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Risk Factors for Postpartum Depression and Severe Distress among Mothers of Very Preterm Infants at NICU Discharge

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Abstract

Objective To identify psychological, medical, and socioenvironmental risk factors for maternal postpartum depression (PPD) and severe psychological distress (SPD) at intensive care nursery discharge among mothers of very preterm infants.

Study Design We studied 562 self-identified mothers of 641 infants born <30 weeks who were enrolled in the Neonatal Neurobehavior and Outcomes in Very Preterm Infants Study (NOVI) conducted in nine university-affiliated intensive care nurseries. Enrollment interviews collected socioenvironmental data, depression, and anxiety diagnoses prior to and during the study pregnancy. Standardized medical record reviews ascertained prenatal substance use, maternal and neonatal medical complications. The Edinburgh Postnatal Depression Scale and Brief Symptom Inventory were administered at nursery discharge to screen for PPD and SPD symptoms, respectively.

Results Unadjusted analyses indicated mothers with positive screens for depression ($n = 76$, 13.5%) or severe distress ($n = 102$, 18.1%) had more prevalent prepregnancy/prenatal depression/anxiety, and their infants were born at younger gestational ages, with more prevalent bronchopulmonary dysplasia, and discharge

Keywords
- postpartum depression
- severe psychological distress
- prenatal marijuana use
- very preterm infants

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after 40 weeks postmenstrual age. In multivariable analyses, prior depression or anxiety was associated with positive screens for PPD (risk ratio [RR]: 1.6, 95% confidence interval [CI]: 1.1–2.2) and severe distress (RR: 1.6, 95% CI: 1.1–2.2). Mothers of male infants had more prevalent depression risk (RR: 1.7, 95% CI: 1.1–2.4), and prenatal marijuana use was associated with severe distress risk (RR: 1.9, 95% CI: 1.1–2.9). Socioenvironmental and obstetric adversities were not significant after accounting for prior depression/anxiety, marijuana use, and infant medical complications.

Conclusion Among mothers of very preterm newborns, these multicenter findings extend others' previous work by identifying additional indicators of risk for PPD and SPD associated with a history of depression, anxiety, prenatal marijuana use, and severe neonatal illness. Findings could inform designs for continuous screening and targeted interventions for PPD and distress risk indicators from the preconception period onward.

Key Points

- Preconceptional and prenatal screening for postpartum depression and severe distress may inform care.
- Prior depression, anxiety, and neonatal complications predicted severe distress and depression symptoms at NICU discharge.
- Readily identifiable risk factors warrant continuous NICU screening and targeted interventions to improve outcomes.

Postpartum depression (PPD) and severe psychological distress (SPD) affect 10 to 15% of mothers,[1] placing them at risk for recurring symptoms,[2–4] threats to positive relationships with their infants,[5–7] and increasing risk for children's poor developmental outcomes.[8–10] PPD and SPD have been associated with a history of depression, anxiety, perinatal loss, obstetric complications, traumatic events, and low social support.[1,11,12] These risk factors are also associated with preterm birth,[13] and among mothers who deliver preterm, reported rates of PPD and SPD range from 18 to 43%.[14–19] At greatest risk are mothers of infants born <30 weeks of gestation, where the infants' immaturity and illness create persistent challenges to maternal coping processes.[17,20]

Previous studies of mothers of preterm infants highlighted the need to detect early, potentially treatable risk factors for PPD and SPD.[6,16,21] Characterizing birthing parents' risk factors and needs at admission to the neonatal intensive care unit (NICU) could expedite the initiation and continuation of supportive interventions beginning early in the infant's stay in the NICU.[14,15,22] Concurrent care for birthing parents and their infants would also benefit from an illumination of specific neonatal medical conditions that may initiate or exacerbate maternal psychological disequilibrium and present cumulative threats to adaptation over time.[8–10]

Toward the goal of informing family-centered practices, the present study was designed to address evidence gaps about birthing parents' needs at NICU admission and discharge by examining *in concert* the parent, infant, and socioenvironmental characteristics associated with postpartum psychological challenges in a large and diverse multicenter sample.

Our own previous work described adverse medical and socioenvironmental conditions, including prenatal depression, anxiety, and substance use associated with neurobehavioral regulation and epigenetic processes in infants born <30 weeks postmenstrual age (PMA).[23–25] The present study extends this work to identify risk factors associated with PPD and SPD at NICU discharge, a point at which important findings about antecedent conditions could inform both preventive and targeted NICU interventions for those with significant risk factors and demonstrated needs. Further, we sought to address a knowledge gap by identifying maternal needs that emerge in the time between routine prenatal care assessments, PPD screening in the context of routine postpartum obstetric follow-up, and in follow-along pediatric care. Building on earlier studies,[17,26] we hypothesized that PPD and SPD would be associated with prior depression and/or anxiety, prenatal substance use, and more extensive medical and socioenvironmental adversities. To our knowledge, this is the first multicenter study to examine these risk factors in concert in a large and diverse sample of mothers who delivered a very preterm infant (<30 weeks gestation), and to describe the relative associations between

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psychological history, substance use, and socioenvironmental conditions, as well as maternal and infant medical complications with PPD and SPD at NICU discharge.[11,12,17,20,27]

Materials and Methods

Participants

From April 2014 through June 2016, the birthing parents who self-identified as mothers of 704 infants were enrolled from nine Level IV NICUs affiliated with six universities across the United States for participation in the Neonatal Neurobehavior and Outcomes in Very Preterm Infants Study (NOVI), a longitudinal multicenter study. NICUs included seven with delivery services and two in children's hospitals, all of which were participating in the Vermont-Oxford Network.[28] NOVI's primary aims have focused on the early and long-term outcomes among very preterm infants and their families, and the present study focuses on early maternal outcomes at NICU discharge.

The sample included 562 mothers of 641 infants with complete maternal assessments (►Fig. 1). Inclusion criteria were: (1) birth <30 weeks PMA determined by available information in order of the following hierarchy: assisted reproduction dates, fetal ultrasonogram, postmenstrual dates, or neonatal physical exam at NICU admission[29]; (2) maternal ability to read and speak English or Spanish (based on discrepancies in requisite interpreter availability across sites); and (3) residence within 3 hours of the NICU and follow-up clinic. Infants were excluded for major congenital anomalies,[30] NICU death, and maternal inability to consent for their infants due to maternal age <18 years, cognitive impairment, or death. Based on longitudinal follow-up aims, parents were invited to participate at 30 to 31 weeks PMA, when survival to NICU discharge was determined to be likely by the attending neonatologist. Informed consent was obtained in accordance with approvals by each site's institutional review board. The present study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

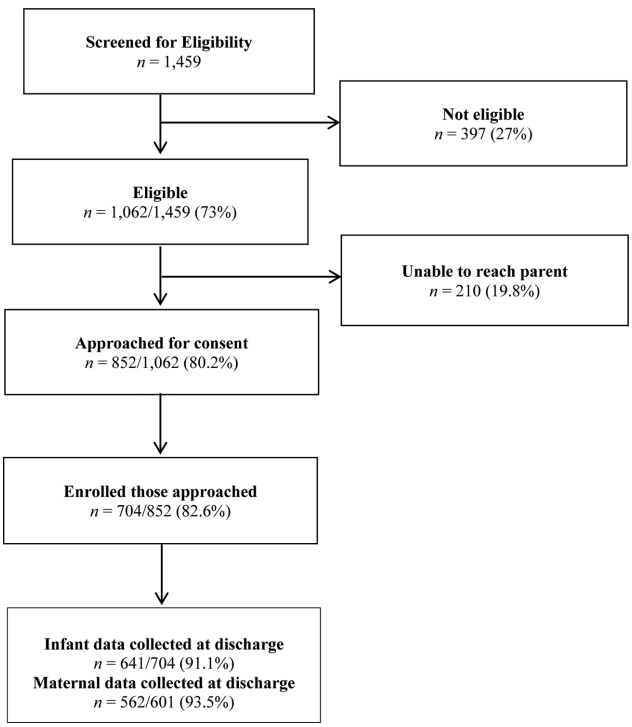

Fig. 1 Study flow and eligibility.

Procedures

Maternal Medical and Socioenvironmental Data Collection

Study Coordinators received training in the reliable implementation of standardized consenting, interviewing, and medical record extraction. In addition, each site's study neonatologist provided oversight to Study Coordinators who completed standardized reviews of infant medical records and maternal delivery admission notes. We also conducted discussions to consensus among the six NOVI Study neonatologists regarding questions about specific variables charted: prenatal and intrapartum conditions, prescribed medications, and the use of alcohol, tobacco, marijuana, and other psychoactive substances including cocaine, opioids, methamphetamine, hallucinogens, and nonprescribed pharmaceuticals (e.g., amphetamines, benzodiazepines). Standardized maternal interviews were administered to collect information about race, ethnicity, partner and cohabitation status, insurance type, education, occupation, and diagnoses of anxiety and depression both (1) prior to and (2) during the pregnancy, as well as counseling and/or medication for either or both of these conditions during either time epoch. For analyses, we identified mothers with a prior diagnosis and treatment of anxiety and/or depression by including either medical record notations or answers to interview questions regarding prior diagnoses, counseling, and/or medication for anxiety and depression.

Maternal Postpartum Depression and Severe Psychological Distress Assessments

To avoid potential variations due to literacy, Study Coordinators were trained to reliably administer the Edinburgh Postnatal Depression Scale (EPDS)[31] to assess PPD risk, and the Brief Symptom Inventory (BSI)[32] to assess SPD risk. Mothers completed the EPDS and BSI by interview during the week of their infant's discharge from the NICU. This assessment point provided information at a standardized point in time that was feasibly integrated into all nine NICUs' routine care protocols, and at a time following maternal transitions through their infants' varied acute and/or chronic medical conditions.

The well-validated EPDS[31] is a self-report screening instrument comprising 10 items related to risk for depression and anxiety. Each symptom is scored on a severity scale ranging from 0 to 3, with "0 = hardly at all/not at all/never" to "3 = quite a lot/most of the time." Total scores range from 0 to 30, where scores ≥12 indicate major depressive disorder risk; scores of 10 to 12 indicate probable mild depression risk requiring monitoring.[33] We adopted the criteria of EPDS

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scores of ≥10[1] to capture a range of severity of PPD risk from mild to severe.[34] The anxiety subscale of the EPDS, EPDS-3A, is the sum of questions 3, 4, and 5 with a range of 0 to 9 and a cut-off score of 6 suggesting symptoms of anxiety, and is distinct from overall EPDS scores among childbearing individuals.[35]

The BSI[32] is a screening instrument composed of 53 item with ratings of 0 to 5 reflecting the extent of symptom distress (i.e., 0 = "not at all" to 5 = "extremely"). Items are grouped into symptom scales (internal consistency >0.70; test–retest reliability 0.68–0.91): Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. Validated criteria for a positive BSI screen were employed to identify SPD risk using composite measures of overall psychological distress, where alpha reliability coefficients ≥0.90 exceeded reliability of individual symptom scales: (1) a Global Severity Index T-score of ≥63, or (2) T-scores ≥63 on any two primary symptom scales.[32,36,37]

Both the EPDS and the BSI include thoughts of self-harm and other symptoms experienced during the previous week. Maternal assessments were administered during the week of NICU discharge, at a time designed to (1) avoid potentially stressful questions and limit measurement variability during periods of the infants' severe and wide-ranging illnesses, (2) standardize the developmental stage for maternal screening to the time at which infants were stable enough for discharge, and (3) identify the range of both maternal post-discharge needs and early and ongoing neonatal risk factors that preceded PPD and SPD. The present study's protocol ensured psychological support referrals for mothers who reported thoughts of self-harm or extreme symptoms on the EPDS or BSI, became distraught completing the questionnaires, or requested help. All data collected for the study remained confidential, including when we implemented referrals for mothers who requested additional services.

Neonatal Medical Complications

Medical record reviews ascertained neonatal characteristics and complications using Vermont-Oxford Network definitions and criteria[38] about infections, retinopathy of prematurity (ROP), and respiratory, renal, neurologic, cardiac, genetic, hematologic, and gastrointestinal morbidities. A validated neonatal medical complications index[39] included one point each for (1) severe brain injury: periventricular leukomalacia, moderate–severe ventricular dilatation, or parenchymal echodensity identified by centralized readings and consensus agreement on diagnoses; (2) culture-positive sepsis; (3) severe ROP; (4) necrotizing enterocolitis (NEC); and (5) bronchopulmonary dysplasia (BPD; supplemental oxygen requirement at 36 weeks PMA).

Statistical Analyses

We compared maternal characteristics for mothers included in analyses based on complete data versus those not included due to missing EPDS and BSI data using one-way analysis of variance (ANOVA) for continuous measures or Chi-square for categorical measures. Unadjusted analyses were conducted to describe maternal and infant correlates of the separate EPDS and BSI outcomes at NICU discharge. To build on findings from previous studies and identify specific risks for PPD and SPD in multivariable model testing, we examined individual covariates based on univariate associations presented in ►Tables 2 and 3 for this sample, as well as on significant predictors of PPD and SPD identified in prior studies.[1,27,40–42]

We examined the multivariable influences of maternal, infant, and socioenvironmental characteristics on maternal EPDS and BSI outcomes using generalized estimating equations (GEEs), where infants from multiple births were nested within families and within site to examine positive EPDS and BSI total scores, and the anxiety symptom subscores for the EPDS (3A) and the BSI separately. Models examined the following risk factors: prepregnancy/prenatal depression/anxiety diagnoses, as well as the influences of socioenvironmental adversities, substance use, maternal and neonatal medical complications, infant sex, as well as PMA at birth and discharge as indicators of the effects of immaturity and duration of illness. GEE procedures using a log link function to obtain beta weights that can be converted to relative risks (RRs) directly produced model convergence issues. Odds ratios (ORs) from the GEE models were converted to RR using the method described by Zhang and Yu[43]: $RR = OR/((1 - P0) + (P0 * OR))$, where P0 is the observed prevalence within the reference group. A priori comparisons were also implemented to determine if prenatal substance use was more prevalent in mothers with a diagnosis of prenatal depression or anxiety.

Prior studies reported disparities and discrimination associated with postpartum distress and depressive symptoms reported by members of racial or ethnic minority groups.[44–47] To examine these influences in our sample, model testing examined self-reported race and ethnicity. Data were analyzed using SPSS 24.0 (Chicago, IL: SPSS, Inc.).

Results

Maternal and Newborn Characteristics

Thirty-seven mothers with missing EPDS and BSI data were excluded from analyses, as were the only two mothers who received prenatal antipsychotic medication for unidentified conditions. Compared with the 562 included mothers, excluded mothers had higher rates of prenatal marijuana and illicit substance use (►Supplementary Table S1, available in the online version).

The included sample (►Table 1) was ethno-racially diverse, with a mean maternal age of 29 years (standard deviation [SD] = 6.3); 25% were neither married nor living with a partner. Thirteen percent of mothers did not complete high school, 29% were high school graduates, 35% attended some college, and 23% graduated from college; however, 64% reported receiving income-based public assistance or health insurance. Prepregnancy or prenatal anxiety or depression diagnoses were reported by 32% of mothers, 61% of whom reported receiving counseling and/or pharmacological treatment (►Table 1).

Table 1 Maternal and infant characteristics

Maternal characteristics ($n = 562$)	n (%) or mean ± SD
Psychological history	
Prepregnancy or prenatal depression and/or anxiety[a]	181 (32.2)
Socioenvironmental risk factors	
No partner	138 (24.6)
Low income-based public assistance/health insurance or uninsured	359 (63.9)
Education < college	435 (77.4)
Race/ethnicity	
Hispanic, any race	114 (20.3)
Non-Hispanic American Indian/Native American	1 (0.2)
Non-Hispanic Asian	37 (6.6)
Non-Hispanic Black	116 (20.7)
Non- Hispanic Native Hawaiian or Pacific Islander	12 (2.1)
Non-Hispanic White	224 (39.8)
Non-Hispanic unknown or not reported	2 (0.4)
Non-Hispanic multiple race	56 (10.0)
Prenatal substance use	
Tobacco	78 (13.9)
Alcohol	16 (2.8)
Marijuana	51 (9.1)
Recreational/illicit substances[b]	20 (3.6)
Prenatal medical risk factors	
Maternal age >35 years	97 (17.3)
Diabetes	34 (6.0)
Vaginal or urinary infection	60 (10.7)
Chronic or pregnancy-induced hypertension	154 (27.4)
Sexually transmitted infection or human immunodeficiency virus	37 (6.6)
Body mass index ≥30 kg/m^2	193 (34.3)
Underweight <18.5 kg/m^2	27 (4.8)
Fetal congenital anomaly	32 (5.7)
Neonatal characteristics ($n = 641$)	
Sex, male	358 (55.9)
Postmenstrual age at birth (wk)	27.0 ± 1.9
Postmenstrual age at discharge >40 wk	264 (41.3)
Multiple gestation	172 (26.9)
Study site	N (%)
1	106 (16.5)
2	126 (19.7)
3	68 (10.6)
4	116 (18.1)
5	126 (19.7)
6	99 (15.4)
Severe neonatal medical conditions	
Brain ultrasound abnormality[c]	81 (12.7)
Bronchopulmonary dysplasia	321 (50.2)
Severe retinopathy of prematurity	40 (6.3)
Necrotizing enterocolitis or sepsis	117 (18.3)

Abbreviation: SD, standard deviation.
[a]Prepregnancy and prenatal depression and anxiety variables were combined due to significant overlap for these diagnoses.
[b]Maternal recreational/illicit substance use included cocaine, methamphetamine, hallucinogens, opioids, and benzodiazepines.
[c]Cranial ultrasound abnormality: periventricular leukomalacia, moderate–severe ventricular dilatation, or parenchymal echodensity identified by centralized readings and consensus agreement on diagnoses.

For 641 newborns born to 562 mothers, 44% were female; there were 492 (87.5%) singletons and 26.9% multiple gestations (64 [11.4%] sets of twins and 6 [1.1%] sets of triplets or more). Mean birth PMA was 27 weeks (SD = 2), mean birth weight was 950 grams (SD = 279), head circumference mean was 24.5 cm (SD = 2.4), and 7% had fetal growth restriction. More than half (52%) of the infants received maternal breast milk during their NICU stay. Thirteen percent of infants had severe brain injuries, 6.9% had NEC, 13.4% had sepsis, and 50% had BPD (24% mild, 26% moderate/severe adapted from Jensen et al's criteria[48]); 23% of infants had two or more of these severe conditions,[39] whereas 41% of the sample had none of these severe conditions (►Table 1). Timing of the EPDS and BSI at NICU discharge reflects a median NICU stay of 85 days; mean PMA at discharge was 40 weeks.

Maternal and Infant Correlates of Postpartum Depression and Severe Psychological Distress

The average EPDS score was 4.6 (SD = 4.1; range 0–21) and 76 mothers (13.5%) had a positive screen (EPDS ≥10). The mean BSI score was 0.29 (SD = 0.34; range 0–2.4); 102 mothers (18.1%) had a positive BSI screen. The average EPDS-3A score was 2.1 (SD = 2.0; range 0–9) and 47 mothers (8.4%) had a positive anxiety screen (EPDS-3A >6). The mean BSI score was 0.29 (SD = 0.34; range 0–2.4) and the mean BSI anxiety symptom dimension was 0.30 (SD = 0.45; range 0–3); 102 mothers (18.1%) had a positive BSI screen and 40 mothers had a positive BSI anxiety screen (7.1%). Fifty-four mothers (9%) screened positive on both the EPDS and the BSI. Thoughts of self-harm were reported by 14 mothers (2.5%); eight (57.1%) of those 14 screened positive on the EPDS or BSI.

Unadjusted analyses indicated that individuals with a positive screen on the EPDS (►Table 2) or the BSI (►Table 3) were more likely to report prepregnancy/prenatal depression and/or anxiety than those with no prior

Table 2 Maternal and infant characteristics by positive screen on the Edinburgh Postnatal Depression Scale (EPDS)

	EPDS > 10 ($n = 76$) n (%) or mean ± SD	EPDS < 10 ($n = 486$) n (%) or mean ± SD	p
Maternal characteristics ($n = 562$)			
Psychological history			
Prepregnancy or prenatal depression and/or anxiety[a]	34 (44.7)	147 (30.6)	0.01
Socioenvironmental risk factors			
No partner	20 (26.3)	118 (24.3)	0.70
Low income-based public assistance/health insurance or uninsured	55 (72.4)	304 (62.6)	0.10
Education < college	63 (82.9)	372 (76.5)	0.22
Member of a minority race or ethnic group[b]	48 (63.2)	277 (57.0)	0.31
Prenatal substance use			
Tobacco	12 (15.8)	66 (13.6)	0.61
Alcohol	2 (2.6)	14 (2.9)	0.62
Marijuana	11 (14.5)	40 (8.2)	0.08
Recreational/illicit substances[c]	2 (2.6)	18 (3.7)	0.48
Prenatal medical risk factors			
Maternal age >35 years	12 (15.8)	85 (17.5)	0.72
Diabetes	4 (5.3)	30 (6.2)	0.51
Vaginal or urinary infection	6 (8.0)	54 (11.1)	0.42
Chronic or pregnancy-induced hypertension	16 (21.1)	138 (28.5)	0.18
Sexually transmitted infection or human immunodeficiency virus	4 (5.3)	33 (6.8)	0.43
Body mass index ≥30 kg/m^2	20 (26.7)	173 (35.6)	0.13
Underweight <18.5 kg/m^2	4 (5.3)	23 (4.7)	0.50
Fetal congenital anomaly	4 (5.3)	28 (5.8)	0.57
Neonatal characteristics ($n = 641$)	($n = 83$)	($n = 558$)	p
Sex, male	55 (66.3)	303 (54.3)	0.04
Postmenstrual age at birth (wk)	26.7 ± 1.9	27.1 ± 1.9	0.06
Postmenstrual age at discharge >40 wk	43 (51.8)	221 (39.7)	0.04
Multiple gestation	18 (21.7)	154 (27.6)	0.25
Study site			0.11
1	16 (19.3)	90 (16.1)	
2	11 (13.3)	115 (20.6)	
3	11 (13.3)	57 (10.2)	
4	22 (26.5)	94 (16.8)	
5	15 (18.1)	111 (19.9)	
6	8 (9.6)	91 (16.3)	
Severe neonatal medical conditions			
Brain ultrasound abnormality[d]	14 (16.9)	67 (12.1)	0.22
Bronchopulmonary dysplasia	51 (61.4)	270 (48.4)	0.03
Severe retinopathy of prematurity	10 (12.0)	30 (5.4)	0.02
Necrotizing enterocolitis or sepsis	9 (10.8)	108 (19.4)	0.06

Abbreviation: SD, standard deviation.

[a]Prepregnancy and prenatal depression and anxiety variables were combined due to significant overlap for these diagnoses.

[b]Self-reported member of the following race or ethnic group: American Indian, Asian, Black, Hispanic, Native Hawaiian, Pacific Islander, or "other" self-specified.

[c]Maternal recreational/illicit substance use included cocaine, methamphetamine, hallucinogens, and nonprescribed pharmaceuticals, e.g., opioids and benzodiazepines.

[d]Cranial ultrasound abnormality: periventricular leukomalacia, moderate–severe ventricular dilatation, or parenchymal echodensity identified by centralized readings and consensus agreement on diagnoses.

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Table 3 Maternal and infant characteristics by positive screen on the Brief Symptom Inventory (BSI)

	Positive BSI screen = yes *n* (%) or mean ± SD	Positive BSI screen = no *n* (%) or mean ± SD	*p*
Maternal characteristics ($n = 562$)	($n = 102$)	($n = 460$)	
Psychological history			
Prepregnancy or prenatal depression and/or anxiety[a]	42 (41.6)	139 (30.5)	0.03
Socioenvironmental risk factors			
No partner	29 (28.4)	109 (23.7)	0.32
Low income-based public assistance/health insurance or uninsured	71 (69.6)	288 (62.6)	0.18
Education < college	85 (83.3)	350 (76.1)	0.11
Member of a minority race or ethnic group[b]	65 (63.7)	260 (56.5)	0.18
Prenatal substance use			
Tobacco	15(14.7)	63 (13.8)	0.80
Alcohol	3 (2.9)	13 (2.8)	0.95
Marijuana	17 (16.7)	34 (7.4)	<0.01
Recreational/illicit substances[c]	4 (3.9)	16 (3.5)	0.77
Prenatal medical complications			
Maternal age >35 years	18 (17.6)	79 (17.2)	0.91
Diabetes	8 (7.9)	26 (5.7)	0.39
Vaginal or urinary infection	9 (8.9)	51 (11.1)	0.52
Chronic or pregnancy-induced hypertension	17 (16.8)	137 (29.8)	<0.01
Sexually transmitted infection or human immunodeficiency virus	5 (5.0)	32 (7.0)	0.46
Body mass index ≥30 kg/m^2	31 (30.7)	162 (35.2)	0.39
Underweight <18.5 kg/m^2	5 (5.0)	22 (4.8)	0.94
Fetal congenital anomaly	8 (7.9)	24 (5.2)	0.29
Neonatal characteristics ($n = 641$)	($n = 114$)	($n = 527$)	*P*
Sex, male	67 (58.8)	291 (55.2)	0.49
Postmenstrual age at birth (mean ± SD)	26.6 ± 1.9	27.1 ± 1.9	0.01
Postmenstrual age at discharge >40 weeks	47 (41.6)	160 (30.7)	0.02
Multiple gestation	28 (24.6)	144 (27.4)	0.54
Study site			0.02
1	15 (13,2)	91 (17.3)	
2	19 (16.7)	107 (20.3)	
3	19 (16.7)	49 (9.3)	
4	29 (25.4)	87 (16.5)	
5	21 (18.4)	105 (19.9)	
6	11 (9.6)	88 (16.7)	
Severe neonatal medical conditions			
Brain ultrasound abnormality[d]	18 (15.9)	63 (12.0)	0.25
Bronchopulmonary dysplasia	68 (59.6)	253 (48.0)	0.02
Severe retinopathy of prematurity	11 (9.6)	29 (5.5)	0.10
Necrotizing enterocolitis or sepsis	17 (14.9)	100 (19.0)	0.31

Abbreviation: SD, standard deviation.

[a]Prepregnancy and prenatal depression and anxiety variables were combined due to significant overlap for these diagnoses.

[b]Self-reported member of the following race or ethnic group: American Indian, Asian, Black, Hispanic, Native Hawaiian, Pacific Islander, or "other" self-specified.

[c]Maternal recreational/illicit substance use included cocaine, methamphetamine, hallucinogens, and nonprescribed pharmaceuticals, e.g., opioids and benzodiazepines.

[d]Cranial ultrasound abnormality: periventricular leukomalacia, moderate–severe ventricular dilatation, or parenchymal echodensity identified by centralized readings and consensus agreement on diagnoses

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diagnosis. Compared to individuals with a negative BSI screen, those with a positive screen had lower rates of chronic or pregnancy-induced hypertension, but higher rates of prenatal marijuana use. Follow-up comparisons examined marijuana use to determine if rates differed in those with versus without preexisting depression or anxiety. Prenatal marijuana use was more prevalent in individuals with prenatal depression or anxiety (15.7%) compared to those without prenatal depression or anxiety (8.7%), but this difference was not significant ($\chi^2 = 2.65$, $p < 0.10$).

Compared to infants born to mothers with negative EPDS or BSI screens, those whose mothers had positive screens were more likely to have been born at younger gestational ages, with BPD prevalence that was 13 and 11% higher, respectively, among infants born to mothers with positive EPDS and BSI screens. Individuals with either positive screen had infants whose NICU stays averaged 14 days longer, and discharge after 40 weeks PMA was 14% more prevalent. There were no significant differences in EPDS or BSI screen rates associated with any adverse socioenvironmental conditions, nor with BPD severity.[48]

Multivariable Analyses of Maternal and Infant Risk Factors

GEE accounted for correlations among multiple births by nesting infants within families and within site to examine EPDS and BSI outcomes tested in the following models separately. Variables were identified based on prior research and the univariate results above: prepregnancy/prenatal depression or anxiety diagnosis, prenatal marijuana use, receipt of income-based public assistance, minority ethnicity, maternal education, and infant PMA at birth, discharge >40 weeks PMA, BPD, and severe ROP. As presented in ►**Table 4**, a positive EPDS screen was associated with prepregnancy/prenatal depression and/or anxiety (RR = 1.6, 95% CI: 1.02,2.1), and male sex (RR = 1.7, 95% CI: 1.1,2.4). A positive BSI screen was associated with prepregnancy/prenatal depression and/or anxiety (RR = 1.6, 95% CI: 1.1,2.2) and prenatal marijuana use (RR = 1.9, 95% CI: 1.1,2.9). Postnatal anxiety as measured by the EPDS-3A was associated only with prepregnancy/prenatal depression and/or anxiety (RR = 1.9, 95% CI: 1.03,3.6) and there were no associations found using the clinical cutoff for the BSI anxiety symptom dimension. As with unadjusted results, there were no significant differences in EPDS or BSI outcomes associated with adverse socioenvironmental conditions.

Discussion

Building on earlier research, this study examined maternal, socioenvironmental, and neonatal risk factors for PPD and severe distress in a large, diverse multicenter sample of mothers of very premature newborns. We found higher PPD and/or SPD rates associated with prior depression or anxiety, prenatal marijuana use, and male sex. In addition, socioenvironmental adversities typically associated with PPD/SPD—i.e., single, low income, or education[11,12,20,49]—while still useful information for screening, were not significant when tested in this study's risk assessment model that also included specific infant medical complications.

Notably, 42 to 46% of mothers who screened positive on either the EPDS or BSI had a prior diagnosis of depression or anxiety. In addition, 8% of mothers had a positive screen on the EPDS anxiety subscale and were significantly more likely to have experienced prior depression or anxiety. These positive screens for mothers with a prior diagnosis are indicative of a high-risk group identifiable in the context

Table 4 Multivariable test statistics for maternal outcome models on the Edinburgh Postnatal Depression Scale (EPDS) and Brief Symptom Inventory (BSI)

Variable	EPDS positive screen (score > 10)			BSI positive screen (positive screen criteria = yes)		
	B	SE	RR (95% CI)	B	SE	RR (95% CI)
Maternal characteristics ($n = 562$)						
Prepregnancy or prenatal depression and/or anxiety[a]	0.57	0.28	1.6 (1.02–2.1)	0.57	0.25	1.6 (1.1–2.2)
Low income-based public assistance/ health insurance or uninsured	0.26	0.33	1.3 (0.7–2.1)	0.07	0.30	1.1 (0.6–1.7)
Minority race or ethnicity[b]	0.8	0.31	1.4 (0.8–2.3)	0.36	0.31	1.3 (0.8–2.1)
Education < college	0.20	0.39	1.2 (0.6–2.2)	0.19	0.34	1.2 (0.6–1.9)
Prenatal marijuana use	0.46	0.41	1.5 (0.7–2.7)	0.82	0.35	1.9 (1.1–2.9)
Infant characteristics ($n = 641$)						
Sex, male	0.57	0.26	1.7 (1.1–2.4)	0.10	0.22	1.1 (0.7–1.5)
Postmenstrual age at discharge >40 weeks	0.10	0.33	1.1 (0.6–2.1)	0.13	0.27	1.1 (0.7–1.7)
Bronchopulmonary dysplasia	0.44	0.30	1.5 (0.9–2.3)	0.38	0.26	1.4 (0.9–2.0)
Severe retinopathy of prematurity	0.77	0.42	1.9 (0.9–3.5)	0.40	0.39	1.4 (0.7–2.4)

Abbreviation: CI, confidence interval; RR, risk ratio; SE, standard error.
[a]Prepregnancy and prenatal depression and anxiety variables were combined due to significant overlap for these diagnoses.
[b]Self-reported member of the following race or ethnic group: American Indian, Asian, Black, Hispanic, Native Hawaiian, Pacific Islander, or "other" self-specified.

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of preconceptional and prenatal care. Conversely, >54% were not identifiable during pregnancy, suggesting additional postnatal needs assessment is warranted, and may be incorporated in the context of family-centered NICU care. Although the present sample's rate of thoughts of self-harm rates at 2.5% was lower than in other samples,[34,50] 43% of mothers reporting thoughts of self-harm did not have positive screens on either the EPDS or BSI. As such, an additional review of self-harm item responses may be warranted to ensure indicated referrals.

Monitoring also appears relevant to pregnant individuals facing multiple risk factors documented here. In particular, the 9% rate of prenatal marijuana use in this sample (confidence interval = 6.8–11.7%) was substantially higher than the reported 4 to 6% in the general population.[51,52] Despite the limitation of potentially underreported use due to being ascertained from medical records rather than toxicology screens, this higher than general use rate may indicate an additional support need in pregnant individuals at risk for SPD associated with varied constellations of complications.[53] Paradoxically, whether marijuana is a form of self-medication used to manage stress, mood, and/or nausea during pregnancy, it has shown no benefit for depression, may contribute to panic when accompanied with anxiety, and safer antinausea treatment alternatives have been available.[52,54,55] Importantly, these contradictions and the findings presented here highlight salient opportunities to overcome biases in substance use assessments and to enhance supportive, nonjudgmental, and widely accessible mental health and substance use services prior to conception, and throughout prenatal and early postpartum care.

Another key finding suggests the importance of measuring both PPD and SPD, as there was only a 9% overlap in positive screens on both the EPDS assessment of depression risk and the BSI assessment of severe distress. Further, these two postpartum outcome measures were predicted by different combinations of prenatal and neonatal conditions. Consequently, each measure appears to offer unique risk detection value concerning both the sources and symptoms of depression and severe distress among birthing parents of very preterm infants.

These multicenter findings expand upon prior work that identified indicators of risk for PPD and SPD. Similar to findings among parents of full-term infants, rates of PPD/SPD were predicted by prior depression or anxiety.[3,33,56] However, this sample's >40% rates of positive EPDS and BSI screens for mothers with prior depression or anxiety are higher than the eported 10 to 25% in the general population.[3] This 15 to 30% elevation of positive screen rates suggests that a prior history combined with severe infant medical complications in this very preterm sample increases vulnerability to recurring symptoms.

Compared to findings from studies involving a wide range of medical variation due to the selection of all "premature" or "NICU" samples, our 13% rate of PPD and 18% rate of SPD are lower than the 18 to 43% previously reported.[14,16,49,57] This difference may have resulted from our decision to complete the BSI and EPDS by interview in order to overcome literacy challenges. However, it is also possible that higher rates of positive screens occurred in more general "NICU samples" where infants had a wider range of major anomalies and acute illnesses with well-established risk for mortality and/or a poor long-term prognosis. Also in contrast to prior work, our rates of PPD and SPD are slightly lower than the 20[20,27] and 27%[19,58] rates reported at comparable postpartum periods, and may reflect study follow-up aims requiring inclusion of infants likely to survive to NICU discharge.

Our findings are similar to PPD[20] and distress[59] in mothers of preterm infants with lengthier ventilation and BPD, and to PPD associated with younger PMA at birth,[17] neonatal medical complications, and lengthier NICU stays.[60] Regarding persisting BPD influences on maternal psychological difficulties in particular, Singer et al[61] reported more prevalent maternal distress in the first 2 years of life, with persisting parenting-specific stress at 3 years of age that was also related to the child's developmental challenges. Importantly, at age 14 follow-up, although mothers of the high-risk children with BPD showed persisting family stress scores, they also demonstrated increases in adaptive coping skills.[59] These findings suggest that the interrelationships observed in our study contribute important information for preventive and targeted interventions to promote multiple aspects of maternal coping strategies and to address family support needs.

It is noteworthy that this sample reported high rates of concurrent prepregnancy and prenatal anxiety and depression diagnoses. As a result, we analyzed global scores for both the EPDS and BSI to examine associations with positive screens on either measure. The EPDS and BSI are screening instruments, rather than diagnostic, and both measures have anxiety symptoms embedded. The global scores were used here to focus on elevated symptom levels that would identify mothers who required more detailed follow-up with specific diagnostic assessments for anxiety, depression, and/or other disorders.

Strengths and Limitations

Study strengths include the large and diverse multicenter sample, rigorously standardized assessments and medical record reviews, with consensus definitions and systematic oversight by site primary investigators, including immediate referrals for indicated maternal needs. The timing of postpartum assessments enabled the identification of both predischarge risk factors and postdischarge referral needs. This was done with the recognition that the postpartum assessments at NICU discharge potentially measured both anxiety around caring for the infant at home[62] and relief at the infant's survival.

Generalizability was enhanced by including mothers of outborn infants admitted to NICUs in children's hospitals. Since prenatal medical records are not uniformly available for infants transported to children's hospitals, and data collection standardization was achieved by abstracting prenatal and intrapartum medical and substance use information from the neonatal medical records including delivery and admission notes, histories, and physicals.

A limitation of the study was that postnatal enrollment was required to determine eligibility, and that timing precluded prenatal maternal interviews and toxicology screens to ascertain prenatal substance use. Postnatal enrollment at varied postnatal ages of outborn infants also precluded an earlier administration of the EPDS and BSI at a standardized time point. However, the statistically significant association between marijuana use and BSI severe distress demonstrates the strength of that association, despite underreported use and without an assessment prior to the week of discharge.

Another issue underlying findings about marijuana use is that legalization of medicinal and/or recreational marijuana use varied by state of residence from 2013 through 2016 during the study of pregnancies in our six sites.[63,64] While legalization may have influenced use, our statistical models adjusted for six sites located in six states prior to examining associations between marijuana use and EPDS and BSI outcomes. This procedure would be expected to adequately adjust for state differences in legalization.

EPDS and BSI positive screen rates may also have been based on potentially underreported symptoms using the interview format to avoid literacy bias. Results may differ from rates obtained by a self-reported questionnaires used in studies that included less diverse samples. Despite these limitations, findings demonstrated the significant strength of relationships between PPD and/or SPD, charted marijuana use, and self-reported prior depression and anxiety diagnoses.

Conclusion

Our findings demonstrate the potential value of incorporating screening and support for psychological well-being that begin in the preconceptional period, with continued services focused on perinatal depression, anxiety, and marijuana use.[14,65–68] Further, extended services could address ongoing needs evidenced by postpartum individuals whose infants have lengthy hospital stays and complex conditions.[69–71] Addressing needs for safer alternatives to marijuana use and personalized approaches to services for pregnant individuals at increased risk for depression and severe distress has demonstrated benefits when integrated into family-centered care.[62,72] These efforts have the potential to improve outcomes for pregnant and postpartum individuals, their infants, and families facing multiple challenges to their well-being and relationships.[73,74]

This study identified early and persisting prepregnancy and prenatal characteristics, and neonatal complications associated with PPD and SPD in a vulnerable sample that represents a population of over 59,000 U.S. families annually,[75] and numbers in the millions worldwide.[76] Programmatic efforts are particularly relevant in light of the current increases in prenatal cannabis use, depression, and anxiety during the on-going coronavirus pandemic, and the cumulative burden of these stressors.[77–79] Addressing risk is clearly warranted,[80] and targeting demonstrated needs continuously and concurrent with infant care has demonstrated potential.

Authors' Contributions

All authors contributed to reviewing, revising, and approval of the final submitted manuscript, and agree to be accountable for all aspects of the work. In addition: J.A.H. conceptualized and designed this manuscript, co-led the overall conceptualization, design, and funding acquisition of the NOVI Study, and led the study site teams in protocol implementation and data collection. E.S.M., L.M.S., B..S.C., and C.R.N. contributed to the conceptualization and design of the manuscript and led their respective site teams in study implementation. S.M.-B. contributed to the design of the maternal data collection protocol and the development of the manuscript. L.M.D. developed the database for this manuscript and conducted statistical analyses. T.M.D.O. and B.M.L. co-led the conceptualization and design of the NOVI study. J.B.H. and S.P. led their respective site teams in study implementation. S.A.D. worked with the study site teams on protocol implementation and designed data collection instruments.

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Conflict of Interest

None declared.

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