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Risk of Spontaneous Preterm Birth in Relation to Maternal Depressive, Anxiety and Stress Symptoms

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Abstract

Objective—To examine the risk of preterm birth (PTB) in relation to maternal psychiatric symptoms during pregnancy in Peruvian women.

Methods—This case control study included 479 PTB cases and 480 term controls. In-person interviews were conducted to assess women's depressive, anxiety and stress symptoms using the Patient Health Questionnaire (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21). Multivariable logistic regression procedures were used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results—Compared with women reporting no or minimal depressive symptoms, the aOR (95% CI) for PTB associated with consecutive severity of depressive symptoms based on the PHQ-9 assessment method were as follows: mild 2.22 (95% CI 1.64–3.00) and moderate-severe 3.67 (95% CI 2.09–6.46). The corresponding aORs for mild, moderate, and moderate- severe depressive symptoms based on the DASS-21 assessment were, 1.00 (reference), 3.82 (95% CI 1.90–7.66) and 2.90 (95% CI 1.66–5.04), respectively. A positive gradient was observed for the odds of PTB with severity of anxiety (p_{trend} <0.001) and stress symptoms (p_{trend} <0.001).

Conclusions—*T*he odds of PTB are increased in pregnant Peruvian women with psychiatric symptoms. Efforts to screen and treat affected women may modify risks of PTB and possibly other associated disorders.

INTRODUCTION

Preterm birth (PTB) complicates 5 to 7% of births in developed countries and is estimated to be even more prevalent in developing countries[1]. PTB is the leading contributor to infant morbidity and mortality, accounting for 42% of neonatal death in the Americas alone[2]. Furthermore, infants born preterm are at increased risks of enduring adverse health sequelae

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including cerebral palsy, blindness, cognitive, sensory, learning, and language deficits[3]. Although the precise etiology of PTB remains elusive, African American race, prior PTB, low maternal pre-pregnancy body mass index, low socioeconomic status, psychosocial stress, genitourinary tract infections, vascular complications, exposure to environmental toxins and polymorphisms in candidate genes, particularly those in inflammatory pathways, have been identified as PTB risk factors[4–6].

Increasingly, maternal psychiatric symptoms, particularly symptoms and or diagnoses of mood and anxiety disorders have been implicated as important PTB risk factors[7–13]. Depression, the fourth highest global disease burden in 2000 [14], psychosocial stress, anxiety, and common psychiatric symptoms, are known to be elevated during pregnancy [15, 16]. For instance, point prevalence estimates for major or minor depression range from 6.5% to 12.9% for women throughout the pregnancy [17, 18]. Notably, investigators have reported that as many as 14.5% of women experience new depressive symptoms during pregnancy [19]. Although data are limited concerning the cumulative incidence of anxiety and stress symptoms during pregnancy, investigators have noted that these symptoms are prevalent among reproductive age women in the US [20–22].

Evidence linking maternal psychiatric symptoms and diagnoses with PTB risk have been conflicting, due in part to variations in study methodologies including the diagnostic criteria and instruments used to define the disorders [9, 23]. Despite these methodological limitations, results from recent literature reviews indicate that maternal psychiatric disorders, particularly mood disorders, are important risk factors of PTB [9, 23]. For example, Orr and colleagues, reported that maternal symptoms of anxiety is associated with a 2.7-fold increased risk (OR=2.73, 95% CI: 1.03, 7.27) of PTB [24]. To the best of our knowledge, no investigators have evaluated risk of PTB in relation to maternal psychiatric symptoms among Peruvian women. Given this gap in the literature, we hypothesized that maternal depressive, anxiety and stress symptoms during pregnancy are associated with increased PTB risks among low income women in Lima, Peru. We tested our hypothesis in a large case-control study of 479 PTB cases and 480 term controls.

METHODS

Study population and selection of cases and controls

This case-control study was conducted among women who delivered live births at the Hospital Nacional Dos de Mayo, the Instituto Nacional Materno Perinatal de Lima, and the Hospital Edgardo Rebagliati Martins in Lima, Peru, from January 2009 through July 2010. This study was approved by the institutional review board of each participating institution. Cases were women with singleton pregnancies who spontaneously delivered before completed 37 weeks of gestation (22–36 weeks of gestation). Spontaneous preterm delivery cases were identified by daily monitoring of all new deliveries at postpartum wards of participating hospitals. Of the 515 eligible cases approached, 479 (93%) agreed to participate in the study. Controls were women who delivered a singleton infant at term (≥37 weeks of gestation) and were selected from the same hospital of delivery. An eligible control, delivering immediately after a case patient, was approached and recruited for the study. Of the 546 eligible controls approached, 480 (88%) agreed to participate in the study. All participants provided written informed consent.

Data collection and analytical variable specification

After obtaining informed consent, enrolled participants were asked to take part in a 45-minute in-person interview in which trained research personnel used a standardized, structured Spanish-language questionnaire to elicit information regarding maternal socio-

demographic, lifestyle habits, medical and reproductive histories. Participants' labor and delivery medical records and prenatal medical records were also reviewed by trained research fellows (obstetricians) who used a standardized abstraction form. Information abstracted from medical records included participants' medical and reproductive histories, blood pressure values, pregnancy complications and condition of the newborn.

The diagnosis of preterm delivery was made using the American College of Obstetricians and Gynecologists (ACOG) guidelines [25]. Gestational age was based on the date of the last menstrual period and was confirmed by an ultrasound examination before 20 weeks. Using detailed information collected from medical records, we categorized preterm delivery cases according to the three pathophysiological groups previously described (i.e., spontaneous preterm labor and delivery and preterm premature rupture of membranes) [26]. Spontaneous preterm labor and delivery cases were comprised of women whose medical records indicated a physician diagnosis of spontaneous labor onset (with intact fetal membranes) and delivery prior to the completion of 37 weeks gestation. Preterm premature rupture of membranes cases were comprised of women whose medical records indicated a physician diagnosis of rupture of fetal membranes (prior to the onset of labor) and delivery prior to the completion of 37 weeks gestation. Women who delivered prior to 37 completed weeks of gestation as a result of medical intervention were not eligible for this study. We also categorized preterm delivery cases according to gestational age at delivery (i.e., very preterm delivery, defined as delivery prior to the completion of 34 weeks gestation; moderate preterm delivery, defined as delivery between 34 and 36 weeks gestation).

Information collected during the interviews included maternal age, marital status, employment status during pregnancy, medical history, and smoking and alcohol consumption during pregnancy. We used the Patient Health Questionaire-9 (PHQ-9) to assess participants' experience of depression or depressive symptoms during pregnancy. The instrument has been demonstrated to be a reliable tool for assessing recent psychosocial stressors among obstetrics-gynecology patients [27] and in Spanish-speaking women [28]. In a recent validation study of the PHQ-9 questionnaire, the authors concluded that the instrument is a reliable and valid measure of depression severity and a useful clinical and research tool [29]. The PHQ-9 scale includes nine items, and choices for responses were (a) never; (b) several weeks over the pregnancy; (c) more than half the pregnancy; or (d) nearly the whole pregnancy. The PHQ-9 total score is the sum of scores for the nine items for each woman, and ranged from 0–27. We categorized participants as exhibiting minimal (PHQ-9 score 0–4), mild (PHQ-9 score 5–9), and moderate-severe (PHQ-9 score ≥10) depressive symptoms.

Maternal depressive, anxiety and stress levels were also characterized using the Depression Anxiety Stress Scales (DASS-21) instrument. The DASS-21 is a 21-item instrument designed to measure the 3 negative affective states of depression, anxiety, and stress. The depression scale assessed dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia, and inertia. The anxiety scale assessed autonomic arousal, situational anxiety, and subjective experience of anxious affect. The stress scale assessed difficulty relaxing, nervous arousal, and being easily upset or agitated, irritable, or over-reactive and impatience [30, 31]. The psychometric properties of the English and Spanish versions of DASS-21 have been extensively evaluated, and there is evidence for the convergent and discriminative validity of data obtained with the instrument[31, 32]. Brown et al. [32] reported that patients meeting the criteria for major depression, based on the DSM-III-R and using a structured interview, had a mean score of 25.3 (SD±10.24) on the DASS depression scale. Using previously suggested cutoff scores [30, 31], participants were categorized as exhibiting normal (DASS score <9), mild (DASS score 10–13), and moderate-severe (DASS score ≥14) depressive symptoms. Subjects were categorized as

exhibiting normal (DASS score <7), mild (DASS score 8–9), and moderate-severe (DASS score ≥10) anxiety symptoms. The corresponding cutoff score for symptoms of stress were as follows: normal (DASS score <14), mild (DASS score 15–18), and moderate-severe (DASS score ≥19).

Other covariates considered in this analysis included maternal age, reproductive and medical histories. Also considered were maternal pre-pregnancy weight, educational attainment, annual household income, occupation, cigarette smoking and alcohol consumption during pregnancy. Maternal age at the time of interview was expressed in years. Parity was reported as the number of previous pregnancies lasting more than 22 weeks of gestation. Maternal educational attainment was based on self-reports.

Statistical analysis

The distribution of maternal socio-demographic characteristics, medical and reproductive histories according to preterm and term delivery status was examined. To estimate the relative association between maternal psychiatric symptoms and risk of preterm delivery, logistic regression procedures were performed to calculate maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (95% CI), adjusted for potential confounding [33]. Confounding was assessed by entering potential confounders into a logistic model one at a time, and then comparing the unadjusted and adjusted ORs. We considered the following variables as possible confounders in these analyses: maternal age, parity, marital status, maternal educational attainment, pre-pregnancy weight, planned pregnancy, use of prenatal care services, employment status, cigarette smoking, alcohol consumption, and use of illicit drugs during pregnancy. Final logistic regression models included covariates that altered unadjusted ORs by at least 10% [33]. These analytical procedures were also used in stratified analyses designed to assess risk of sub-types of preterm delivery (i.e., spontaneous preterm labor and delivery, preterm premature rupture of membranes, very preterm delivery, moderate preterm delivery and mild preterm delivery). All analyses were performed using STATA 9.0 statistical software (Stata, College Station, Texas, USA). All continuous variables are presented as mean ± standard deviation (SD). All reported *P*-values are two tailed, and confidence intervals were calculated at the 95% level. Prior to initiating the study, we estimated that a study size of 400 cases and an equal number of controls would be sufficient (>85% power) for estimating odds ratios of ≥2.0 if exposure frequencies were ≥10%, and if significance was set at 0.05.

RESULTS

Sociodemographic and reproductive characteristics of PTB cases and controls are presented in Table 1. Cases and controls were statistically similar with regards to maternal age, parity, educational attainment, employment status, smoking, alcohol use, and pre-pregnancy weight. Compared with controls, cases were less likely to have received prenatal care, plan the pregnancy, or take vitamins. Unadjusted and adjusted odds ratios of PTB according to varying levels of depression, anxiety and stress symptoms, respectively, are summarized in Table 2. The odds of PTB increased with increasing severity of depressive, anxiety, and stress symptoms as measured by both the PHQ-9 and the DASS questionnaire.

Depression

After adjusting for confounding by maternal age, pre-pregnancy weight, unplanned pregnancy, prenatal vitamin and alcohol consumption during pregnancy, mild (aOR=2.22; 95% CI 1.64–3.00) and moderate-severe (aOR=3.67; 95% CI 2.09–6.46) depressive symptoms, determined using the PHQ-9 instrument, were statistically significantly associated with increased odds of PTB, compared with minimal depressive symptoms

(Table 2). The corresponding aORs for mild and moderate-severe depressive symptoms based on the DASS-21 assessment were (aOR=3.82, 93%; 1.90–7.66) and (aOR=2.90; 95% CI 1.66–5.04), respectively. Strong positive and statistically significant associations of PTB categorized by sub-type (SPTL or PPROM) or severity of preterm birth (<34 weeks, or 34–36 weeks) were evident and are summarized in Tables 3 and Table 4, respectively.

Anxiety and Stress

The odds of PTB were also positively and statistically significantly associated with anxiety and stress symptoms as measured using the DASS-21 questionnaire (Table 2). Compared with the reference group (anxiety symptom score ≤7) women with mild (DASS score 8–9) anxiety symptoms had a modest increased odds of PTB (aOR=1.72; 95% CI 1.11–2.67). Women with moderate-severe anxiety symptoms (DASS score ≥10), as compared with the reference group, had a greater than 2-fold odds of PTB (aOR=2.76; 95% CI 1.83–4.16). Associations of similar directions and magnitudes were observed when sPTB were sub-categorized according to clinical presentation (SPTL or PPROM, Table 3) or severity (very PTB vs. moderate PTB, Table 4). The odds of PTB increased with increasing severity of stress symptoms as measured by the DASS-21 subscale (p for trend<0.001). After adjusting for confounding by maternal age, pre-pregnancy weight, unplanned pregnancy, prenatal vitamin and alcohol consumption during pregnancy, mild (aOR=2.40; 95% CI 1.16–4.95) and moderate-severe stress (aOR=11.07; 95% CI 5.64–21.71) were statistically significantly associated with increased odds of PTB. Associations were similar when analyses were repeated after stratification by PTB subtype (Table 3) or severity (Table 4).

DISCUSSION

Women with depressive, anxiety and stress symptoms during pregnancy had higher odds of PTB when compared with women without such symptoms. To the best of our knowledge, this is the first study examining associations of depressive, anxiety and stress symptoms with PTB among Peruvian women. Our findings are largely consistent with other studies reporting positive associations of psychiatric disorders and psychosocial stress with PTB [7, 9–13, 24]. For instance, in their hospital-based medical records of over 32 million births to women in the US, Bansil and colleagues reported that women with a diagnosis of depression had an increased odds of PTB (aOR=1.71; 95% CI 1.65–1.77) [7]. In their study of women residing in Baltimore, Maryland, USA, Orr et al observed that maternal anxiety symptoms were positively associated with the odds of PTB. The authors reported that the odds of PTB was increased 2.7-fold for mothers with the highest levels anxiety symptoms as compared with minimal symptoms (aOR=2.73; 95% CI 1.03–7.27)[24]. Of note, in a recent meta-analysis of 20 studies focused on the assessment of PTB risk in relation to maternal antepartum depression, Grote and colleagues [9] reported that antepartum depression, regardless of the type of antenatal depression measurement, is associated with modest but statistically significant increased risks of PTB. Point estimates of associations of maternal psychological stress and psychiatric symptoms and PTB are larger (stronger associations) for our present study than many of the prior studies. However, these stronger associations are consistent with results reported by Grote et al [9] who noted that relative risk estimates for adverse pregnancy outcomes associated with depression were higher among women from developing countries. The authors also noted that relative risk estimates for PTB in relation to maternal depression and depressive symptoms were stronger for women of predominantly lower SES but not in women of middle- or upper-income status [9].

Several potential limitations should be taken into consideration when interpreting the results of our study. First, our analyses are based on cross-sectionally collected data, which may be subject to recall bias. Second, we used two depression screening instrument to categorize participants according to symptoms of depression, anxiety and stress. Participants did not

have formal diagnostic examinations. As a result, some misclassification is possible. However, both the PHQ-9 and DASS-21 have been shown to have good-to-excellent psychometric properties when compared with the Structured Clinical Interview for DSM-IV mood disorder module [28, 29, 31]. As well, the findings from both sets of analyses are consistent with each other, providing some robustness to the study. Lastly, although we adjusted for multiple confounding factors, as with all observational studies, we cannot exclude the possibility of some residual confounding.

Associations between depression and increased odds of PTB are biologically plausible. Psychiatric disorders have been associated with hypothalamic-pituitary-adrenal (HPA) axis hyperactivity[34]. Maternal depression, for example, is thought to activate the mother's HPA axis and, in turn, is regulated by peptides derived from the activated HPA axis. Depression may cause an increase in the release of corticotropin-releasing hormone (CRH) from the placenta via the actions of catecholamines and cortisol [35–40]. Smith and colleagues examined the relationships between mood changes, obstetric experience, and alterations in plasma cortisol, beta-endorphin, and CRH[36]. Plasma levels of these hormones were obtained throughout pregnancy, at delivery, and postpartum. Smith and colleagues reported that the prevalence of mood disturbances found in the late antenatal period was higher than the level found in the postnatal period; the prevalence correlated with hormone levels, which peaked in late pregnancy and fell postpartum[36]. These data suggest a role for CRH and the HPA axis in the relationship between antenatal mood states and obstetric events. Depression may be mediated by an altered excretion of vasoactive hormones and other neuroendocrine transmitters. This may in turn cause vasoconstriction and uterine artery resistance and, therefore, premature labor[39]. Available evidence also implicates pro-inflammatory cytokines in the pathogenesis of psychiatric disorders, particularly major depression. The stress hormones may facilitate inflammation through induction of interleukins (IL) such as IL-1, IL-6, tumor necrosis factor-alpha, and C-reactive protein production [41] and contribute to the pathogenesis of PTB [42].

Our results, combined with those reported by others, suggest that the risk of PTB is increased in women experiencing psychological stress and symptoms of mood and anxiety disorders during pregnancy. Additional efforts are required to carefully characterize the sequelae of psychiatric illnesses among pregnant women. Longitudinal studies, with prospective assessment of clinical and sub-clinical psychiatric illnesses in ethnically and racially diverse populations are warranted. Efforts to screen and treat affected women may modify risks of PTB and possibly other associated disorders.

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Table 1

Socio-Demographic and Reproductive Characteristics and Infant Outcomes in the Study Population, Lima, Peru, 2009–2010

	Preterm Birth				
	Control (N=480)		Case (N=479)		
Characteristics	**n**	**%**	**n**	**%**	**p-value**
Maternal Age at delivery (years)	28.3 ± 6.5		28.2 ± 6.6		0.74
Maternal Age at delivery (years)					
<20	42	8.8	49	10.2	0.49
20–29	235	49.0	228	47.6	
30–34	94	19.6	107	22.3	
≥35	109	22.7	95	19.8	
Missing	199	41.5	205	42.8	0.68
Primiparity	335	69.8	319	66.6	0.29
High School Education or lower	195	40.6	177	37.0	0.24
Employed during Pregnancy	209	43.5	152	31.7	<0.001
Planned Pregnancy	19	4.0	75	15.7	<0.001
No Prenatal Care	68	14.2	119	24.8	<0.001
No Prenatal Vitamin					
Smoking during Pregnancy					
No	426	88.8	410	85.6	0.14
Yes	54	11.2	69	14.4	
Alcohol use during Pregnancy	157	32.7	150	31.3	0.64
Illicit Drug use during Pregnancy	0	0.0	3	0.6	---
Pre-pregnancy weight (kg)	58.0 ± 9.8		56.7 ± 10.0		0.04
Infant Birth Weight (grams)	3393 ± 462		1999 ± 663		<0.001
Low Birth Weight Infant (<2500grams)	14	2.9	381	76.5	<0.001

*Mean ± SD (SD: standard deviation)

Table 2

Odds Ratio and 95% CI of Preterm Birth According to Levels of Depression, Anxiety and Stress Symptom Scores Assessed Using the Patient Health Questionnaire-9 (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21), Lima, Peru, 2009–2010

	Controls (n = 480)		ALL PTB (n = 479)		Unadjusted OR		Adjusted OR	
(Instrument) & Psychiatric Symptom	**n**	**%**	**n**	**%**		**(95% CI)**		**(95% CI)**
(PHQ-9) Depression								
Minimal (0–4)	339	70.6	239	49.9	1.00	referent	1.00	referent
Mild (5–9)	122	25.4	188	39.3	2.19	(1.65–2.90)	2.22	(1.64–3.00)
Moderate-Severe (≥10)	19	4.0	52	10.9	3.88	(2.24–6.73)	3.67	(2.09–6.46)
P-value for Trend						<0.001		<0.001
(DASS-21) Depression								
Normal (0–9)	450	93.7	387	80.8	1.00	referent	1.00	referent
Mild (10–13)	11	2.3	38	7.9	4.02	(2.03–7.97)	3.82	(1.90–7.66)
Moderate-Severe (≥14)	19	4.0	54	11.3	3.30	(1.93–5.67)	2.90	(1.66–5.04)
P-value for Trend						<0.001		<0.001
(DASS-21) Anxiety								
Normal (0–7)	401	83.5	329	68.7	1.00	Referent	1.00	referent
Mild (8–9)	40	8.3	56	11.7	1.71	(1.11–2.63)	1.72	(1.11–2.67)
Moderate-Severe (≥10)	39	8.1	94	19.6	2.94	(1.97–4.39)	2.76	(1.83–4.16)
P-value for Trend						<0.001		<0.001
(DASS-21) Stress								
Normal (0–14)	458	95.4	359	75.0	1.00	Referent	1.00	referent
Mild (15–18)	12	2.5	23	4.8	2.45	(1.20–4.98)	2.40	(1.16–4.95)
Moderate-Severe (≥19)	10	2.1	97	20.2	12.4	(6.36–24.07)	11.07	(5.64–21.71)
P-value for Trend						<0.001		<0.001

*Adjusted for maternal age, pre-pregnancy weight, unplanned pregnancy, prenatal vitamin and alcohol consumption during pregnancy

Table 3

Odds Ratio and 95% CI of Preterm Birth Sub-Types According to Levels of Depression, Anxiety and Stress Symptom Scores Assessed Using the Patient Health Questionnaire-9 (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21), Lima, Peru, 2009–2010

	Controls (N=480)	SPTL (N = 245)		PPROM (N = 234)	
(Instrument) & Psychiatric Symptom	**n**	**n**	**OR* (95% CI)**	**n**	**OR* (95% CI)**
(PHQ-9) Depression					
Minimal (0–4)	339	129	1.00 (referent)	110	1.00 (referent)
Mild (5–9)	122	86	1.96 (1.37–2.82)	102	2.50 (1.75–3.59)
Moderate-Severe (≥10)	19	30	4.13 (2.21–7.70)	22	3.20 (1.65–6.22)
P-value for Trend			<0.001		<0.001
(DASS-21) Depression					
Normal (0–9)	450	200	1.00 (referent)	187	1.00 (referent)
Mild (10–13)	11	18	3.56 (1.63–7.76)	20	4.09 (1.89–8.81)
Moderate-Severe (≥14)	19	27	2.89 (1.55–5.41)	27	2.90 (1.55–5.44)
P-value for Trend			<0.001		<0.001
(DASS-21) Anxiety					
Normal (0–7)	401	165	1.00 (referent)	164	1.00 (referent)
Mild (8–9)	40	28	1.77 (1.05–2.98)	28	1.67 (0.99–2.83)
Moderate-Severe (≥10)	39	52	3.15 (1.99–5.01)	42	2.39 (1.47–3.87)
P-value for Trend			<0.001		<0.001
(DASS-21) Stress					
Normal (0–14)	458	193	1.00 (referent)	166	1.00 (referent)
Mild (15–18)	12	10	2.04 (0.86–4.85)	13	2.79 (1.23–6.33)
Moderate-Severe (≥19)	10	42	8.89 (4.32–18.27)	55	13.67 (6.73–27.76)
P-value for Trend			<0.001		<0.001

*Adjusted for maternal age, pre-pregnancy weight, unplanned pregnancy, prenatal vitamin and alcohol consumption during pregnancy

Table 4

Odds Ratio and 95% CI of Preterm Birth Severity According to Levels of Depression, Anxiety and Stress Symptom Scores Assessed Using the Patient Health Questionnaire-9 (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21), Lima, Peru, 2009–2010

	Controls (N=480)	<34 weeks (N = 213)		34-<37 weeks (N = 266)	
(Instrument) & Psychiatric Symptom	**n**	**n**	**OR* (95% CI)**	**n**	**OR* (95% CI)**
(PHQ-9) Depression					
Minimal (0–4)	339	105	1.00 (referent)	134	1.00 (referent)
Mild (5–9)	122	85	2.27 (1.56–3.30)	103	2.18 (1.54–3.09)
Moderate-Severe (≥10)	19	23	3.69 (1.90–7.13)	29	3.67 (1.96–6.86)
P-value for Trend			<0.001		<0.001
(DASS-21) Depression					
Normal (0–9)	450	164	1.00 (referent)	223	1.00 (referent)
Mild (10–13)	11	23	5.35 (2.52–11.33)	15	2.64 (1.18–5.92)
Moderate-Severe (≥14)	19	26	3.37 (1.79–6.36)	28	2.55 (1.37–4.75)
P-value for Trend			<0.001		<0.001
(DASS-21) Anxiety					
Normal (0–7)	401	144	1.00 (referent)	185	1.00 (referent)
Mild (8–9)	40	26	1.83 (1.07–3.13)	30	1.64 (0.98–2.74)
Moderate-Severe (≥10)	39	43	2.86 (1.76–4.63)	51	2.68 (1.69–4.26)
P-value for Trend			<0.001		<0.001
(DASS-21) Stress					
Normal (0–14)	458	166	1.00 (referent)	193	1.00 (referent)
Mild (15–18)	12	11	2.43 (1.04–5.68)	12	2.38 (1.04–5.47)
Moderate-Severe (≥19)	10	36	8.68 (4.16–18.09)	61	13.21 (6.56–26.61)
P-value for Trend			<0.001		<0.001

*Adjusted for maternal age, pre-pregnancy weight, unplanned pregnancy, prenatal vitamin and alcohol consumption during pregnancy