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ARTICLE *in* NORDIC JOURNAL OF PSYCHIATRY · APRIL 2014

Impact Factor: 1.5 · DOI: 10.3109/08039488.2013.789073 · Source: PubMed

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Finnish Prenatal Study of Bipolar Disorders (FIPS-B): Overview, design and description of the sample

ROSHAN CHUDAL[1], DAN SUCKSDORFF[1], AULI SUOMINEN[1], VENLA LEHTI[1], SUSANNA HINKKA-YLI-SALOMÄKI[1], JUKKA HUTTUNEN[1], TERJA RISTKARI[1], MIKA GISSLER[1,3,4], IAN W. MCKEAGUE[5], ALAN S. BROWN[6,7], ANDRE SOURANDER[1,2,6]

Chudal R, Sucksdorff D, Suominen A, Lehti V, Hinkka-Yli-Salomäki S, Huttunen J, Ristkari T, Gissler M, McKeague IW, Brown AS, Sourander A. Finnish Prenatal Study of Bipolar Disorders (FIPS-B): Overview, design and description of the sample. Nord J Psychiatry 2013;Early Online:1–11.

Background: Bipolar disorders (BPD) are chronic mental illnesses, the development of which involves genetic factors and environmental influences. *Aims*: The aim of this paper is to provide an overall description of the Finnish Prenatal Study of Bipolar Disorders (FIPS-B), including the study design, national registers and linkage of the registers. *Methods*: FIPS-B is a population-based prenatal epidemiological study of BPD with a nested case–control study design using several national registers. The registers used are: the Finnish Medical Birth Register (FMBR), the Finnish Hospital Discharge Register (FHDR), the Population Central Register and the Finnish Maternity Cohort (FMC), which are linked using the unique personal identity code (PIC). FIPS-B includes all children born from January 1, 1983 to December 31, 1998 and diagnosed with BPD in Finland by December 31, 2008. *Results*: The total number of cases included in the FIPS-B is 1887. The age at first diagnosis ranged from 4 to 25 years. Half (50.4%) of the cases utilized only outpatient services, 12.7% only inpatient services and the rest (36.9%) utilized both services. Offspring of mothers with the lowest educational level had an increased odds of BPD (OR = 1.46, 95% CI 1.13–1.88). The cumulative incidence of BPD in the population aged 25 years or younger was 11.6/10,000 in 2008. *Conclusions*: FIPS-B has all the strengths of a register-based prenatal epidemiological study, along with the availability of maternal biomarkers, enabling it to examine several prenatal, perinatal and familial risk factors for BPD.

• *Bipolar disorder, Methodology, Prenatal, Register-based study, Risk factors.*

Andre Sourander, Research Centre for Child Psychiatry, Institute of Clinical Medicine, Faculty of Medicine, University of Turku, Itäinen pitkäkatu 1/Varia, 20014 Turku, E-mail: andsou@utu.fi;
Accepted 20 March 2013.

Bipolar disorders (BPD) are frequent, severe and often chronic mental illnesses associated with considerable morbidity and mortality (1). The development of BPD involves both genetic factors and environmental influences (2). Few clinical studies have shown that prenatal risk factors (family history of BPD, obstetric complications) (3–6) are associated with development of BPD. However, clinical studies of BPD have varied considerably as many studies were retrospective (4, 5), had no comparison subjects (7) and had small sample sizes (4, 5, 7) with consequently limited statistical power. The population-based epidemiological studies, many of which were carried out in the Nordic countries, make use of the population-based nationwide registers, which have several advantages over previous studies. These include: availability of large, representative sample of pregnancies from national medical birth register, comparison subjects drawn from the same population and comprehensive prospective data on pregnancy events and birth complications from birth records or registers.

The existing literature on prenatal and perinatal risk factors of BPD from population-based studies is limited and the findings are inconsistent. These studies vary considerably in terms of sample size, age range of subjects and potential confounders used. Five studies (8–12) examined the association between family history of psychiatric illness and BPD in offspring while the association with parental age was studied in four previous

DOI: 10.3109/08039488.2013.789073

studies (13–16). Two previous studies have examined the association of fetal growth indicators (14, 17), while only a single study (18) investigated BPD risk associated with obstetric complications. There has been one previous study that has examined association between parental education and wealth (19), urbanicity at birth (20) and neonatal seropositivity with infectious agents (21) and BPD risk. In addition, only one previous study made use of maternal serological biomarkers for examining maternal exposure to HSV-2 and BPD risk (22). No previous study has examined the association between maternal smoking or alcohol use during pregnancy and BPD risk.

In Finland, significant regional differences have been seen in the prevalence of psychiatric disorders (23), schizophrenia (24) and the use of psychiatric hospital beds (25). Studies on the association between parental education and BPD in offspring are few and the findings are inconsistent. While one study showed that higher educational level (Bachelor degree and above) in both parents was associated with increased risk of BPD (19), another study (26) showed BPD to be more common in offspring of parents without a college or professional degree.

The Finnish Prenatal Study of Bipolar Disorders (FIPS-B) aims to enhance our understanding of the association of various familial (parental age and psychopathology), prenatal/perinatal (maternal risk behavior including smoking and alcohol use, intrauterine growth retardation, hypoxia at birth) and postnatal (developmental milestones) risk factors with development of BPD in offspring. The FIPS-B, along with the advantages of population-based epidemiological studies, has two unique advantages: 1) the possibility of prospective assessment *in utero* of potential environmental risk factors validated by maternal biomarkers using archived maternal serum; and 2) in future, access to comprehensive data from child health clinics, allowing characterization of early developmental growth trajectories, in relation to perinatal events and risks of BPD. Furthermore, this study reports the age- and sex-specific distribution of BPD subjects utilizing specialized mental health services in Finland during the study period. This, along with the availability of data on regional variation of BPD could be helpful for estimating the disease burden on specialized mental health services and planning for the optimal utilization of available healthcare resources.

Aim

The objective of this paper is to provide an overall description of the FIPS-B, including the study design, description of the national registers included in the study and linkage of the registers. Furthermore, we report: 1) a brief description of the study sample; 2) cumulative incidence of diagnosed BPD cases; 3) regional variation of BPD risk, and 4) association between parental educational level and BPD in offspring.

Materials and Methods

Diagnosis and treatment of BPD in Finland

Mental health services are an essential part of the public healthcare system in Finland. They are provided by municipal primary healthcare centers and specialized services at different levels. The typical pathway to psychiatric services begins with the general practitioner who screens for BPD and refers the patient to specialized mental health services, where diagnosis is made and treatment initiated. The assessment in specialized mental healthcare services, both inpatient and outpatient is led by a Physician specialized in adult, adolescent or child psychiatry, depending on the age of the patient. The role of the specialized services is essential, first and foremost due to the severity of the disease, but also because of some national compensation policies requiring statement from a psychiatrist for sick leaves and medications. Psychiatric inpatient units are solely run by public means and are part of the public healthcare system. The outpatient specialist care is given in public outpatient units, or sometimes, if the patient wishes and can afford, in the private sector.

Overview of design

Figure 1 shows the design of the FIPS-B. The FIPS-B is based on a nested case–control study design. Different national registers are used to identify cases, controls and their parents and obtain their psychiatric history. They are also used to obtain maternal serum specimens for assays, evaluate complications during pregnancy and labor and examine developmental antecedents. Linkages have been made, and future linkages are planned, between different nationwide registers and child health clinics using a unique personal identity code (PIC). The PIC is a unique number provided for all residents of Finland since 1964 and does not change over the lifespan of the individual. The sampling frame for this study includes 1,009,846 offspring consisting of all live births in Finland between January 1, 1983 and December 31, 1998 (an average of 63,115 births per year). The information about the births is ascertained from computerized data in the Finnish Medical Birth Register (FMBR) since 1987. Approval for the utilization of the health registers data and linkage of the data for scientific research was obtained from the data protection authority. Ethical approval for the study was provided by the Ethics Committee of the Hospital District of Southwest Finland.

All diagnoses are based on the *International Statistical Classification of Diseases* (ICD). Healthcare personnel routinely enter the diagnoses in the Finnish Hospital

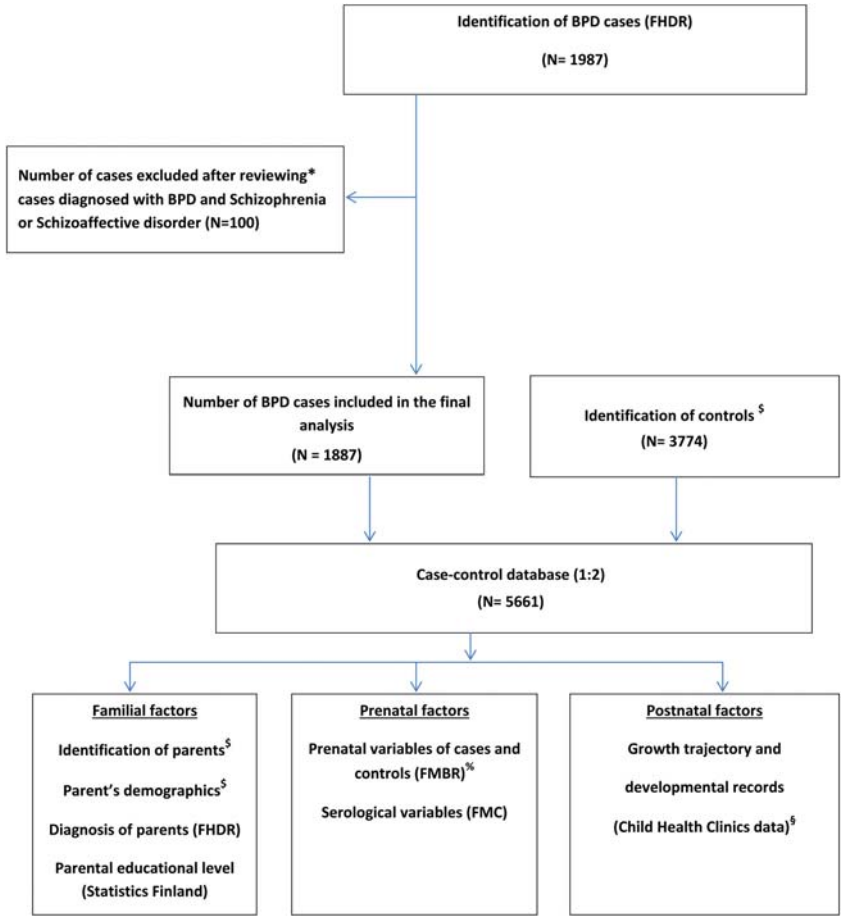

Fig. 1. Study design of Finnish prenatal study of Bipolar Disorder (FIPS-B). *As explained in "Case identification and inclusion criteria" in text. †From the Finnish Central Population Register. %FMBR data from 1987–2008, manual data collection from medical records of births between 1983–1986. §Intend to use child health clinics data; FHDR, Finnish Hospital Discharge Register; FMBR, Finnish Medical Birth Register; FMC, Finnish Maternity Cohort.

Discharge Register (FHDR). This and several other nationwide registers and biobank—FMBR, the Finnish Maternity Cohort (FMC), and the Finnish Central Population Register are used in the FIPS-B. The Central Population Register is maintained by the Population Register Centre and local register offices. The other registers and biobank are maintained by the National Institute for Health and Welfare (THL), a Finnish research and development institute aiming at promoting the well-being and health of the population, which is also the statistical authority for health and welfare in Finland. In the FIPS-B, we also intend to make use of the information collected at the child health clinics. Each of these registers is described in more detail below.

The Finnish Hospital Discharge Register (FHDR).

The FHDR is used in FIPS-B, for identification of cases. It contains information about the patient's PIC, date of birth, sex, dates of admission and discharge, and primary diagnosis along with up to three subsidiary diagnoses for each inpatient and outpatient care. The diagnoses are coded according to the World Health Organization (WHO) ICD-8 (27) from 1969 to 1986, ICD-9 (28) from 1987 to 1995 and ICD-10 (29) from 1996 onwards. This register has been maintained in Finland since the 1960s and since 1969, complete computerized data with PICs is available for all medical diagnoses, both somatic and psychiatric. Initially it covered information from all inpatient wards in somatic and psychiatric hospitals, local health centers, military wards, prison hospitals and private hospitals, and since 1998 covers the outpatient care in public hospitals. The FHDR has full coverage of inpatient BPD diagnoses and has outpatient coverage of specialized hospital units since 1998. A data quality study of the FHDR (30) has shown that the main hospital treatment-based psychiatric diagnosis was correctly reported at the three-digit ICD code level for 98% of the cases**.** A recent review of the quality of the FHDR showed that the positive predictive value for common diagnoses ranged between 75% and 99% (31). The diagnostic validity of the FHDR has

previously been shown to be good for schizophrenia (32, 33) and childhood autism (34). Specifically, the diagnostic validity of the FHDR examined against *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised (DSM III-R) (35) criteria found 92% specificity for BPD I diagnosis (36). A recent study examining FHDR diagnoses of psychotic disorders including BPD I against *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (37) criteria found high concordance for FHDR diagnosis of psychotic disorders with a kappa value of 0.8 and 99.7% specificity (38).

The Finnish Medical Birth Register (FMBR)

The FMBR was established in 1987 for the purpose of collecting statistical data for research, development and provision of maternity care, obstetrics services and care of newborn infants. It contains data from mothers and newborns in Finland up to the age of 7 days with 100% coverage (39, 40). The register contains comprehensive and standardized data on pregnancy, prenatal period, and neonatal period up to age 7 days for all live births, and stillbirths of fetuses with birth weight of at least 500 g or gestational age of at least 22 weeks. This register is based on standardized forms, completed for each newborn by the attending midwife or physician and sent by the hospital to the register within 7 days of birth. The definitions and variables used in the register are in accordance with established international concepts and based on ICD classification. The provision of the PIC of mothers and liveborn infants enables the data from this register to be used with all other databases in this study. The different categories of data in the FMBR, which will be used in the FIPS-B, are: demographic characteristics, reproductive history, maternal health-related behaviors, complications during pregnancy and perinatal/neonatal events (41). The information about the births between 1987 and 1998 is ascertained from computerized data in the FMBR. In future, we intend to collect the data for all births between 1983 and 1987 manually from the medical birth records.

The Finnish Maternity Cohort (FMC) and the Prenatal Serology Laboratory

The Finnish maternity cohort (FMC) contains blood samples from virtually all (more than 98%) pregnant women in Finland. The collection of blood samples of pregnant women in the first and early second trimester, at the maternity clinics for the purpose of screening for congenital infections (HIV, hepatitis B and syphilis) started in 1983 and is ongoing. Approximately 1.5–3 ml of serum from each pregnancy are collected and stored at −25°C in polypropylene cryovials at the Prenatal Serology Laboratory (PSL) in Oulu, Finland (42), where the serologic assays will be performed. In 2010, the repository contained more than 1.6 million samples from over 810,000 women (43). The FMC will be used in the FIPS-B for measurement of specific maternal biomarkers, including those for infections, immune function, toxins and hormones of all subjects in the study.

Child Health Clinics

The child health clinic system in Finland is a population-based municipal service for every child below school age (i.e. until age 7 years). They form part of the primary healthcare services. Public health nurses collaborating with physicians are the primary caregivers at these clinics. They monitor children's physical, cognitive and social development as well as implement the national vaccination programme. Trained public health nurses examine the child six times during the first year with physician examinations done four times during the first 1.5 years. Thereafter, annual physical examinations are done by public health nurse and physician from age 2 to 6 years until school age. In the FIPS B, we intend to use the child health clinic records to ascertain the various growth measurements including head circumference in relation to risk of BPD.

The Finnish Central Population Register

This computerized national register, is maintained by the Finnish Population Register Centre and local register offices, and contains basic information about Finnish citizens and foreign citizens residing permanently in Finland. Registration of information is based on statutory notifications made by private individuals and public authorities. Personal data recorded in the system includes name, PIC, address, citizenship and native language, family relations and date of birth and death (if applicable). The FIPS-B will make use of this register for identification of controls and parents.

Birthplace

The data on birth municipalities of the cases and controls was obtained from the Population Register Centre. The birth municipality information was used to group the study sample into four regions in Finland based on population data at Statistics Finland (44). The four regions used are: southern Finland (which includes the capital city Helsinki), western Finland, eastern Finland and northern Finland. Subjects from Åland province (six cases and 14 controls) were included in western Finland, due to the small number of subjects and geographic proximity to western Finland.

Parental educational level

The Finnish education system comprises 9-year basic education (comprehensive school), upper secondary education and higher education. Upper secondary education includes general upper secondary education, giving eligibility for further university studies and polytechnic studies, which provide vocational education and training. Polytechnics

and the universities make up the Finnish higher education system. Polytechnics provide professional training leading to Bachelors or Master's degree. Universities conduct scientific research and provide undergraduate (Bachelor's and Master's degrees) and postgraduate (licentiate and doctoral degrees) education based on it (45). Data on educational level of the parents was obtained from Statistics Finland. While data on maternal educational level was available for all cases and controls, paternal educational level data was not available for 2.1% of the cases and 1.1% controls. The reason for missing data on paternal educational level was unknown paternity. The husband of the married mother is automatically registered as the father in Finland. In other situations such as cohabiting relationships among unmarried mothers, paternity has to be confirmed in a legal process.

STATISTICS FINLAND

Statistics Finland, established in 1865, is the only public authority established specifically for statistical services in Finland (44). Statistics Finland was used in the FIPS-B to ascertain the data on educational level of the parents of cases and controls. The available information is based on various data sources available to Statistics Finland on educational level of the population. In FIPS-B, data on the educational level of parents was obtained from the staff at Statistics Finland based on the PIC of the parents.

Linkage of the registers

All of the previously described national registers can be linked with one another using the PIC, assigned to all residents of Finland from 1964 onwards. It includes the date of birth and sex, and is unique for each person, and does not change over the lifespan of the individual. All the data in these registers are organized by this identifier. Using the PIC, we acquired the following data from the Finnish Central Population Register about the cases, controls and their parents: 1) date of birth; 2) place of birth; 3) country of birth and native language as a proxy of ethnicity; and 4) information on residency in Finland.

Data sources

Table 1 shows the different variables used in this study along with the data sources from which they were ascertained.

Table 1. The different variables used in this study along with the data sources from which they were ascertained.

Time point of variable	Sources
1) Preconception	
Parents psychiatric history	FHDR
Reproductive history	FHDR
Parents demographic variables	Finnish Central Population Register
Parental educational level	Statistics Finland
2) Prenatal/perinatal	
A) Maternal	
Gestational diabetes	FMBR
Maternal hypertension	FMBR
Maternal proteinuria	FMBR
Maternal anemia	FMBR
Smoking	FMBR
Maternal weight/BMI	FMBR*
Pre-eclampsia	FMBR
Excessive bleeding	FMBR
Breech presentation	FMBR
Prolonged delivery	FMBR
Anesthesia during delivery	FMBR
Serological variables	FMC
B) Child	
Low birth weight/IUGR	FMBR
Gestational age	FMBR
APGAR score	FMBR
Birth province	Finnish Central Population Register
3) Postnatal	
Height/weight/head circumference	Child health clinics†
Developmental milestones	Child health clinics†
Vaccinations	Child health clinics†

FHDR, Finnish Hospital Discharge Register; FMBR, Finnish Medical Birth Register; BMI, body mass index; IUGR, intrauterine growth restriction.

*Data available from FMBR from 2004 onwards.

†We intend to use Child health clinics data in the study.

Case identification and inclusion criteria

All diagnosed cases of BPD ($n = 1887$) born in Finland between January 1, 1983, and December 31, 1998, who have been treated in Finland for BPD according to the FHDR before December 31, 2008 (age range up to 25 years) were identified. Among them, 26 cases were twin births. The cases were diagnosed with ICD codes 2962, 2963, 2964, 2967 (ICD 9) from January 1, 1987, to December 31, 1995, and F31x (ICD 10), from January 1, 1996, onwards and the most recently registered diagnosis was used for identification. Of the total, only one case had an ICD-9 diagnosis as the most recently registered. The remaining cases ($n = 1886$) were diagnosed with an ICD-10 code. We upgraded the single diagnosis recorded in ICD 9 to the latest ICD 10 diagnostic classification. There were 140 cases, diagnosed with BPD and schizophrenia and/or schizoaffective disorder. These case diagnosis records were then further evaluated by two senior authors (AS, AB). After evaluation, only 40 of those cases classified as BPD were included in the final analysis (i.e. 1887 BPD cases). Of the remaining cases, 47 were classified as schizophrenia or schizoaffective disorder, and the remaining 53 cases comprised other diagnoses and were excluded from the final analysis.

Identification of controls

Controls are defined as offspring born in Finland who are without any diagnosis in the FHDR of psychosis

spectrum disorder or BPD. Controls were matched 1:2 ($n = 3774$) to the cases on date of birth (± 30 days) and gender. Among them, 79 controls were twin births. Furthermore, controls were alive and residing in Finland on the first day of diagnosis of the matched case. Date of birth was included as a matching factor in order to control for secular changes in prevalence of exposures, and for potential confounding by seasonality of birth. Data for the controls was ascertained from the Finnish Central Population Register.

Statistical analysis

Cumulative incidence of BPD

The inclusion of diagnosed BPD cases born between 1983 and 1998 and treated between 1983 and 2008 meant that the oldest subjects were 25 years old at the end of follow-up. We evaluated the cumulative incidence of diagnosed BPD cases, over an 11-year period (1998–2008) in the population aged 25 years or younger. The cumulative incidence of BPD in three age group categories, i.e. less than 15 years, 15–19 years and 20–25 years was calculated separately for males and females. The numerator was the number of cases of BPD during each year from 1998 to 2008. The denominator was the total population, calculated separately in each age group for males and females i.e. <15 years, 15–19, 20–25 years for every year from 1998 to 2008. The number of cases of BPD (numerator) was ascertained from the FHDR. Data on the total number of individuals in every age group category from 1998 to 2008 (denominator) was ascertained from the database of Statistics Finland (44). The odds ratios (OR) for the cumulative incidence were calculated using Poisson-regression model assuming a Poisson error distribution. Statistical analysis was performed with SAS statistical software (SAS Institute Inc. SAS Version 9.2. Cary, NC).

The analyses of the association between birth regions and the development of BPD were performed by conditional logistic regression. Associations were quantified using odds ratios with 95% confidence interval (CI). The calculation of odds ratios with CI was repeated with each region as the reference category. Statistical analysis was performed with SAS statistical software (SAS Institute Inc. SAS Version 9.3. Cary, NC).

Parental 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 highest educational level i.e. Master/Licentiate/Doctoral degree was used as the reference category. The associations between parental education and development of BPD were performed by conditional logistic regression using odds ratios with 95% CI and the *P*-values were calculated by the χ^2-test with the limit of statistical significance $P < 0.05$.

Power analysis

We calculated the detectable odds ratios as a function of prevalence of exposure with the correlation between matched subjects fixed at 0.2. The detectable odds ratios for unmatched subjects in case cohort design were also calculated. The power calculations were performed with the R packages epicalc (http://cran.r-project.org/web/packages/epicalc/epicalc.pdf) and epiR (http://cran.r-project.org/web/packages/epiR/epiR.pdf).

Results

Table 2 shows the sex distribution, age at diagnosis and service utilization of BPD cases. It also reports birthplace distribution and the association between parental educational level and BPD. Of 1887 BPD cases, 68.4% were females and 31.6% males. The age when BPD was diagnosed ranged from 4 to 25 years (mean $\pm$ standard deviation $= 19.3 \pm 3.1$). The age range was 4–25 years (mean $= 19.2 \pm 3.7$) among males and 7–25 years (mean $= 19.3 \pm 2.9$) in females. Altogether 50.5% were 20–25 years old at first diagnosis of BPD, 43.9% were 15–19 years old and 5.6% were younger than 15 years. Half (50.4%) of the cases utilized the outpatient services only and 12.7% inpatient services only, while 36.9% utilized both outpatient and inpatient services.

As shown in Table 2, the regional distribution of birthplace, showed that the highest number of BPD subjects were born in southern Finland (40.4%) and the lowest in eastern Finland (12.9%). Offspring of mothers with only basic comprehensive school education had a 1.5-fold increased odds (OR = 1.46, 95% CI 1.13–1.88) of BPD compared with mothers with master's degree or higher level of education. Father's educational level was not associated with the risk of BPD in offspring.

Table 3 shows the comparative association between birth in different regions and the risk of developing BPD. Children born in eastern Finland had significantly increased odds of developing BPD compared with those born in all other regions. Being born in southern Finland was associated with increased odds of BPD compared with those born in all other regions except eastern Finland. The highest odds were seen in children born in eastern Finland compared with those in western Finland (OR = 2.02, 95% CI 1.69–2.42).

Figure 2 shows age- and sex-specific cumulative incidence of BPD from 1998 to 2008. The cumulative incidence of BPD in the population aged 25 years or younger was 11.6/10,000 in 2008. The incidence in cases aged below 15 years remained more or less stable over the 11-year period. However, there was a linear increase in incidence among subjects 15 years or older. The incidence in subjects 15 years or older was higher in female than male subjects. The incidence in 2008 in the 15–19-year age group was 13.4/10,000 among males and

Table 2. A) Gender distribution, age at diagnosis and service utilization in the study sample, B) regional distribution of birthplace of study subjects, C) parental educational level and risk of bipolar disorder (BPD).

A) Gender, age at diagnosis and service utilization of BPD cases	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)
Number of BPD cases	597 (31.6)	1290 (68.4)	1887 (100)
Age at first diagnosis (years)			
Mean (standard deviation)	19.2 (3.7)	19.3 (2.9)	19.3 (3.1)
Median (range)	20 (4–25)	19 (7–25)	
Age range at first diagnosis (years)			
< 15	53 (8.9)	53 (4.1)	106 (5.6)
15–19	231 (38.7)	598 (46.4)	829 (43.9)
20–25	313 (52.4)	639 (49.5)	952 (50.5)
Services utilization			
Only outpatient services	289 (48.4)	663 (51.4)	952 (50.4)
Only inpatient services	89 (14.9)	150 (11.6)	239 (12.7)
Both outpatient and inpatient services	219 (36.7)	477 (37.0)	696 (36.9)
Total	597 (31.6)	1290 (68.4)	1887 (100)
B) Regional distribution of birthplace in the study sample	**Cases, *n* (%)**	**Controls, *n* (%)**	**Total, *n* (%)**
Southern Finland	867 (46.0)	1417 (37.5)	2284 (40.4)
Western Finland*	487 (25.8)	1343 (35.6)	1830 (32.3)
Eastern Finland	310 (16.4)	421 (11.2)	731 (12.9)
Northern Finland	223 (11.8)	593 (15.7)	816 (14.4)
C) Parental educational level and BPD	**Cases, *n* (%)**	**Controls, *n* (%)**	**Odds ratios (95% CI)**
Father's educational level†			
Master degree/Licentiate degree/Doctoral degree (Reference)	174 (9.4)	362 (9.7)	1
University/Polytechnics Bachelor degree	151 (8.2)	342 (9.2)	0.91 (0.70–1.19)
Upper secondary school/equivalent vocational degree	975 (52.8)	2038 (54.6)	0.996 (0.82–1.21)
Basic education (comprehensive school)	547 (29.6)	989 (26.5)	1.16 (0.94–1.43)
Mother's educational level			
Master degree/Licentiate degree/Doctoral degree (Reference)	109 (5.8)	258 (6.8)	1
University/polytechnics Bachelor degree	201 (10.7)	488 (12.9)	0.98 (0.74–1.30)
Upper secondary school/equivalent vocational degree	1078 (57.1)	2208 (58.5)	1.16 (0.92–1.48)
Basic education (comprehensive school)	499 (26.4)	820 (21.7)	1.46 (1.13–1.88)‡

CI, confidence interval.
*Six cases and 14 controls from Åland province included in western Finland.
†Missing data (father's educational level): cases—40 (2.1%), control—43 (1.1%).
‡Statistically significant.

36.5/10,000 in females. In the 20–25-year age group, the incidence was 15.4 and 33.0/10,000 in males and females respectively.

Discussion

The main findings are: 1) the cumulative incidence of BPD by age 25 years was 11.6/10,000; 2) majority of the cases (68%) were females; 3) significant regional differences, based on birthplace, were seen in the risk of BPD, and 4) offspring of mothers with the lowest educational level had the highest risk of BPD.

There is wide variation in incidence and prevalence estimates of BPD worldwide. A recent study (46) showed that the lifetime prevalence of BPD in adults varied from 0.1% in India to 4.4% in the USA. A previous Finnish study utilizing hospital inpatient data showed the incidence of BPD to be 3/10,000 among population aged over 15 years (47). Of note, that study did not include outpatient cases of BPD. When comparing our results with previous studies, it should be noted that our sample is limited to those diagnosed by age 25 years. Therefore, it cannot be compared with total population incidence rates from other studies including a broader age range of subjects. Furthermore, because of incomplete outpatient coverage in the FHDR, the incidence figure in this study will somewhat be an underestimation.

The finding of BPD being more common in females is similar to that seen in previous population-based studies (13–16, 18, 21). The abundance of female subjects could be a true finding seen among young BPD subjects. A study in Finland (48) found that females account for 72% of the early onset BPD cases (< 18 years). However, gender differences in treatment seeking behavior could also to some extent, account for this increased occurrence of BPD in females. Women seem to seek psychiatric help more often (49) and earlier (50) than males. Thus, young study sample, gender difference in treatment seeking

Table 3. Birth region and the risk of BPD in Finland.

	Reference region			
Birth region	Southern Finland*	Western Finland*	Eastern Finland*	Northern Finland*
Southern Finland†	N/A	1.70 (1.49–1.95)‡	0.84 (0.71–0.999)‡	1.64 (1.37–1.96)‡
Western Finland†	0.59 (0.51–0.67)‡	N/A	0.50 (0.41–0.59)‡	0.96 (0.80–1.16)
Eastern Finland†	1.19 (1.001–1.41)‡	2.02 (1.69–2.42)‡	N/A	1.95 (1.57–2.41)‡
Northern Finland†	0.61 (0.51–0.73)‡	1.04 (0.86–1.25)	0.51 (0.42–0.64)‡	N/A

Odds ratios and 95% confidence intervals of the risk of BPD based on birth provinces. Risk of BPD among persons born in different provinces (shown in the vertical axis), compared with persons born in the other provinces (shown in the horizontal axis).
*Reference province.
†Birth province.
‡Statistical significance.

behavior or some other factors could explain this gender difference among BPD cases in our sample.

Subjects born in eastern Finland had significantly increased odds of developing BPD compared with those born in any other regions. Similar findings of regional differences in the prevalence (23) and treatment rates (25) have been seen, with highest risk of schizophrenia seen in populations of eastern Finland (24, 51). Relative genetic isolation and thereby enrichment of the genes that predispose to schizophrenia has been suggested as a possible explanation (51). This could be because of the stable regional population isolate formed by the settlement of founder populations in those regions some 500 years ago with rather little genetic admixture. The genetic association between BPD and schizophrenia (8, 52, 53) could thus, explain similar findings seen in this sample. In addition, subjects born in southern Finland had increased odds of BPD than all other regions except eastern Finland. This could be due to the trend of internal migration of the Finnish population with an increasing number of people migrating after World War II, especially to the urban areas in the south. In addition, Finland experienced a substantial increase in birth rates in the late 1940s, especially in eastern and northern Finland, with many in that generation migrating towards Helsinki area in southern Finland (54–56).

Offspring of mothers in the lowest educational level category had significantly increased odds of developing BPD. Low parental education has been associated with lower scores on psychological wellbeing, moods and emotions in children (57) and shown to influence, to some extent the mental health of adolescents (58). Lower educational status of both parents has been shown to be associated with schizophrenia (59). Less educated mothers are more likely to have risk factors including: smoking during pregnancy, exposure to second-hand smoke,

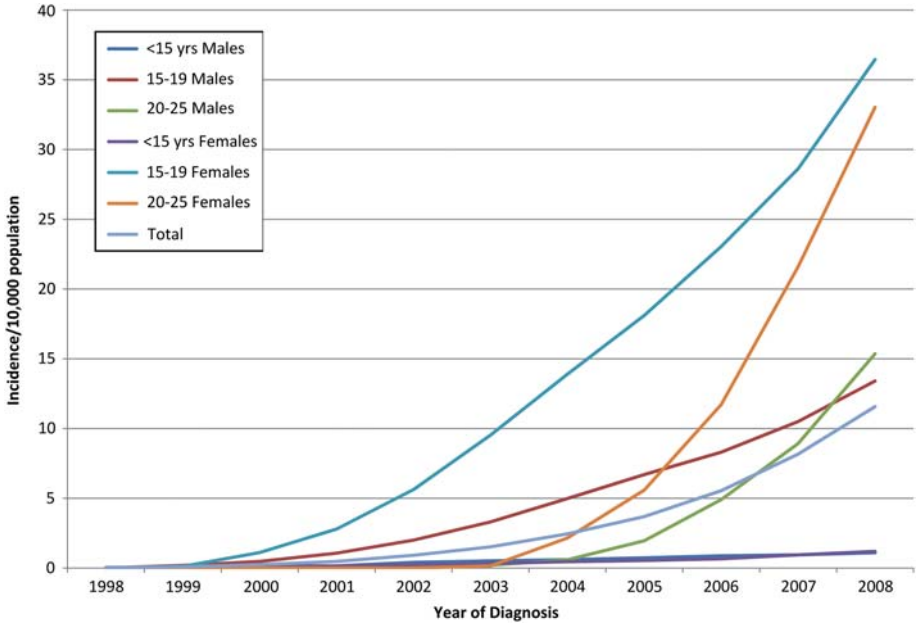

Fig. 2. Cumulative incidence of bipolar disorder (BPD) cases per 10,000 population by gender, age group and year of diagnosis in the study sample (1998–2008).

problems in breastfeeding and lack of social support (60). Low birth weight, increased risk of being born small for gestational age (SGA) have also been associated with lower parental education, and more strongly with maternal education (61). However, this finding is in contrast to a Danish study (19), which showed increased risk of BPD in offspring of highly educated parents. Thus, further studies would be needed to clarify these inconsistent findings.

The FIPS-B is a population-based prenatal epidemiological study of BPD, which has the potential for identification of early biological risk factors, childhood predictors of later psychopathology and providing important information about the prenatal and early developmental risk factors of BPD. This includes information about the parental demographics and health risk behaviors, various risk factors occurring during pregnancy, childbirth and the neonatal/perinatal period. In addition, we intend to ascertain valuable information regarding the postnatal period, such as growth characteristics of the study subjects including the developmental milestones up to the age of 6 years. This helps to characterize the growth trajectory in relation to various perinatal events. The large sample size, availability of data from several registers, archived maternal serum specimens drawn during pregnancy, population-based sampling and ascertainment of all diagnosed cases from the source population over the follow-up interval are important strengths of the study. The use of prospectively collected data from medical records as data source prevents any recall bias. Using matched controls from the source population minimizes selection bias. All of this information will be supplemented by the availability of archived prenatal serum specimens of the mothers, which will enable the study of the association between prenatal maternal biomarkers and BPD. This study has 80% power to detect small effect sizes for exposure with BPD prevalence of at least 1% with the range of odds ratios less than 2. Figure 3 shows the detectable odds ratios as a function of prevalence of exposure for matched and unmatched subjects.

Limitations

Like in other register-based studies, there is lack of complete representation of the cases in the population. Our sample includes only cases utilizing specialized mental health services and because of complete inpatient coverage, we assume that it represents rather well more severe cases of BPD. However, subjects having less severe BPD may not utilize specialized mental health services and will not be found in the nationwide registers. Similarly, BPD cases treated in private health clinics are not recorded in the register and if they have no contact with public health services, they are not included in our study. The diagnoses in the FHDR are not based on standardized interviews, but are hospital-based clinical diagnoses, which usually have lower diagnostic validity. However, the validity of the FHDR has been good for diagnosis of mental disorders in general (30) and particularly for schizophrenia (32, 33), childhood autism (34) and BPD I (36, 38). BPD with very early onset may be hard to differentiate from organic developmental disorders, particularly ADHD. However, in our sample, only 5.6% of the cases were younger than 15 years, so it is unlikely that these differential diagnoses would have substantially affected results in this study. The subjects included were identified until age 25 years and therefore, the findings are applicable for BPD cases diagnosed before the age of 25 years.

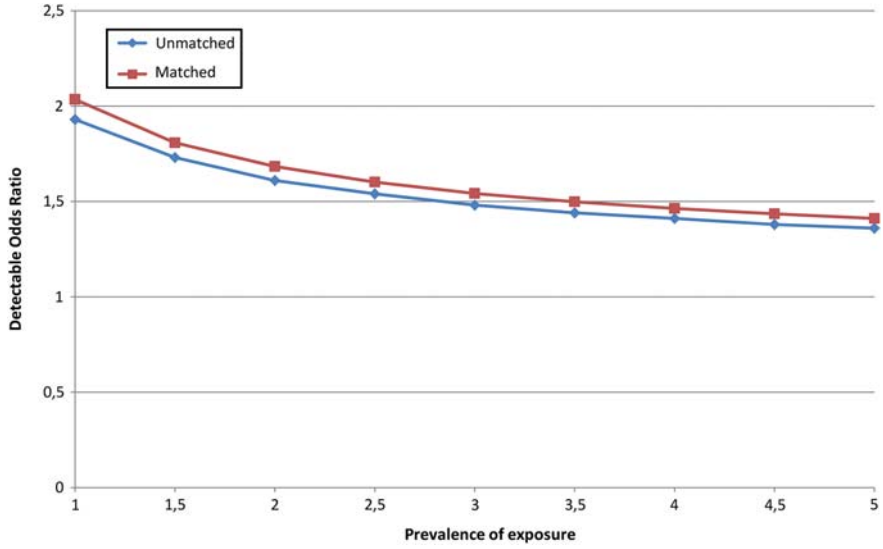

Fig. 3. Power analysis. Detectable odds ratios by prevalence/100 (for 1887 bipolar disorder cases and 3774 matched controls) of exposure for unmatched and matched design.

Conclusion

The strengths of FIPS-B include availability of maternal serum biomarkers archived during pregnancy, possibility of utilizing longitudinal child development data, large sample size with population-based sampling and availability of various time point data from several registers that can be linked together. FIPS-B will enable us to examine BPD risk factors, e.g. parental age, parental and family psychopathology, obstetric complications, health risk behaviors (i.e. smoking, alcohol use), and maternal exposure to infections, autoimmune conditions and environmental toxins during pregnancy. In future, FIPS-B provides a possibility for further studies investigating the role of genetic factors, epigenetic mechanisms and gene–environment interactions in the development of BPD.

Acknowledgement—We thank the study investigators and staff at medical centers involved in this research. Specifically we would like to thank the members involved in the data collection process including: Juha-Pekka Virtanen, Pyry Kantanen, Kristiina Saanakorpi, Ulla Kulmala, Tanja Sarlin, Jarna Lindroos and Lauri Sillanmäki from Research Institute of Child Psychiatry, Turku University and Pilar Cordova from Columbia University.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The study was supported by grants from NARSAD Independent Investigator Award, USA (A.S) and Sigrid Juselius Foundation, Finland (A.S). The study was conducted at University of Turku, Finland.

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Roshan Chudal, Department of Child Psychiatry, University of Turku, Finland.
Dan Sucksdorff, Department of Child Psychiatry, University of Turku, Finland.
Auli Suominen, Department of Child Psychiatry, University of Turku, Finland.
Venla Lehti, Department of Child Psychiatry, University of Turku, Finland.
Susanna Hinkka-Yli-Salomäki, Department of Child Psychiatry, University of Turku, Finland.
Jukka Huttunen, Department of Child Psychiatry, University of Turku, Finland.
Terja Ristkari, Department of Child Psychiatry, University of Turku, Finland.
Mika Gissler, Department of Child Psychiatry, University of Turku, Finland; Nordic School of Public Health, Gothenburg, Sweden; and National Institute for Health and Welfare, Finland.
Ian W. McKeague, Mailman School of Public Health, Department of Biostatistics, Columbia University College of Physicians and Surgeons, New York, NY, USA.
Alan S. Brown, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA; Department of Epidemiology, Columbia University, Mailman School of Public Health, New York, NY, USA.
Andre Sourander, Department of Child Psychiatry, University of Turku, Finland; Department of Child Psychiatry, Turku University Hospital, Finland; and Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA.