biceps, triceps and subscapular sites.

Anthropometry. Adult anthropometry: After ensuring that the scale was placed on a level ground, the research staff would view 'zero' reading. After ensuring that the respondent would remove heavy outer clothing and shoes, two readings to the nearest 10 gram were taken. Further, we used SECA 213 portable stadiometer for measuring height to the nearest 0.1 cm. This was measured by requesting the respondent to stand straight with her feet together, ensuring the posterior surface of the head and heels was applied to the stadiometer. The head was positioned in an imaginary line joining the upper margin of the external auditory meatus and the lower border of the orbit of the eye (Frankfurt plane). The head plate of the stadiometer would then be pulled down to ensure that it rests on the crown of the head[26].

Baby anthropometry: Newborn anthropometry was performed using SECA 354 Weighing Scale and SECA 417 Infantometer. The baby was placed naked on the digital weighing scale and readings are taken to the nearest 0.5g. For measuring infant length, the baby's head is held against the end of the head plate and the legs extended until they are flat. The foot plate is brought up to the heels ensuring that feet and knees were flat, the length is recorded. Chasmors body circumference tape was used to measure the circumferences. Head circumference is measured with the baby's head on the side, so that the maximum occipito-frontal circumference could be found. The tape was placed on

the forehead, on the most anterior point (just above the eyebrows) and passed around the head to the most posterior part of the head making sure the maximum circumference is found. Waist circumference was taken by placing the tape around the abdomen immediately above the umbilicus ensuring that it is horizontal and marked at the end of expiration. Chest circumference is measured by placing the tape around the chest at the level of xiphisternum ensuring that it is placed horizontal and marked at the end of expiration. MUAC was recorded with the arm bent, allowing the measurement to be taken with the baby in its natural position. Skinfold thickness is measured on the left side of the body using the Holtain Calipers. Three readings to the nearest 0.2mm were taken unless this caused too much distress, in which case, a single measurement was taken. For triceps skinfold thickness, the tape is placed around the upper arm at the level of the mark done while measuring MUAC. With the tape in position, a horizontal line is drawn on the skin posteriorly at the level of the mark. Another vertical line is marked on this line at the most dorsal part of the upper arm. This level was determined by 'eyeballing' the mid-point. The point at which the fold is to be measured was then marked; the skin was lifted over the posterior surface of triceps muscle, above the marked point, on a vertical line passing upward from the olecranon to the acromion. The calipers are applied below the fingers such that the marked cross was at the apex of the fold. Biceps skinfold is measured in the anterior midline of the arm over the biceps on the same level as the triceps skinfold. For subscapular skinfold thickness, the inferior angle of the scapula was identified and the skin is marked immediately below the angle. The skinfold was picked up above the mark with the fold slightly inclined downward and laterally, in the natural cleavage of the skin. The caliper jaws are applied below the fingers, such that the marked point is at the apex of the fold[26].

The weight of infant was classified into percentiles based on the Indian standards for birth weights of newborns based on the sex and order of the baby[27]. Anything less than 10 percentile were classified as SGA, between 10 to 90th percentile was appropriate for gestational age (AGA) and greater than 90th percentile was large for gestational age (LGA). Babies born before 37 weeks of gestation were considered as premature. Other details of neonatal morbidity and hospitalization were obtained from the family members and medical records.

Statistical analysis

We used logistic regression analysis to assess the association between SGA and EPDS score. The association with SGA was examined using the 3 categorical variables based on the cut-off scores of 11, 12 and 13. This was adjusted for known confounders based on literature review for maternal age, religion, respondent's and husband's incomes, gravida, parity, husband's current consumption of tobacco and alcohol and respondent's sum of skinfold thickness. These variables were adjusted based on the priori information[28–33]. Goodness of fit of the models were assessed using Hosmer-Lemeshow statistic and AUROC curves formed from predicted probabilities. Statistical analysis was performed using Stata/IC 14.2 for Mac (Revision 19 Dec 2017, Copyright 1985-2015 StataCorp LLC) and SPSS version 23. Descriptive analysis was done for maternal and neonatal characteristics for both women with and without mental depressive symptoms.

Results

A total of 654 pregnant mothers who completed the EPDS questionnaire were taken into consideration for analysis in the present study. The mean maternal age of the study sample at baseline was 23.6 ± 3.9 years. Mothers with depressive symptoms had lower mean social support scores compared to mothers without depressive symptoms (Table 1). The study found that overall 16.51% (n=108) of the antenatal mothers had depressive symptoms (EPDS score of >11).

Among mothers with depressive symptoms (EPDS score >11), 43 (39.8%) mothers were below the age of 22 years. Depressive symptoms affected predominately young mothers and the symptoms decreased with increase in age of the women. The majority of the study sample comprised of Muslim women and they were the most afflicted with depressive symptoms (65.7%), followed by mothers belonging to Hindu religion (32.4%). Pregnant women with high school education had a high proportion of depressive symptoms (44.3%) compared to other levels of educational attainment. Among the pregnant women, the depressive symptoms in the women with first pregnancy were high (41.7%) and decreased with an increase in the number of times conceived and delivered. The results indicate that 60% of husbands of the pregnant women with depressive symptoms were consuming tobacco and 21% were consuming alcohol (Table 1).

Women with depressive symptoms delivered a greater proportion of SGA (21.3 *vs* 15.8%) and LGA (9.3 *vs* 3.3%) babies compared to women with no symptoms. While there were no major differences for normal term delivery, women with depressive symptoms had a slightly elevated proportion of caesarian section delivery (31.5 *vs* 24.2%) (Table 2).

Maternal and neonatal characteristics in relation to SGA and AGA status are summarized in Table 3.

No major variation was found between the mean and standard deviation for age, gravida, parity and abortion status of mothers with relation to SGA and AGA category. A higher proportion of SGA was found in male babies compared to female babies. Mothers who delivered SGA babies had greater mean EPDS scores during pregnancy (6.27 *vs* 5.73%) and at the time of delivery (21.1 *vs* 14.5%) compared to the mothers who delivered AGA babies. Among the mothers who delivered SGA babies, a majority (68.8%) were younger (under 25 years) and the SGA proportion decreased with the increase in age. Hindus had a higher proportion of delivering SGA babies (49.5%) followed by Muslims (45.9%) and Christians (4.6%) (Table 3). Education of the partners with higher than high school level had a lesser chance of delivering SGA babies compared to their counterparts.

Adjusted odds ratio (OR) and 95% confidence interval (CI) for EPDS cut off 11, 12, 13 and SGA is presented in Table 4.

Table 1. Maternal characteristics in relation to depressive symptoms during pregnancy.

Characteristic	EPDS ≤ 11 (without depressive symptoms) [N = 546]	EPDS >11 (with depressive symptoms) [N = 108]	Total [N =654]
Age (years)	23.66 ± 3.83	23.43 ± 4.31	23.62 ± 3.91
Respondent's income	450.92 ± 1980.19	333.33 ± 1334.31	431.50 ± 1888.46
Husband's income	11613.47 ± 6061.27	10893.52 ± 4878.93	11493.85 ± 5884.02
Gravida	1.94 ± 0.89	1.91 ± 0.93	1.93 ± 0.90
Parity	0.69 ± 0.65	0.68 ± 0.72	0.69 ± 0.67
Social support	25.49 ± 10.65	20.88 ± 12.24	24.73 ± 11.05
Age (years)			
<22	173 (31.7)	43 (39.8)	216 (33.0)
22 – 25	223 (40.8)	32 (29.6)	255 (39.0)
26 – 30	117 (21.4)	27 (25.0)	144 (22.0)
31 – 35	29 (5.3)	4 (3.7)	33 (5.0)
>35	4 (0.7)	2 (1.9)	6 (0.9)
Religion			
Hinduism	245 (44.9)	35 (32.4)	280 (42.8)
Christianity	17 (3.1)	2 (1.9)	19 (2.9)
Islam	284 (52.0)	71 (65.7)	355 (54.3)
Respondent's education			
Illiterate	15 (2.7)	4 (3.7)	19 (2.9)
Primary school	33 (6.0)	3 (2.8)	36 (5.5)
Middle school	88 (16.1)	25 (23.1)	113 (17.3)
High school	241(44.1)	49 (45.4)	290 (44.3)
Pre-university	136 (24.9)	17 (15.7)	153 (23.4)
Graduate or above	33 (6.1)	10 (9.3)	43 (6.6)
Consanguineous Marriage			
Yes	167 (30.6%)	37 (34.3%)	204 (31.2%)
No	379 (69.4%)	71 (65.7%)	450 (68.8%)
Kuppuswamy scale			
Upper	4 (0.7)	0	4 (0.6)
Upper middle	495 (90.7)	99 (91.7)	594 (90.8)
Lower middle	43 (7.9)	9 (8.3)	52 (8.0)
Lower	4 (0.8)	0	4 (0.6)
Gravida			
1	189 (34.6)	45 (41.7)	234 (35.8)
2	238 (43.6)	35 (32.4)	273 (41.7)
3	93 (17.0)	21 (19.4)	114 (17.4)
More than 3	26 (4.7)	7 (6.5)	33 (5.1)
Parity			
0	224 (41.0)	51 (47.2)	275 (42.0)
1	272 (49.8)	41 (38.0)	313 (47.9)
2 or more	50 (9.1)	16 (14.8)	66 (10.1)

Characteristic	EPDS ≤ 11 (without depressive symptoms) [N = 546]	EPDS >11 (with depressive symptoms) [N = 108]	Total [N =654]
Anaemia Status			
Present	253 (46.3%)	47 (43.5%)	300 (45.9%)
Absent	293 (53.7%)	61 (56.5%)	354 (54.1%)
Tobacco consumption among husbands			
Yes	230 (42.1)	65 (60.2)	295 (45.1)
No	316 (57.9)	43 (39.8)	359 (54.9)
Alcohol consumption among husbands			
Yes	68 (12.5)	23 (21.3)	91 (13.9)
No	478 (87.5)	85 (78.7)	563 (86.1)
Women with depressive symptoms (EPDS >11)	546 (83.5)	108 (16.5)	654 (100)

Values are presented as mean ± standard deviation or n (%); EPDS: Edinburgh Postnatal Depression Scale

Table 2. Neonatal characteristics in relation to depressive symptoms during pregnancy.

Characteristic	EPDS ≤ 11 (without depressive symptoms) [N = 546]	EPDS >11 (with depressive symptoms) [N = 108]	Total [N =654]
Gender of baby			
Female	277 (50.7)	60 (55.6)	337 (51.5)
Male	269 (49.3)	48 (44.4)	317 (48.5)
Delivery type			
Normal	286 (52.4)	55 (50.9)	341 (52.1)
Primary C-section	132 (24.2)	34 (31.5)	166 (25.4)
Repeated C-section	128 (23.4)	19 (17.6)	147 (22.5)
Weight categories			
SGA	86 (15.8)	23 (21.3)	109 (16.7)
AGA	442 (81.0)	75 (69.4)	517 (79.1)
LGA	18 (3.3)	10 (9.3)	28 (4.3)
Premature delivery			
Yes	52 (9.5)	9 (8.3)	61 (9.3)
No	494 (90.5)	99 (91.7)	593 (90.7)

Values are presented as mean ± standard deviation or n (%); EPDS: Edinburgh Postnatal Depression Scale; C-section: caesarian delivery; SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age

A significant association was found between EPDS 11 cutoff and SGA. Women with EPDS scores of above 11 had a twice as high risk of giving birth to a child who would be SGA (Adjusted OR = 2.03; 95% CI = 1.12 - 3.70) compared to the women with EPDS scores of 11 and below. The EPDS 12 (Adjusted OR = 1.96; 95% CI = 1.04 – 3.69) and EPDS 13 (Adjusted OR = 2.42; 95% CI = 1.24 – 4.70) cut-off categories also proved to be a risk factor for SGA with significant p value (0.0006 and 0.0003) and the individuals with more than 13 EPDS score is found to have the highest risk of SGA

Table 3. Maternal and neonatal characteristics in relation to small for gestational age (SGA) babies.

Characteristic	SGA (N = 109)	AGA (N = 517)
Maternal characteristics		
Age at the baseline	24.12 ± 3.76	23.55 ± 3.93
Gravida	1.93 ± 0.80	1.93 ± 0.93
Parity	0.73 ± 0.56	0.68 ± 0.69
Abortion	0.28 ± 0.58	0.28 ± 0.56
EPDS Score (Pregnancy)	6.27 ± 5.71	5.73 ± 5.20
BMI (kg/m2)	22.67 ± 3.64	24.42 ± 4.32
Maternal anthropometric measurements		
Weight (kg)	52.87 ± 8.76	58.51 ± 10.79
Height (cm)	152.78 ± 5.77	154.77 ± 5.17
Mid-upper arm circumference (cm)	24.89 ± 2.96	26.15 ± 3.55
Biceps skinfold thickness (mm)	8.57 ± 3.38	9.59 ± 3.66
Triceps skinfold thickness (mm)	18.87 ± 5.30	20.59 ± 5.89
Subscapular skinfold thickness (mm)	15.08 ± 5.36	16.88 ± 5.78
Sum of skinfold thickness (mm)	42.53 ± 12.71	47.06 ± 13.73
Gestational age at delivery (weeks)	39.22 ± 1.14	38.65 ± 1.43
Neonatal anthropometric measurements		
Weight (Kg)	2.31 ± 0.23	2.80 ± 0.29
Length (cm)	47.29 ± 2.43	48.30 ± 2.49
Crown-rump length (cm)	30.69 ± 2.84	31.63 ± 3.25
Head circumference (cm)	32.32 ± 1.34	32.99 ± 1.37
Chest circumference (cm)	29.75 ± 1.82	31.17 ± 1.72
Waist circumference (cm)	26.45 ± 2.57	28.23 ± 2.34
Hip circumference (cm)	23.51 ± 5.43	25.77 ± 5.07
Mid-upper arm circumference (cm)	10.88 ± 5.43	11.15 ± 4.99
Biceps skinfold thickness (mm)	3.48 ± 0.71	3.78 ± 0.69
Triceps skinfold thickness (mm)	4.23 ± 0.92	4.89 ± 0.92
Subscapular skinfold thickness (mm)	4.04 ± 0.84	4.79 ± 0.89
Sum of skinfold thickness (mm)	11.74 ± 2.22	13.47 ± 2.07
EPDS score of mother (post-natal)	14.24 ± 10.58	10.98 ± 11.00
Mother's age at baseline (years)		
< 22	28 (25.7)	177 (34.2)
22 – 25	47 (43.1)	199 (38.5)
26 – 30	28 (25.7)	110 (21.3)
31 – 35	4 (3.7)	27 (5.2)
> 35	2 (1.8)	4 (0.8)
Religion		
Hinduism	54 (49.5)	215 (41.6)
Islam	50 (45.9)	288 (55.7)
Christianity	5 (4.6)	14 (2.7)
Occupation		
Unemployed	97 (89.0)	483 (93.4)

Characteristic	SGA (N = 109)	AGA (N = 517)
Unskilled	7 (6.4)	23 (4.4)
Semi-skilled and skilled	2 (1.8)	11 (2.2)
Husband's occupation		
Unemployed	2 (1.8)	1 (0.2)
Unskilled	55 (50.5)	264 (51.1)
Semi-skilled	33 (30.3)	136 (26.3)
Skilled	18 (16.5)	94 (18.2)
Clerical/Semi-professional	1 (0.9)	22 (4.3)
Kuppuswamy scale		
Upper	0	4 (0.8)
Upper middle	103 (94.5)	466 (90.1)
Lower middle	5 (4.6)	44 (8.5)
Upper lower	1 (0.9)	3 (0.6)
Gravida		
1	33 (30.3)	191 (36.9)
2	56 (51.4)	206 (39.8)
3	16 (14.7)	92 (17.8)
More than 3	4 (3.7)	28 (5.5)
Parity		
0	35 (32.1)	227 (43.9)
1	68 (62.4)	232 (44.9)
2 or more	6 (5.5)	58 (11.2)
EPDS score (>11) at delivery	23 (21.1)	75 (14.5)
Gender of baby		
Female	50 (45.9)	276 (53.4)
Male	59 (54.1)	241 (46.6)

Values are presented as mean ± standard deviation or n (%); SGA: small for gestational age; AGA: appropriate for gestational age; EPDS: Edinburgh Postnatal Depression Scale; BMI: body mass index

Table 4. Association between maternal depressive symptoms during pregnancy and SGA.

EPDS score	*Adjusted OR (95% CI) for SGA*	*p-value (EPDS score in the model)*	*p-value (Model)*
EPDS 11	2.0322 (1.1179 – 3.6947)	0.0201	0.00047
EPDS 12	1.9624 (1.0429 – 3.6927)	0.0366	0.00061
EPDS 13	2.4193 (1.2442 – 4.7044)	0.0092	0.00034

SGA: small for gestational age; EPDS: Edinburgh Postnatal Depression Scale.

Adjusted for maternal age, religion, consanguineous marriage, respondent and husband's education, occupation and income, gravida, parity, anaemia, husband's current tobacco and alcohol consumption and respondent's sum of skinfold thickness.

EPDS categories are defined as follows:

EPDS 11 – EPDS score of either more than 11 or 11 and below.

EPDS 12 – EPDS score of either more than 12 or 12 and below.

EPDS 13 – EPDS score of either more than 13 or 13 and below

Figure 2 displays EPDS with three cut off scores (EPDS 11, EPDS 12 and EPDS 13) against the target diagnosis. The accuracy of the model including EPDS scale, using three cut-off points was estimated by using the area under the ROC curve (AUC). The accuracy in predicting SGA by using EPDS scale improves after accounting for other confounders. In terms of AUC, EPDS 11 cut off (AUC: 0.757, CI 0.707-0.806) same as that of EPDS 12 cut-off (AUC: 0.757, CI 0.708-0.807), which is slightly lower than EPDS 13 cut off (AUC: 0.759 CI 0.709-0.809) for predicting the chance of having SGA.

Discussion

By means of a longitudinal study, we found that a relationship may exist between the symptoms of mental distress in pregnant women and SGA babies. Using a validated EPDS questionnaire, appropriate for the India populace, we were able to capture scores from 654 expectant mothers during and post pregnancy. We also found that the prevalence of depressive symptoms was relatively high (16.5%; n=108/654). This was higher compared to our previous study using the Kessler-10 scale (prevalence of 8.7%) across Bangalore[34], and is comparable to other Asian countries (20%) and LMICs (15.6%)[35,36].

Further, more salient findings from our analysis showed that pregnant women with depressive symptoms in the second trimester exhibited an increased likelihood of giving birth to SGA infants, when assessed using a cut-off value of 11 or above of the EPDS. This association was observed after adjusting for possible confounders: maternal age, religion, consanguineous marriage, respondent and husband's education, occupation, and income, gravida, parity, anaemia, husband's current tobacco and alcohol consumption, and respondent's sum of skinfold thickness. Significant association between scores of 11 or above and SGA were noted ($p \leq 0.005$) that were further corroborated with OR and AUC values, while lower EPDS scores were not significantly associated. Thus, it is possible that the peak adversities of SGA with depressiveness are around a score of 11 in EPDS[37–40]. However, it is possible that very low and very high score on EPDS might have different effects on the continuum of weight gain of the fetus. In the absence of diagnostic accuracy, it is difficult to comment on threshold cut-off level of EPDS, beyond which depressiveness might have some effect is difficult. We believe that mental health problems faced by pregnant women may not be simply and completely measured by EPDS alone, as the perception of stressors may vary and there may be varying levels of buffer mechanisms[41,42]. Thus it is important to further explore these findings based on perception, coping, and interpersonal attitudes[42–44].

Our findings are in concurrence with evidence from other South Asian countries such as Bangladesh[16,45–47] while the results from high-income countries and sub-Saharan Africa were mostly negative[48–50]. The conflicting geographical variations of this association needs further exploration. Also, if proven, this understanding of the life-course perspective of mental health of women in India,may help in reducing the prevalence of LBW[51,52].

Earlier studies have shown maternal nutrition to be an important predictor of LBW[53]. In our study, after adjusting for anaemia, the results from our study suggest that maternal antepartum depression might act independently in causing LBW. While the largest proportion of LBW in India results from poor maternal nutritional status[50], there are possibilities that antepartum depression may add to the significant burden of LBW. Evidences from neighbouring countries as Pakistan and Bangladesh supports this finding[45,46]. Further proof/evidence that delineates causative pathways leading to LBW and its interactions will provide a unique, compelling opportunity to inform the development of

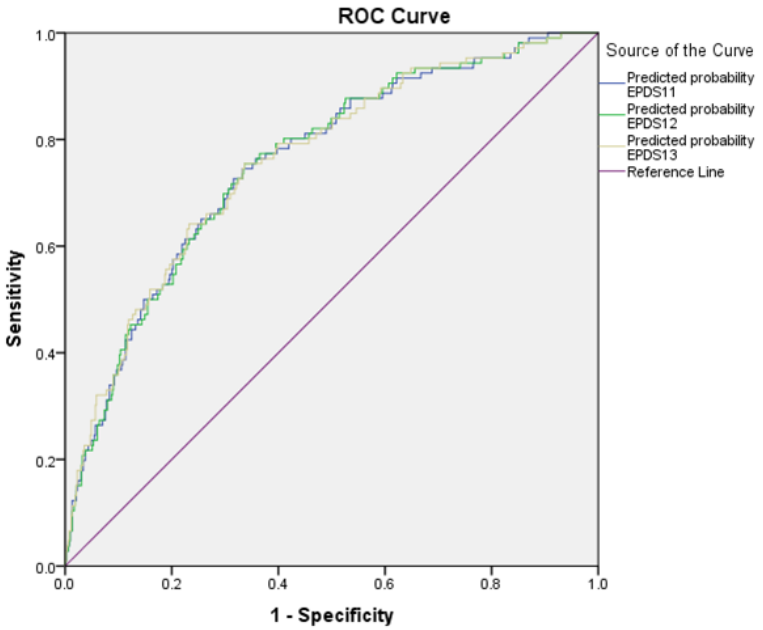

Figure 2. Receiver operating characteristic (ROC) curve for assessing predictability of the models.

specific preventive interventions for childhood malnutrition. Since LBW is multifactorial in origin and can lead to childhood obesity and its complications, our results indicate psychosocial environment as a potential, contextually important risk factor for LBW.

There is a need for establishing the causal association, after which the policymakers can prioritize screening pregnant women for mental health problems. The governments can modify and or/ incorporate mental health screening within the existing provisions of the national health mission.

In summary, we were successful in using a simple screening method at primary care level for screening depression in the antenatal population. Healthcare workers at primary health care levels can thus efficiently screen pregnant women for depression and refer those in need of further care.

There are three potential explanations for the association of antenatal depression and SGA. One, antenatal depression might result in dysregulation of the hypothalamic-pituitary-adrenocortical axis, thereby releasing stress hormones. For example, cortisol levels might mediate this association[54], possibly resulting in decreased blood flow to the placenta and consequent restriction of oxygen and nutrients to the fetus leading to intrauterine growth retardation[55–59]. In order to explore this possibility further, mediation mechanisms by cortisol and other catecholamines prospectively is necessary. Two, it is possible that there might be an interaction between the association of antenatal depression and other maternal antecedents, such as maternal undernutrition, poor access to healthcare facilities, smoking, alcohol and substance abuse, which are independent known risk factors of LBW[60]. It is possible that such an association is generally seen in women of disadvantaged social groups, therefore poverty might confound the association between mental health and LBW. Although we have adjusted for income, there might be a possibility of residual confounding distorting the association.

Strengths and limitations

There are various strengths of our study: First, our study is a birth cohort with real-time data quality monitoring. Second, our prospective examination of antenatal depression with SGA has been carried out in a sufficiently large study sample; third, we were able to adjust for several potential confounders; fourth, have also demonstrated the usefulness of the 10-item EPDS screening tool in screening for antenatal depression that can be used even at primary care level. Further there were few limitations: first, despite being the most commonly used screening tool[61,62], we are yet to demonstrate the diagnostic accuracy of EPDS in the study sample. Second, since our study is not immune to the source of systematic error similar to all other observational studies, we are not providing any causal inference regarding the association between EPDS and SGA. Third, we did not assess violence which is a considerable risk factor; and finally, we have not assessed anxiety as part of the screening and it might be a limitation given that anxiety and depression are known to be co-morbid[63,64]

Conclusion

Our findings indicate that maternal distress due to depression can lead to the birth of SGA babies. There is a need to universally screen women for depression during pregnancy. The causal links and mediation by other factors have to be delineated before policymakers can consider to prioritize screening and care for mental health, especially in the women belonging to vulnerable or lower socioeconomic backgrounds.

Ethics and consent

The study was reviewed and approved by the institutional ethical review board at Bangalore campus of IIPH-H (Ref No: IIPHHB/TRCIEC/091/2015 Dated 13/11/2015).

Written informed consent has been obtained from all the enrolled participants of the study.

Data availability

Dataset 1: Raw data for the study 'Small for gestational age babies and depressive symptoms of mothers during pregnancy: Results from a birth cohort in India' available on OSF: http://doi.org/10.17605/OSF.IO/BV8F6[65].

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Supplementary material

Supplementary File 1. SGA and EPDS_Supplementary tables and graph.

Click here to access the data.

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http://www.doi.org/10.17605/OSF.IO/BV8F6

Open Peer Review

Current Referee Status: ✔ ? ✘

Version 2

Referee Report 24 April 2019

https://doi.org/10.21956/wellcomeopenres.16498.r35333

? **Howard Cabral**
Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

This paper examines the association of maternal depressive symptoms during pregnancy and small for gestation age delivery in a birth cohort in India from April 2016 to October 2017. The paper is generally well written and the tables and figures are well done and informative.

There are several points raised in the prior review that have not been addressed in the revised text.

Among the important confounding variables not included in the analysis would indeed be exposure to violence, a factor that is often not included in similar studies, though it clearly should be if available given that depressive symptomatology is the primary independent variable here. Checking the effects of applying different cutoffs to the Edinburgh (EPDS) score is helpful from a clinical standpoint, though the intent of developing a score is to be able to identify risk that is subclinical. Hence, analyses that use the EPDS score as continuous would also be informative. Women with scores less than a cutoff are indeed not “without mental depressive symptoms”. The authors note that they have performed analyses using the continuous score but this is not apparent in the Methods or Results but in a Supplemental file. If this is the accepted approach of the publishing platform, this is fine but a link to this information of results should be included in the main text also.

The authors state that additional statistical analyses checked for effect modification (interaction) with depressive symptoms for salient variables on intrauterine growth. The methods and results of these models are not shown in the main text. Are these included in the Supplemental File also? If so, the recommendation above applies here also. If the interactions were found to be statistically and clinically significant, then showing the main effects only model as the primary set of results is inappropriate.

As noted above with respect to exposure to violence, very important confounders are not included in the statistical models that could alter the estimation of the effect of depressive symptoms on intrauterine growth. These would include maternal pre-pregnancy weight or BMI, as well as maternal health habits that have been shown to have associations with depressive symptoms, including maternal substance use of various kinds and the quality of prenatal care. A list of the most important confounders that were not examined in this study should be included in the limitations.

The English grammar in the text should be thoroughly re-checked.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics, statistical modeling, maternal and child health.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Referee Report 14 November 2018

https://doi.org/10.21956/wellcomeopenres.15915.r33919

Nisreen A. Alwan
Academic Unit of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, University of Southampton, Southampton, UK

This is an observational study which measured maternal depressive symptoms during pregnancy using the Edinburgh Postnatal Depression Scale (EPDS), and examined if this is linked to having a small for gestational age (SGA) birth in the MAASTHI birth cohort in India.

The stated study aim in the manuscript is to “replicate the association between antepartum depression and SGA in the setting of a public hospital in India”, however the abstract conclusion seems to comment on the validity of using EPDS as a screening tool for antenatal depression. The study does not explicitly state the aim of examining the validity of EPDS as a screening tool. The abstract also reports values for the AUC using different cut-offs of EPDS for the diagnosis of antenatal depression. These values are only in relation to the SGA outcome examined in this study and does not compare EPDS to a ‘gold standard’ or another screening test for antenatal depression. Therefore, it is not accurate to comment of the “usefulness of using 10-item EPDS screening tool” in relation to other outcomes other than SGA, or for use as a screening tool in general.
The manuscript needs to be clear about this, and if the authors would like to keep the ‘prediction’ element of EPDS in relation to SGA as an outcome, they need to be clear about this in the aims and methods.

Under the Methods section-Measurement, the authors state that they “aimed to assess the exact EPDS score cut-off value (11,12 or 13) as a better predictor of association between antenatal depression and SGA”. Firstly, this statement needs to move to the aims section at the end of the Introduction section, and also needs to be clearly stated in the abstract. Secondly, this aim is not interchangeable with testing if EDPS is a valid screening tool for antenatal depression in the population the study is trying to generalise results to.

Under the Statistical Analysis section, it is not clear whether the association with SGA was examined using the continuous EPDS score or the 3 categorical variables based on the cut-off scores of 11, 12 and 13, or both.

Was maternal body mass index taken into account as a confounder?

Under the Results section, second paragraph: "among mothers with depressive symptoms….” using what EPDS cut-off? This applies to all the descriptive findings.

It is strange that the direction of effect is so different between using a cut-off of 11 versus 12 or 13 of the same scale (aOR 2.18 versus 0.46 and 0.41). Please check your categories and what you have assigned as a reference in your models.

Last paragraph of the results section, 'accuracy of EPDS scale' in relation to what? Are you saying that the strength of association with one outcome (SGA) a measure of accuracy of the screening test? Please clarify. If you are trying to predict the outcome then that is a function of other factors accounted for in the prediction model (if it is adjusted), not just the EPDS cut-off.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

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Are the conclusions drawn adequately supported by the results?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 12 Feb 2019

Giridhara R Babu, Public Health Foundation of India, India

1. The stated study aim in the manuscript is to "replicate the association between antepartum depression and SGA in the setting of a public hospital in India", however the abstract conclusion seems to comment on the validity of using EPDS as a screening tool for antenatal depression. The study does not explicitly state the aim of examining the validity of EPDS as a screening tool. The abstract also reports values for the AUC using different cut-offs of EPDS for the diagnosis of antenatal depression. These values are only in relation to the SGA outcome examined in this study and does not compare EPDS to a 'gold standard' or another screening test for antenatal depression. Therefore, it is not accurate to comment of the "usefulness of using 10-item EPDS screening tool" in relation to other outcomes other than SGA, or for use as a screening tool in general.

Thank you for the comments. We have modified the abstract conclusion and result section as per the suggestion.

2. The manuscript needs to be clear about this, and if the authors would like to keep the 'prediction' element of EPDS in relation to SGA as an outcome, they need to be clear about this in the aims and methods.

We have used antenatal depression as the exposure and SGA as an outcome. We have mentioned it clearly in the aims and methods.

3. Under the Methods section-Measurement, the authors state that they "aimed to assess the exact EPDS score cut-off value (11,12 or 13) as a better predictor of association between antenatal depression and SGA". Firstly, this statement needs to move to the aims section at the end of the Introduction section, and also needs to be clearly stated in the abstract. Secondly, this aim is not interchangeable with testing if EDPS is a valid screening tool for antenatal depression in the population the study is trying to generalise results to.

We sincerely thank the reviewer for the comment. The aim of the study is now modified as per the suggestion of the reviewer. We agree with the reviewer that the aim is not interchangeable with testing if EDPS as a valid screening tool for antenatal depression in the population. Clearly, we do not have the intent of doing so. There is no external validity (generalization) without meeting the internal validity. Since our study not immune to the source of systematic error similar to all other observational studies, we are not providing any causal inference regarding the association between EPDS and SGA. We have included this limitation in the revised manuscript.

4. Under the Statistical Analysis section, it is not clear whether the association with SGA was examined using the continuous EPDS score or the 3 categorical variables based on the cut-off scores of 11, 12 and 13, or both.

- The legends of tables contain the categorical classification of EPDS score as per the cut-offs as 11, 12 and 13

- Association with SGA was examined using EPDS score as categorical variable based on the cut off values. We have updated the details in the Statistical Analysis section as well **.(Page 9 Line 6)**

5. Was maternal body mass index taken into account as a confounder?

As we have no data on pre-pregnancy BMI we have not considered the body mass index obtained during different trimester of pregnancy as a confounder, but we have taken sum of skinfold thickness into account. (1)

6. Under the Results section, second paragraph: "among mothers with depressive symptoms….” using what EPDS cut-off? This applies to all the descriptive findings.

Here depressive symptom is defined as EPDS score >11 as we have mentioned in Table 1 and it applies for all descriptive findings. In the present study the cutoff score 13 showed highest OR compared to rest two categories, however, we have shown the descriptive statistics with cutoff of 11 since it is the minimum value at which we got statistically significant results.

7. It is strange that the direction of effect is so different between using a cut-off of 11 versus 12 or 13 of the same scale (aOR 2.18 versus 0.46 and 0.41). Please check your categories and what you have assigned as a reference in your models.

We sincerely thank the reviewer for this input. Please note that there was a mistake in coding the variable (EPDS score cut off 11, 12, 13). We recoded the entire data set and have thoroughly checked the entire analysis after redoing it. The resulted OR changes gradually from one cut off category to another. (OR : 2.03 ,1.96, 2.42 respectively)

8. Last paragraph of the results section, ‘accuracy of EPDS scale’ in relation to what? Are you saying that the strength of association with one outcome (SGA) a measure of accuracy of the screening test? Please clarify. If you are trying to predict the outcome then that is a function of other factors accounted for in the prediction model (if it is adjusted), not just the EPDS cut-off.

In our study, the use of EPDS score without adjusting for its confounders resulted in very low specificity in predicting SGA. The area under ROC curve using EPDS score alone in predicting SGA was 0.515. EPDS is a screening tool and hence may not fare well as a diagnostic test. However, after adjusting for confounders, the accuracy improved. Therefore, we meant that accuracy in predicting SGA by using EPDS scale improves after accounting for other variables confounders. This section is modified. (Page 18 Line 1)

1. Piers L, Soares M, Frandsen S, O'dea K. Indirect estimates of body composition are useful for groups but unreliable in individuals. International journal of obesity. 2000;24(9):1145.

Competing Interests: No competing interests were disclosed.

Referee Report 08 October 2018

https://doi.org/10.21956/wellcomeopenres.15915.r33915

Howard Cabral
Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

This paper examines the association of maternal depressive symptoms during pregnancy and small for gestation age delivery in a birth cohort in India from April 2016 to October 2017. The paper is generally well written and the tables and figures are well done and informative.

A number of points of concern, however, can be raised regarding this paper. Among these are points raised in a prior review by Dr. Desai, all of which are very pertinent. The inclusion of fetal loss deliveries would not be appropriate. If these were excluded the sample should be described as one comprised of livebirths only. Also, the inclusion of multiples would render as inappropriate analyses that assume independent observations. Not accounting for potential clustering by clinical site would additionally be inappropriate should such effects be observed (standard errors would likely be too small without such adjustment for site). Among the important confounding variables not included in the analysis would indeed be exposure to violence, a factor that is often not included in similar studies, though it clearly should be if available given that depressive symptomatology is the primary independent variable here.

In terms of additional comments, the following can be listed:

1. The data analyzed should be described as the “study sample” and not the “study population”.

2. Checking the effects of applying different cutoffs to the Edinburgh (EPDS) score is helpful from a clinical standpoint, though the intent of developing a score is to be able to identify risk that is subclinical. Hence, analyses that use the EPDS score as continuous would also be informative. Women with scores less than a cutoff are indeed not “without mental depressive symptoms”.

3. The statistical analyses did not include checks of effect modification (interaction) with depressive symptoms for salient variables on intrauterine growth.Such effects should be checked at a minimum to verify that the main effects only model is valid. Any effect modification identified would be useful in delineating the mechanism of how depressive symptoms affect intrauterine growth.

4. Very important confounders are not included in the statistical models that could alter the estimation of the effect of depressive symptoms on intrauterine growth.These would include maternal pre-pregnancy weight or BMI, as well as maternal health habits that have been shown to have associations with depressive symptoms, including maternal substance use of various kinds and the quality of prenatal care.

5. The fit of the logistic regression models with respect to calibration should include the Hosmer-Lemeshow statistic and its associated degrees of freedom and p-value. A good fitting model should have both good calibration and discrimination.

6. The discrimination abilities of the models (c statistics or area under the ROC curve) are poor and barely above the null value of 0.5.The lack of additional confounding control also likely contributed to this under-fitting. In addition, there must be some recoding of the data that somehow has resulted in c statistics less than 0.5. The authors should carefully check this. There should not be values less than 0.5. Moreover, such a coding problem has likely resulted in the stark change in the direction of the odds ratios as shown in Table 4. There should not be such a drastic change from an odds ratio of 2.18 for the EPDS cutoff of 11 that indicates higher risk of SGA to one of 0.46 for a cutoff of 0.46. This kind of error markedly reduces the confidence of the reader in the overall analysis.

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Are the conclusions drawn adequately supported by the results?
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Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Feb 2019

Giridhara R Babu, Public Health Foundation of India, India

1.This paper examines the association of maternal depressive symptoms during pregnancy and small for gestation age delivery in a birth cohort in India from April 2016 to

October 2017. The paper is generally well written and the tables and figures are well done and informative.

We sincerely thank the reviewer for the encouraging review with very constructive suggestions.

2. **A number of points of concern, however, can be raised regarding this paper. Among these are points raised in a prior review by Dr. Desai, all of which are very pertinent. The inclusion of fetal loss deliveries would not be appropriate. If these were excluded the sample should be described as one comprised of livebirths only. Also, the inclusion of multiples would render as inappropriate analyses that assume independent observations. Not accounting for potential clustering by clinical site would additionally be inappropriate should such effects be observed (standard errors would likely be too small without such adjustment for site).**

Thank you for the very useful comment. We have provided the responses for each point.

- Twin deliveries and stillbirths were excluded from the study analysis. We have now mentioned this in the Methods. (Page 6 and Line 10)
- Women with Multiple viable wombs are excluded from the study and analysis
- We have conducted the study in only one hospital. Therefore, there is no possibility of errors induced due to clustering.

3. Among the important confounding variables not included in the analysis would indeed be exposure to violence, a factor that is often not included in similar studies, though it clearly should be if available given that depressive symptomatology is the primary independent variable here.

We understand and agree that exposure to domestic violence was not measured in our study. However, the assessment of the psychosocial environment in the pregnant women was clearly directed **at the end result of many factors** resulting in stress/depression in pregnant women such as domestic violence might have resulted in. For example, if the women is a victim of domestic violence, the questions in the questionnaire would definitely indicate that she would not have slept well or felt low or has suicidal tendencies etc. Including the assessment of domestic violence as an antecedent was not done as it would have amounted to include other sources of maternal stress/depression such as job stress, social settings, poverty etc.

In terms of additional comments, the following can be listed:
4.The data analyzed should be described as the "study sample" and not the "study population".

Thank you for the comment, we have made the necessary change.

5.Checking the effects of applying different cutoffs to the Edinburgh (EPDS) score is helpful from a clinical standpoint, though the intent of developing a score is to be able to identify risk that is subclinical. Hence, analyses that use the EPDS score as continuous would also be informative. Women with scores less than a cutoff are indeed not "without mental depressive symptoms".

We sincerely appreciate this comment and do agree that it is useful to examine the risk of a sub-clinical group. In this regard, we have provided a graph indicating the relation between EPDS as a continuous variable and the proportion of women delivered with SGA. (**Supplementary File:**

Figure 1, Page 2)

6.The statistical analyses did not include checks of effect modification (interaction) with depressive symptoms for salient variables on intrauterine growth. Such effects should be checked at a minimum to verify that the main effects only model is valid. Any effect modification identified would be useful in delineating the mechanism of how depressive symptoms affect intrauterine growth.

We sincerely thank for this suggestion. As per the advice, we have run separate models including interaction effect. The results are provided in (**Supplementary File: Table 1, Page 1**)
We considered skinfold thickness as a continuous variable and excluded BMI to avoid the problem of multicollinearity.

7.Very important confounders are not included in the statistical models that could alter the estimation of the effect of depressive symptoms on intrauterine growth. These would include maternal pre-pregnancy weight or BMI, as well as maternal health habits that have been shown to have associations with depressive symptoms, including maternal substance use of various kinds and the quality of prenatal care.

We have not measured the maternal pre-pregnancy weight, however, have adjusted for the maternal sum of skinfold thickness. Maternal substance use is very minimal (less than 1%) in the study sample, we have adjusted for the husband's current tobacco and alcohol consumption.

8.The fit of the logistic regression models with respect to calibration should include the Hosmer-Lemeshow statistic and its associated degrees of freedom and p-value. A good fitting model should have both good calibration and discrimination. The discrimination abilities of the models (c statistics or area under the ROC curve) are poor and barely above the null value of 0.5.The lack of additional confounding control also likely contributed to this under-fitting. In addition, there must be some recoding of the data that somehow has resulted in c statistics less than 0.5. The authors should carefully check this. There should not be values less than 0.5. Moreover, such a coding problem has likely resulted in the stark change in the direction of the odds ratios as shown in Table 4. There should not be such a drastic change from an odds ratio of 2.18 for the EPDS cutoff of 11 that indicates higher risk of SGA to one of 0.46 for a cutoff of 0.46. This kind of error markedly reduces the confidence of the reader in the overall analysis.

Thank you for pointing out this. We sincerely thank you for pointing to the error; it is very useful insight and we realized that there was a mistake in coding the variable (EPDS score cut off 11, 12, 13). We recoded the entire data set and have thoroughly checked the entire analysis after redoing it. The resulted OR changes gradually from one cut off category to other and the AUROC curves obtained from the predicted probabilities of each model are above the null value. We sincerely apologize for the mistake. Hosmer-Lemeshow test statistic indicated model is a good fit. Overall model predictability is 83.6% for EPDS cut off category 11. We tried performing discriminant analysis, but the factors found to have a significant deviation from the multivariate normal distribution.

Competing Interests: No competing interests were disclosed.

Referee Report 03 September 2018

https://doi.org/10.21956/wellcomeopenres.15915.r33687

Geetha Desai
Department of Psychiatry , National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India

It is well written report. Few clarifications may be added to methods. EPDS is a self rated instrument, how was it administered to women who could not rate the tool due to illiteracy. How was the tool translated?

Please mention that there are different cut offs that have been established for different samples (Shrestha et al. 2016[1])

In the flow chart, can you make it clear on how many had delivered when this report was written (was it 763?) or were there any exclusions due to fetal loss or twins?

Since there is a mention of women being referred to psychiatrist if the score was more than >13 , is there a possibility that they took treatment and hence there was no link to SGA? Can you describe the public hospital, was it just one or many centers?

Was violence assessed? As it is considered a risk factor.

Since many of the public hospitals do not have adequate space, how was privacy ensured?

Did any of the women have hyperemesis?

References

1. Shrestha SD, Pradhan R, Tran TD, Gualano RC, Fisher JR: Reliability and validity of the Edinburgh Postnatal Depression Scale (EPDS) for detecting perinatal common mental disorders (PCMDs) among women in low-and lower-middle-income countries: a systematic review.*BMC Pregnancy Childbirth*. 2016; **16**: 72 PubMed Abstract | Publisher Full Text
2. Ing H, Fellmeth G, White J, Stein A, Simpson JA, McGready R: Validation of the Edinburgh Postnatal Depression Scale (EPDS) on the Thai-Myanmar border.*Trop Doct*. 2017; **47** (4): 339-347 PubMed Abstract | Publisher Full Text

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Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Feb 2019

Giridhara R Babu, Public Health Foundation of India, India

1.It is a well-written report. Few clarifications may be added to methods.
Many thanks for the encouraging review.

2. EPDS is a self-rated instrument, how was it administered to women who could not rate the tool due to illiteracy. How was the tool translated?
EPDS tool was translated into the local language (Kannada) and then back-translated to English for accuracy. Through this, efforts were made to ensure a clear and conceptually accurate translation that was easily understood by the local population. The Questionnaire was then administered to the respondents by trained Research Assistants who would interview without altering the actual meaning. The response score is quantified by asking the frequency of occurrence of depressive symptoms for the number of days.

3. Please mention that there are different cutoffs that have been established for different samples

(Shrestha et al. 2016[1])Thank you for this comment. We have included this in the manuscript now. (Page 5, Line 32)

4. In the flow chart, can you make it clear on how many had delivered when this report was written (was it 763?) or were there any exclusions due to fetal loss or twins?
Five cases were excluded as it was a twin delivery and there were four stillbirths. We have updated the flow chart.

5. Since there is a mention of women being referred to a psychiatrist if the score was more than > 13, is there a possibility that they took treatment and hence there was no link to SGA? Can you describe the public hospital, was it just one or many centres?
We have referred the women with a higher score to the psychiatrist, but we have not tracked them to ascertain the treatment that they may have received. There may be a chance that they have approached a specialist and have taken treatment. Jayanagar General Hospital; a secondary level public hospital was chosen to conduct this study.

6. Was violence assessed? As it is considered a risk factor.
No, violence was not assessed as part of this study. We have mentioned this under the limitations now.

7. Since many of the public hospitals do not have adequate space, how was privacy ensured?
We thank the reviewer for this rightful concern. The research team is allotted a separate room for administering the interview and carrying out other research activities at the hospital. Thereby, efforts are consciously made to ensure that the privacy of the respondents is assured during the interviews.

8. Did any of the women have hyperemesis?
Seven women had hyperemesis in the study sample.

Competing Interests: No competing interests were disclosed.