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Maternal stress, prenatal medical illnesses and obstetric complications: Risk factors for schizophrenia spectrum disorder, bipolar disorder and major depressive disorder

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ABSTRACT

Maternal stress and medical illnesses during early life are well-documented environmental indicators of an increased risk of schizophrenia. Few studies, conversely, have confirmed an association with major affective disorders. The present study examined the impact of maternal stress, medical illnesses and obstetric complications on the development of severe mental disorder in 240 patients with a diagnosis of schizophrenia spectrum disorder, bipolar disorder, or major depressive disorder and matched with 85 controls. Mothers of participants were asked about stressful events during pregnancy using the Social Readjustment Scale; information on prenatal/perinatal illnesses were acquired from medical records. Schizophrenia spectrum disorder was positively associated with maternal stress (OR = 2.16), infections (OR = 7.67), inadequate weight gain (OR = 9.52) during pregnancy, and peripartum asphyxia (OR = 4.00). An increased risk of bipolar disorder was associated with head circumference $<$ 32 cm at birth (OR = 5.40) and inversely with inadequate weight gain (OR = 0.29). Major depressive disorder diagnosis was inversely related to inadequate weight gain (OR = 0.22). These results support a role for maternal stress, medical illnesses and obstetric complications as risk factors for subsequent severe mental illness in adulthood. Further research is needed, especially with regard to affective disorders.

1. Introduction

Severe mental illness, including schizophrenia, bipolar disorder and major depressive disorder, are among the most burdensome diseases of the whole medicine (Global Burden of Disease Study 2013 Collaborators, 2015).

A number of environmental risk factors play an important role in the development of severe mental illness, such as prenatal exposure to infection, lack of nutrients, preterm birth, obstetric complications, maternal stress, perinatal complications, social disadvantage, urban upbringing, ethnic minority status, childhood maltreatment, bullying, traumatic events, and cannabis use during adolescence (Fusar-Poli et al., 2017; Marangoni et al., 2016).

Epidemiological studies have documented the role of the prenatal environment in the development of severe mental disorders (Rice et al., 2010). In particular during the first or second trimester of pregnancy, a vulnerable brain development may be due to maternal exposure psychological stress (e.g., due to bereavement, unwanted pregnancy, death of relatives, or other serious life events) (Meyer and Feldon, 2010). Prenatal stress is known to influence function of the hypothalamic-pituitary-adrenal (HPA) axis and secretion of glucocorticoid hormones as well as the protective capacity of the placenta (Owen et al., 2005). In addition to the effects on stress hormones, prenatal stress influences the fetal transcriptome through microRNA regulation as an epigenetic mechanism, which links environmental factors to altered gene expression in the pathophysiology of schizophrenia and bipolar disorder (Hollins and Cairns, 2016).

Prenatal exposure to a range of bacterial, respiratory or genital infections and inflammatory responses may be associated with 2- 5-fold increased risk of schizophrenia. The evidence for herpes simplex virus (HSV) type 2 and *toxoplasma gondii* is not clear, while prenatal HSV type 1 or cytomegalovirus infections are not associated with an increased risk. Exposure to influenza or other infections during early pregnancy may be more harmful than later exposure (Khandaker et al., 2013).

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Maternal infection or increased inflammatory cytokines during pregnancy are reported to be associated with both structural and functional brain phenotypes relevant to schizophrenia in the offspring (Brown and Derkits, 2013).

Some studies found that maternal influenza (Parboosing et al., 2013) as well as prenatal exposure to *toxoplasma gondii* (Hamdani et al., 2013) may be a risk factor for bipolar disorder, while other studies do not support this link (Mortensen et al., 2011). The role of prenatal exposure to viral infections in the etiology of depressive disorders is still unknown: a cohort study did not support the hypothesis that in-utero exposure to viral infection is associated with an increased risk of affective disorder in later life (Pang et al., 2009).

The evidence supporting a role of prenatal malnutrition in schizophrenia derives from studies on in utero exposure to famine (St Clair et al., 2005; Susser et al., 1996). In addition, maternal micronutrient deficiencies, including folate/homocysteine, iron, vitamin D deficiencies, which are frequent in both developed and developing countries, are viewed as more prominent risk factors for schizophrenia (Brown, 2011). Only a few studies have investigated the possible association between prenatal malnutrition and affective disorders. Furthermore, the results of these studies have been contradictory. A cohort-study showed an association between late gestational malnutrition and both bipolar and unipolar affective disorders (Brown et al., 2000), while a national population case-control study carried out in Denmark showed that none of the indicators of fetal growth could be identified as risk factors for bipolar disorder (Øgendahl et al., 2006). Deficiency of iron during development, but not in prenatal life, increased the risk of mental illnesses, including bipolar disorder and major affective disorder (Chen et al., 2013).

Several meta-analyses have shown an association between complications during pregnancy and delivery and schizophrenia. This applies to obstetric complications such as preeclampsia, bleeding, rhesus incompatibility, diabetes, asphyxia, uterine atony, emergency caesarian section, and fetal abnormalities such as low birth weight, congenital malformations, and small head circumference. Effect sizes have been estimated between two and three, with the highest effect for emergency caesarian section, placental abruption, and low birth weight (Forsyth et al., 2013). A common factor of all these complications is perinatal hypoxia, which in animal models induced altered cell proliferation in the anterior cingulate cortex (Schaeffer et al., 2013) and decreased *N*-methyl-D-aspartate (NMDA) receptor binding in the anterior cingulate cortex, frontal regions, nucleus accumbens, and hippocampus, as well as a deficit in prepulse inhibition of acoustic startle response (Schmitt et al., 2007). The role of obstetric complications in the etiology of bipolar disorder is controversial: a meta-analysis did not support the association between exposure to obstetric complications and subsequent development of bipolar disorder (Scott et al., 2006). However, in a large cohort study, preterm birth was significantly associated with affective disorders: those with a gestation less than 32 weeks had a 2.9-fold higher risk of developing major depression and were 7.4% more likely to have bipolar disorder (Nosarti et al., 2012). Perinatal asphyxia induced smaller amygdala and hippocampal volumes in patients with bipolar disorder (Haukvik et al., 2014), alterations considered to be the key components in the pathophysiology of these disorders (Hajek et al., 2012; Hallahan et al., 2011).

This study aims to investigate the association between maternal psychological stress and medical illnesses during prenatal/perinatal period and the development of severe mental disorders, such as schizophrenia, bipolar disorder, and major depressive disorder. Our primary hypothesis was that prenatal and perinatal exposure to development perturbations would account for the increased risk among cases that later developed severe mental illnesses. We also hypothesized a difference in the prevalence of these early environmental risk factors in relation of the disorder developed.

2. Methods

2.1. Subjects and procedures

Participants were outpatients aged 18–65 years afferent to the Department of Psychiatry of the University of Catanzaro, between 2014 and 2016. We included all patients admitted in the unit for at least twelve months with a diagnosis of Schizophrenia Spectrum Disorder (SDD), Bipolar Disorder (BD) type 1 or 2, and Major Depressive Disorder (MDD) according to DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000). Diagnoses were made through the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1995) by experienced psychiatrists who were trained in administration of neuropsychiatric tests and used these tools in their daily clinical practice.

A control sample was also collected from the local community via Internet advertisements and from local university working staff and was chosen to reflect the group of patients on the basis of age, social class and gender. Prior the assessment, they were all interviewed and asked about the lifetime presence of schizophrenia spectrum disorder or affective disorder and were excluded if so. A prior history of other psychiatric disorders was not an exclusion criteria.

Inclusion criteria in the clinical groups were: diagnosis of Schizophrenia Spectrum Disorder (SDD), Bipolar Disorder (BD) type 1 or 2, and Major Depressive Disorder (MDD) according to DSM-IV-TR. All participants were subject to the following exclusion criteria: 1) age younger than 18 or older than 65 years; 2) diagnosis of dementia, intellectual disabilities or other medical conditions associated with psychiatric symptoms; 3) drug dependence; 4) undocumented anamnestic elements not supported by medical records.

The final sample ($N = 333$) consisted of 91 patients with a diagnosis of SSD, 74 patients with BD, 83 patients with MDD and 85 Healthy Controls (HC).

The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the local research ethics committee. All patients and controls signed a written informed consent according to the Ethical Committee's guidelines.

2.2. Measures

An ad-hoc schedule was administered in order to assess socio-demographic and clinical characteristics. Collected data included school performance at age 16, psychiatric familiarity, onset characteristics (age, insidious or acute, significant life events in the 12 months prior to the onset), longitudinal course of the disorder, previous suicide attempts, suicidal ideation, and previous psychiatric hospitalizations. A close relative (parent or sibling) was asked to assist patients during the assessment in order to verify the correctness of the answers.

2.2.1. Maternal psychological stress, prenatal medical illnesses and obstetric complications

Maternal psychological stress: The Social Readjustment Rating Scale (SRRS) (Holmes and Rahe, 1967) is a 53-item stimulus-event measure of environmental stress, experienced by an individual within 12-month; a total score of 300 or more suggests a high level of stressors experienced in the period explored. Mothers of participants were asked about their experience of negative life events occurred in the months prior to giving birth including: death/illness of a close someone, health problems, serious disagreements with partner or with someone else, financial problems, major employment change of partner, serious problems with housing or accommodation, and serious problems with the law.

Prenatal medical illnesses and obstetric complications: Data on exposure to medical illnesses in the prenatal period (inadequate weight gain, lack of nutrients, infections) and to obstetric complications during pregnancy (rhesus incompatibility, bleeding, diabetes, preeclampsia),

Table 1
Socio-demographic characteristics for schizophrenia spectrum disorder, bipolar disorder, major depressive disorder compared to healthy controls.

		Group 1 SSD $N = 91$		Group 2 BD $N = 74$		Group 3 MDD $N = 83$		Group 4 HC $N = 85$		Statistics	***p***
Age[a]		39.5	(10.8)	48.2	(12.4)	48.9	(12.2)	45.3	(12.3)	$F = 11.065$	**0.001**
Gender[b]	Male	55	(60.4)	29	(39.2)	27	(32.5)	40	(47.1)	$\chi^2 = 15.098$	**0.002**
	Female	36	(39.6)	45	(60.8)	56	(67.5)	45	(52.9)		
Civil status[b]	Single	68	(74.7)	21	(28.4)	11	(13.3)	22	(25.9)	$\chi^2 = 116.344$	**0.001**
	Married	9	(9.9)	40	(54.1)	58	(69.9)	59	(69.4)		
	Stable relationship	0	(0.0)	1	(1.4)	3	(3.6)	0	(0.0)		
	Divorced	14	(15.4)	10	(13.5)	6	(7.2)	3	(3.5)		
	Widower	0	(0.0)	2	(2.7)	5	(6.0)	1	(1.2)		
Education[b]	Primary	9	(9.9)	9	(12.2)	17	(20.5)	6	(7.1)	$\chi^2 = 17.960$	0.117
	Intermediate	24	(26.4)	23	(31.1)	24	(28.9)	29	(34.1)		
	Secondary	44	(48.4)	27	(36.5)	31	(37.3)	32	(37.6)		
	University	11	(12.1)	15	(20.3)	11	(13.3)	17	(20.0)		
	Postgraduate	3	(3.3)	0	(0.0)	0	(0.0)	1	(1.2)		
School performance at age 16[b]	Low	44	(48.4)	38	(51.4)	45	(54.2)	40	(47.1)	$\chi^2 = 13.266$	0.151
	Medium	17	(18.7)	10	(13.5)	15	(18.1)	8	(9.4)		
	Good	25	(27.5)	20	(27.0)	18	(21.7)	22	(25.9)		
	Excellent	5	(5.5)	6	(8.1)	5	(6.0)	15	(17.6)		
Occupation[b]	Unemployed	47	(51.6)	26	(35.1)	14	(16.9)	6	(7.1)	$\chi^2 = 65.072$	**0.001**
	Unpaid activity	18	(19.8)	22	(29.7)	27	(32.5)	24	(28.2)		
	Student	6	(6.6)	2	(2.7)	6	(7.2)	3	(3.5)		
	Part-time	11	(12.1)	5	(6.8)	9	(10.8)	14	(16.5)		
	Full-time	9	(9.9)	19	(25.7)	27	(32.5)	38	(44.7)		
Urbanicity[b]	Urban	54	(59.3)	36	(48.6)	37	(44.6)	20	(23.5)	$\chi^2 = 40.023$	**0.001**
	Suburban	24	(26.4)	32	(43.2)	40	(48.2)	62	(72.9)		
	Rural	13	(14.3)	6	(8.1)	6	(7.2)	3	(3.5)		
Living status[b]	Alone	10	(11.0)	10	(13.5)	4	(4.8)	7	(8.2)	$\chi^2 = 111.47$	**0.001**
	Partner	9	(9.9)	42	(56.8)	61	(73.5)	57	(67.1)		
	Parents	57	(62.6)	15	(20.3)	11	(13.3)	16	(18.8)		
	Other relatives/friends	7	(7.7)	7	(9.5)	6	(7.2)	5	(5.9)		
	Psychiatric facility	8	(8.8)	0	(0.0)	1	(1.2)	0	(0.0)		

(SSD): Schizophrenia Spectrum Disorder; (BD): Bipolar Disorder; (MDD): Major Depressive Disorder; (HC): Healthy controls.
[a] Data are expressed as means and (SD).
[b] Data are expressed as frequencies and (%).

and at childbirth and peripartum (emergency caesarian section/application of forceps, uterine atony, fetal abnormalities such as birth weight < 2500 g, head circumference < 32 cm, asphyxia), were acquired by medical records. Subjects were rated as having either a definite prenatal/perinatal medical illness or no prenatal/perinatal medical illness.

2.2.2. Clinical assessment

Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987): The PANSS is a 30-item, seven-point rating instrument rates the presence and severity of positive and negative symptoms, as well as general psychopathology for people with schizophrenia within the past week. Of the 30 parameters assessed, seven were chosen to constitute a Positive Scale (score range 7–49), seven a Negative Scale (7–49), and the remaining 16 a General Psychopathology Scale (16–112).

Hamilton Depression Rating Scale (HDRS or HAM-D) (Hamilton, 1967): The HDRS is an observer-rated scale that evaluates core symptoms of depression consisting of 17–21 items (including two, two-part items, weight and diurnal variation). Scoring ranges on a 0 to 4 spectrum (0 = none/absent and 4 = most severe) and total score can range from 0 to 54.

Young Mania Rating Scale (YMRS) (Young and Biggs, 1978): The YMRS is a rating scale used to evaluate manic symptoms at baseline and over time in individuals with mania. The scale has 11 items: four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0–4 scale.

2.3. Statistical analyses

A statistical power analysis was performed for sample size estimation. With an alpha = 0.05 and power = 0.85, the projected sample size needed with an effect size = 0.25 (GPower 3.1 or other software) is approximately $N = 299$ for this simplest between/within group comparison.

Data were analyzed using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago Illinois) and are presented as means, standard deviations, and frequency of occurrence (%).

Comparisons among groups have been performed using ANOVA for continuous variables and by Chi-squared test for categorical ones, where appropriate.

A logistic regression analysis was performed in order to identify the possible predictors for the diagnosis of Schizophrenia Spectrum Disorders (SSD), Bipolar Disorder (BD), and Major Depressive Disorder (MDD). Possible predictors were initially identified by comparing the rates of obstetric complications between the four groups. To assess independent variables for the diagnoses of SSD, BD, and MDD, variables that differed at $p < 0.01$ were entered into a forward stepwise multivariate logistic regression model. Independent variables included obstetric complications during pregnancy: stressful events, inadequate weight gain, lack of nutrients, infections, Rh incompatibility, bleeding, diabetes, preeclampsia, and obstetric complications during birth and the peripartum, emergency caesarian section or application of forceps, uterine atony, birth weight < 2500 g, head circumference < 32 cm, and asphyxia (all variables: yes = 1, no = 0). Probabilities for stepwise entry and removal were 0.2 and 0.4. The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Clinical characteristics

The final sample included 333 subjects divided in four groups:

- Group 1: 91 patients with a diagnosis of Schizophrenia Spectrum

Table 2
Distribution of family history, onset characteristics and longitudinal course.

		Group 1 SDD *N* = 91		Group 2 BD *N* = 74		Group 3 MDD *N* = 83		Group 4 HC *N* = 85		Statistics	*p*
Family history[a]	Negative	45	(49.5)	24	(32.4)	43	(51.8)	75	(88.2)	χ^2 = 119.196	0.001
	Depressive disorder	15	(16.5)	23	(31.1)	29	(34.9)	7	(8.2)		
	Bipolar disorder	3	(3.3)	17	(23.0)	1	(1.2)	1	(1.2)		
	Anxiety disorder	2	(2.2)	4	(5.4)	2	(2.4)	1	(1.2)		
	Substance use disorder	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)		
	Schizophrenia spectrum disorder	23	(25.3)	5	(6.8)	6	(7.2)	1	(1.2)		
	Eating disorder	0	(0.0)	1	(1.4)	1	(1.2)	0	(0.0)		
First degree relatives with SSD[a]		22	(24.2)	5	(6.8)	7	(8.4)	1	(1.2)	χ^2 = 27.430	**0.001**
Mean age at onset in years[b]		23.5	(6.9)	30.3	(13.0)	36.4	(13.0)			*F* = 28.786	**0.001**
Onset[a]	Insidious	43	(47.3)	30	(40.5)	54	(65.1)			χ^2 = 10.314	**0.006**
	Acute	48	(52.7)	44	(59.5)	29	(34.9)				
Life events in the 12 months prior to the onset[a]		75	(82.4)	59	(79.7)	60	(72.3)			χ^2 = 2.754	0.252
Previous suicide attempts[a]		28	(30.8)	20	(27.0)	15	(18.1)			χ^2 = 3.840	0.147
Suicidal ideation[a]		26	(28.6)	31	(41.9)	15	(18.1)			χ^2 = 10.788	**0.005**
Previous voluntary psychiatric hospitalizations[a]		60	(31.0)	29	(45.0)	14	(69.0)			χ^2 = 43.275	**0.001**
Previous involuntary psychiatric hospitalizations[a]		25	(27.5)	10	(13.5)	4	(4.8)			χ^2 = 17.198	**0.001**

(SSD): Schizophrenia Spectrum Disorder; (BD): Bipolar Disorder; (MDD): Major Depressive Disorder; (HC): Healthy controls.
[a] Data are expressed as frequencies and (%).
[b] Data are expressed as means and (SD).

Disorders (SSD), including schizophrenia (*N* = 56), schizophreniform disorder (*N* = 1), schizoaffective disorder (*N* = 17), delusional disorder (*N* = 6), and psychotic disorder not otherwise specified (NOS) (*N* = 11).

- Group 2: 74 patients with Bipolar Disorders (BD); 40 had bipolar disorder I and 34 bipolar disorder II.
- Group 3: 83 patients with Major Depressive Disorder (MDD).
- Group 4: 85 healthy controls (HC).

The sociodemographic characteristics of the sample are shown in Table 1. Significant differences between groups are evident regarding age, gender, marital status, occupation, and living status: patients from group 1 are younger, males and more frequently single, unemployed, living in urban areas, and still living with parents. The family history, the characteristics of onset and the longitudinal course of the disorders are shown in Table 2.

3.2. Maternal psychological stress, prenatal medical illnesses and obstetric complications

Table 3 summarizes the maternal psychological stress, prenatal medical illnesses and obstetric complications reported by mothers of patients during pregnancy, birth, and peripartum. Maternal psychological stress during pregnancy is described with similar frequency by mothers of patients from Groups 1, 2, and 3; inadequate weight gain of mothers is significantly higher in Group 1; nutritional deficits are more frequent in Groups 1 and 2; bleeding during pregnancy is more frequent in Groups 1 and 3. Emergency caesarian section is more frequently observed in Group 3, while Groups 1 and 2 report a higher frequent application of forceps. Uterine atony is more frequent in Group 1; head circumference < 32 cm and asphyxia are more frequent in Groups 1 and 2.

The results of the Regression Logistic Analysis are reported in Table 4. Three models were run to assess the independent predictors associated with the SSD, BD, and MDD diagnosis. Maternal psychological stress, mother's inadequate weigh gain, infections during pregnancy, and peripartum asphyxia were associated with the diagnosis of SSD (–2 Log-likelihood = 324.905; χ^2 = 65.696; $p < 0.001$). BD diagnosis (–2 Log-likelihood = 330.454; χ^2 = 22.331; $p < 0.001$) was positively associated with head circumference <32 cm and negatively associated to mother's inadequate weigh gain. Finally, MDD diagnosis was negatively associated with mother's inadequate weigh gain (–2 Log-likelihood = 358.02; χ^2 = 15.944; $p < 0.001$).

4. Discussion

The main findings of this study are that prenatal exposure to maternal psychological stress and medical illnesses during pregnancy – mother's inadequate weight gain and infections - and peripartum asphyxia were associated with an increased risk of schizophrenia spectrum disorder in later life. Conversely, abnormal fetal growth – head circumference < 32 cm – is associated with increased risk of bipolar disorder. Furthermore, our study shows a negative correlations between maternal inadequate weight gain and bipolar and major depressive disorder diagnosis.

Obstetric complications and maternal illness during pregnancy are among the strongest putative antecedents of schizophrenia (Brown, 2011; Cannon et al., 2002; Laurens et al., 2015; Matheson et al., 2011; Réthelyi et al., 2013; Suvisaari et al., 2013) while there is no robust evidence that exposure to obstetric complications increases the risk of developing bipolar disorder (Demjaha et al., 2012; Murray et al., 2004; Scott et al., 2006). Data concerning the effects of maternal stress during pregnancy as a risk factor for schizophrenia spectrum disorders in the offspring were available from three birth cohorts (Dorrington et al., 2014; Herman et al., 2006; Mäki et al., 2010) and one high-risk cohort (Niemi et al., 2004). One study found that maternal psychological factors did not confer a significant increase in risk for psychosis, with the exception of a medium sized effect for depressed mood during pregnancy, only when either parent had a psychotic disorder (Mäki et al., 2010). Another study, however, found a 2-fold increased risk for psychosis in offspring whose mothers were exposed to death of relatives during the first trimester (Khashan et al., 2008), like to the increased risk we found.

In major depressive disorder, maternal psychosocial stress exposure during pregnancy and the perinatal period is an important trigger and several studies do suggest that exposure to gestational stress can indeed increase the risk of later life depression and anxiety-related disorders (Brown et al., 2000).

Prenatal stress is known to cause increased basal secretion or enhanced stress-related secretion of glucocorticoid hormones and to reprogram the function of the HPA axis as well as the protecting capacity of the placenta (Owen et al., 2005; Weinstock, 2008, 2005). Moreover,

Table 3

Comparison of maternal stress, prenatal medical illnesses and obstetric complications between Schizophrenia Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder and Healthy Controls.

		Group 1 SDD $N = 91$		Group 2 BD $N = 74$		Group 3 MDD $N = 83$		Group 4 HC $N = 85$		Statistics	*p*
		Fr	(%)	*Fr*	(%)	*Fr*	(%)	*Fr*	(%)		
Maternal stress		23	(25.3)	15	(20.3)	12	(14.5)	2	(2.4)	$\chi^2 = 19.091$	**0.001**
Prenatal medical illnesses											
Inadequate weight gain		28	(30.8)	4	(5.4)	3	(3.6)	3	(3.5)	$\chi^2 = 46.587$	**0.001**
Nutritional deficits		20	(22.0)	10	(13.5)	6	(7.2)	0	(0.0)	$\chi^2 = 23.738$	**0.001**
Infections		6	(6.6)	1	(1.4)	1	(1.2)	1	(1.2)	$\chi^2 = 7.213$	0.065
Obstetric complications during pregnancy											
Rhesus incompatibility		2	(2.2)	0	(0.0)	1	(1.2)	0	(0.0)	$\chi^2 = 3.246$	0.355
Bleeding		11	(12.1)	1	(1.4)	8	(9.6)	2	(2.4)	$\chi^2 = 11.473$	**0.009**
Diabetes		5	(5.5)	1	(1.4)	1	(1.2)	0	(0.0)	$\chi^2 = 7.442$	0.059
Preeclampsia		6	(6.6)	3	(4.1)	1	(1.2)	1	(1.2)	$\chi^2 = 5.562$	0.135
Obstetric complications at birth and peripartum											
Delivery	Spontaneous	78	(85.7)	66	(89.2)	79	(95.2)	83	(97.6)	$\chi^2 = 17.482$	**0.008**
	Emergency caesarian section	3	(3.3)	1	(1.4)	4	(4.8)	0	(0.0)		
	Application of forceps	10	(11.0)	7	(9.4)	0	(0.0)	2	(2.4)		
Uterine atony		9	(9.9)	3	(4.1)	3	(3.6)	1	(1.2)	$\chi^2 = 7.940$	**0.047**
Birth weight < 2500 g		6	(6.6)	8	(10.8)	9	(10.8)	4	(4.7)	$\chi^2 = 3.160$	0.368
Head circumference < 32 cm		3	(3.3)	5	(6.8)	0	(0.0)	0	(0.0)	$\chi^2 = 10.430$	**0.015**
Asphyxia		16	(17.6)	8	(10.8)	2	(2.4)	1	(1.2)	$\chi^2 = 20.788$	**0.001**

(SSD): Schizophrenia Spectrum Disorder; (BD): Bipolar Disorder; (MDD): Major Depressive Disorder; (HC): Healthy controls

abnormalities in DNA methylation have been described in GABAergic neurons after prenatal stress in mice and have been related to schizophrenia-like behavioral phenotypes (Matrisciano et al., 2013).

The association between prenatal malnutrition and schizophrenia risk is supported by robust evidence both in large cohort and review studies (Kyle and Pichard, 2006; Lumey et al., 2011; Wang and Zhang, 2017). Severe famine during the time of conception or early pregnancy was related to a 2-fold increase in the risk of schizophrenia in the offspring (Brown and Susser, 2008) and some epigenetic changes during this same period of pregnancy may provide a potential mechanism to explain these specific associations (Lumey et al., 2011). Our study confirms a 9-fold increased risk of psychosis in offspring of mothers that reported inadequate weight gain during pregnancy.

Prenatal protein-calorie malnutrition is associated with increased dopamine and serotonin release and turnover and this dysfunction in the hippocampus reduced dendritic branching, establishment and maintenance of long-term potentiation (Xu et al., 2015), and increased binding of the NMDA receptors, which have been implicated in the pathophysiology of schizophrenia (Palmer et al., 2008).

Few studies have investigated the possible association between prenatal malnutrition and affective disorders. A cohort-study showed an association between late gestational malnutrition and affective disorders (Brown et al., 2000) while a case-control study explained that none of the indicators of fetal growth could be identified as risk factors for bipolar disorder (Nosarti et al., 2012). Deficiency of iron during development, but not in prenatal life, increased the risk of mental illnesses, including bipolar disorder and major affective disorder (Chen et al., 2013). Recent studies have been conducted on the association between maternal pregnancy over-weight and mental outcomes for offspring (Rodriguez, 2010). One study found a higher risk of affective problems, including depression, among children of women who were overweight and obese during pregnancy while there were no significant associations for women with a body mass index in the underweight weight range (Robinson et al., 2013). Our study shows a negative correlation between maternal inadequate weight gain and affective disorders diagnosis. Having only investigated the presence of maternal inadequate weight gain and not the presence of over-weight or obesity during pregnancy in our study, we cannot overlap our results.

A recent meta-analysis highlighted that the evidence for gestational influenza as a psychosis risk factor is insufficient (Selten and Termorshuizen, 2017), while many other studies confirmed the association between prenatal exposure to maternal infection and risk of schizophrenia (Brown, 2011; Brown and Derkits, 2013; Matheson et al., 2014; Nielsen et al., 2016). Exposure to a range of infections and inflammatory responses has been associated with a 2- to 5-fold increased risk for schizophrenia (Khandaker et al., 2013). In our study, infections

Table 4

Logistic Regression analysis. Dependent variables: diagnosis of schizophrenia spectrum disorder, bipolar disorder or major depressive disorder. Independent variables: maternal stress, prenatal medical illnesses, obstetric complications.

Dependent variable	Independent variables	B	Standard Error	*p*	Odds Ratio	95% Confidence Interval	
						Min	Max
Schizophrenia Spectrum Disorder[a]	Maternal stress	0.770	0.350	**0.028**	2.160	1.087	4.291
	Inadequate weight gain	2.253	0.410	**0.001**	9.517	4.259	21.269
	Infection	2.038	0.746	**0.006**	7.673	1.778	33.120
	Asphyxia	1.388	0.456	**0.002**	4.006	1.639	9.788
	Constant	−1.666	0.175	**0.001**	0.189		
Bipolar Disorder[b]	Inadequate weight gain	−1.234	0.604	**0.041**	0.291	0.089	0.951
	Head circumference < 32 cm	1.687	0.796	**0.034**	5.404	1.136	25.710
	Constant	−1.272	0.154	**0.001**	0.280		
Major Depressive Disorder[c]	Inadequate weight gain	−1.523	0.629	**0.015**	0.218	0.064	0.748
	Constant	−0.971	0.138	**0.001**	0.379		

[a] Model 1. Dependent variable: Schizophrenia Spectrum Disorder; –2 Log-likelihood = 324.905; $\chi^2 = 65.696$; $p < 0.001$.
[b] Model 2. Dependent variable: Bipolar Disorder; –2 Log-likelihood = 330.454; $\chi^2 = 22.331$; $p < 0.001$.
[c] Model 3. Dependent variable: Major Depressive Disorder; –2 Log-likelihood = 358.021; $\chi^2 = 15.944$; $p < 0.001$.

during pregnancy increased 8-fold the risk of psychosis in later life.

Epidemiological study failed to support the association between prenatal infections and risk of affective disorders (Cannon et al., 1996). Only a birth cohort study found an increased risk of bipolar disorder after exposure to maternal influenza during pregnancy (Parboosing et al., 2013).

Prenatal immune activation can negatively affect early fetal brain development and change the offspring's neurodevelopmental trajectories which can lead to the emergence of behavioral and cognitive disturbances in later life (Meyer, 2014). Indeed, infection during early life, induces stable epigenetic modifications in offspring (Weber-Stadlbauer, 2017), such as a down-regulation of genes critical to synaptic transmission and plasticity (Kentner et al., 2016) and modifications of prefrontal GABAergic system which induced impairments of working memory and social cognition (Labouesse et al., 2015).

Several studies and reviews have determined that fetal asphyxia is involved in some of the obstetric complications associated with a risk of schizophrenia (Byrne et al., 2007) such as bleeding during pregnancy, pre-eclampsia, traumatic birth (Cannon et al., 2002; Haukvik et al., 2012; McNeil et al., 2000; Mittal and Ellman, 2008). The probability of developing schizophrenia after exposure to perinatal asphyxia was increased 5-fold (Zornberg et al., 2000) similar to the result shown in our study. The consequences of asphyxia comprise neuronal death, white matter damage, reduced growth of dendrites (Rees et al., 2008), altered cell proliferation in the anterior cingulate cortex (Schaeffer et al., 2013), and decreased NMDA receptor binding in the frontal regions, nucleus accumbens, anterior cingulate cortex, and hippocampus, as well as a deficit in prepulse inhibition of acoustic startle response (Schmitt et al., 2007). Studies on animal models have also demonstrated that perinatal asphyxia caused a shrinkage of the prelimbic cortex and consequently a deterioration in social interaction (Vázquez-Borsetti et al., 2016).

One study found that preterm birth has been associated with a risk for affective disorders (Nosarti et al., 2012) and another study showed that children delivered by planned cesarean section had a 2-fold increased risk of bipolar disorder while none of the other perinatal complications were associated with this risk (Chudal et al., 2014). The lack of association between several delivery complications and affective disorders in our study is in line with previous studies.

Small head circumference at birth was related to an increased risk of developing schizophrenia (Hultman et al., 1997; McNeil et al., 2000) through other studies found no association (Wahlbeck et al., 2001) or relationships that were restricted to females (Lahti et al., 2011). A recent study reported an abnormal head circumference growth acceleration during early life in female patients with pre-schizophrenia (Brown et al., 2017). Few minor malformations, and no major malformations have been associated with a later diagnosis of bipolar disorder (Sanches et al., 2008) as well as dermatoglyphic changes (Vonk et al., 2014). To our knowledge, our study is the first to report associations between small head circumference at birth and increased risk of bipolar disorder. Reduced head circumference at birth may be an expression of abnormal fetal growth (Cannon et al., 2002). Abnormal fetal growth can induce widespread structural brain alterations in specific regions of interest, such as the hippocampus and thalamus (Beauchamp et al., 2008), and also deficits in myelin integrity and cortical circuit connectivity (McNamara et al., 2015).

The originality of the present research is represented by the inclusion of different diagnostic groups with the aim of studying the role of maternal psychological stress and medical illnesses during prenatal/perinatal period in the etiology of schizophrenia and mood disorders.

The most important limits of this study are the retrospective design and the recruitment process. The use of maternal recall as a method of collecting pregnancy and birth information data has been criticized for potential bias (McIntosh et al., 2002). Mothers of patients with schizophrenia could have poorer recall because of cognitive impairment or psychiatric illness (Mechri et al., 2010), and a tendency to false positive responses in order to attribute a cause for the illness of their offspring (McIntosh et al., 2002). However, studies showed that obstetric complications data collected by maternal report is largely consistent with that recorded in contemporaneous medical records (Walshe et al., 2011). In our study the data potentially subject to recall bias concern maternal psychological stress during pregnancy, since the stressful experiences were reported directly by the mothers of the patients (recall-based). Data on exposure to medical illnesses in the prenatal period and to obstetric complications were acquired by only medical records, so they were not influenced by a recall bias.

The demographic characteristics including age, gender, civil status, education and employment were significantly different between groups. Regarding the control group it was impossible to get a sample to could match with each clinical group in terms of socio-demographic characteristics as patients with Schizophrenia, Bipolar Disorder or Major Depressive Disorder. So we decided to recruit a convenient sample that could embrace the majority of these variables.

During the last decades, schizophrenia has been regarded as a neurodevelopmental disorder and genetic risks, environmental risks, and vulnerability factors are cumulative and interactive with each other and with critical periods of neurodevelopment vulnerability (Davis et al., 2016). Considerable evidence also supports a neurodevelopmental contribution to bipolar disorder, although studies of perinatal/prenatal medical problems have not identified a strong association with an increased risk for this disorder (O'Shea and McInnis, 2016). However, evidence suggest that, in early-onset bipolar disorder with psychotic symptoms, early insults could produce deviant neurodevelopmental trajectories, similar to what occurs in schizophrenia (Arango et al., 2014). Gene-environment interactions may potentially explain a large proportion of cases of schizophrenia and bipolar disorder since their probands are more vulnerable to the effects of prenatal and postnatal environmental exposure (Fusar-Poli et al., 2017).

The main findings of this study are that prenatal exposure to psychological stress and medical illnesses during prenatal/perinatal period were associated with an increased risk of severe mental illness in later life.

Our study suggests that exposure to early development perturbations needs more attention in psychiatric clinical practice and scientific research, especially with regard to major affective disorders. It may be possible to decrease the risk of severe mental illness in some genetically at risk individuals with careful prenatal and perinatal monitoring. Further, including prenatal/perinatal stress in models combining multiple risk factors may enhance our ability to identify those individuals who stand to most benefit from early intervention.

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Conflict of interest

None.

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