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Perinatal factors and the risk of bipolar disorder in Finland

Roshan Chudal¹, Andre Sourander^{1,2,3,4}, Päivi Polo-Kantola⁵, Susanna Hinkka-Yli-Salomäki¹, Venla Lehti¹, Dan Sucksdorff¹, Mika Gissler^{1,6,7}, and Alan S. Brown^{3,8}

¹Department of Child Psychiatry, University of Turku, Finland ²Department of Child Psychiatry, Turku University Hospital, Finland ³Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA ⁴Regional Centre for Child and Youth Mental Health and Child Welfare, University of Tromsø, Norway ⁵Department of Obstetrics and Gynecology, Turku University Hospital and University of Turku, Turku Finland ⁶Nordic School of Public Health, Gothenburg, Sweden ⁷National Institute for Health and Welfare, Finland ⁸Department of Epidemiology, Columbia University, Mailman School of Public Health, New York, NY, USA

Abstract

Background—Complications during the perinatal period have been associated with neurodevelopmental disorders like schizophrenia and autism. However, similar studies on bipolar disorder (BPD) have been limited and the findings are inconsistent. The aim of this study was to examine the association between perinatal risk factors and BPD.

Methods—This nested case-control study, based on the Finnish Prenatal Study of Bipolar Disorders (FIPS-B), identified 724 cases and 1419 matched controls from population based registers. Conditional logistic regression was used to examine the associations between perinatal factors and BPD adjusting for potential confounding due to maternal age, psychiatric history and educational level, place of birth, number of previous births and maternal smoking during pregnancy.

Results—Children delivered by planned cesarean section had a 2.5-fold increased risk of BPD (95% CI: 1.32–4.78, $P < 0.01$). No association was seen between other examined perinatal risk factors and BPD.

Limitations—The limitations of this study include: the restriction in the sample to treated cases of BPD in the population, and usage of hospital based clinical diagnosis for case ascertainment. In addition, in spite of the large sample size, there was low power to detect associations for certain exposures including the lowest birth weight category and pre-term birth.

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Corresponding Author: Roshan Chudal, Research Centre for Child Psychiatry, Institute of Clinical Medicine, Faculty of Medicine, University of Turku, Lemminkäisenkatu 3 / Teutori (3rd floor), 20014 Turku, Tel: +358-2-3337394, roschi@utu.fi.

Contributors:

Authors AS, ASB, MG, RC, SHY designed the study. RC did the literature search and wrote the first draft of the manuscript. SHY conducted the statistical analysis. All authors contributed to the interpretation of the data and critically revised the initial manuscript. All authors gave their approval for the final version submitted.

Conflict of interest:

The authors report no conflict of interest.

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Conclusions—Birth by planned caesarean section was associated with risk of BPD, but most other perinatal risk factors examined in this study were not associated with BPD. Larger studies with greater statistical power to detect less common exposures and studies utilizing prospective biomarker-based exposures are necessary in the future.

Keywords

obstetric complications; perinatal complications; gestational age; fetal growth; bipolar disorder

Introduction

Bipolar disorder (BPD) is a chronic disabling psychiatric condition characterized by recurrent episodes of mania or hypomania and depression in a cyclical course (Barnett et al., 2009). Complications during the perinatal period have been associated with psychiatric disorders like schizophrenia (Byrne et al., 2007; Abel et al., 2010; Cannon et al., 2002), autism (Kolevzon et al., 2007; Glasson et al., 2004) and affective disorders (Abel et al., 2010). However, studies on BPD have been inconsistent with some studies showing an increased risk in children exposed to perinatal complications (Kinney et al., 1993, 1998), while other studies failed to show similar associations (Verdoux and Bourgeois, 1993; Martelon et al., 2012). These complications include a variety of factors; some of the most noteworthy are indicators of fetal growth including birth weight, gestational age, and weight for gestational age (WGA), and what are often termed “obstetric complications,” including uterine bleeding, birth presentation, birth type, and Apgar score.

Six population-based epidemiological studies have examined the association between perinatal risk factors and BPD in the offspring (Nosarti et al., 2012; Øgendahl et al., 2006; Eaton et al., 2000; Laursen et al., 2007; Hultman et al., 1999; Bain et al., 2000). Three of these studies included cases with affective psychosis including BPD (Eaton et al., 2000; Hultman et al., 1999; Bain et al., 2000). Among the indicators of fetal growth, birth weight was examined in only three studies (Øgendahl et al., 2006; Eaton et al., 2000; Bain et al., 2000), and was shown not to be associated with BPD in two Danish studies (Øgendahl et al., 2006; Eaton et al., 2000) and one Scottish study (Bain et al., 2000). Findings of the studies on gestational age and on birth weight adjusted for gestational age have been inconsistent. A Swedish study (Nosarti et al., 2012) found preterm birth to be associated with increased risk of BPD, while two Danish studies (Øgendahl et al., 2006; Eaton et al., 2000) failed to show similar associations. A Danish study (Laursen et al., 2007) showed increased risk in preterm children born small for gestational age (SGA) whereas SGA was not associated with BPD in two Swedish studies (Nosarti et al., 2012; Hultman et al., 1999) and a Scottish study (Bain et al., 2000). Only three of these six population based studies included information on obstetric complications (Nosarti et al., 2012; Hultman et al., 1999; Bain et al., 2000). The study by Bain et al, (2000) showed abnormal fetal presentation and artificial rupture of membranes to be associated with BPD, whereas the Swedish study only found the association with uterine atony and late winter birth (Hultman et al., 1999). However, Nosarti et al (2012) did not find any association between Apgar score and BPD. Several methodological issues could explain the inconsistency in the results of the population based studies. First, the sample size in the studies varied widely from 69 (Eaton et al., 2000) to 4490 (Laursen et al., 2007). Second, there was wide variation in the categorization of the perinatal risk factors (Nosarti et al., 2012; Laursen et al., 2007; Øgendahl et al., 2006; Eaton et al., 2000; Bain et al., 2000; Hultman et al., 1999) thereby resulting in lack of uniformity in interpreting the findings. Lastly, there were extensive differences in adjustment for confounding factors with only three studies (Laursen et al., 2007; Øgendahl et al., 2006; Nosarti et al., 2012) adjusting for the effects of parental age and psychiatric history and only two studies adjusting for some measure of maternal socioeconomic status (Øgendahl et al., 2006; Nosarti et al., 2012).

The aim of this study was to examine the association between perinatal risk factors and the subsequent risk of BPD. Only one previous population based study (Bain et al., 2000) has examined a similar range of perinatal risk factors as in this study. However, that study did not adjust for any confounders. This study utilizes a nationwide population based sample and includes information about several potential perinatal risk factors. In addition, the availability of data on several possible confounding factors further adds to the strength of this study.

Methods

This study is based on the Finnish Prenatal study of Bipolar Disorders (FIPS-B), a nested case-control study derived from all singleton live births in Finland between January 1, 1983 and December 31st, 1998 (N=1,009,846). Cases included in this study were all offspring born in Finland between January 1st 1987 and December 31st 1998 (N=754,450) who were diagnosed and/or treated for BPD by December 31, 2008. The Finnish Medical Birth Register (FMBR), the data source for perinatal risk factors, was established in 1987. Thus, only offspring born 1987 onwards were included in this study. The cases were identified from the Finnish Hospital Discharge Register (FHDR) and the controls, identified from the Finnish Central Population Register, were also born during the study years, not diagnosed with BPD or psychotic disorder, and matched to cases on selected factors (sex, date of birth and residence in Finland on the first date of diagnosis of the case). Data on all the newborns and their mothers during the study period were ascertained from the Finnish Medical Birth Register (FMBR).

Ethical approval for the study was provided by the Institutional Ethical Review Board at Turku University Hospital, Turku University, and the Institutional Review Board of the New York State Psychiatric Institute. Approval was obtained from the data protection authority in Finland for the utilization of the health registers data and linkage of the data for scientific research

National register information

This study is based on data from four nationwide registers. The registers include: the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR), the Register of Education at Statistics Finland and the Finnish Central Population Register. Detailed descriptions of the Finnish Hospital Discharge Register (FHDR) and the Finnish Medical Birth Register (FMBR) have already been reported elsewhere (Chudal et al., 2013) and will only be briefly described here. The FHDR contains all medical diagnoses given in hospitals in Finland from 1969 to the present. It initially covered all diagnoses from inpatient wards, in both somatic and psychiatric hospitals, local health centers, military wards, prison hospitals and private hospitals, and since 1998, also covers outpatient care in public specialized hospital units. The diagnostic classification in Finland is based on the International Classification of Diseases (ICD); ICD-8 (WHO, 1967) from 1969 to 1986, ICD-9 (WHO, 1977) from 1987 to 1995 and ICD-10 (WHO, 1992) from 1996 onwards. The Finnish public health care covers both primary health care and specialized services, and the care is provided by local health centers, district, central and university hospitals. Typically patients are referred to specialized mental health services within the public health care system by a general practitioner based on suspicion of BPD. The diagnostic assessment is led by an adult or child/adolescent psychiatrist, depending on the age of the patient. The FMBR was established in 1987 and includes comprehensive and standardized data on the perinatal period for all live births, and stillbirths of fetuses with birth weight of at least 500 g or gestational age of at least 22 weeks.

Statistics Finland

Statistics Finland is the public authority established particularly for statistical services in Finland. Information on maternal educational level of cases and controls was taken from the Register of Education at Statistics Finland.

The Finnish Central Population Register

The Finnish Population Register Centre and local register offices maintain this computerized national register. It contains basic information about Finnish citizens and foreign citizens residing permanently in Finland. This information is based on statutory notifications made by private individuals and public authorities. Personal data recorded in the system includes name, personal identity code (PIC), address, citizenship and native language, family relations and date of birth and death (if applicable). These registers were linked using the PIC, assigned to all residents of Finland since 1964. The PIC includes the date of birth, sex and a control number which is unique for each person, and does not change over the lifetime of an individual.

Identification of study subjects

The cases for this study include all diagnosed BPD subjects born singleton between January 1, 1987 and December 31, 1998 and diagnosed and/or treated by December 31, 2008. They were identified from the FHDR using ICD diagnostic codes 2962, 2963, 2964, 2967 (ICD-9) and F31.X (ICD-10). The total number of cases identified was 724.

Controls for this study were offspring who were without BPD, schizophrenia or diagnoses related to these disorders {ICD-10 diagnoses: F20–29 (schizophrenia, schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders, unspecified nonorganic psychosis), F30 single manic episode, F31 BPD, F34.0 cyclothymia, F38.0 other mood disorders; mixed affective episode, F39 unspecified mood disorder, F60.0 paranoid personality disorder and F60.1 schizoid personality disorder}; ICD-9 diagnoses {2962A-G, 2963A-G, 2964A-G, 2967A BPD, 295 schizophrenic psychoses, 297 paranoid states, 298 psychoses aliae, 3010A paranoid personality, 3012A schizoid personality and 3012C schizotypal personality. Two matched controls were identified from the Finnish Central Population Register randomly for each case (N= 1448). Among 1448 control subjects, 29 were excluded as they belonged to a twin pair resulting in 1419 controls included in the final analyses.

Perinatal risk factors

“Perinatal period” is defined as the time period from 22 completed weeks of gestation until 7 completed days after birth (WHO, 1992). In this study, we classified the perinatal risk factors into two categories: 1) Indicators of fetal growth (birth weight, gestational age and WGA) and 2) Obstetric complications (e.g. uterine bleeding, birth presentation, birth type and Apgar score).

Indicators of fetal growth

Birth weight was categorized as: < 1500, 1500 to 2499, 2500 to 3999, 4000 to 4499 and 4500 grams. Gestational age was classified into four categories: < 32, 32 to 37, 38 to 41 and 42 weeks. The calculation of birth weight for gestational age [(small for gestational age (SGA)/ appropriate for gestational age (AGA) and large for gestational age (LGA)] was made according to national sex-specific weight distribution standards at a given gestational age. The growth curves were derived from data on 75 061 singleton children, with a

gestational age of 24 to 43 weeks, born between 1979 and 1983 in Helsinki University maternity hospitals in Uusimaa, Finland. The gestational age was calculated mainly based on the information of the last menstruation period, and corrected by ultrasound measurement only in unclear cases (Pihkala et al., 1989). WGA was categorized into three groups: SGA, < -2 SD; AGA, -2 SD - $+2$ SD and LGA: $> +2$ SD. The classifications used for the indicators of fetal growth were similar to a previous population based prenatal study on autism (Lampi et al., 2012).

Obstetric complications

Maternal risk factors included uterine bleeding that required hospitalization and maternal hypertension. Uterine bleeding was classified as a binary variable (yes/no). Between January 1, 1987 and September 30, 1990, this information was ascertained based on the ICD-9 codes (640, 6400A, 6408X, 6409X, 641, 6410A, 6410B, 6411A, 6411B, 6412A, 6412B, 6413A, 6413B, 6418A, 6418B, 6419A, 6419B) as the FMBR did not have information on this variable during this period. From October 1st 1990 onwards the FMBR contains information about "hospital care due to bleeding during pregnancy" as a "Yes/ No" variable recorded during the maternal visit to the health centres. However, no information was available about the etiology of uterine bleeding or in what trimester the bleeding occurred. Maternal hypertension was also classified as a binary variable (yes/no) with blood pressure higher than 140/90 mm Hg during pregnancy considered as "high". The information on this variable was obtained from the FMBR based on the maternal visits to the health centres. However, no information was available about the etiology or the time frame of occurrence of maternal hypertension during pregnancy.

Birth factors included birth presentation, birth type, induced labour and Apgar scores (1 minute). Birth presentation was classified into three categories: cephalic, breech or other (e.g. transverse, oblique, upper or lower limb). Birth type was classified into five categories: vaginal cephalic, suction or forceps, planned caesarean section, emergency or other caesarean section and unknown. Induced labour was classified as a binary variable (Yes/ No). Apgar scores were measured at one minute and classified as 9–10, 7–8 or less than 7. Neonatal treatment included neonatal monitoring or intensive care of the infant at the neonatal intensive care unit (NICU treatment), and was classified as a binary variable: Yes/ No. Information on these birth factors was obtained from the FMBR.

Confounding factors

Six potential confounding factors that have been shown to be associated with both perinatal risk factors and BPD were included in the analyses: maternal age (Newburn et al., 2005; Frans et al., 2008), maternal psychiatric history (Lee et al., 2010; Mortensen et al., 2003), maternal education level (Tsuchiya et al., 2004; Mortensen et al., 2008) and place of birth (Thomson et al., 2005; Pedersen et al., 2006), number of previous births (Aliyu et al., 2005; Frans et al., 2008) and maternal smoking during pregnancy (Agrawal et al., 2010; Talati et al., 2013). Maternal age was classified in the following categories: less than 20, 20–24, 25–29, 30–34, 35–39 and over 40 years. A mother was classified as having a psychiatric history if she had any mental health disorder of F10–99, based on the ICD-10 classification, excluding mental retardation (F70–79). Corresponding diagnoses based on the ICD-9 (291–316) and the ICD-8 (291–309) were also included for those diagnosed during the periods in which those diagnostic systems were in use. Maternal psychiatric history was classified as a binary variable (yes/no). Maternal educational level was classified into four categories: 1) Master / Licentiate / Doctoral degree, 2) University/ Polytechnics bachelor degree, 3) Upper secondary school/equivalent vocational degree and 4) Basic education (comprehensive school). The place of birth variable (southern Finland, western Finland, eastern Finland and northern Finland) was derived from the birth municipality information of cases and controls,

obtained from the Population Register Centre. Number of previous births was classified as 0 and 1. Smoking during pregnancy was classified as a binary variable (Yes/No). Data on maternal age were available from the Finnish Central Population Register, data on maternal psychiatric diagnoses were obtained from the FHDR and maternal educational level data were obtained from the Register of Education at Statistics Finland. Data on number of previous births and smoking during pregnancy was derived from FMBR.

Statistical analyses

Conditional logistic regression models were used to examine the associations between the BPD outcome and perinatal risk factors. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were first calculated. In the adjusted model, possible confounders (maternal age, psychiatric history, educational level and place of birth) were controlled. In all analyses, a two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS statistical software (SAS Version 9.3; SAS Institute Inc., Cary, NC).

Results

The mean age of diagnosis of BPD in the sample was 16.9 years (SD: 2.6, range: 4–21 years). Table 1 shows the unadjusted and adjusted odds ratios (OR) for the association between indicators of fetal growth and BPD. In the unadjusted analyses, post-term birth (i.e. gestational age of 42 weeks or more) was associated with a 1.7-fold increased risk of BPD. However, the association was not significant following adjustment for all potential confounders (OR= 1.52, 95% CI: 0.93–2.45). No significant associations were observed between other gestational age categories, birth weight and their combinations and BPD.

Table 2 shows the unadjusted and adjusted ORs for the various potential obstetric complications and BPD. Children delivered by planned caesarean section had a 2-fold increased risk of BPD in the unadjusted analyses. The risk increased to 2.5-fold (OR= 2.51, 95% CI: 1.32–4.78, $P < 0.01$) following adjustment for potential confounders. Birth presentation other than cephalic or breech (i.e. transverse, oblique, upper or lower limb) was associated with a 5.3-fold increased risk of BPD in the unadjusted analyses. However, the association failed to reach statistical significance following adjustment for all potential confounders (OR= 5.12, 95% CI: 0.95–27.54). No significant associations were seen between maternal hypertension (OR= 1.84, 95% CI 0.78–4.33, $p = 0.17$), uterine bleeding during pregnancy (OR= 2.77, 95% CI 0.39–19.66, $p = 0.31$), induced labor (OR= 0.73, 95% CI 0.43–1.23, $p = 0.23$), low Apgar scores (OR= 1.17, 95% CI 0.66–2.05, $p = 0.59$) and neonatal treatment (OR= 1.46, 95% CI 0.73–2.90, $p = 0.28$) and BPD. Furthermore, we conducted a sub-analysis of the sample of BPD cases diagnosed after 1998 when the FHDR had coverage of both inpatient and outpatient cases. The results remained the same as seen in the total sample.

Discussion

Birth by planned caesarean section was associated with an increased risk of BPD. The only previous population based study (Bain et al., 2000) to have examined this question found no association. The association between planned caesarean section and BPD should be interpreted with caution as it may be a proxy of another risk factor. While common indications for a planned caesarean section include previous caesarean section and twin delivery (Penn et al., 2001), caesarean section can also be requested by the mother without any medical indication (Wiklund et al., 2012; Lee et al., 2008). Mothers requesting caesarean section have been shown to be more anxious, depressed, and to have low self-

esteem, lack social support and personality traits such as neuroticism (Saisto et al., 2001; Storksen et al., 2012). These maternal characteristics could contribute to the increased risk of BPD in offspring through genetic factors or by affecting the childhood environment. However, further studies are needed to clarify these associations.

No association was seen between birth weight, gestational age and their combinations and the risk of BPD. The lack of association between birth weight and BPD has been seen in three previous studies (Øgendahl et al., 2006; Bain et al., 2000; Eaton et al., 2000). Similarly, three previous population-based studies (Nosarti et al., 2012; Eaton et al., 2000; Øgendahl et al., 2006) have examined the association between gestational age and BPD and found no association. However, these negative findings are in contrast to a study showing increased risk of BPD in children born preterm (Nosarti et al., 2012). Being born SGA was not associated with BPD, similar to three previous studies (Nosarti et al., 2012; Hultman et al., 1999; Bain et al., 2000). However, an increased risk of BPD was found in preterm children born SGA in another study (Laursen et al., 2007). The study failed to show any association between several obstetric risk factors (e.g. uterine bleeding, birth type and 1 minute Apgar score) and BPD.

The lack of association between several perinatal risk factors and BPD is in line with similar previous studies. Several studies have shown an association between adverse events in pre-, peri- and postnatal period and subsequent risk of schizophrenia (Rifkin et al., 1994; Sacker et al., 1996; Byrne et al., 2007; Hultman et al., 1999; Abel et al., 2010; Cannon et al., 2002) and autism (Hultman et al., 2002; Glasson et al., 2004; Larsson et al., 2005; Buchmayer et al., 2009; Karmel et al., 2010; Eaton et al., 2001). This suggests that the role of complications during pregnancy and perinatal period as a potential environmental risk factor is different for BPD as compared to schizophrenia and autism.

Limitations

Some limitations of this study should be noted. First, our study sample includes only cases utilizing specialized mental health services and we assume that it represents rather well more severe cases of BPD in the population. Subjects having less severe BPD often do not utilize specialized mental health services and are therefore not found in nationwide registers. BPD cases treated in private health clinics are not recorded in the register and if they have no contact with public health centers, they are not included in this study. The healthcare services in Finland, however, are universal, financed by the state and municipalities. In addition, children are exempted from the generally low patient fees, and the overall health coverage is good. Thus, the number of BPD cases missing due to lack of access to health services is expected to be small. Second, the diagnoses of BPD used in the FHDR are hospital based clinical diagnosis, which usually have lower diagnostic validity than those based on standardized interviews. However, the validity of the FHDR has been good for diagnoses of mental disorders in general (Keskimäki and Aro 1991) and particularly for BPD I (Kieseppä et al., 2000; Perälä et al., 2007). Third, the diagnoses in the FHDR are based on ICD classification, which does not differentiate between DSM-IV subtypes bipolar I and II. Fourth, Apgar scores information was available only at 1 minute with no information for 5 minute Apgar scores. Fifth, BPD subjects included in this study were aged 21 years or younger, and thus the findings, or lack thereof, may be specific to early onset cases. Sixth, despite a large sample size, there was low power to detect associations for certain exposures including the lowest birth weight category (26%) and pre-term birth (13%). Lastly, the study could not examine all the perinatal outcomes, but only those that existed in the registers. However, the coverage of these existing outcomes was as complete as previous register based studies.

Conclusion

Birth by planned caesarean section was associated with subsequent risk of BPD. Increased risk of BPD was seen in children born post-term and with birth presentation other than cephalic or breech, although it failed to reach statistical significance. Thus, despite having a large sample size, effects of uncommon outcomes cannot be ruled out due to low power in the study to detect significant associations for certain exposures. This study is consistent to some degree with the existing literature, which overall has demonstrated associations between a relatively modest number of perinatal risk factors and BPD. Nonetheless, in spite of the large sample size in this study, statistical power was not sufficient to detect associations between less common perinatal outcomes such as very low birth weight and preterm birth.

It is possible that the investigation of prenatal factors and BPD may prove to be a more fruitful area of endeavor. Notably, prenatal exposure to famine (Brown et al., 2000), and advanced paternal age (Frans et al., 2008) have been associated with BPD. Few previous studies have utilized maternal biological specimens to evaluate these prenatal risk factors. Hence, rigorous studies that capitalize on prospective biomarkers of prenatal exposures and detailed clinical data on prenatal experiences are worthy of future investigation.

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Table 1

Birth weight, gestational age, weight for gestational age and risk for BPD

Risk factors	Bipolar Disorder							
	Frequencies				Unadjusted model			
	Cases (N= 724) (%)	Control (N= 1419) (%)	OR	95 % CI	p-value	OR	95 % CI	p-value
Birth weight (grams)*								
<1500	6 (0.8)	5 (0.4)	2.40	0.73–7.88	0.15	1.51	0.41–5.57	0.53
1500–2499	29 (4.1)	38 (2.7)	1.43	0.87–2.32	0.15	1.28	0.74–2.21	0.37
2500–3999	553 (77.7)	1070 (77.4)	Ref			Ref		
4000–4499	101 (14.2)	221 (16.0)	0.88	0.68–1.14	0.34	0.90	0.68–1.20	0.47
4500 or more	23 (3.2)	49 (3.5)	0.90	0.54–1.50	0.69	1.04	0.60–1.79	0.89
Gestational age (weeks)**								
<32	8 (1.1)	8 (0.6)	2.17	0.81–5.8	0.12	1.41	0.47–4.18	0.54
32–37	74 (10.4)	117 (8.5)	1.30	0.95–1.77	0.11	1.20	0.85–1.69	0.29
38–41	590 (83.1)	1208 (87.5)	Ref			Ref		
42 or more	38 (5.3)	47 (3.4)	1.70†	1.08–2.66	0.02	1.52	0.93–2.48	0.09
Weight for gestational age***								
SGA	16 (2.2)	20 (1.4)	1.46	0.75–2.84	0.26	1.35	0.64–2.85	0.43
AGA	674 (94.9)	1305 (94.6)	Ref			Ref		
LGA	20 (2.8)	54 (3.9)	0.73	0.43–1.24	0.25	0.83	0.47–1.46	0.52

missing data:

* cases: 1.6%, control: 2.5% ;

** cases: 1.9%, control: 2.7% ;

*** cases: 1.9%, control: 2.8% ;

† adjusting for maternal age, psychiatric history, education level, birth place, **maternal smoking during pregnancy and number of previous births** ‡ statistically significant

Table 2

Obstetric complications and risk for BPD

Risk factors	Frequencies		Unadjusted model			Adjusted model ^L		
	Cases (N=724) (%)	Controls (N=1419) (%)	OR	95 %CI	p-value	OR	95 %CI	p-value
Maternal Risk Factors								
High blood pressure*								
No	707 (98.3)	1389 (99.0)	Ref			Ref		
Yes	12 (1.7)	14 (1.0)	1.71	0.77–3.77	0.19	1.89	0.74–4.84	0.18
Uterine Bleeding*								
No	716 (99.6)	1401 (99.9)	Ref			Ref		
Yes	3 (0.4)	2 (0.1)	2.64	0.43–16.02	0.29	2.76	0.38–20.13	0.31
Birth factors								
Birth presentation*								
Cephalic	706 (98.2)	1382 (98.5)	Ref			Ref		
Breech	7 (1.0)	18 (1.3)	0.75	0.31–1.82	0.52	0.65	0.24–1.73	0.39
Other presentation	6 (0.8)	3 (0.2)	5.31[†]	1.06–26.77	0.04	5.12	0.95–27.54	0.06
Birth type*								
Vaginal cephalic	568 (79.0)	1132 (80.7)	Ref			Ref		
Suction+forceps	26 (3.6)	66 (4.7)	0.78	0.49–1.24	0.29	0.73	0.44–1.21	0.22
Planned C-section	25 (3.5)	24 (1.7)	2.04[†]	1.15–3.65	0.01	2.51[†]	1.32–4.78	<0.01
Emerg+other C-section	97 (13.5)	174 (12.4)	1.10	0.84–1.44	0.47	1.03	0.77–1.39	0.85
Unknown	3 (0.4)	7 (0.5)	0.84	0.22–3.27	0.06	0.57	0.05–6.70	0.65
Induced Labor*								
No	692 (96.2)	1340 (95.5)	Ref			Ref		
Yes	27 (3.8)	63 (4.5)	0.81	0.50–1.32	0.40	0.63	0.36–1.10	0.10
Hypoxia Related Factors								
Apgar-scores at 1 minute**								
9–10	553 (78.1)	1078 (78.0)	Ref			Ref		
7–8	130 (18.4)	269 (19.4)	0.96	0.76–1.21	0.73	0.93	0.72–1.20	0.59
<7	25 (3.5)	36 (2.6)	1.42	0.84–2.40	0.20	1.11	0.62–2.00	0.72

Risk factors	Frequencies		Unadjusted model			Adjusted model [/]		
	Cases (N =724) (%)	Controls (N= 1419) (%)	OR	95 %CI	p-value	OR	95 %CI	p-value
Neonatal treatment								
Monitoring/NICU[*]								
No	701 (97.5)	1379 (98.3)	Ref			Ref		
Yes	18 (2.5)	24 (1.7)	1.51	0.8–2.87	0.21	1.42	0.69–2.95	0.33

missing data:

* cases: 0.7 %, control: 1.1 % ;

** cases: 2.2%, control: 2.5% ;

[/] adjusting for maternal age, psychiatric history, education level and birth place, **maternal smoking during pregnancy and number of previous births** † statistically significant