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ORIGINAL ARTICLE

Perinatal risk factors for the onset of bipolar disorder in young adulthood: a 22-year birth cohort

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Objective: Bipolar disorder (BD) is a major cause of disability-adjusted life years in young adults. Pregnancy complications have previously been associated with BD. The current study aimed to examine the association between perinatal factors and BD.
Methods: We included 3,794 subjects from the 1993 Pelotas population-based birth cohort study. We assessed 27 variables at birth and modeled BD onset at 18 and 22 years. Bivariate analysis was performed by means of binomial logistic regression models. The variables with p-values less than 0.05 were included in a multiple regression with confounders.
Results: Maternal smoking was associated with a 1.42-fold increased risk of BD at 18 or 22 years old (95%CI 1.091-1.841), and maternal passive exposure to tobacco with a 1.43-fold increased risk (95% CI 1.086-1.875). No association was found between other perinatal factors and BD after controlling for confounders.
Conclusion: The results of the present cohort study corroborate previous reports in the literature indicating a negative effects of maternal smoking during pregnancy. These findings can be further tested and support the development of strategies to prevent the onset development of BD.

Keywords: Bipolar disorder; perinatal factors; risk markers; maternal smoking; cohort study

Introduction

Bipolar disorder (BD), a severe multifactorial disorder affecting more than 1% of the global population, is one of the main causes of disability worldwide.[1] Individuals with BD have increased suicide rates (7.8% in men and 4.9% in women) and decreased quality of life, even in euthymia.[2] Because of the pronounced negative impacts of BD on the individual, family, and social spheres,[3] preventive measures and early diagnosis and interventions are needed to improve the long-term prognosis of individuals with BD. Similarly, evidence suggests that individuals with BD who are treated early in the course of illness may respond better to available treatment options and require less aggressive therapeutic regimens.[4] However, despite advances in the understanding of the neuropathophysiology of BD, the etiology of the disease remains largely unknown. Therefore, efforts have been made to identify more distal risk factors, as early as the prenatal and perinatal periods.[5]

Evidence suggests that the trajectory of BD involves a link between risk and severity.[6] This can be observed in both the disorder's clinical course, as described in neuroprogression models,[7,8] as well as in its prodromal history, with distal factors associated with the condition. Furthermore, the earlier an individual experiences stressful events in life, the greater his or her risk of developing a neurodevelopmental disorder over the life course.[9,10]

Several perinatal factors are known to be associated with serious general mental illness[11] as well as the suicide risk.[12] A recent meta-analysis also found dozens of prenatal and perinatal factors associated with psychotic disorders,[13] suggesting that prenatal and perinatal factors may also be associated with BD. Therefore, the present

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study aims to assess perinatal and prenatal factors and their potential association with the onset of BD in a birth cohort followed up to 22 years of age.

Methods

Sample

We included 3,794 individuals from the 1993 Pelotas Birth Cohort, a population-based prospective study conducted in Pelotas, Brazil. All births occurring in Pelotas from January 1 to December 31, 1993 (n=5,265) were eligible, and 5,249 newborns participated in the longitudinal study with their mother's consent. The initial goals of the cohort were to evaluate trends in maternal and child health indicators by comparing the results with those of an earlier cohort established in 1982.[14] Participants were followed at birth and at 11, 15, 18, and 22 years of age.[15] The retention rate was 81.4% at the 18-year follow-up and 76.3% at the 22-year follow-up visit, including 3,810 individuals interviewed at these two time points. These participants answered the Mini-International Neuropsychiatric Interview (MINI) (Brazilian version 5.0 for DSM-IV), an instrument used to operationalize psychiatric diagnoses, including BD type I and BD type II. The present study included data from 3,794 participants, as MINI results were missing for 16 subjects. By age 22 years, 268 participants met criteria for a diagnosis of BD. The control group (n=3,526) comprises individuals without BD, including healthy individuals and individuals with other diagnoses.

Procedures

Mental health assessments were conducted by trained psychologists. The variables described below were selected based on those reported in previously published studies regarding BD. We also included variables selected *a priori* by convenience (availability of information in the cohort data) as part of the study protocol: sociodemographic data, perinatal and prenatal variables, social support/family variables, and diagnosis according to DSM-IV. A detailed description of the variables is provided in Box 1.

Statistical analysis

Descriptive univariate analysis was performed, using relative and absolute frequencies for categorical variables and mean and median values for numerical variables, followed by SD and minimum and maximum values. P-values for the descriptive tables were estimated using Student's *t*-tests and chi-square tests of independence.

We assessed the association between BD diagnosis (at 18 or 22 years of age) and perinatal factors using bivariate analysis with binomial logistic regression models. We used the Bonferroni correction to account for multiple comparisons. As 25 crude models were fitted, we considered a p-value below 0.002 (0.05/25 given that α = 0.05) to perform further adjusted analyses. Out of these, the risk factors with an unadjusted p-value below 0.002 were included in a multiple regression model along with the following confounders: sex, maternal age ($<$ 20 and $>$ 34), maternal years of education, parity ($\geqslant$ 4), and family income.

For multiple regression, we used binomial logistic regression while incorporating the confounding variables. To calculate the odds ratio (OR), we applied the exponential function to the regression coefficients and determined 95%CIs using standard errors. These calculations were performed while controlling for the sociodemographic and environmental variables described above.

All analyses were performed with scripts written in the R programming language (version 4.2.3) using the RStudio integrated development environment.[18] The following packages were used: *dplyr* (for data wrangling), *haven* (for data import), *ggplot2* (for creating data visualizations), *purrr* (for functional programming tools), *magrittr*, *tidyr*, *broom*, *table1*, and *flextable* (for descriptive tables).

Box 1 Variables included in the study

- Pregnancy: arterial hypertension,[†] diabetes mellitus,[†] gestational infection,[†] gestational anemia,[†] intrapartum hemorrhage, maternal smoking (in any amount and at any time during pregnancy), maternal passive exposure to tobacco, heavy drinking[‡] (defined as consuming any amount of alcohol more than once a day).
- Delivery: cesarean, induced labor (by amniotomy or administration of an oxytocin pump).
- Childbirth: prematurity, trauma during labor, respiratory dysfunction, malformations, fetal distress, hospitalization in neonatal intensive care unit (ICU), low birth weight, low birth length, head circumference,[§] 1st minute APGAR,[‖] 5th minute APGAR.[‖]
- Socioeconomic status: parental structure (whether parents lived together or not), paternal education level, maternal education level, family support, maternal age at birth ($<$ 20 years old or $>$ 34 years old),[¶] and intention to breastfeed.
- Outcome at 18 years and 22 years: diagnosis of BD type I or type II – variable created by algorithm based on the patients' responses to th MINI.

[†] Three levels (no disease, treated, and untreated).
[‡] Heavy drinking, used as a dichotomous variable due to the lack of reliable data on the timing and amount of alcohol consumption, which precluded a linear analysis of consumption and the increased risk.
[§] Head circumference, dichotomized as $<$ 33 cm or $\geqslant$ 33 cm.
[‖] Appearance, pulse, grimace, activity, and respiration (APGAR) score, dichotomized as $<$ 7 and $\geqslant$ 7.2.
[¶] Maternal age, dichotomized according to maternal groups considered at risk for various diseases in their offspring).[16,17]

Ethics statement

The 1993 Pelotas Birth Cohort study was approved by the Ethics Committee of the Faculdade de Medicina, Universidade Federal de Pelotas. All participants provided fully informed consent for inclusion in the study.

Results

We included 3,794 individuals from the birth cohort according to the inclusion and exclusion criteria. Of the 3,794 participants who answered the MINI, 268 (7.06%) were diagnosed with BD (110 [2.90%] at age 18 and 158 [4.16%] at age 22). A total of 192 (5.06%) were diagnosed with BD type I and 76 (2%) with BD type II. Table 1 shows the sociodemographic characteristics of the cohort at age 22 years. A statistically significant difference was noted in the incidence of lifetime marijuana and cocaine use in BD patients when compared to individuals without BD. The groups also differed in terms of sex, socioeconomic status, and years of education. Supplementary Table S1 shows the results of perinatal exposures. Supplementary Figure S1 shows the frequency of missing values for all variables.

Most comparisons did not reach statistical significance in either bivariate analysis or after adjustment for potential confounders, as shown in Table 2. However, four variables were statistically different in the bivariate analysis: maternal smoking (OR = 1.648; 95%CI 1.279-2.118; $p < 0.001$), maternal passive exposure to tobacco (OR = 1. 635; 95%CI 1.259-2.132; $p < 0.001$), paternal education level (OR = 0.919; 95%CI 0.883-0.955; $p < 0.001$), and maternal education level (OR = 0.909; 95%CI 0.875-0.944; $p < 0.001$). After controlling for confounders, only maternal smoking (OR = 1.419; 95%CI 1.091-1.841; p = 0.009) and maternal passive exposure to tobacco (OR = 1.425; 95%CI 1.086-1.875; p = 0.010) remained statistically significant as risk factors for BD, whereas paternal education level (OR = 0.977; 95%CI 0.928-1.03; p = 0.365) and maternal education level (OR = 0.950; 95%CI 0.902-1.000; p = 0.053) did not.

Based on the present results, maternal smoking and maternal passive exposure to tobacco were identified as the main risk factors. We examined whether these variables could explain lifetime smoking during childhood or adolescence. After analyzing data collected at age 15, we concluded that individuals whose mothers smoked (OR = 1.71; 95%CI 1.44-2.04; $p < 0.001$) or were exposed to tobacco during pregnancy (OR = 1.65; 95%CI

Table 1 Sociodemographic characteristics of the cohort at age 22

Variables	Individuals without BD (n=3,526)	Onset of BD in young adulthood (n=268)	p-value
Sex			
Male	1,690 (47.9%)	109 (40.7%)	0.026
Female	1,836 (52.1%)	159 (59.3%)	
Socioeconomic status			
Upper	1,386 (39.3%)	51 (19.0%)	< 0.001
Middle	1,761 (49.9%)	148 (55.2%)	
Lower	330 (9.4%)	45 (16.8%)	
Missing	49 (1.4%)	24 (9.0%)	
Marital status			
Married/Stable union	534 (15.1%)	45 (16.8%)	0.664
Divorced/Separated	18 (0.5%)	1 (0.4%)	
Single	2,946 (83.6%)	202 (75.4%)	
Widowed	1 (0.0%)	0 (0%)	
Missing	27 (0.8%)	20 (7.5%)	
Years of education			
Mean (SD)	9.86 (2.43)	8.67 (2.50)	< 0.001
Median (min, max)	11.0 (0, 12.0)	8.50 (4.00, 12.0)	
Missing	30 (0.9%)	20 (7.5%)	
Currently working			
No	1,045 (29.6%)	92 (34.3%)	0.057
Yes	2,220 (63.0%)	149 (55.6%)	
Missing	261 (7.4%)	27 (10.1%)	
Lifetime cannabis use			
No	2,103 (59.6%)	123 (45.9%)	< 0.001
Yes	1,200 (34.0%)	116 (43.3%)	
Missing	223 (6.3%)	29 (10.8%)	
Lifetime cocaine use			
No	2,794 (79.2%)	168 (62.7%)	< 0.001
Yes	500 (14.2%)	72 (26.9%)	
Missing	232 (6.6%)	28 (10.4%)	

P-values were calculated by using Student's t-tests and chi-square tests.

Table 2 Variables not significantly associated with bipolar disorder

Variables	OR	95% CI	p-value
Maternal hypertension			
Treated	0.77	0.49-1.16	0.23
Untreated	0.78	0.35-1.50	0.49
Maternal diabetes mellitus			
Treated	1.08	0.42-2.30	0.86
Untreated	1.52	0.24-5.29	0.58
Gestational infection			
Treated	1.23	0.80-1.82	0.32
Untreated	1.62	0.55-3.75	0.32
Gestational anemia			
Treated	1.24	0.96-1.61	0.09
Untreated	1.25	0.52-2.58	0.58
Intrapartum hemorrhage	1.60	0.48-4.07	0.38
Heavy drinking	0.73	0.12-2.40	0.67
Cesarean section	0.77	0.58-1.01	0.07
Induced labor	0.92	0.69-1.20	0.55
Trauma during labor	4.39	0.22-34.48	0.20
Respiratory dysfunction	1.77	0.81-3.40	0.11
Admission to neonatal ICU	1.52	0.70-2.89	0.25
Low birth weight	1.37	0.91-2.00	0.11
Low birth length	1.35	0.96-1.85	0.07
Head circumference	1.22	0.79-1.80	0.35
One-minute Apgar	0.74	0.37-1.32	0.34
Parental structure	1.27	0.88-1.79	0.19
Family support	0.91	0.62-1.38	0.64
Maternal age at delivery $<$ 20 years old	1.26	0.92-1.70	0.14
Maternal age at delivery $>$ 34 years old	0.78	0.49-1.18	0.27

ICU = intensive care unit; OR = odds ratio.

1.37-1.98; $p < 0.001$) were more likely to smoke during adolescence. We examined the effect of lifetime smoking at age 15 on the development of BD in early adulthood. The results showed a statistically significant effect (OR = 1.59; 95%CI 1.17-2.13; p = 0.002), which was lost after adjustment for confounders (OR = 1.34; 95%CI 0.97-1.84; p = 0.074). The frequency distributions of maternal smoking, maternal exposure to tobacco during pregnancy, and lifetime smoking at age 15 are shown in Supplementary Figure S2.

Some perinatal characteristics were found to be extremely rare, precluding their inclusion in our modeling analyses – prematurity (n=3 [0.08% of the total sample]), malformations (n=3 [0.08% of the total sample]), fetal distress (n=15 [0.39% of the total sample]), 5-minute APGAR score (n=28 [0.74% of the total sample]), intention not to breastfeed (n=21 [0.55% of the total sample]).

Discussion

Although there is growing interest in the identification of early risk factors for BD to support early intervention and the development of potential prevention strategies, few well-designed studies have been conducted so far. The present study identified maternal exposure to tobacco during pregnancy as a potential risk factor for the development of BD in offspring. This was found in of women who smoked during pregnancy and women exposed to tobacco through partner use. Because few previous studies were well-designed, and given the dearth of longitudinal data in this topic, the present findings represent a consistent contribution to the evidence on perinatal factors associated with BD.

Previous studies have reported that smoking exposure is associated with adverse effects on the developing brain.[19] Results from animal studies demonstrate that prenatal exposure to nicotine can significantly affect the development of axons and synapses in neural cells.[20] Moreover, studies in rodents have shown that nicotine can both modify and impair the process of brain development.[21-23] In addition, similar effects have been observed in first-trimester human fetal brain cell cultures.[24] Thus, the current literature reinforces the potential for prenatal smoking exposure to have long-lasting effects and a pronounced impact on individual developmental trajectories.

Previous data also show maternal exposure to tobacco during pregnancy as a risk factor for offspring mental health outcomes. A Finnish population-based study collected information on prenatal smoking exposure and assessed the risk of psychiatric morbidity[25] – the study detected that risk was significantly higher in exposed than unexposed individuals, even after adjustment for confounders. There is some evidence that changes in DNA methylation caused by maternal smoking during prenatal development may increase susceptibility to psychiatric disorders,[26] and recent evidence suggests that maternal smoking may enrich genes related to growth factor signaling and inflammation,[27] both of which have been

implicated in BD.[7] Nicotine and carbon monoxide are also known to cross the placenta and may directly and indirectly (e.g., through hypoxia) affect fetal neurodevelopment.[28] A population-based study found that children born to mothers who smoked heavily during pregnancy were approximately 1.5 time more likely to develop BD than children born to mothers who did not smoke during pregnancy.[28] Our findings are also supported by an American case-control study published in 2013, in which maternal smoking was associated with a 2-fold increased risk of developing BD, even after adjusting for confounders.[29] However, a nested case-control study derived from the Finnish population born between 1983 and 1998 found no significant association between maternal smoking and BD, attributing the finding to confounders.[30]

We raised the possibility that maternal smoking might be associated with smoking in offspring. This could be a factor mediating the effect of our study. Indeed, there is a primary association, but offspring smoking was not statistically significant as a risk factor for BD after adjustment for confounders. This leads us to believe that maternal exposure to tobacco is independently associated with the diagnosis of BD, as also observed in an American cohort.[31] A study evaluated the association between maternal and offspring smoking, which was statistically significant, but also found that maternal smoking was independently associated with BD onset.[31]

In a recently published meta-analysis by our group, investigating pre- and perinatal factors for BD, maternal smoking was not significantly associated with increased risk of BD.[32] However, only two case-control studies with small sample sizes were analyzed, resulting in insufficient statistical power to make significant claims on tobacco use during pregnancy.[33,34] Differently from the present study, the meta-analysis identified obstetric complications, peripartum asphyxia, maternal stress, and low birth weight as associated risk factors. Regarding ''obstetric complications,'' the meta-analysis did not specify which complications were studied. Considering that we evaluated different types of complications as independent variables in our study, the combination of multiple outcomes may have produced significant effect in the meta-analysis. Data on peripartum asphyxia and maternal stress were not available in our sample, which precluded these analyses. The main difference is for low birth weight, for which our study found no statistical significance, consistent with previous reports.[35-38]

Our study should be interpreted considering its strengths and limitations. Our findings were derived from a cohort with a large sample size, allowing robust analyses of perinatal factors. In addition, most previous studies on the topic relied on case-control designs, whereas a cohort study has greater associative potential in the hierarchy of evidence of observational studies. However, we must acknowledge certain important limitations inherent to the epidemiological nature of our study. Primarily, our investigation focused exclusively on the onset of BD up to the age of 22 years, limiting our inclusion criteria to individuals with an early diagnosis. Furthermore, there may be an overdiagnosis in our sample because the cohort used the MINI, a highly sensitive scale, as a diagnostic method for BD.[39] This would explain the high rate of BD diagnoses compared with previous studies.[40] Moreover, the possibility of attrition bias cannot be ignored. Individuals experiencing mental distress may have been more adherent to the study because they felt it was a form of supportive care, whereas healthy individuals may have discontinued participation due to a lack of perceived benefit. Additionally, our study was not specifically designed to assess mental health. Consequently, we lack data on other established factors associated with BD onset, such as parental diagnosis of BD within the cohort. Because of the substantial genetic component of BD, eliminating this confounder from our study was not possible.

In conclusion, identifying distal factors associated with BD is crucial in the search of preventive strategies for the disorder. Our study sheds light on one such critical factor, tobacco exposure during pregnancy, which holds a potential for effective intervention. Bipolar disorder is known to have multifaceted origins, and understanding these risk factors allows us to address them before the onset of the disorder. By addressing this link, we provide an opportunity for early intervention, thereby potentially reducing the risk of BD in offspring. The present research underscores the importance of public health interventions to reduce maternal tobacco use, not only for the immediate well-being of pregnant individuals but also for the long-term mental health outcomes of their offspring. It is another step toward a future in which psychiatric conditions can be prevented through evidence-based, targeted interventions.

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Disclosure

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Author contributions

VG: Conceptualization, Methodology, Project administration, Writing – original draft.
BBM: Data curation, Formal analysis, Methodology, Writing – original draft.
DPB: Methodology, Supervision, Visualization, Writing – original draft.
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