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PRENATAL AND PERINATAL RISK FACTORS FOR BIPOLAR DISORDER

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"It always seems impossible until it's done."

Nelson Mandela

To

Hajurama,

All I am and will ever be, I owe it all to you.

ABSTRACT

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Prenatal and perinatal risk factors for bipolar disorder
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Bipolar disorder (BPD) is a severe mental disorder associated with considerable morbidity and mortality. Prenatal insults have been shown to be associated with later development of mental disorders and there is a growing interest in the potential role of prenatal and perinatal risk factors in the development of BPD.

The aims of this thesis were to describe the overall study design of the Finnish Prenatal Study of Bipolar Disorders (FIPS-B) and demographic characteristics of the sample. Furthermore, it was aimed to examine the association of parental age, parental age difference, perinatal complications and maternal smoking during pregnancy with BPD. This thesis is based on FIPS-B, a nested case-control study using several nationwide registers. The cases included all people born in Finland between January 1st 1983 and December 31st 1998 and diagnosed with BPD according to the Finnish Hospital Discharge Register (FHDR) before December 31st 2008. Controls for this study were people who were without BPD, schizophrenia or diagnoses related to these disorders, identified from the Population Register Centre (PRC), and matched two-fold to the cases on sex, date of birth (+/- 30 days), and residence in Finland on the first day of diagnosis of the matched case. Conditional logistic regression models were used to examine the association between risk factors and BPD.

This study included 1887 BPD cases and 3774 matched controls. The mean age at diagnosis was 19.3 years and females accounted for 68% of the cases. Mothers with the lowest educational level had the highest odds of having BPD in offspring. Being born in Eastern and Southern region of Finland increased the odds of having BPD later in life. A U-shaped distribution of odds ratio was observed between paternal age and BPD in the unadjusted analysis. Maternal age and parental age difference was not associated with BPD. Birth by planned caesarean section was associated with increased odd of BPD. Smoking during pregnancy was not associated with BPD in the adjusted analyses.

Region of birth and maternal educational level were associated with BPD. Both young and old father's age was associated with BPD. Most perinatal complications and maternal smoking during pregnancy were not associated with BPD. The findings of this thesis, considered together with previous literature, suggest that the pre- and perinatal risk factor profile varies among different psychiatric disorders.

Key words: risk factors, prenatal, perinatal, bipolar disorder, parental age, obstetric complications, smoking during pregnancy, nationwide registers, case-control study.

TIIVISTELMÄ

Roshan Chudal
Kaksisuuntaisen mielialahäiriön pre- ja perinataaliset riskitekijät
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Kaksisuuntainen mielialahäiriö on vakava mielenterveyden häiriö, johon liittyy merkittävä sairastuvuus ja kuolleisuus. Syntymää edeltävien tekijöiden on osoitettu olevan yhteydessä mielenterveyden häiriöiden kehittymiseen. Kiinnostus myös kaksisuuntaisen mielialahäiriön mahdollisten pre- ja perinataaliajan riskitekijöiden löytämiseksi on lisääntynyt.

Väitöskirjatyön tavoitteena oli kuvata Finnish Prenatal Study of Bipolar Disorders (FIPS-B) -tutkimuksen tutkimusasetelma ja otoksen väestöpohjaisia ominaisuuksia. Lisäksi tavoitteena oli tutkia vanhempien iän ja ikäeron, perinataaliajan tekijöiden sekä äidin raskaudenaikaisen tupakoinnin yhteyttä kaksisuuntaiseen mielialahäiriöön. Väitöskirjatyö perustuu FIPS-B -tutkimukseen. Tutkimus on pesitetty tapaus-verrokkitutkimus, joka hyödyntää kansallisia rekisteritietoja. Tapaukset olivat Suomessa 1.1.1983–31.12.1998 syntyneitä henkilöitä, joille oli 31.12.2008 mennessä annettu kaksisuuntaisen mielialahäiriön diagnoosi kansallisessa hoitoilmoitus-rekisterissä. Väestörekisterikeskuksesta poimitut verrokit olivat henkilöitä, joilla ei ollut kaksisuuntaisen mielialahäiriön tai skitsofreniaryhmän diagnooseja. Tapaukset ja kutakin tutkittavaa varten poimitut kaksi verrokkia olivat kaltaistettuja iän, sukupuolen ja syntymäajan (+/- 30 päivää) sekä asuinpaikkakunnan suhteen. Asuinpaikkakunta määriteltiin sen mukaan, missä tutkittava oli saanut ensimmäisen kerran kaksisuuntaisen mielialahäiriön diagnoosin. Riskitekijöiden ja kaksisuuntaisen mielialahäiriön yhteyttä tutkittiin ehdollisen logistisen regressioanalyysin avulla.

Tutkimus käsitti 1887 kaksisuuntaisen mielialahäiriön diagnoosin saanutta tapausta sekä 3774 verrokkia. Tapausten keski-ikä diagnoosin asettamisen hetkellä oli 19.3 vuotta ja naisten osuus kaikista tapauksista oli 68 %. Matalimmin koulutettujen äitien jälkeläisillä oli korkein todennäköisyys sairastua kaksisuuntaiseen mielialahäiriöön. Itä- ja Etelä-Suomessa syntyminen lisäsi todennäköisyyttä sairastua kaksisuuntaiseen mielialahäiriöön. Korjaamattomassa analyysissä havaittiin U-muotoinen yhteys kaksisuuntaisen mielialahäiriön ja isän iän välillä. Äidin iällä, eikä vanhempien ikäerolla ollut yhteyttä kaksisuuntaiseen mielialahäiriöön. Syntyminen suunnitellulla keisarinleikkauksella oli yhteydessä kaksisuuntaiseen mielialahäiriöön. Äidin raskaudenaikainen tupakointi ei ollut yhteydessä kaksisuuntaiseen mielialahäiriöön monimuuttuja-analyyseissä.

Syntymäpaikka ja äidin koulutustaso olivat yhteydessä kaksisuuntaiseen mielialahäiriöön. Sekä isän alhainen että korkea ikä olivat yhteydessä kaksisuuntaiseen mielialahäiriöön. Useimmat perinataaliajan komplikaatiot tai äidin raskaudenaikainen tupakointi eivät olleet yhteydessä kaksisuuntaiseen mielialahäiriöön. Tämän väitöskirjatutkimuksen löydökset ja aikaisempi kirjallisuus viittaavat siihen, että pre- ja perinataaliriskitekijöiden merkitys psykiatristen häiriöiden välillä vaihtelee.

Avainsanat: riskitekijät, prenataalinen, perinataalinen, kaksisuuntainen mielialahäiriö, vanhempien ikä, synnytyskomplikaatio, raskauden aikainen tupakointi, kansallinen rekisteri, tapaus-verrokkitutkimus.

CONTENTS

ABBREVIATIONS

APA	American Psychiatric Association
ASD	Autism spectrum disorders
BPD	Bipolar disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision
FHDR	The Finnish Hospital Discharge Register
FIPS-B	Finnish Prenatal Study of Bipolar Disorders
FMBR	The Finnish Medical Birth Register
ICD	International Classification of Diseases
NICU	Neonatal intensive care unit
PIC	Personal identity code
PRC	Finnish Population Register Centre
SCID	Structured Clinical Interview for DSM-IV
SD	Standard Deviation
SES	Socioeconomic status
SGA	Small for gestational age
THL	The National Institute for Health and Welfare
WGA	Weight for gestational age
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV.

I. 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. 2014a;68:169-79.

II. Chudal R, Gissler M, Sucksdorff D, Lehti V, Suominen A, Hinkka-Yli-Salomäki S, Brown AS, Sourander A. Parental age and the risk of bipolar disorders. Bipolar Disord. 2014b;16:624-32.

III. Chudal R, Sourander A, Polo-Kantola P, Hinkka-Yli-Salomäki S, Lehti V, Sucksdorff D, Gissler M, Brown AS. Perinatal factors and the risk of bipolar disorder in Finland. J Affect Disord. 2014c;155:75-80.

IV. Chudal R, Brown AS, Gissler M, Suominen A, Sourander A. Is maternal smoking during pregnancy associated with bipolar disorder in offspring? J Affect Disord. 2015;171:132-6.

1. INTRODUCTION

An increasing body of evidence suggests that changes in the environment during the period from conception until infancy can result in permanent changes to the structure and physiological mechanisms of the human body (Gluckman *et al*. 2007). This concept "developmental origins of health and disease'' (DOHaD)" originated based on the observations of association between birth size and later risk of cardiovascular diseases (Barker & Osmond 1986) and type 2 diabetes (Haig & Graham 1991). Along similar lines, an association has been suggested between fetal growth and mental health (Schlotz & Phillips 2009). There is also a growing interest in the role of social determinants in the development of mental health problems such as anxiety and depression. Studies suggest that various social, economic and physical environments in different stages of life affect and shape the mental health of an individual (Patel *et al*. 2010, Allen *et al*. 2014).

Studies have shown prenatal insults to be associated with mental disorders with a neurodevelopmental component. The studies showing an association between exposure to prenatal influenza (Mednick *et al*. 1988) and prenatal famine (Susser *et al*. 1996) and schizophrenia later in life provided one of the earliest epidemiological evidence supporting the potential role of prenatal insults in the development of severe mental disorders. Several studies have shown an association between other prenatal and perinatal risk factors, e.g. prenatal iron, vitamin A and vitamin D deficiency (Insel *et al*. 2008, Bao *et al*. 2012, McGrath *et al*. 2010), maternal stress during pregnancy (Khashan *et al*. 2008), seasonality of birth (Davies *et al*. 2003), low birth weight, diminished head circumference (Jones *et al*. 1998, McNeil *et al*. 1993) obstetric complications (Cannon *et al*. 2002), and subsequent development of schizophrenia. Similarly, a range of prenatal and perinatal risk factors have also been implicated in the development of Autism spectrum disorders (ASD) (Kolevzon *et al*. 2007, Guinchat *et al*. 2012). However, majority of previous studies on prenatal and perinatal risk factors have been focused on schizophrenia and ASD and it is less clear if these results can be extended to other psychiatric disorders, e.g. bipolar disorder (BPD). Therefore, it is important to investigate whether several psychiatric disorders have a common prenatal risk profile or have certain specific profiles. This has important implications on developing research strategies and conceptualizing the causes of psychiatric problems.

Two major views have been postulated as the causal mechanisms for the influence of prenatal insults on health later in life. First, specific prenatal factors, either alone or in combination with other factors result in the structural or functional damage to organs

important in the pathophysiology of the disease condition. For instance, the influence of intrauterine factors resulting in hypoplasia or dysplasia of key cerebral structures e.g. limbic system and prefrontal cortex, and its interaction with normal brain maturation later in life could lead to the manifestation of psychiatric symptoms (Sanches *et al*. 2008). Second, prenatal insults result in a general impairment in fetal health, thereby affecting the general indicators of growth and development. This, in turn predisposes the child to ill health later in life (Susser *et al*.1999).

BPD is a severe mental disorder characterized by mood swings towards mania and depression, and associated with considerable morbidity and mortality, often evolving into life-long illness (Bauer & Pfennig 2005, Ortiz *et al*. 2011). The clinical manifestation of BPD includes very intense emotional states during periods called "mood episodes". An extremely joyful or overexcited state is called a "manic episode" (or "hypomanic episode" when symptoms are less severe) whereas a considerably sad and hopeless state is called a "depressive episode". A "mixed state" includes symptoms of both mania and depression occurring in a mood episode (NIMH. 2008). Patients with BPD have a much higher risk of suicide (Isometsä *et al*. 1994) with the absolute risk among subjects with BPD followed up over 18 years shown to be 7.8 % in males and 4.8 % in females (Nordentoft *et al*. 2011). Compared to the general population, people with BPD have a 10 to 30-fold greater risk of suicide (Crump *et al*. 2013, Pompili *et al.* 2013). The lifetime prevalence of BPD varies from 0.1% to 4.4% worldwide (Merikangas *et al*. 2011).

The development of BPD has a strong genetic component with the heritability estimated to be between 59% and 89% (Lichtenstein *et al*. 2009, McGuffin *et al*. 2003). However, the concordance within monozygotic (MZ) twin pairs of far less than 100% (Craddock & Jones 1999) points towards the importance of non-genetic factors in the development of BPD. There is a growing interest in the role of epigenetic dysfunction as a potential explanation for phenotypic differences between MZ twins (Pidsley & Mill 2011). It has been shown that DNA methylation could play a role in the etiology of schizophrenia and BPD (Dempster *et al*. 2011). Environmental risk factors have also been implicated in the development of BPD. Clinical studies have shown obstetric complications (Kinney *et al*. 1993, 1998) and higher parental education (Lewinsohn *et al*. 1995) to be associated with BPD. On the other hand, systematic reviews have been inconclusive regarding obstetric complications and BPD (Scott *et al*. 2006). The findings of previous clinical studies have been limited due to the use of a clinical sample increasing the chances of selection bias, retrospective study designs with subsequent recall bias, small sample sizes and thus limited statistical power and lack of healthy controls for comparisons. More recently, nationwide population-based epidemiological studies have provided new insights on the association of prenatal and perinatal risk factors including parental age (Frans *et al.* 2008, Laursen *et al.*

2007), obstetric complications (Nosarti *et al.* 2012, Øgendahl *et al.* 2006) and parental socioeconomic status (Tsuchiya *et al.* 2004) with BPD.

Population-based studies making use of nationwide registers have immensely helped epidemiological psychiatric research. These studies, conducted mostly in the Nordic countries, are based on several nationwide registers manually collected initially and computerized subsequently. These registers contain individual health data over the entire life span of the individual and the availability of unique national personal identifier helps in the linkage of data from several registers. The collection of individual health data runs throughout the lifespan with the earliest data recorded even before birth i.e. during pregnancy (Pukkala 2011). The subsequent collection of personal health data continues at childbirth, during each visit to the national health care system, during use of prescribed medication for any illness until the death of the individual. Overall, this system of registers provides the overall picture of the health, illness, and the socio demographic status of an individual and thereby the entire population. This thesis uses several Finnish Nationwide Registers to examine the association between prenatal and perinatal risk factors and the development of BPD. The exploration of potential prenatal and perinatal risk factors in the development of BPD would help to better understand the causation of BPD. It also lays the groundwork to possible development of selected interventions aimed at population at risk of specific prenatal and/or or perinatal risk factors for the development of BPD.

1.1 Diagnostic Classification

Globally, there are two main systems of classification for the diagnosis of mental disorders: the International Classification of Diseases (ICD) (WHO 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA 1994). There is some heterogeneity in the criteria for the diagnosis of BPD in the two diagnostic classifications. The ICD-10 classification requires two discrete mood episodes, out of which at least one must be manic (or hypomanic). However, in DSM-IV, a single episode of mania (or hypomania), even without any previous mood episodes would result in a diagnosis of bipolar disorder (NICE 2006). Few changes have been made in the diagnostic criteria of BPD in the recently introduced DSM-5, such as: a) an emphasis on changes in activity and energy and mood has been included in criteria A for manic and hypomanic episodes and b) removal of bipolar I disorder, mixed episode diagnosis in DSM-IV requiring the individual meet full criteria for both mania and a major depressive episode at the same time (APA 2015). In Finland, hospital diagnoses are based on ICD: ICD-8 from 1969 to 1986, ICD-9 from 1987 to 1995 and ICD-10 from 1996 onwards. Table 1 shows the ICD-10 diagnostic criteria for BPD.

Table 1. ICD-10 diagnostic criteria for BPD. Modified and reproduced with permission from WHO. 2015.

Bipolar affective disorder

Definition: A disorder characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others of a lowering of mood and decreased energy and activity (depression). Repeated episodes of hypomania or mania only are classified as bipolar.

Including: manic depression, manic-depressive: a) illness, b) psychosis, c) reaction.

Excluding: bipolar disorder, single manic episode (F30.-), cyclothymia (F34.0)

F31.0 Bipolar affective disorder, current episode hypomanic

The patient is currently hypomanic, and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.

F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms

The patient is currently manic, without psychotic symptoms (as in F30.1), and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.

F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms

The patient is currently manic, with psychotic symptoms (as in F30.2), and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.

F31.3 Bipolar affective disorder, current episode mild or moderate depression

The patient is currently depressed, as in a depressive episode of either mild or moderate severity (F32.0 or F32.1), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.

F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms

The patient is currently depressed, as in severe depressive episode without psychotic symptoms (F32.2), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.

F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms

The patient is currently depressed, as in severe depressive episode with psychotic symptoms (F32.3), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.

F31.6 Bipolar affective disorder, current episode mixed

The patient has had at least one authenticated hypomanic, manic, depressive, or mixed affective episode in the past, and currently exhibits either a mixture or a rapid alteration of manic and depressive symptoms.

Excluding: single mixed affective episode (F38.0)

F31.7 Bipolar affective disorder, currently in remission

The patient has had at least one authenticated hypomanic, manic, or mixed affective episode in the past, and at least one other affective episode (hypomanic, manic, depressive, or mixed) in addition, but is not currently suffering from any significant mood disturbance, and has not done so for several months. Periods of remission during prophylactic treatment should be coded here.

F31.8 Other bipolar affective disorders

Bipolar II disorder; Recurrent manic episodes NOS

F31.9 Bipolar affective disorder, unspecified

Manic depression NOS

2. REVIEW OF THE LITERATURE

2.1 Epidemiology of Bipolar Disorder

2.1.1 Global distribution

Mental health problems are one of the most common causes of morbidity globally. Mental and substance use disorders accounted for 7.4% of all Disability adjusted life years (DALYs) globally in 2010 (Whiteford *et al*. 2013). DALY is a measure used to quantify the burden of a disease resulting from its mortality and morbidity. The WHO defines DALY as "the sum of the years of life lost (YLL) due to premature mortality in the population and the years lost due to disability (YLD) for people living with the health condition or its consequences" (WHO 2014). In the year 2010, BPD accounted for 7% of the DALYs caused by mental and substance use disorders. BPD, due to its early onset and chronic life course results in more DALYs loss than all forms of cancer combined (WHO 2002).

The incidence and prevalence of BPD varies widely worldwide. The variation could be due to the differences in actual disease burden, cultural differences to mental illness, varying availability of diagnostic and treatment services and differences in the study design and the target population used in different studies. The lifetime prevalence of BPD varied from 0.3% in Taiwan to 1.5% in New Zealand when using population-based interviews (Weissman *et al*. 1996). Another recent study using cross sectional, face to face household surveys conducted in 11 countries found the aggregate lifetime prevalence of 0.6% for bipolar type I disorder (BPD-I) and 0.4% for bipolar type II disorder (Merikangas *et al*. 2011). The prevalence of BPD varied from 0.1% in India to 4.4% in the USA. The lifetime prevalence of BPD-I was 0.24% in a Finnish study (Perälä *et al.* 2007). The study by Perälä *et al*. (2007) was based on an extensive general population survey using Composite International Diagnostic Interview (CIDI), self-reported diagnoses, medical examination, and nationwide registers. Another Finnish study using hospital inpatient data over 8 years, found the incidence of BPD to be 0.03% among population aged more than 15 years (Räsänen *et al.* 1998). Räsänen *et al.* (1998) identified cases from the Finnish Hospital Discharge Register (FHDR), based on first admission of patients to psychiatric inpatient wards nationwide between 1987 and 1994, and used the Finnish Population statistics to estimate the overall incidence of BPD in 1994.

2.1.2 Age and sex

The mean age of onset of BPD in an epidemiological survey in 10 countries ranged from 18 to 27 years (Weissman *et al*. 1996). A hospital inpatient and outpatient study of BPD

in Finland had a mean age of onset of 23.7 years, standard deviation (SD) 9.8 years for first affective episode (Suominen *et al.* 2007). The classification of BPD by age of onset has not been uniform. While some have classified BPD cases as early onset (≤ 18 years) and later onset (> 18 years) (Suominen *et al.* 2007, Carter *et al.* 2003), others have classified the age of onset of BPD into four categories: childhood onset: onset at age 0 to 12 years; adolescent onset: 13 to 18 years; early-adult onset: 19 to 29 years and late-adult onset for onset after 30 years (Perlis *et al*. 2004). Cases with an early onset i.e. before the age of 18 years have been shown to be associated with greater heritability, increased illness severity, higher comorbidity, and an overall poorer outcome (Carter *et al.* 2003, Suominen *et al.* 2007, Somanath *et al.* 2002).

Similarly, there are conflicting findings regarding the distribution of early onset BPD cases in the US as compared to Europe. While few studies have suggested that the rates of early onset BPD are much higher in the US as compared to Europe (Post *et al.* 2008, James *et al*. 2014), others did not find such differences (Van Meter *et al.* 2011, Oedegaard *et al.* 2009). Several possible explanations have been suggested to explain the finding of an increased occurrence of early onset BPD cases in the US. First, there are differences in the study design and methodology in the studies, e.g. age range, rating scales and duration of assessment in the interviews. Second, the differences in the diagnostic classification i.e. ICD vs DSM may be relevant, as the ICD requires more than one manic episode for BPD diagnosis. Third, early onset BPD cases could be underdiagnosed outside US, with a bias among clinicians towards making a diagnosis instead of hyperkinetic disorder, conduct disorder or major depressive disorder. Fourth, early onset BPD cases could be over- diagnosed in the US. Finally, early onset BPD may actually be rarer outside the US due to some environmental or cultural differences (Soutullo *et al*. 2005).

Most previous studies suggest that BPD occurs almost equally among men and women (Weissman *et al.* 1996, Mitchell *et al.* 2004). However, other studies have shown some differences in BPD based on gender. One study suggested that bipolar I occurs approximately equally among men and women, whereas bipolar II disorder may be more common in women than in men (Bauer & Pfennig 2005). While some clinical studies suggest that females with BPD experience more depressive episodes and less manic episodes as compared to males (Robb *et al.* 1998), others do not report such differences (Hendrick *et al.* 2000). The nationwide register based studies show BPD to be slightly more common among females, accounting for 54% (Laursen *et al.* 2007) to 58% (Frans *et al.* 2008) of the total cases. Previous studies from Finland report similar distribution among females of 53-54% (Suominen *et al.* 2007). Interestingly, early onset BPD cases (before the age of 18 years) are much more common among females, accounting for 72% of total cases in one Finnish study (Suominen *et al.* 2007).

2.2 Risk factors for BPD

2.2.1 Place of birth

Table 2 summarizes the findings of previous studies on birthplace and parental socioeconomic status (SES) and the risk of BPD. Few previous studies have examined the association between urban birth and residence and subsequent risk of BPD (Mortensen *et al.* 2003, Pedersen & Mortensen 2006, Laursen *et al.* 2007). A study found birth in a provincial city to be associated with an increased risk of BPD (Mortensen *et al.* 2003). Another study showed place of residence in a provincial city at 15th birthday to be associated with increased risk of BPD (Pedersen & Mortensen 2006). It did not find any association between urbanicity at birth and BPD. Another study showed that being born in larger cities as compared to rural areas was associated with greater risk of BPD (Laursen *et al*. 2007).

Studies have shown an association between region of birth and the subsequent risk of psychosis in Finland. Perälä *et al.* (2008) showed that region of birth, notably in the East or North, was associated with increased risk of any psychotic disorder and schizophrenia but not with affective psychosis. Other studies have also shown similar increased clustering of psychosis or schizophrenia in Eastern Finland (Haukka *et al.* 2001, Lehtinen *et al*. 1990). A similar trend is observed in the treatment rates with rates of new admissions for psychosis and affective disorders shown to be significantly higher in Eastern Finland as compared to other regions (Korkeila *et al.* 1998).

2.2.2 Parental socioeconomic status

Several studies have shown an association between measures of socioeconomic status and several health outcomes (Bradley & Corwyn 2002, Adler *et al*. 1993) including mental disorders (Van Oort *et al.* 2011, Fryers *et al.* 2003). Socioeconomic status is a complex measure resulting from an intricate combination of various variables, mostly derived as a combination of three components: education, occupation and income. There seems to be a general agreement that all three components put together represent SES better than each individual component (White 1982). There is a lack of consensus on which measure individually best predicts the overall SES (Winkleby *et al.* 1992).

There are limited previous studies examining parental socioeconomic status in association with BPD in offspring. Only one previous study has examined the association between parental educational level and income and BPD in offspring (Tsuchiya *et al*. 2004). It showed higher paternal and maternal educational level to be associated with increased BPD risk. Furthermore, higher level of paternal wealth was also associated with BPD.

2.2.3 Parental age

The average age of being a parent has been increasing over the last three decades in many high-income countries (OECD 2014a, Eurostat 2014). In the European Union (EU), the mean maternal age at childbirth increased by 1.5 years (from 27.1 to 28.6 years) between 1980 and 1993 (Breart 1997) and by 3.1 years until 2012 (Eurostat 2014). Similarly, in the United States of America (USA), the average age of first time mothers increased by 3.6 years, from 21.4 years in 1970 to 25.0 years in 2006 (Mathews & Hamilton 2009). During the same time period, the proportion of first time birth among women aged 35 years or older increased almost 8-fold (Martin *et al*. 2009, Mathews 2001). Similar trend has been observed with paternal age as well. The mean age of fathers in England and Wales increased from 29.2 to 32.6 between 1980 and 2011 (ONS 2011). In Australia, the median age of fathers increased by almost 3 years from 31.4 to 34 years between 1990 and 2010 (ABS 2010). In Finland, the mean age of becoming a father and mother for first live birth was 30.4 and 28.6 years respectively in 2013. The corresponding figures for all births in 2013 were 30.7 years for fathers and 30.4 years for mothers (Statistics Finland. 2015).

This change in the demographics of parents has been attributed to economic, technologic and social changes in the developed world (Huang *et al.* 2008). An increasing number of years spent in education, combined with years spent on achieving a stable work environment, in search for financial stability has resulted in an increasing number of people opting to have children later in life. Along similar lines, a recent study suggested that the optimal age for women to be a parent while achieving a balance between education, career, and family would be between 25 to 35 years (Heffner 2004). Thus, it seems that there is a trend of increasing normative age of being a parent. During the same period, teenage pregnancy has declined, especially in the Nordic countries. In Finland, women younger than 20 years accounted for 8.2% of all pregnancies in 1975, the corresponding value has declined to 2.3% in 2010 (Heino & Gissler.2012).

Table 2. Population-based studies on birth place, parental socioeconomic status and BPD.

Author, Publication year, Country	Study design	Diagnostic criteria; Data source	Sample size; age range	Covariates	Results	Measure of association and risk of BPD
1.Tsuchiya *et al*. 2004, Denmark	Nationwide Population-based case-control study	ICD-8, ICD-10; Nationwide registers	947 BPD cases, 47350 control (1:50); 10-38 years	Marital status, occupation, education, annual income and wealth of subject and parents, sex, citizenship, country of birth, place of residence, age of parents, lack of link with parents in the previous year, number of siblings, history of psychiatric diagnoses in first degree relatives.	Mother's and father's higher education and higher level of paternal wealth were associated with increased risk of BPD.	Mother's higher education level, **OR_{adj}=1.59 95% CI: 1.31–1.94,** Father's **higher** education level, **OR_{adj}= 1.24, 95% CI: 1.01–1.52,** higher level of paternal wealth **OR_{adj}= 1.29, 95% CI: 1.09–1.52.**
2.Mortensen *et al*. 2003, Denmark	Nationwide Population-based cohort study	ICD-8, ICD-10, Nationwide registers	2299 BPD cases; 15-48 years	Age, sex, interaction between age and sex, calendar year of diagnosis, age of the mother and father at the time of birth, history of mental illness in parent or siblings, history of loss of a parent or sibling.	Urbanicity at birth i.e. being born in a provincial city was associated with an increased risk of BPD.	Being born in a provincial city, **OR_{adj}=1.21, 95% CI: 1.06- 1.39.**
3.Pedersen & Mortensen. 2006, Denmark	Nationwide Population-based cohort study	ICD-8, ICD-10, Nationwide registers	2232 BPD cases. 15-45 years	Age and its interaction with sex, birth year, parental age, history of mental illness in a parent or sibling.	Place of residence in a provincial city at 15th birthday was associated with increased risk of BPD. Urbanicity at birth was not associated with BPD.	Place of residence at 15th birthday **(P=0.02)**, Urbanicity at birth **(P=0.13)**
4.Laursen *et al.* 2007, Denmark	Nationwide Population-based cohort study	ICD-8, ICD-10, Nationwide registers	4490 BPD cases, 18-50 years	Age, birth year, sex, family history of psychiatric admission, maternal age, loss of parent, paternal age, place of birth.	Being born in larger cities as compared to rural areas was associated with greater risk of BPD	RR for being born in Copenhagen, **RR_{adj}=1.20, 95%CI: 1.09-1.31**, city with >100,000 population **RR_{adj}=1.33, 95 %CI: 1.20-1.47**, city with >10,000 population **RR_{adj}=1.12, 95% CI: 1.04-1.22.**

OR_{adj}: Adjusted odds Ratio, RR_{adj}: Adjusted Relative Risk, 95% CI: 95% confidence Interval

Several epidemiological studies (Durkin *et al.* 2008, Croen *et al*. 2007) and meta-analyses (Sandin *et al.* 2012, Gardener *et al.* 2009) have shown an association between advanced maternal age and ASD. However, studies examining the association between maternal age and schizophrenia have been inconsistent with one study showing an association with teenage mothers (McGrath *et al.* 2014), whereas another study did not show any association (Byrne *et al.* 2003). The possible mechanisms for the association with advanced maternal age include: First, advanced maternal age has been suggested to be an important risk factor for chromosome abnormalities, e.g. aneuploidy (Martin 2008) and genomic modifications, e.g. trinucleotide repeat instability (Kaytor *et al.* 1997). Interestingly, genomic alterations including copy number variations have been associated with autism and schizophrenia (Cook & Scherer 2008, Sebat *et al.* 2007). Second, epigenetic dysfunction could explain some of the parental age effect (Sandin *et al.* 2012). Third, prenatal exposure to toxins, e.g. lead and polychlorinated biphenyls (PCBs) have been shown to affect brain development and have long term developmental consequences in offspring (Williams & Ross 2007). Lastly, older mothers have an increased risk of obstetric complications (Berkowitz *et al.* 1990) and that could explain the association with psychiatric disorders (Kolevzon *et al.* 2007).

Increasing paternal age has been associated with an increased risk of various adverse outcomes in children including cleft lip and palate (Bille *et al*. 2005) and various forms of cancer (Hemminki *et al.* 1999). Advanced paternal age has been associated with an increased risk of schizophrenia (Malaspina *et al.* 2001, Byrne *et al.* 2003) and ASD (Croen *et al.* 2007, Durkin *et al.* 2008). The possible mechanisms for the association with advanced paternal age include: a) increase in *de novo* mutations in the male germline with advancing age due to the repeated cell divisions occurring during the normal development of sperm (Malaspina 2001), b) epigenetic dysregulation such as DNA-methylation changes as an important non genetic factor (Dempster *et al.* 2011), c) the accumulation of exposure to various environmental toxins over the life time resulting in genomic and/or epigenetic changes in the germ cells (Yauk *et al.* 2008) and d) heritable traits in the old fathers, e.g personality traits leading to reduced social interaction skills and thus leading to delayed age at parenthood (Hare & Moran 1979).

Young parental age has been associated with psychiatric disorders in offspring in general (McGrath *et al.* 2014), with schizophrenia (Wohl & Gorwood 2007) and ASD (Lundström *et al*. 2010). Young parents are a special group with increased tendency to early reproduction, among other things, due to their personality (Lundström *et al.* 2010). Young parents are likely to have higher chances of transmitting genetic risk of neurodevelopmental disorders due to the higher rates of psychiatric disorders among them (Lundström *et al.* 2010). Using the "Finnish 1981 Birth Cohort Study" (Sourander *et al*. 2009), childhood conduct and hyperactive problems were demonstrated to be associated with becoming a teenage mother (Lehti *et al.* 2012a). Similarly, childhood conduct

problems were associated with becoming a young father (Lehti *et al.* 2012b). Young parents are more likely to have lower education and belong to a low socioeconomic status (Kiernan 1997) and may more likely have poor access to prenatal care (D'Ascoli *et al.* 1997). Subsequently, the offspring are likely to be at an increased risk of complications during pregnancy. In turn, these complications during pregnancy have been associated with neurodevelopmental disorders (Rapoport *et al.* 2012, Kolevzon *et al.* 2007). Also, offspring of young fathers have an increased risk of *de novo* genetic disorders due to immaturity of spermatids or impaired DNA repair (Malaspina 2001).Young fathers are more likely to be exposed to health risk behaviors, e.g. drug abuse, which have been linked with germline *de novo* mutations (Robbins *et al.* 2005). Young mothers are more likely to smoke during pregnancy and most of them continue it through the whole pregnancy (Vuori & Gissler. 2012). Smoking during pregnancy has been associated with attention-deficit/hyperactivity disorder (ADHD) (Button *et al.* 2005), conduct disorder (Fergusson *et al.* 1998) and ASD (Hultman *et al.* 2002) in offspring.

2.2.3.1 Paternal age and BPD

As shown in Table 3, several previous studies have examined the association between paternal age and BPD. Out of a total of seven studies, five were based on nationwide population-based registers from the Nordic countries (McGrath *et al.* 2014, D'Onofrio *et al.* 2014, Menezes *et al*. 2010, Frans *et al.* 2008, Laursen *et al.* 2007). The remaining two were population-based studies from the Netherlands (Voskamp *et al.* 2011) and the USA (Brown *et al*. 2013). Four of the studies (McGrath *et al*.2014, D'Onofrio *et al.* 2014, Laursen *et al.* 2007, Menezes *et al.* 2010) were based on a cohort design whereas the remaining three were case-control studies (Brown et al. 2013, Frans et al. 2008, Voskamp *et al.* 2011). Three studies focused specifically on the risk of BPD in association with paternal age (Menezes *et al.* 2010, Frans *et al.* 2008, Brown *et al.* 2013), whereas the remaining four examined the relationship between paternal age and a range of other disorders. The number of BPD cases included in the studies varied from 94 (Brown *et al*. 2013) to 13,428 (Frans *et al*. 2008). Five out of seven studies showed a positive association between advanced paternal age and BPD (McGrath *et al.* 2014, D'Onofrio *et al.* 2014, Menezes *et al.* 2010, Frans *et al.* 2008, Laursen *et al.* 2007). The remaining two (Voskamp *et al*. 2011, Brown *et al*. 2013) did not find any association.

A Danish cohort study using nationwide registers showed an association between paternal age and BPD (Laursen *et al.* 2007). It showed that fathers aged 31-40 years and 50-55 years had an increased risk of BPD in offspring. Offspring of fathers aged 50-55 years had 1.7-fold increased risk of BPD. Frans *et al*. (2008) demonstrated an increased risk of BPD among offspring of fathers aged 30-34 years, 40-44 years and >55 years. Offspring of fathers aged more than 55 years had a 1.4-fold increased risk of

BPD. On evaluating cases of BPD with an early onset (i.e. before the age of 20 years), the risk among offspring of fathers aged >55 years was 2.6-fold. Another Swedish study (Menezes *et al.* 2010) demonstrated an increased risk of BPD among offspring of fathers aged 35 years or older. The risk was highest among offspring of fathers aged 40-44 years showing a 1.8-fold increased risk. A recent Swedish study examined the association between paternal age and a range of offspring psychiatric disorders and academic morbidity (failing grades and low educational attainment) (D'Onofrio *et al.* 2014) and showed more than 5-fold increased risk of BPD among offspring of fathers older than 45 years. A Danish study used a similar cohort design examining the association between parental age and a range of psychiatric disorders in the offspring (McGrath *et al.* 2014) and showed that offspring of fathers aged over 45 years had a 1.2-fold increased risk of BPD.

A Dutch case-control study using psychiatric case registry from central Netherlands examined the association between paternal age and schizophrenia, ASD, major depressive disorder, and BPD (Voskamp *et al.* 2011). The study did not find any association between parental age and BPD in offspring. Another case-control study in the USA, used a population-based study design (Brown *et al.* 2013) and did not find any association between paternal age and BPD.

2.2.3.1 Maternal age and BPD

Four previous population-based epidemiological studies have examined the association between maternal age and BPD (Table. 3). Three of the studies were based on the Nordic nationwide registers (Menezes *et al.* 2010, Frans *et al.* 2008, McGrath *et al.* 2014) whereas one was a population-based study from the USA (Brown *et al.* 2013). Two studies showed an association between maternal age and BPD (Frans *et al*. 2008, McGrath *et al*. 2014) whereas the other two did not find any association (Menezes *et al*. 2010, Brown *et al*. 2013). A Swedish nationwide case-control study showed an increased risk of BPD among offspring of mothers aged 30-39 years (Frans *et al*. 2008). Offspring of mothers aged 35-39 years had a 1.16-fold increased risk of BPD. However, unlike the findings with paternal age, no association was found between maternal age and BPD when the study included early onset BPD cases. Another Danish nationwide cohort study showed an association between young maternal age and the risk of BPD (McGrath *et al*. 2014). Mothers aged younger than 20 years had a 1.2-fold increased risk of BPD in the offspring.

2.2.4 Perinatal complications

The World Health Organization (WHO) defines the perinatal period as period commencing at 22 completed weeks (154 days) of gestation and ending at seven

completed days after birth (WHO 1992). Complications occurring during the perinatal period include those occurring during the later period of pregnancy, during childbirth and until 7 days during the postnatal period. Prenatal and perinatal complications have been suggested as risk factors for schizophrenia (Rapoport *et al.* 2012) and ASD (Kolevzon *et al.* 2007, Guinchat *et al*. 2012). However, despite sharing a genetic overlap with schizophrenia (Lichtenstein *et al*. 2009, Mortensen *et al*. 2010, Lencz *et al*. 2013) and having a neurodevelopmental origin (Sanches *et al.* 2008), the evidence for an association between pre and perinatal risk factors and BPD is much more inconsistent (Haukvik *et al.* 2014).

Preterm birth is defined as birth occurring prior to 37 completed weeks of gestation and is associated with increased mortality in infancy (Moster *et al*. 2008, Fellman *et al.* 2009, Crump *et al.* 2011), as well as with increased morbidity including psychiatric disorders (Crump *et al*. 2011, Doyle & Anderson 2010) later in life. Small for gestational age (SGA) refers to a neonate whose birth weight or birth length is at least two standard deviations (SD) below the mean for the infant's gestational age, based on data derived from a reference population (Lee *et al*. 2003). SGA is a measure of size of infant at birth and should not be considered synonymous to intrauterine growth restriction (IUGR), which suggests diminished growth velocity in the fetus (Lee *et al*. 2003). Being born SGA has been shown to be associated with cognitive and attention problems in adolescence (O'Keeffe *et al.* 2003) and drug and alcohol dependency (Nosarti *et al*. 2012). Low birth weight is considered as a marker of high-risk newborns and has been associated with prenatal risk factors, complications during pregnancy and increased morbidity and mortality (Class *et al.* 2014a).

It has been suggested that deviation in fetal somatic growth occurs along with abnormalities in the fetal brain development. These growth abnormalities are subsequently linked with ASD (Abel *et al*. 2013). Furthermore, early placental programming of fetal development and placental functioning has been increasingly implicated in fetal somatic and brain growth (Abel & Allin 2005).

Table 3. Population-based studies on parental age and BPD.

Author, Publication year, Country	Study design	Diagnostic criteria, Data source	Sample size Age range	Covariates	Results	Measure of association and risk of BPD
1. McGrath *et al.* 2014, Denmark	Nationwide Population-based cohort study	ICD-8, ICD-10, Nationwide registers	7309 BPD cases, 0-56 years	Age at onset, year at onset, sex of offspring, degree of urbanization of the place of birth and history of mental illness in a parent or sibling.	Young maternal age and advanced paternal age was associated with increased BPD risk.	Mother's age < 19 years, **IRR_{adj}= 1.20, 95 % CI: 1.08-1.33.** Father's age ≥ 45 years, **IRR_{adj} = 1.24, 95% CI: 1.05-1.45.**
2. D'Onofrio *et al.* 2014, Sweden	Nationwide Population-based cohort study	ICD-8, ICD-9, ICD-10, Nationwide registers	6819 BPD cases, 12-36 years	Offspring covariates: sex, parity, year of birth; Parental covariates: Swedish nationality, educational level, lifetime history of psychiatric hospitalization, lifetime history of any criminal conviction, maternal age at childbirth, paternal disposable household-level income in the proband birth year.	Advanced paternal age was associated with increased risk of BPD.	Father's age >45 years, **HR > 5-fold**.
3. Brown *et al.* 2013, USA	Population-based nested case-control study	DSM-IV TR, Medical records database and mailed questionnaire	94 BPD cases, 746 matched controls (1:8), age range N/A	Paternal/ maternal education, paternal/ maternal ethnicity and gestational age.	No association between parental age and BPD.	Mother's age ≥ 45 years, OR_{adj}=1.46, 95%CI: 0.52-4.11. Father's age ≥ 45 years, ORadj= 1.45, 95% CI: 0.51, 4.11,
4. Menezes *et al.* 2010, Sweden	Nationwide Population-based cohort study	ICD-9, ICD-10, Nationwide registers	493 BPD cases, 16-29 years	Age, sex, maternal age, place of birth, obstetric characteristics, family history of psychosis and of BPAD, parental death before age 15 years, childhood SES.	Offspring of fathers aged 35-44 years had an increased risk of BPD. Every 10 years increase in paternal or maternal age was not associated with BPD risk. Having both parents older than 30 years was associated with increased risk of BPD.	Father's age 35-39 years, **HR_{adj} = 1.68, 95% CI:1.09-2.61,** 40-44 years, **HR_{adj}= 1.85, 95% CI:1.04–3.30.** Both parents older than 30 years, **HR= 1.45, 95% CI: 1.16-1.81.**
5. Frans *et al.* 2008, Sweden	Nationwide Population-based nested case-control study	ICD-8, ICD-9, ICD-10, Nationwide registers	13428 BPD cases, 67140 controls (1:5), 0-69 years	Parity, SES, family history of psychotic disorders.	Advanced paternal age was associated with increased risk of BPD in offspring. Offspring of mothers aged 30-39 years also had an increased risk.	Mother's age 35-39 years, **OR_{adj} = 1.16,95%CI: 1.06-1.26.** Father's age >55 years, ORadj= 1.37, 95% CI: 1.02-1.84.

IRR_{adj} : Adjusted Incidence Rate Ratios , HR: Hazard Ratio, HR_{adj}: Adjusted Hazard Ratio, OR_{adj}: Adjusted Odds Ratio ,RR_{adj}: Adjusted Relative risk, SES: Socioeconomic status, N/A: Not available, [1] 50 years and 6 months, [2] Mean age : 40.71 years, standard deviation: 10.03. 95% CI: 95% confidence Interval. *Continued on the next page.*

Table 3. Population-based studies on parental age and BPD

Author, Publication year, Country	Study design	Diagnostic criteria, Data source	Sample size Age range	Covariates	Results	Measure of association and risk of BPD
6. Laursen *et al.* 2007, Denmark	Nationwide Population-based cohort study	ICD-8, ICD-10, Nationwide registers	4490 BPD cases. 18-50 years[1]	Age, birth year, sex, family history of psychiatric admission, maternal age, loss of parent, paternal age, place of birth.	Increased risk of BPD observed in offspring of Fathers aged 31-40 years and 51-55 years.	Father's age 51-55 years, **RR_{adj}=1.71, 95% CI:1.21-2.41.**
7. Voskamp *et al.* 2011, Netherlands	Population-based case-control study	DSM-IV-TR, Regional registers	1121 BPD cases and 4484 controls (1:4). 40.71 years[2]	SES, ethnic background.	No association of father's age with BPD in offspring.	Father's age ≥ 40 years, OR_{adj}=1.14, 95% CI: 0.84-1.55.

[1] 50 years and 6 months, [2] Mean age : 40.71 years, standard deviation: 10.03, RR_{adj}: Adjusted Relative risk, OR_{adj}: Adjusted Odds Ratio , SES: Socioeconomic status, 95% CI: 95% confidence Interval

Several perinatal conditions indicating acute or prolonged oxygen deprivation i.e. hypoxia to the fetal brain have been suggested as a major risk factor for the development of schizophrenia (Dalman *et al.* 1999, 2001). Three possible mechanisms have been considered in explaining the association between obstetric complications and schizophrenia: a) a chronic fetal hypoxia like state resulting in reduction in supply of nutrients, e.g. oxygen, glucose to the fetus resulting in impaired CNS development and IUGR, b) hypoxia due to complications during delivery that could result in brain damage especially in hippocampus and the cortex and c) increased risk of complications due to prematurity such as intracranial hemorrhages causing brain damage (Dalman *et al*. 1999). Indeed, neuroimaging studies have shown reduction in the hippocampal volumes in schizophrenia patients with a history of complications during delivery (McNeil *et al*. 2000, Stefanis *et al*. 1999). In addition, an interaction has been seen between schizophrenia susceptibility genes and exposure to hypoxia in influencing hippocampal volume (Van Erp *et al.* 2002).

The earlier studies on prenatal and perinatal complications and neurodevelopmental disorders used scales of various obstetric complications, e.g. Murray-Lewis Obstetric Complications Scale, Mirdal's score (Murray & Lewis 1987, Mirdal *et al.* 1974). These scales provided summary scores for obstetric complications based on the number and relative severity of various complications (Kinney *et al*. 1998). The use of such summary scales combining a range of exposures together as "obstetric factors" has been questioned regarding their assumption of all the risk factors having a unitary and a dose-response effect (Zornberg *et al*. 2000). The direction forward has been the use of clearly defined distinct exposures as obstetric risk factors, which are quantified by standardized measurements (Cannon *et al*. 2002). The earlier studies used retrospectively collected obstetric complications data, based on maternal interviews (Kinney *et al*. 1993, 1998), which are prone to recall bias. More recent studies using documented measures of perinatal complications collected during antenatal visits and during childbirth have improved our understanding of the role of perinatal complications in development of neurodevelopmental disorders (Nosarti *et al*. 2012, Øgendahl *et al.* 2006).

2.2.4.1 Obstetric complications and BPD

Previous studies have examined the association between obstetric complications and the risk of affective disorders. A Scottish study (Bain *et al.* 2000) examined the association between obstetric complications and affective psychosis using two birth cohorts (1971-74 and 1975-78) and found inconsistent results. Abnormal presentation of the fetus was more common among cases as compared to controls in the 1971-74 cohort and was associated with a 2.6-fold increased risk of affective psychosis. However, abnormal presentation was more common among controls in the 1975-78 cohort. Similarly, artificial rupture of membranes was more common among cases in the 1975-78 cohort with a 2.5-fold increased risk of affective psychosis. It was more common among controls in the 1971-74 cohort. A Swedish

study (Hultman *et al.* 1999) showed uterine atony to be associated with affective psychosis. Exposure to uterine atony was associated with 2.2-fold increased risk of affective psychosis.

Four previous clinical studies have examined the association between obstetric complications and BPD. Kinney *et al.* (1993) examined the association between obstetric complications and BPD based on a proband-sibling study design. Using maternal interview based scores of obstetric complications (Mirdal *et al.* 1974), the total sum score of obstetric complications was significantly higher among probands as compared to siblings. Another study (Kinney *et al*. 1998) using a similar study design and summed scores of obstetric complications showed similar results. Both prenatal and perinatal complications were significantly higher among cases as compared to siblings. Another case-control study (Verdoux & Bourgeois 1993) compared obstetric complications among BPD, schizophrenia and normal controls using summary scores. They did not find any difference among cases and controls in the frequency, severity and summary scores of obstetric complications, collected by maternal interviews. However, they found significantly higher complications among schizophrenia cases as compared to BPD and controls. A recent case-control study compared obstetric and perinatal complications among BPD cases, siblings and controls (Martelon *et al*. 2012). The questions regarding obstetric (breech delivery, cesarean section, and other difficulties (e.g. cord around the neck, or labor greater than 24 hours) and perinatal difficulties (placement in an incubator, weight of less than 5 lbs=2.2 kg, required hospital stay, and needed surgery) were based on maternal interview based on Diagnostic Interview for Children and Adolescents-Parent Version (DICA-P) (Herjanic *et al*. 1982). They did not find any significant association between obstetric and perinatal complications and BPD on comparison with neither siblings nor controls. Only one previous population-based study has examined the association between obstetric complications and BPD (Table. 4). A Swedish nationwide register based study examined the association between Apgar score at 5 minutes and BPD (Nosarti *et al*. 2012). Neither Apgar scores of less than 3 nor 4-6 were not associated with BPD.

2.2.4.1 Indicators of growth and development and BPD

Few previous studies have examined the association between indicators of fetal growth and affective disorders. The study outcomes in the studies have varied, with some studies examining the association specifically for affective disorder. Few other studies have combined affective disorders and schizophrenia whereas others have grouped BPD, schizophrenia and other non-organic psychotic disorders together.

A Danish nationwide case-control study (Larsen *et al*. 2010) examined the association between low birth weight, prematurity and risk of affective disorders and/or schizophrenia. Prematurity or low birth weight was not associated with affective disorders (ICD-10, F30–F39). However, both low birth weight and prematurity was associated with an increased risk of affective disorders and schizophrenia (ICD-10, F20–F29) combined together. In another

Swedish cohort study (Abel *et al.* 2010), low birth weight was associated with increased risk of affective disorders (ICD-10, F30–F39). Birth weight less than 3000 grams was associated with an increased risk, with the highest risk of affective disorders (1.6-fold) among birth weight less than 1500 grams. Being small for gestational age (SGA) (defined as birth weights in the population less than 2 SDs less than the mean birth weight for a particular gestational age) was associated with 1.16-fold increased risk of affective disorders.

A Danish case-control study (Eaton *et al*. 2000) found no association between gestational age, weight for gestational age (WGA) or number of prior pregnancies with manic-depressive psychosis and other affective psychosis combined together. A Swedish cohort study (D'Onofrio *et al*. 2013) examined the association between preterm birth and BPD grouped together with schizophrenia and other non-organic psychotic disorders as "psychotic or bipolar disorder". Extreme preterm birth (i.e. gestational age 23-27 weeks) was associated with a 3.2-fold increased risk of psychotic or bipolar disorder. Another recent Swedish cohort study examined the association between birth weight and psychiatric and socioeconomic problems (Class *et al*. 2014). The study also grouped BPD together with schizophrenia and other non-organic psychotic disorders as "psychotic or bipolar disorder". It showed low birth weight (less than 2500 grams) to be associated with a 1.19-fold increased risk of psychotic or bipolar disorder.

Three previous studies (Table 4) have specifically examined the association between indicators of fetal growth and development and BPD (Øgendahl *et al*. 2006, Nosarti *et al*. 2012, Laursen *et al*. 2007). All the three studies were based on nationwide registers, including two Danish (Øgendahl *et al.* 2006, Laursen *et al*. 2007) and one Swedish study (Nosarti *et al.* 2012). Two of the studies were cohort studies (Nosarti *et al*. 2012, Laursen *et al*. 2007) while one study was based on a case-control study design (Øgendahl *et al*. 2006). One Danish case-control study examined the association between birth weight, gestational age and WGA with BPD and did not find any association (Øgendahl *et al*. 2006). Another Danish cohort study used a combined measure of gestational age and weight for gestational age while examining their association with BPD (Laursen *et al*. 2007). They initially classified gestational age as born before or after 37 weeks of gestational age. Subsequently, in each gestational age category, they classified birth weight into lower 10% and upper 90%. It showed that preterm children born small for gestational age (i.e. lower 10% birth weight among less than 37 weeks gestational age group) had more than 5-fold increased risk of BPD. A Swedish study examined the association between gestational age and a range of psychiatric disorders (Nosarti *et al*. 2012). They showed that gestational age of less than 37 weeks is associated with an increased risk of BPD. Children born with a gestational age of 32-36 weeks had a 2.7-fold increased risk of BPD. The risk increased even further among children who were born with a gestational age less than 32 weeks. They had a 7.4-fold increased risk of BPD as compared to children born with a gestational age of 37-41 weeks.

Table 4. Population-based studies on perinatal complications and BPD.

Author, Publication year, Country	Study design	Diagnostic criteria, Data source	Sample size, Age range	Covariates	Results	Measure of association and risk of BPD
1. Nosarti *et al*. 2012, Sweden	Nationwide Population-based cohort study	ICD-8,ICD-9, ICD-10, Nationwide registers	217 BPD cases, 11.8-23 years (SD: 4.1)[1]	Gestational age, non-optimal fetal growth, and Apgar score, sex, parity, mother's age at delivery, mother's educational level, and maternal psychiatric history.	Preterm birth was associated with BPD risk. Weight for gestational age and Apgar scores were not associated with BPD.	Gestational age <32 weeks, **(HR_{adj}= 7.4, 95 % CI: 2.7-20.6,** 32-36 weeks, **HR_{adj}=2.7, 95 % CI: 1.6-4.5.5 min Apgar score (0-3):** HRadj= 3.8, 95% CI:0.9-15.5; (4-6): HRadj=0.5, 95% CI: 0.1-3.6
2.Laursen *et al.* 2007, Denmark	Nationwide Population-based cohort study	ICD-8,ICD-10, Nationwide registers	4490 BPD cases. 18-50 years[2]	Age, birth year, sex, family history of psychiatric admission, maternal age, loss of parent, paternal age, place of birth.	Preterm children born small for gestational age had increased risk of BPD.	Preterm and SGA **(RR_{adj}= 5.32, 95 % CI: 2.75-10.29).**
3.Øgendahl *et al.* 2006, Denmark	Nationwide Population-based nested case-control study	ICD-8,ICD-10, Nationwide registers	196 BPD cases, 4900 controls (1:25). 12-26 years	Parental age, SES, parental psychiatric history.	No association between birth weight, birth length, gestational age and number of previous pregnancies in the mother and development of BPD in offspring.	Low birth weight (<2500grams), OR_{adj}=0.92, 95 % CI:0.46–1.87; Gestational age <37 weeks, OR_{adj}= 1.58, 95 %CI: 0.67–3.75; low birth weight (<2500 grams) and preterm birth (<37 weeks gestational age): OR_{adj}= 2.10, 95% CI:0.86–5.15.

HR_{adj}: Adjusted Hazard Ratio SES: socioeconomic status, OR_{adj}: Adjusted Odds Ratio, [1] mean: 23 years, SD: standard deviation: 4.1, [2] 50 years and 6 months, RR_{adj}: Adjusted Relative risk, 95% CI: 95% confidence Interval.

2.2.5 Maternal smoking during pregnancy

Smoking during pregnancy is an important global health problem. There is a wide variation in the number of women who smoke during pregnancy, ranging from 13.2% (Martin *et al.* 2009) to 36% (Ward *et al*. 2007) of total pregnancies worldwide.

Among the Nordic countries, all countries except Finland have a declining trend of maternal smoking during pregnancy. In Finland, the rate of maternal smoking during pregnancy has remained more or less stable at around 15% over last 20 years (Heino & Gissler 2012). Since the year 2000, there has been a greater decrease of 2.6% annually among mothers who smoke throughout pregnancy, as compared to 0.5% among mothers who smoke only in the first trimester. During the same period, rates of smoking among mothers older than 25 years have been similar to the overall trend, whereas, smoking rates have increased among mothers younger than 20 years (Ekblad *et al*. 2014). Women in the lowest SES category were 6-7 times more likely to smoke during pregnancy than women with the highest SES. Similarly, single women were 2-3 times more likely to smoke than women who were married or in a cohabiting relationship (Ekblad *et al.* 2014).

Exposure to maternal smoking affects the growth and development of the fetus including alterations in the brain structure and functions (Ekblad *et al*. 2015) and subsequently leads to an increased risk of prematurity (Fantuzzi *et al.* 2007) and intrauterine growth retardation (Jaddoe *et al*. 2007). Smoking during pregnancy has also been associated with increased risk of ADHD (Langley et al. 2005), conduct disorder (Fergusson *et al.* 1998) and ASD (Hultman *et al*. 2002). It has also been shown to be associated with psychiatric morbidity and use of psychotropic medication until young adulthood (Ekblad *et al*. 2010, 2011). However, a systematic review did not find an association with schizophrenia (Cannon *et al*. 2002).

Among thousands of potentially harmful chemicals in tobacco smoke, the two most important components shown to affect fetal development are nicotine and carbon monoxide (CO) (Hoffmann & Hoffmann 1997). A sustained exposure to exogenous nicotine leads to increased affinity to and subsequent desensitization of the nicotinic acetylcholine receptors (nAChRs) (Cohen *et al.* 2005). These receptors are essential in regulating the axonal guidance, synapse formation and cell survival during fetal brain development (Huang *et al.* 2007). The loss of function of specific nicotinic receptors due to desensitization has been associated with adverse neonatal outcomes including growth restriction (Cohen *et al.* 2005). CO binds to hemoglobin in fetal blood resulting in formation of carboxyhemoglobin (COHb), which reduces the delivery of oxygen to fetal tissues. In addition, animal studies have shown, nicotine to affect contraction of uterine arteries and thus decrease the uterine blood flow (Xiao *et al*. 2007). Thus prenatal smoking exposure could affect fetal brain development by fetal hypoxia and ischemia.

2.2.5.1 Maternal smoking during pregnancy and BPD

Two previous studies (Ekblad *et al*. 2010, Talati *et al.* 2013) have examined the association between maternal smoking in pregnancy and mood disorders in the offspring and only one previous study specifically on BPD (Talati *et al*. 2013). In a Finnish nationwide population-based cohort study, Ekblad *et al*. (2010) showed that maternal smoking during pregnancy is associated with increased risk of mood disorders (F30-39). Smoking less than 10 cigarettes/ day was associated with a 1.6-fold increased risk, which increased to 1.9-fold among mothers who smoked more than 10 cigarettes/ day. The only previous study on maternal smoking and BPD was a population-based case-control study in the US (Talati *et al*. 2013). It showed more than 2-fold increased risk of BPD among offspring exposed to maternal smoking during pregnancy. However two previous studies did not find any association between maternal smoking in pregnancy and anxiety disorders or major depression (Fergusson *et al*.1998, Weissman *et al.* 1999).

2.3 Gaps in the existing literature

There has been growing interest in research on fetal origins of mental health. Most of the studies on prenatal and perinatal risk factors have focused on schizophrenia and ASD with a relative paucity of studies on BPD. Among the existing large population-based studies, parental age has been examined most frequently but only one previous study has examined the role of prenatal maternal smoking. No previous study has examined the association between parental age difference and BPD. Similarly, previous studies on perinatal complications have been few, examining limited risk factors, inconsistent grouping of risk factors studied and mostly having small sample sizes.

3. AIMS OF THE STUDY

The main objective of this thesis was to improve our understanding of the role of prenatal and perinatal risk factors in the development of BPD. The specific aims of this thesis included:

1) To provide an overview of the Finnish Prenatal Study of Bipolar Disorders (FIPS-B) and report the demographic characteristics of the sample. A further aim was to examine the association between parental educational level, region of birth and BPD (I).

2) To study the association of paternal age, maternal age and parental age difference with BPD (II). The study hypothesis was that there is an association between both young and advanced paternal age and BPD.

3) To examine the association between perinatal risk factors and the subsequent risk of BPD (III). The study hypothesis was that perinatal risk factors, in general are weakly associated with BPD.

4) To study the association between maternal smoking during pregnancy and the risk of BPD (IV). The study hypothesis was that there is an association between maternal smoking during pregnancy and BPD.

4. MATERIALS AND METHODS

4.1 Study design

Figure 1 shows the overall study design of the Finnish prenatal study of Bipolar Disorder (FIPS-B). This is a nested case-control study based on all live births in Finland between January 1st 1983 and December 31st 1998. The source population included 1,009,846 live births. The cases included in this study were all subjects diagnosed with BPD in the FHDR among the subjects from the source population before 31st December 2008. The cases were identified from the FHDR based on the ICD diagnostic codes and the last registered diagnosis was used for identification (Table. 5). ICD-9 classification was used between January 1st 1987 and December 31st 1995 and ICD-10 from January 1st 1996 onwards. The total number of identified BPD cases was 1887, out of which 26 cases were twins.

The controls in this study were defined as those born in Finland during the study period and without any diagnosis in the FHDR of BPD, schizophrenia or any diagnoses related to these disorders (Table. 5). Two randomly selected controls were identified from the Finnish Population Register Centre (PRC) and were matched to cases (2:1) on selected factors including: sex, date of birth (±30 days) and the controls had to be alive and living in Finland on the date of diagnosis of the matched case. Matching for date of birth ensured was aimed at controlling for any secular changes over study period among the prevalence of exposures in the study and controlling for the effects of seasonality of birth. Matching for the date of diagnosis of the case ensured that the controls were followed up at least for the same time period. Matching for residency in Finland was aimed at controlling for emigration out of Finland among controls, thereby lacking the relevant information in the health registers. The total number of controls identified was 3774. Among them 79 controls were twins.

Table 5. ICD-10 and ICD-9 diagnostic codes for cases and exclusions for controls

Diagnostic classification	Cases	Controls excluded the following diagnoses
ICD-10	**F 31X** BPD	**F20–29** schizophrenia, schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders, and unspecified nonorganic psychosis; **F30** single manic episode; **F31X** BPD; **F34.0** cyclothymia; **F38.0** other mood disorders or mixed affective episode; **F39** unspecified mood disorder; **F60.0** paranoid personality disorder; and **F60.1** schizoid personality disorder
ICD-9	**2962 A–G, 2963 A–G, 2964 A–G, 2967A** BPD	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

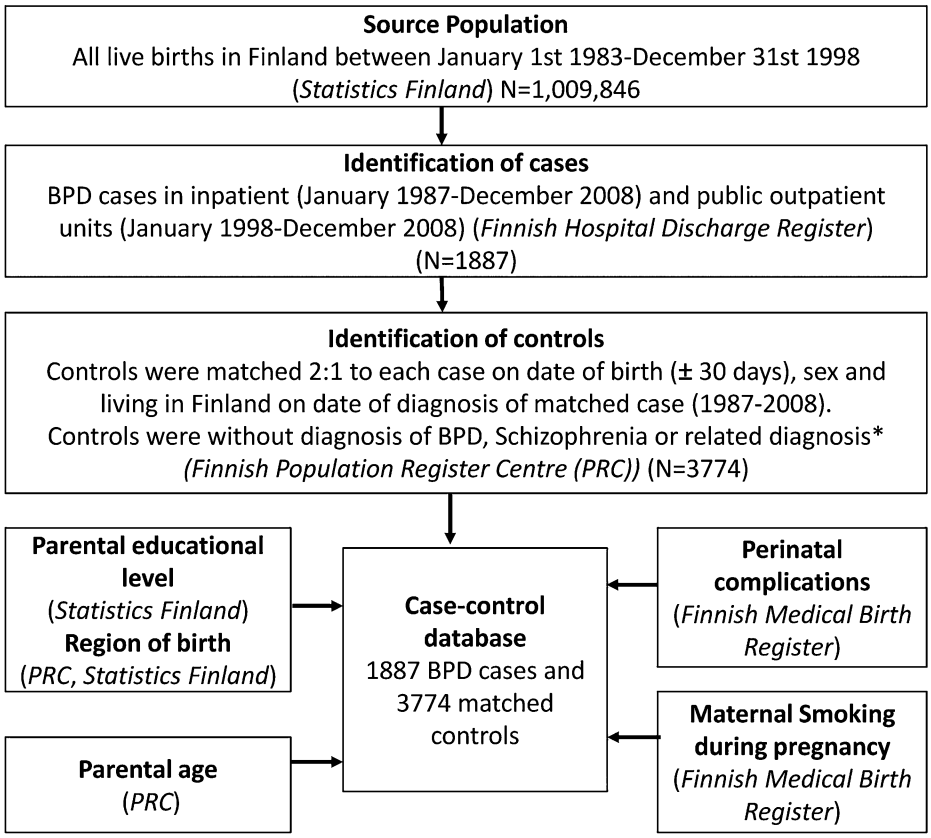

Figure 1. Flowchart of the study design of Finnish Prenatal Study of Bipolar Disorders (FIPS-B). *Listed in description of diagnostic codes excluded for controls in page 38. Modified from Chudal et al. 2014a, study I.

4.2 Overview of the Finnish Healthcare system

Mental health services in Finland are an integral part of the public health care system, provided by municipal primary healthcare centres and various levels of specialized services. The municipalities, with support of the government, employers and taxpayers are responsible for organizing social welfare and health care of the population. They provide basic social welfare and health care services either alone, or together with other municipalities. Hospital districts organize specialized medical care. (Ministry of Social Affairs and Health 2013). Finland is divided into 20 hospital districts and every municipality has to be a member of such a district. It is the responsibility of each district to provide hospital services and to coordinate specialized public hospital care within its area. The municipalities are responsible for social services such as nursing homes, child day care, social assistance, basic education and services for the elderly (Häkkinen 2005). Recently there have been attempts to renew the legislation for Social welfare and health care organization (SOTE *in Finnish*) and a new system is likely to come into place in Finland in the coming years.

The mental health services are provided by the municipal primary health care centres, district, central and the University Hospitals. The primary health care centres provide the basic primary health care services. The next level of health care is provided by the district hospitals, which are somewhat smaller than the central hospitals. The central hospitals form the next level of health care provider, which are smaller than the University hospitals. Finally, the five university hospitals provide the most challenging specialized health care services (Saarivirta *et al*. 2010). The typical pathway to psychiatric services starts with a visit to the primary health care centre. The general practitioner on suspicion of BPD refers the patient to specialized health care, where the diagnosis is specified and treatment started. The role of specialized services in mental health care services is two-fold. First, they are responsible for the provision of specialist care required due to the severity of the disease. Second, national compensation policies concerning sick leaves and medications warrant a statement from a specialist psychiatrist. The psychiatric inpatient units are part of the public health care system. The outpatient specialist care is provided through public outpatient units, or sometimes in the private sector, depending on the wish and affordability of the patient.

4.3 Overview of the Finnish Nationwide Registers

Finland has a long history of record keeping and the earliest form of registers was the registration of vital statistics, e.g. births, deaths and marriages that already started as early as the year 1749. The earliest system of record keeping was established for administrative purposes and this tradition of record keeping has gradually evolved over time. The earliest computerized nationwide disease register was the Cancer Register,

which started in 1952. Today there are several nationwide registers on health and social welfare in Finland (Gissler & Haukka 2004). The availability of several nationwide registers having good data quality, governed by strict data protection laws, have for long been a valuable source of information for research and improvement of health and social welfare.

4.4 The National Institute for Health and Welfare (THL)

The National Institute for Health and Welfare (THL) is a research and development institute established for promoting the welfare and health of the population, work on preventing diseases and social problems and developing social and healthcare services (THL 2014). The THL, as part of its role as the major statistical authority for health and welfare maintains several nationwide registers with comprehensive databases of health and welfare statistics. The registers maintained by the THL that are used in this study include: the Finnish Hospital Discharge Register (FHDR) and the Finnish Medical Birth Register (FMBR).

4.4.1 Finnish Hospital Discharge Register (FHDR)

The Finnish Hospital Discharge Register (FHDR) is one of the oldest hospital discharge registers covering the whole country in the world. This register has been maintained in Finland since 1967 and since 1969, contains complete computerized data of all medical diagnosis, both somatic and psychiatric. Since 1994, the FHDR has been replaced with The Care Register for Health Care and contains additional information on: patient count in inpatient care in hospitals at the end the year, day surgeries and specialized outpatient care (THL. 2015). In order to maintain uniformity with the manuscripts included, FHDR is used to denote The Care Register for Health Care in this thesis. The FHDR contains data on hospital discharge with information about patient's personal identity code (PIC) (including date of birth and sex), area of residence, hospital ID, admission and discharge days, and diagnosis of patient's medical problems at discharge with three subsidiary diagnoses coded according to the International classification of Disease (ICD) (Sund 2012). All diagnoses are based on the International Statistical Classification of Diseases (ICD): ICD-8 from 1969 to 1986, ICD-9 from 1987 to 1995 and ICD-10 from 1996 onwards. The FHDR initially included information from all inpatient wards of local health centers, military wards, prison hospitals, and private hospitals and since 1998 also includes outpatient care in specialized hospital units (University hospitals or hospitals serving several municipalities). However, it should be noted, that there are regional differences regarding the coverage in the FHDR of the specialized outpatient services from 1998 onwards. The primary care outpatient visits have been included in the FHDR from 2011 onwards (Sund 2012). The information in the FHDR has been repeatedly

shown to be of a good quality. Keskimäki & Aro (1991) showed that, when examined against the medical records of the patients, 98% of the main diagnoses of mental disorders at the 3-digit ICD code level had been correctly reported in the FHDR. More recently, a review of the quality of the FHDR concluded that the completeness and accuracy of the register varied from satisfactory to very good (Sund R 2012). The validity of the diagnoses in the FHDR has been repeatedly shown to be of a good quality. Kieseppä *et al.* (2000) demonstrated the validity of the FHDR diagnosis of BPD-I to be between 87% and 92%. Another study (Perälä *et al*. 2007) showed that the FHDR had a sensitivity of 75.3 % and specificity of 99.7% for diagnosis of psychotic disorders including BPD-I. The FHDR has been used in this study for the identification of BPD subjects.

4.4.2 Finnish Medical Birth Register (FMBR)

The FMBR was established in 1987 for collecting statistical data for research, development and provision of maternity care, obstetrics services and the care of newborn infants. The Register includes data on live births and stillbirths of fetuses with a birth weight of at least 500 grams or with a gestational age of at least 22 weeks, and data on the mothers. The information included in the register include: a) personal data of mother including the personal identity code (PIC), b) data on previous pregnancies and deliveries, c) data on current pregnancy and its monitoring including the health check-ups and maternal smoking during pregnancy, d) data on delivery including method of delivery and other procedures related to delivery, e) data on infant including PIC, birth weight and Apgar scores at 1 and 5 minutes and f) data on infant at age 7 days or at discharge including care interventions and diagnoses of the infants during that period (Medical Birth Register 2013). This information in the register is based on the standardized forms, completed for each born infant by the attending midwife or physician and sent by the hospital to the register within 7 days of birth. The data are initially entered into local electronic databases and submitted to the THL by the delivery hospitals. The review of the completeness of the data shows that less than 0.1% of the total births are missing (Gissler & Shelley 2002). The FMBR is used in this study for obtaining information on maternal smoking during pregnancy, indicators of fetal growth and development and obstetric complications.

4.5 Finnish Population Register Centre (PRC)

The Finnish Population Register Centre was established in 1969 and along with the local register offices, is responsible for the usage and maintenance of the data contained in the Population Information System (PRC 2014). The Finnish Population Information System (PIS 2014) is a computerized National register containing basic information about Finnish citizens and foreign citizens residing permanently in Finland. The

registration of information in the system is based on statutory notifications made by private individuals and public authorities. The personal data included in the system include: name, PIC, address, citizenship and native language, family relations and date of birth and death (if applicable). The population register centre data are used in this study to obtain information on: parents of cases and controls, identification of controls and information on the place of birth of cases and controls in the study.

4.6 Statistics Finland

Statistics Finland is the only public authority established particularly for statistical services in Finland. It is responsible for the production of the vast majority of Finnish official statistics (Statistics Finland 2014). The statistics Finland was used in this study for obtaining information on: source population of the study sample, classifying birth municipality information into four different regions (i.e. Southern, Western, Eastern and Northern Finland) and information on parental educational level of cases and controls.

The Finnish education system is comprised of nine-years of basic education, followed by, upper secondary education, which can be either, general education or vocational education, and higher education, provided by universities and polytechnics. Children permanently residing in Finland have the statutory right and obligation to complete the comprehensive school and almost all complete the basic education (99.7%). This is followed by upper secondary education, in either general education or vocational education and training (VET). Two complementary sectors comprise the Finnish higher education system, polytechnics and the universities. Polytechnics provide a bachelor's level polytechnic degree and a polytechnic 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 (Ministry of Education and Culture 2012).

4.7 Linkage of the Registers

The linkage of the information from the above-mentioned registers is achieved through the PIC. The PIC is a unique code issued to all Finnish citizens and foreign residents registered in the population information system. The PICs were introduced in Finland in the 1960s and consist of date of birth, sex and a control number, which is unique for each person. The PIC does not change over the lifetime of an individual, with the only exceptions being, e.g. to provide protection to individuals when the health and safety of a person is under permanent threat i.e. the PIC is abused by someone other than the one issued with the code and in case of change of the sex of the individual, in accordance with the Gender Confirmation of Transsexual Individuals Act (563/2002) (PIS 2014).

4.8 Overview, design and description of the FIPS-B (study I)

4.8.1 Study subjects

The subjects included in this study were 1887 BPD cases and 3774 matched controls identified from the FHDR and the PRC respectively.

4.8.2 Parental educational level, region of birth and BPD

Information on parental educational level was obtained from the Register of education at Statistics Finland. Linkage of the parental information from the PRC with the educational level data at the Statistics Finland was achieved using the PIC. The educational level of the parents was classified into four categories: (1) Master/Licentiate/Doctoral degree, (2) University/Polytechnic bachelor's degree, (3) Upper secondary school/equivalent vocational degree, and (4) Basic education (comprehensive school).

Information on region of birth was obtained based on information from PRC and Statistics Finland. Initially the information on birth municipalities was obtained from the PRC. That information was used to classify the study sample into four regions based on the information obtained from Statistics Finland. The four regions were: Southern Finland (including capital city Helsinki), Western Finland, Eastern Finland and Northern Finland.

The cumulative incidence of BPD according to the year of diagnosis in the sample was estimated, stratified by sex and age groups. Information on the numerator, i.e. BPD subjects stratified by age and sex were obtained from the FHDR and the denominator, i.e. total population in each age group stratified by sex was obtained from Statistics Finland.

4.9 Parental age and BPD (study II)

4.9.1 Study subjects

The cases included in this study were all diagnosed with BPD in Finland before December 31st 2008, among all singleton live births in Finland between January 1st 1983 and December 31st 1998. The number of BPD cases was 1861. The controls were matched 2:1 for each case, thereby resulting in 3722 controls. Among them, 79 controls born in a twin pair were excluded, thereby resulting in 3,643 controls. The cases were identified from the FHDR and the controls from the PRC.

4.9.2 Paternal age, maternal age, parental age difference and BPD

Information on age of both the parents was obtained from the PRC. Maternal age was classified into the following categories: <20, 20-24, 25-29, 30-34, 35-39, and ≥40 years. Similarly, paternal age was classified into: <20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and ≥50 years. The age difference between parents was estimated as a categorical variable with the difference classified into three categories: no difference (parental age difference less than 1 standard deviation (SD)), small difference (1-2 SD) and large difference (more than 2 SD). The age difference analyses were estimated separately for couples with older fathers/younger mothers and older mothers/younger fathers. Information on maternal age was available for all cases and controls. Paternal age information was missing for 2.1% of the cases and 1.1% of the controls. The missing information on paternal age was due to unknown paternity. In Finland, the husband of a married mother is registered as the father of the child automatically. In other cases of child birth, e.g. unmarried mothers who are cohabiting or in a relationship, the child welfare officer of the municipality established the paternity. The identity of paternity is established by initially contacting the mother for details regarding the father. Free services for DNA testing are also available for establishing paternity. The failure to establish paternity despite these measures resulted in the missing information on paternal age.

4.10 Perinatal complications and BPD (study III)

4.10.1 Study subjects

The source population in this study was all singleton born live births in Finland between January 1st 1987 and December 31st 1998 (N=754,450). As the FMBR was established in 1987, therefore only cases born 1987 onwards were included in this study. The cases included all diagnosed BPD subjects identified from the FHDR before 31st December 2008. The number of BPD cases identified was 724. Two controls born during the same period and matched 2:1 for each case were identified resulting in 1448 controls. Among them, 29 controls born to a twin pair were excluded, thereby resulting in 1419 controls. The cases and controls were identified from the FHDR and PRC respectively.

4.10.2 Indicators of fetal growth, obstetric complications and BPD

In this thesis, the perinatal complications have been classified as: a) obstetric complications (e.g. uterine bleeding, birth type, birth presentation) and b) indicators of fetal growth and development (i.e. birth weight, gestational age and weight for gestational age (WGA)). Information on the perinatal complications was obtained from the FMBR. Birth weight

was classified in the following categories: <1500 grams, 1500-2499, 2500-3999, 4000-4499 and ≥4500 grams. Gestational age was classified into the following four categories: <32 weeks, 32-37, 38-41 and ≥42 weeks. The calculation of birth weight for gestational age was based on the national sex specific weight distribution standards for a given gestational age. The national standard distributions of weight for gestational age were derived in a previous study based on 75,061 singleton children born with a gestational age of 24-43 weeks in Helsinki University maternity hospitals (Pihkala *et al*. 1989). The WGA was classified into three categories: small for gestational age (SGA): <-2 SD; appropriate for gestational age (AGA): -2 SD to +2 SD and large for gestational age (LGA): >+2 SD.

The obstetric complications examined was subdivided into: 1) maternal risk factors, 2) birth factors, 3) hypoxia related factors and 4) neonatal treatment. The risk factors included in maternal factors were uterine bleeding requiring hospitalization, and maternal hypertension. The information on uterine bleeding was obtained from two sources. Initially, the information was obtained based on ICD-9 codes (640, 6400A, 6408X, 6409X, 641, 6410A, 6410B, 6411A, 6411B, 6412A, 6412B, 6413A, 6413B, 6418A, 6418B, 6419A and 6419B) between January 1st 1987 and September 30th 1990. From October 1st 1990, it was based on a variable in the FMBR "hospital care due to bleeding during pregnancy" which was recorded as a yes/no variable. In Finland, maternal blood pressure of more than 140/80 mm Hg during pregnancy is considered high. Information on maternal hypertension was classified as a binary variable yes/no. The variables included in birth factors were birth presentation, birth type, and induced labour. Birth presentation was classified as cephalic, breech, or other (e.g. transverse, oblique, upper or lower limb). Birth type included five categories: vaginal cephalic, suction or forceps, planned cesarean section, emergency or other cesarean section and unknown. Induced labour was classified as a binary variable: yes/no. The hypoxia related factor included in this study was Apgar score at 1 minute. The Apgar score at 1 minute was classified as: <7, 7-8 and 9-10. The last component of the obstetric complications in this study included neonatal treatment. Neonatal monitoring or intensive care in the neonatal intensive care unit (NICU treatment) constituted neonatal treatment. It was classified as a binary variable yes/no.

4.11 Maternal smoking during pregnancy and BPD (study IV)

4.11.1 Study subjects

The source population in this study was similar to that in the study on the perinatal complications. The cases included all diagnosed BPD subjects identified from the FHDR before 31st December 2008 among singletons born in Finland between January 1st 1987

and December 31st 1998. The total number of BPD cases was 724. Two controls born during the same period were matched 2:1 for each case resulting in 1448 controls. 29 controls born to a twin pair were excluded resulting in 1419 controls. The cases and controls were identified from the FHDR and PRC respectively.

4.11.2 Prenatal maternal smoking and BPD

Information on maternal smoking during pregnancy was obtained from the FMBR. This was based on the information obtained from the mothers while visiting the maternal health clinics during second trimester of pregnancy. Information on maternal smoking was recorded in two different methods during this study period. Initially, between January 1st 1987 and September 30th 1990, this information was recorded as non-smokers, smoking less than 10 cigarettes/ day or more than 10 cigarettes/ day. From October 1st 1990 to December 31st 1998 the information was classified as non-smokers, smoking during the first trimester only, and smoking throughout pregnancy.

4.12 Study Ethics

The Finnish Data Protection Board approved the utilization of the health registers data and their linkage for current study. The institutions responsible for the registers used in this study (Statistics Finland, PRC, THL) provided approval for the utilization of the sensitive health register data in line with the national data-protection legislation. The ethical approval for the study was obtained from the Ethics committee of the Hospital district of Southwest Finland and the Institutional Review Board of the New York State Psychiatric Institute.

4.13 Statistical analyses

Conditional logistic regression models were used to examine the associations between exposure variables and BPD in all four studies. Initially unadjusted odds ratios and 95% confidence intervals were estimated. Subsequently adjustment was made for available potential confounders. In all analyses, a two-sided p-value of <0.05 was considered statistically significant. The statistical analyses were conducted with SAS statistical software (SAS version 9.3) (SAS Institute Inc.; Cary, NC, USA). Table 6 summarizes the statistical analyses used in the individual studies.

Table 6. Summary of the statistical analyses used in the studies

Study	Exposure variable	Strength of association	Covariates	Statistical method
I	Birth region	OR (Unadjusted); 95% CI	None	Conditional logistic regression analysis
	Mother's educational level	"	"	"
	Father's educational level	"	"	"
II	Father's age	OR (Unadjusted, adjusted); 95% CI	Age of other parent, parental psychiatric history, parental educational level and place of birth	Conditional logistic regression analysis
	Mother's age	"	"	"
	Age difference between parents	"	Father's age and parental psychiatric history	"
III	Indicators of fetal growth and development	OR (Unadjusted, adjusted); 95% CI	Maternal age, psychiatric history, educational level and place of birth.	Conditional logistic regression analysis
	Obstetric complications	"	"	"
IV	Maternal smoking during pregnancy	OR (Unadjusted, adjusted); 95% CI	Maternal age, maternal educational level and maternal and paternal psychiatric history	Conditional logistic regression analysis
	Smoking during pregnancy (yes/no)	"	"	"
	Smoking during pregnancy (no, < 10/ day, > 10 /day)	"	"	"
	Smoking during pregnancy (no, during first trimester only, throughout pregnancy)	"	"	"

OR: Odds Ratio, adjusted: adjusted for covariates,**":**same as above, 95% CI:95% confidence Interval

Additionally, in study I, the cumulative incidence of BPD in the sample stratified by age group and sex was estimated. The numerator was the number of diagnosed BPD cases every year between 1998 and 2008, separately for males and females and in three age group categories (less than 15 years, 15-19 years and 20-25 years). The denominator was the total population in Finland in each age group category separately for males and females during the same time period.

The association between birth regions (Northern, Eastern, Western and Southern Finland) and BPD were examined by comparing the risk of BPD on being born in any one region, against the risk on being born in the other three regions. Parental educational level classified into four categories was examined for their association with BPD.

In study IV, bivariate analyses were conducted initially to test the significance of association between covariates and maternal smoking during pregnancy among controls as well as between covariates and BPD. Using Pearson's chi squared test, only covariates significantly associated (at p- value <0.1) with both maternal smoking among controls and BPD were identified as potential confounders to be adjusted for in the analyses. Initially, smoking during pregnancy was examined as a binary variable (yes/no) for the total sample. Using conditional logistic regression, unadjusted ORs and 95% CIs were estimated. The association was adjusted in subsequent models for maternal age, maternal educational level and maternal and paternal psychiatric history. In the final model, adjustment was made for all the above-mentioned covariates together. In addition, adjustment was also made for a combination of any two covariates. Unadjusted OR and 95% CI were calculated for the association between maternal smoking during pregnancy and BPD separately for two classifications of maternal smoking status. Subsequently, adjustment was made for potential confounding due to maternal age, maternal educational level and maternal and paternal psychiatric history. The FIPS-B overall had 80% power to detect effect sizes between 1.9 and 2.0, for exposure with the prevalence of BPD set at 1 %. The power to detect significant association was 38% for birth weight less than 2500 grams and 26% in the lowest birth weight category (less than 1500 grams), with prevalence set at 0.4% and minimal detectable odds ratio of 1.4. Similarly, the power for preterm birth (less than 32 weeks) was 13% with prevalence set at 0.6%, with an odds ratio greater than 1.4.

5. RESULTS

5.1 Overview, design and description of the study sample

5.1.1 Descriptive

The FIPS-B study included 1887 BPD cases and 3774 matched controls (Table. 7). BPD was more common among females than males with females accounting for 68.4% of the cases. The mean age of diagnosis of BPD in the sample was 19.3 years with age of subjects ranging from 4 to 25 years. Almost half (50.5%) of the cases were aged 20-25 years at first diagnosis and only 5.6% were younger than 15 years at first diagnosis. Information on health service utilization showed that half of the cases (50.4%) utilized outpatient services only and 12.7 % of the total had used inpatient care only. The remaining 36.9% had used both inpatient and outpatient services.

5.1.2 Parental educational level and region of birth

Table 7 also shows the distribution of the region of birth and parental educational level in the study sample.

Table 7. Frequency of region of birth and parental educational level. (Modified from Chudal et al. 2014a, study I).

		Cases (N=1887) (%)	**Controls** (N=3774) (%)
1.	**Region of birth**		
	Southern Finland	867 (46)	1417 (37.5)
	Western Finland	487 (25.8)	1343(35.6)
	Eastern Finland	310 (16.4)	421 (11.2)
	Northern Finland	223 (11.8)	593 (15.7)
2.	**Parental educational level**		
A	**Father's educational level**		
	Master/ Licentiate / Doctoral degree	174 (9.4)	362 (9.7)
	Bachelor degree	151 (8.2)	342 (9.2)
	Upper secondary school	975 (52.8)	2038 (54.6)
	Comprehensive school	547 (29.6)	989 (26.5)
B	**Mother's educational level**		
	Master/ Licentiate / Doctoral degree	109 (5.8)	258 (6.8)
	Bachelor degree	201 (10.7)	488 (12.9)
	Upper secondary school	1078 (57.1)	2208 (58.5)
	Comprehensive school	499 (26.4)	820 (21.7)

Figure 2 shows the association between parental educational level and BPD. The findings from this study showed that offspring of mothers with the lowest educational level i.e. only comprehensive school had an increased odd of BPD (OR= 1.46, 95% CI: 1.13-1.88). Father's educational level was not associated with BPD.

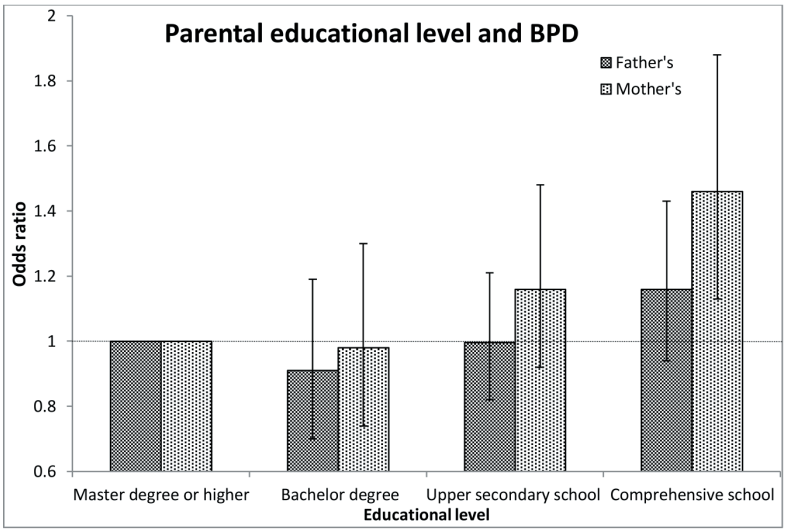

Figure 2. Parental educational level and BPD.

Figure 3 shows the association between birth in different regions in Finland and the risk of BPD. People born in Eastern Finland had the highest odds of BPD (OR= 2.02, 95% CI: 1.69-2.42), whereas being born in Western Finland was associated with the lowest odds (OR=0.50, 95% CI: 0.41-0.59) of BPD.

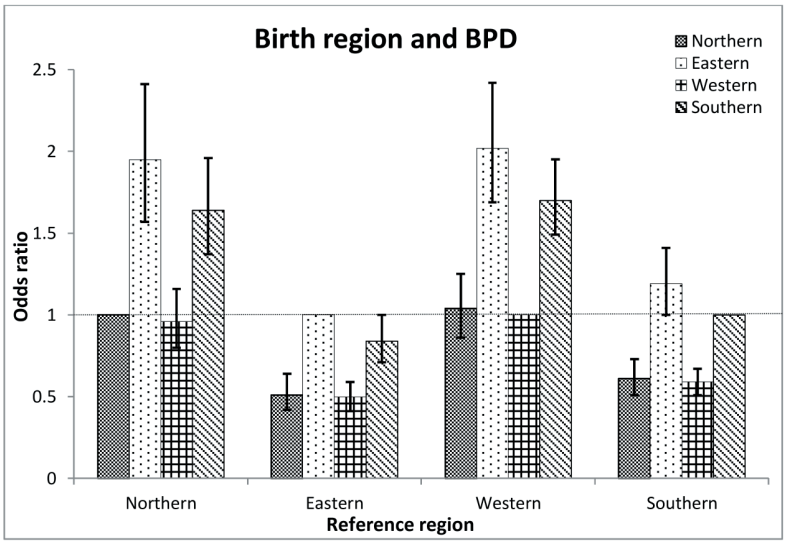

Figure 3. Birth region and BPD.

5.1.3 Cumulative Incidence

Figure 4 shows the cumulative incidence by sex and year of diagnosis in the sample. The cumulative incidence of BPD in 2008 was 7.1 and 16.5 per 10,000 population among males and females respectively.

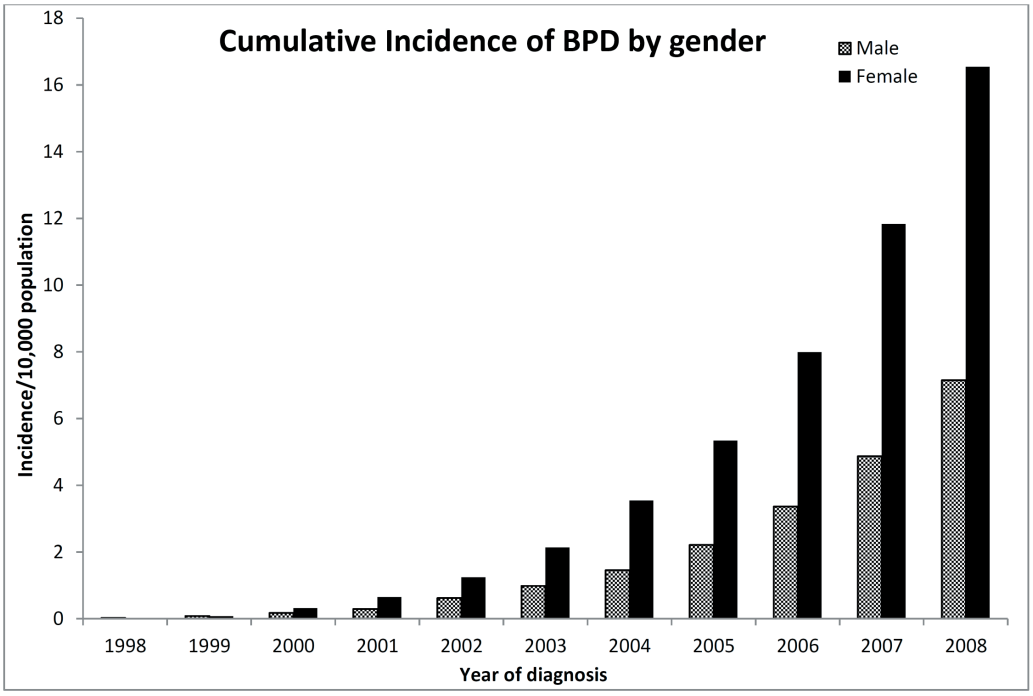

Figure 4. Cumulative Incidence of BPD/10,000 population by sex and year of diagnosis in the sample. Modified from Chudal et al. 2014a, study I.

Figure 5 shows the cumulative incidence among three age groups. The cumulative incidence in the youngest age group remained almost the same throughout the period of follow up. Among BPD cases aged 15-19 years, the cumulative incidence of BPD had a linear increase over the 11-year period. The cumulative incidence of BPD in the total sample was 11.6 per 10,000 population in 2008. The incidence of BPD in the three age groups was: 1.1 (less than15 years), 25.1 (15-19 years) and 24.2 per 10,000 population (20-25 years).

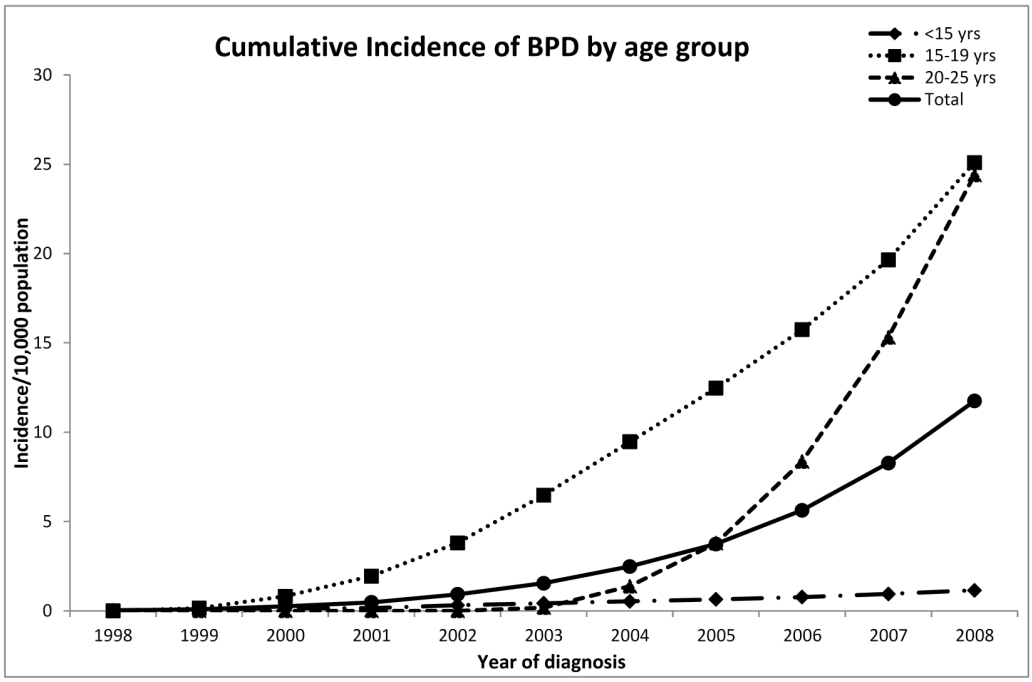

Figure 5. Cumulative Incidence of BPD/10,000 population in total sample and by age group and year of diagnosis in the sample. Modified from Chudal et al. 2014a, study I.

5.2 Parental age at birth

The father's age of cases in this study ranged from 17 to 63 years with the mean age of 30.4 years (SD 6.4). Mother's age ranged from 15 to 47 years with a mean of 27.8 years (SD 5.6). Table 8 shows the frequency of cases and controls in different paternal and maternal age categories. It also shows the distribution of the age difference between parents among case and controls. There was a strong correlation between paternal and maternal age categories with the Pearson's correlation coefficient, r=0.68 for cases and 0.69, for controls.

Table 8. Distribution of paternal and maternal age and parental age difference among cases and controls. Modified from Chudal et al. 2014b, study II.

		Cases (N= 1861) (%)	Controls (N= 3643) (%)
1.	**Paternal age**		
	<20	25 (1.4)	35 (1.0)
	20–24	298 (16.4)	434 (12.0)
	25–29	567 (31.1)	1149 (31.9)
	30–34	499 (27.4)	1134 (31.5)
	35–39	285 (15.7)	609 (16.9)
	40–44	102 (5.6)	177 (4.9)
	45–49	28 (1.5)	49 (1.4)
	≥ 50	17 (0.9)	14 (0.4)
2.	**Maternal age**		
	<20	107 (5.8)	128 (3.5)
	20–24	456 (24.5)	790 (21.7)
	25–29	616 (33.1)	1303 (35.8)
	30–34	433 (23.3)	955 (26.2)
	35–39	206 (11.1)	389 (10.7)
	≥40	43 (2.3)	78 (2.1)
3.	**Father's age > Mother's age**	N= 1391	N= 2760
	< 1 SD (No difference)	778 (55.9)	1,603 (58.1)
	1-2 SD	391 (28.1)	778 (28.2)
	> 2SD	222 (16.0)	379 (13.7)
4	**Mother's age > Father's age**	N= 437	N= 864
	< 1 SD (No difference)	275 (64.0)	551 (65.6)
	1-2 SD	85 (19.8)	195 (23.2)
	> 2SD	70 (16.3)	94 (11.2)

Figure 6 shows the association between paternal age and BPD. An increased odd of BPD was found among offspring with fathers aged 20-24 years and 50 years or older. Offspring of fathers aged greater than or equal to 50 years had a 2.7-fold (95% CI: 1.31-5.64) increased odd of BPD in comparison to those with fathers aged 30-34 years. Similar associations were observed when adjusting for confounding due to maternal age. In the final model adjusting for all available confounders, oldest fathers had a 2.8-fold (95% CI: 1.32-6.12) increased odd of having BPD in offspring. The corresponding odd was 1.35-fold (95% CI: 1.06-1.72) among fathers aged 20-24 years.

As shown in Figure 7, offspring of mothers aged younger than 24 years had an increased odd of BPD. Offspring of mothers aged younger than 20 years had 1.8-fold (95% CI: 1.40-2.44) increased odd of BPD on comparing with mothers aged 30-34 years. No association was observed between advanced maternal age and BPD. On adjusting for paternal age, there was no significant association between maternal age and BPD in offspring. In the final model when adjusting for all available confounders, there was no significant association.

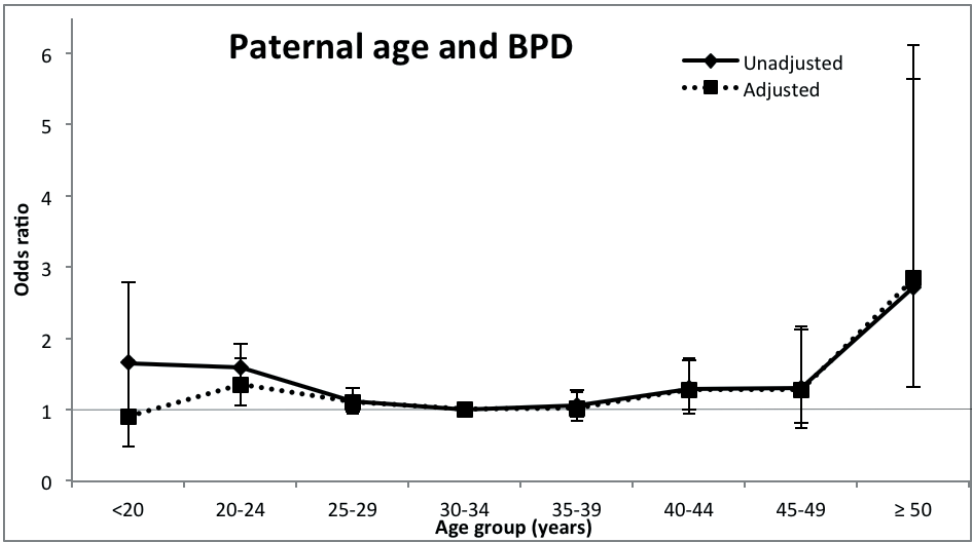

Figure 6. Odds ratio and 95% confidence interval of association between paternal age and BPD. Modified from Chudal et al. 2014b, study II.

The analysis of association between age difference between parents showed that having an age difference of eight years (2 SDs) or more with older father and a younger mother was associated with increased odd of BPD in offspring. As shown in Figure 8, offspring with fathers more than 2SDs (i.e. 8 years) older than mothers had 1.3-fold (95% CI:1.07-1.62) increased odds. However, there was no significant association when the results were adjusted for father's age and parental psychiatric history. No similar association was found with an older mother and a younger father (Figure 9).

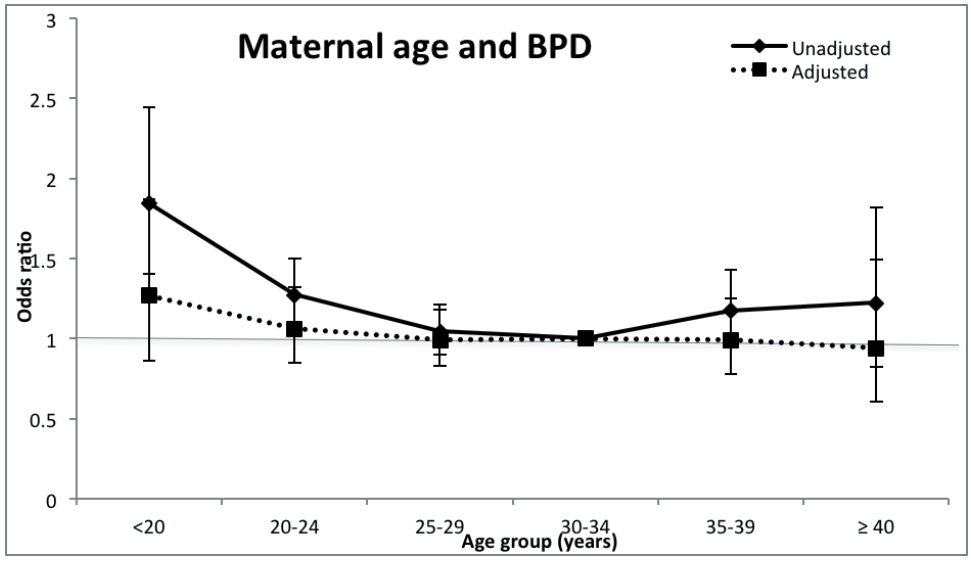

Figure 7. Odds ratio and 95% confidence interval of association between maternal age and BPD. Modified from Chudal et al. 2014b, study II.

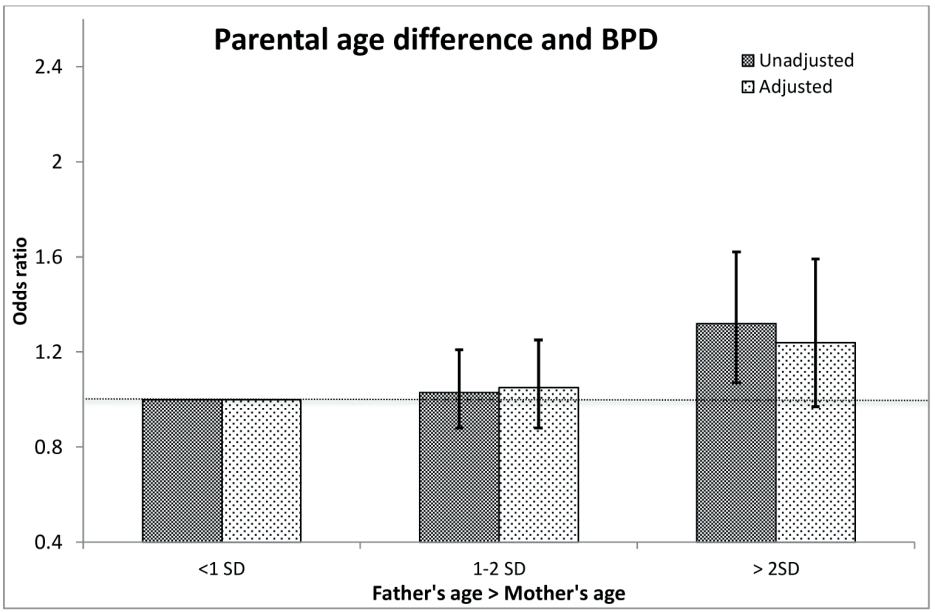

Figure 8. Age difference between parents (father's age > mother's age) and BPD.

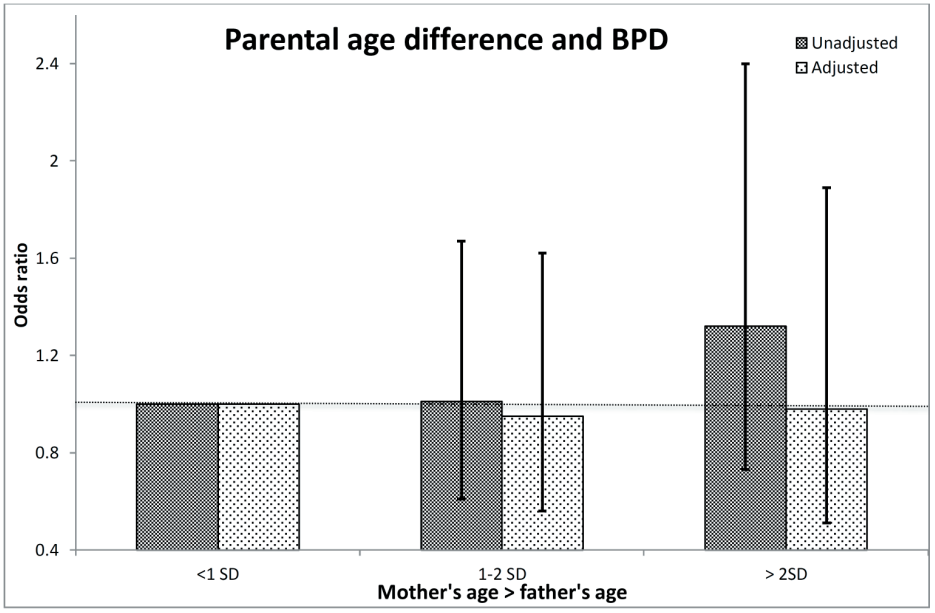

Figure 9. Age difference between parents (mother's age > father's age) and BPD.

5.3 Perinatal complications

The association between perinatal complications and BPD was examined in a subset of the total FIPS-B sample including 724 cases and 1419 controls. The BPD cases ranged

from 4 to 21 years. Table 9 shows the distribution of cases and controls in the different birth weight, gestational age and WGA categories.

Table 9. Distribution of indicators of fetal growth and development among cases and controls. Modified from Chudal et al. 2014c study III.

		Cases (N= 724) (%)	**Controls** (N= 1419) (%)
1.	**Birth weight (grams)**		
	<1500	6 (0.8)	5 (0.4)
	1500-2499	29 (4.1)	38 (2.7)
	2500-3999	553 (77.7)	1070 (77.4)
	4000-4499	101 (14.2)	221 (16.0)
	≥ 4500	23 (3.2)	49 (3.5)
2.	**Gestational age (weeks)**		
	<32	8 (1.1)	8 (0.6)
	32-37	74 (10.4)	117 (8.5)
	38-41	590 (83.1)	1208 (87.5)
	≥ 42	38 (5.3)	47 (3.4)
3.	**Weight for gestational age (WGA)**		
	SGA	16 (2.2)	20 (1.4)
	AGA	674 (94.9)	1305 (94.6)
	LGA	20 (2.8)	54 (3.9)

Birth weight, gestational age and WGA were examined as indicators of fetal growth and development for their association with BPD later in life. Children born with a gestational age of 42 weeks or more were associated with a 1.7-fold (95% CI: 1.08-2.66) increased odd of BPD as compared to those born with gestational age of 38-41 weeks. On adjusting for potential covariates, the odds decreased to 1.5-fold (95% CI: 0.93-2.48) and were statistically insignificant. No association with BPD was observed between birth weight, gestational age and WGA in the adjusted analyses.

A range of risk factors was examined as obstetric risk factors for their association with subsequent risk of BPD (Table. 10).

Table 10. Frequency of obstetric complications among cases and controls. Modified from Chudal et al. 2014c, study III.

		Cases (N= 724) (%)	**Controls** (N= 1419) (%)
1.	**Maternal risk factors**		
A	**High blood pressure**		
	No	707 (98.3)	1389 (99.0)
	Yes	12 (1.7)	14 (1.0)
B	**Uterine bleeding**		
	No	716 (99.6)	1401 (99.9)
	Yes	3 (0.4)	2 (0.1)
2.	**Birth factors**		
A	**Birth presentation**		
	Cephalic	706 (98.2)	1382 (98.5)
	Breech	7 (1.0)	18 (1.3)
	Other	6 (0.8)	3 (0.2)
B	**Birth type**		
	Vaginal cephalic	568 (79.0)	1132 (80.7)
	Suction+ forceps	26 (3.6)	66 (4.7)
	Planned C- section	25 (3.5)	24 (1.7)
	Emerg + other C-section	97 (13.5)	174 (12.4)
	Unknown	3 (0.4)	7 (0.5)
C	**Induced labour**		
	No	692 (96.2)	1,340 (95.5)
	Yes	27 (3.8)	63 (4.5)
3.	**1 minute Apgar score**		
	9-10	553 (78.1)	1078 (78.0)
	7-8	130 (18.4)	269 (19.4)
	<7	25 (3.5)	36 (2.6)
4	**Neonatal monitoring/NICU**		
	No	701 (97.5)	1379 (98.3)
	Yes	18 (2.5)	24 (1.7)

Figure 10 shows the association between maternal high blood pressure, uterine bleeding, induced labour, neonatal treatment and BPD. Maternal high blood pressure was associated with 1.8- fold (95% CI: 0.74-4.84), uterine bleeding 2.7-fold (95% CI: 0.38-20.13), induced labour 0.6-fold (95% CI: 0.36-1.10), and neonatal treatment 1.4-fold (95% CI: 0.69-2.95) increased odd of BPD. None of the examined risk factors were significantly associated with BPD.

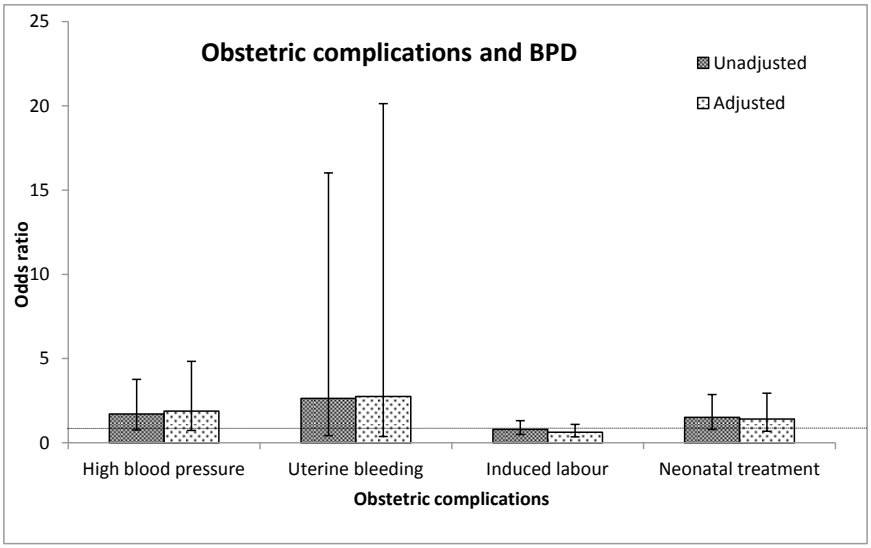

Figure 10. Obstetric complications (binary) and BPD.

In the unadjusted analyses, children born with a birth presentation other than cephalic or breech i.e. transverse, oblique, upper or lower limb, were associated with a 5.3-fold increased odd of BPD (Figure 11). The odds were not significant on adjusting for available confounders. Birth by planned cesarean section was associated with a 2-fold (95% CI: 1.15-3.65) increased odd of BPD in the unadjusted analyses (Figure 11). The odds increased to 2.5-fold (95% CI: 1.32-4.78) on adjusting for confounders.

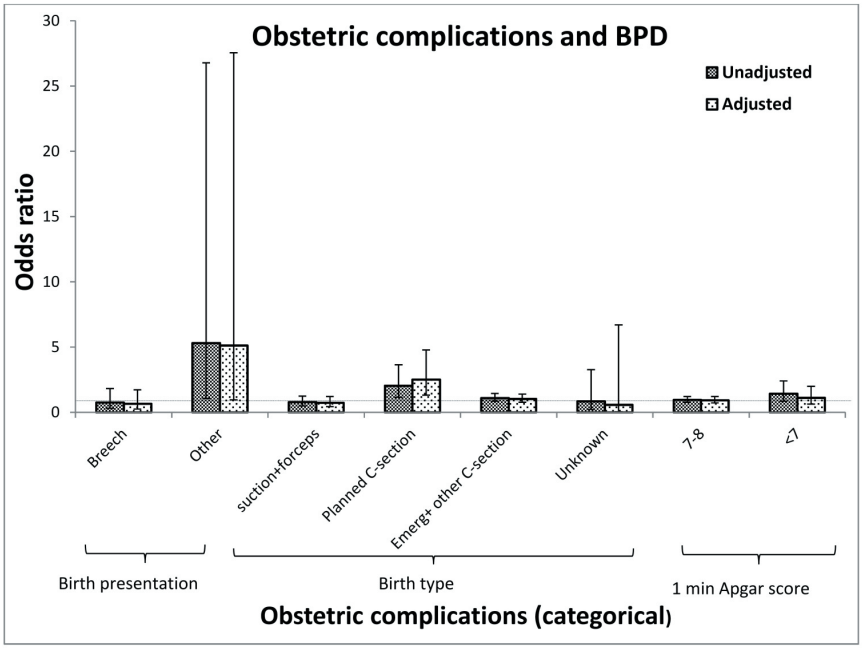

Figure 11. Obstetric complications (categorical) and BPD.

5.4 Maternal smoking during pregnancy

The association between maternal smoking during pregnancy and BPD was examined in a sample of 724 BPD cases and 1419 controls. Information on maternal smoking status was available for 698 cases and 1352 controls. Among the study subjects, 18.5% were exposed to maternal smoking during pregnancy. Initially, on analyzing the smoking exposure as a binary variable, exposure to prenatal smoking was associated with a 1.4-fold (95% CI: 1.12-1.79) increased odd of BPD. No association was seen on adjusting for potential confounders (Table 11).

Subsequently smoking exposure during pregnancy was examined as a quantitative measurement i.e. less than 10 cigarettes/day and more than 10 cigarettes /day against no smoking exposure. Smoking more than 10 cigarettes/ day was associated with a 1.5-fold (95% CI: 1.01-2.13) increased odd of BPD in the unadjusted analyses. The association was not significant on adjusting for confounders. No association was found between smoking less than 10 cigarettes/ day and BPD in offspring. Lastly smoking during pregnancy was analyzed based on the timing of smoking exposure during pregnancy i.e. only during first trimester/ continuing throughout pregnancy. Offspring of mothers who smoked throughout the pregnancy had a 2.1-fold (95% CI: 1.29-3.55) increased odd of BPD in the unadjusted analyses. The association was not significant on adjusting for confounders.

Table 11. Smoking during pregnancy and BPD. OR[1] adjusting for all available confounders. Modified from Chudal et al. 2015, study IV.

		Cases (N) (%)	**Controls** (N) (%)	OR (95% CI)	OR[1] (95% CI)
1	**Smoking during pregnancy (total sample)**	N = 698	N= 1352		
	No	546 (78.2)	1125 (83.2)	Reference	Reference
	Yes	152 (21.8)	227 (16.8)	**1.41(1.12-1.79)**	1.14 (0.88-1.49)
2	**Smoking during pregnancy (sub sample Jan 1987- Sept 1990)**	N= 531	N= 1021		
	No	422 (79.5)	848 (83.1)	Reference	Reference
	< 10 cigarettes/day	55 (10.4)	97 (9.5)	1.14 (0.79-1.64)	1.02 (0.69-1.51)
	> 10 cigarettes/day	54 (10.2)	76 (7.4)	**1.47 (1.01-2.13)**	1.29 (0.87-1.92)
3	**Smoking during pregnancy (sub sample Oct 1990- Dec 1998)**	N= 167	N= 331		
	No	124 (74.3)	277 (83.7)	Reference	Reference
	Only in first trimester	2 (1.2)	8 (2.4)	0.63 (0.13-3.06)	0.38 (0.07-2.04)
	Continued after first trimester	41 (24.6)	46 (13.9)	**2.14 (1.29-3.55)**	1.38 (0.78-2.43)

6. DISCUSSION

6.1 Main findings

This thesis examined several prenatal and perinatal risk factors in relation to BPD and the main findings are: 1) the diagnosis of BPD in Finland among population younger than 25 years is more common among females as compared to males, 2) mothers with the lowest educational level have the highest odds of having BPD in offspring, 3) being born in the Eastern and Southern region of Finland increased the odds of having BPD later in life, 4) offspring of young fathers and very old fathers had increased odds of BPD. Mother's age was not associated with BPD in offspring. Age difference between parents (i.e. older fathers and younger mothers; older mothers and younger fathers) was not associated with BPD. 5) Children born by a planned cesarean section had increased odds of BPD later in life. In addition, the study showed a lack of association between perinatal complications in general and BPD. 6) Maternal smoking during pregnancy was not associated with BPD in the offspring.

6.2 Methodological discussion

6.2.1 Study design

The studies included in the thesis are based on a nested case-control study design. The nested case- control study involves initial selection of a cohort, which forms the source population, and subsequent identification of cases from the cohort. Subsequently, controls are selected among the rest of the cohort who are at risk of the disease but have not developed the disease of interest by the time of occurrence of disease in the cases (Ernster 1994). An additional important component of the nested case-control study design involves time matching. This means the controls are matched to the cases on the age, date of entry into the cohort and the duration of stay in the cohort or a combination of these factors (Wacholder 1991). In this thesis, the initial cohort included all people born in Finland between January 1st 1983 and December 31st 1998. Among them, cases were those diagnosed with BPD, identified from the FHDR before December 31st 2008. Subsequently, among the rest of the people in the cohort, two controls were identified for each case matched on sex and date of birth (± 30 days). The controls had to be alive and living in Finland until the date of diagnosis of the matched case, thereby ensuring time matching.

A nested case-control study design is used when the disease outcome is rare, the outcome of the disease is known for all the subjects in the cohort, and it is highly expensive to collect and process the information on the covariates from all members of the cohort.

Thus, it is a cost effective way of examining the association between exposures and disease by sampling a fraction of the controls (Langholz 2005). The disadvantages of nested case-control studies include: 1) only an association between exposures and outcomes can be interpreted from this study design. It is not possible to measure and control for all the confounders that affect the association, therefore causation cannot be inferred (Sedgwick 2014). 2) There is reduced statistical power in these studies. The selection of case and controls from the predefined larger cohort means that only a fraction of the source population is included (Wacholder 2009). 3) In the nationwide register based studies, as a result of involvement of many clinicians in the care process, there may be differences in the accuracy and consistency of the recording of both exposures and outcomes of the study (Sedgwick 2014).

6.2.2 Data sources

The thesis is based on data obtained from the Finnish Nationwide Registers. The availability of registers on various aspects of health and social welfare enables studying the entire country as a source population. The availability of information on all the cases of BPD diagnosed and/or treated in the specialized health care services provides an inclusive sample of BPD cases. The strengths of the use of nationwide registers in this prenatal epidemiological study include: 1) nationwide representative population-based sampling, 2) information on potential risk factors at various time points of development with linkage of data from various sources, 3) prospectively collected data on potential risk factors thereby eliminating any recall bias and, 4) a large sample size thereby increasing the statistical power for the analyses.

The register based study design has several limitations that need to be considered. First, the FHDR used for case ascertainment in this study covered inpatient diagnosis over the complete period. A Finnish study has shown that more than half of BPD II cases and more than a quarter of BPD I cases are never hospitalized (Mantere *et al.* 2004). Therefore, a significant proportion of BPD cases do not have an inpatient diagnosis. The FHDR included the diagnoses in the outpatient services only after 1998. Although the coverage of outpatient services started from the year 1998, it only includes the specialized outpatient services at public hospitals (University hospitals or hospitals serving several municipalities) and its coverage is not consistent throughout the country. The primary care outpatient visits have been included in the FHDR only from the year 2011 (Sund 2012) and are thus not covered in this study. The coverage in the FHDR of BPD is most likely to have an overrepresentation of moderate to severe cases and does not identify many milder BPD cases in the population. In addition, patients with BPD utilizing private health sector are not included in the FHDR and are therefore missed from the sample. Due to the long term nature of BPD, it is possible that many of the cases treated only in outpatient services before 1998 would be included in the registers during

follow up visits after 1998. The healthcare system in Finland is generally financed by the municipalities with highly subsidized patient fees and the overall care coverage is good. The number of cases missing due to lack of access to healthcare services is likely to be small in comparison to other countries with high healthcare fees and majority of payments being made by the patients themselves (OECD 2014b).

Second, the diagnosis of BPD in the study is based on the hospital based clinical diagnosis and not on standardized interviews. It has been shown that the validity of hospital diagnosis is lower than the interviews (Rettew *et al.* 2009). However, previous studies have shown that the validity of the diagnosis recorded in the FHDR is good for mental disorders in general. A data quality study of the FHDR showed, that 99% of mental disorders related hospitalizations were recorded in the correct ICD chapter. The main diagnoses had been correctly reported at the 3-digit ICD code level for 98% of the diagnoses (Keskimäki & Aro 1991). A recent quality review showed the positive predictive value for common diagnoses recorded in the FHDR to range between 75% and 99% (Sund 2012). Kieseppä *et al.* (2000) examined the validity of BPD-I diagnosis in the FHDR using two twin samples. The Finnish Population Register and FHDR were used to identify BPD-I cases (DSM-III-R) among twin births born between 1940 and 1969. Fourty-two twins born 1940-1959 and fifteen twins born 1961-1969 were identified. The best estimate diagnosis of the proband was made according to DSM-IV criteria using all available medical records. Subsequently, diagnoses of the probands were confirmed using Structured Clinical Interview (SCID) I and II interviews (Spitzer *et al.* 1997). False positive diagnosis accounted for 6.8% of the cases in the first sample (1940-59). The second sample (1961-69) had no false positive diagnosis, but 13% of the cases were erroneously coded at discharge. The study showed the validity of the FHDR diagnosis of BPD-I to be 92% and 87% in the two samples.

Perälä *et al.* (2007) screened a nationally representative sample of 8,028 persons aged 30 years or older for psychotic disorder and BPD-I using Composite International Diagnostic Interview (CIDI), self-reported diagnoses, medical examination and information from nationwide registers. The subjects selected from the screen were then interviewed again using Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.* 2001). Finally, the best estimate diagnosis was made using the information from interview and/or case records. The study then estimated the concordance between different screens used including the FHDR diagnosis and the best estimate diagnosis. The FHDR was the most sensitive screen for psychotic disorders including BPD-I with a kappa (κ) value of 0.8. The FHDR had high specificity (99.7%) and negative predictive value (99.2%) but a relatively lower sensitivity of 75.3 %. It should be noted that no separate validation study for BPD diagnosis was conducted as part of this study.

Third, the information on maternal smoking during pregnancy was based on maternal self-report during maternal visits to the health care centre (study IV). It has been suggested that maternal self-reports tend to underestimate the actual smoking exposure (Ford *et al*. 1997). The social stigmatization of smoking may contribute to the underreporting of smoking behaviour during pregnancy (Ananth *et al.* 1999). A previous study has examined the validity of maternal smoking self-report in the FMBR by comparing it with the information on smoking habits during pregnancy obtained by a questionnaire. It showed a high concordance between the two data sources with a kappa (κ) value of 0.84 (Jaakkola *et al.* 2001). Serum measurement of cotinine, a major nicotine metabolite, has been used as a more reliable marker of maternal smoking. A cross sectional analysis of validity of smoking status in a random sample of 5846 persons aged 25 to 64 years in Finland, using serum cotinine measurements demonstrated a high validity of smoking self-report (Vartiainen *et al.* 2002). Similar studies with pregnant mothers in Finland have been inconsistent in results. Bardy *et al.* (1993) showed that 38% of mothers with high cotinine levels reported themselves as non-smokers. Another study demonstrated a good correlation between self-reported number of cigarette smoked and serum cotinine levels with a Spearman's correlation coefficient, $r = 0.68$, $p < 0.001$ (Tikkanen *et al.* 2010). However, the wide variation in the cut off concentration levels of cotinine in the two studies between 6 µg/l (Bardy *et al.* 1993) and 15ng/ml (Tikkanen *et al.* 2010), could explain the inconsistent findings. In addition, the FMBR does not contain information on the alcohol or substance abuse during pregnancy, information on postnatal smoking exposure and smoking status among fathers.

Fourth, the FMBR lacks adequate information regarding categorization of indications for caesarean birth i.e. either due to obstetric causes or out of fear of childbirth in the mother. Similarly, information is lacking regarding the causes of maternal hypertension and uterine bleeding during pregnancy.

6.2.3 Study sample

The source population of FIPS-B included 1,009,846 live births in Finland between January 1st 1983 and 31st December 1998. The cases were identified from the source population and two randomly selected controls were matched to cases on sex and date of birth (±30 days). Furthermore, the controls had to be alive and living in Finland on the date of diagnosis of the matched case. In studies II, III and IV only singleton born cases and controls were included. A sample size of 1887 BPD cases and 3774 matched controls and the availability of information on various covariates were the strengths of the study sample. The predefined years of birth and follow up of the study meant that the oldest cases of BPD in were younger than or equal to 21 years (study III, IV) and younger than or equal to 25 years (study I, II). Therefore, the findings in these studies may be more specific for early onset BPD cases. Despite the large sample size in the

study, the numbers in certain exposure groups were very small, therefore may lack the statistical power to detect associations.

6.3 Discussion of results

6.3.1 Characteristics of the study sample (study I)

6.3.1.1 Age at diagnosis

The mean age of diagnosis of BPD in this study was 19.3 years with no difference between males and females in the age of onset. Despite the narrow age range of the subjects, the mean age of onset of BPD is in line with previous studies (Weissman *et al.* 1996, Mantere *et al.* 2004). A cross-national epidemiological study using DSM III criteria showed the mean age of onset of BPD to range from 18 to 27 years (Weissman *et al.* 1996). A study from Finland showed the average age of onset of DSM IV BPD cases to be around 20 years (Mantere *et al.* 2004).

The mean age of diagnosis in this sample is based on the age at first diagnosis from the FHDR. Most previous studies also use age at first hospitalization and age at first treatment as a measure of age at onset. However, age at first identified major affective episode has been considered a more reliable indicator of the start of the illness (Leboyer *et al.* 2005). Globally there is a lengthy delay between onset of mental disorders and seeking treatment (Wang *et al.* 2007). A study from Finland has shown two delays in diagnosis of BPD, a delay in seeking treatment and receiving the correct diagnosis. It reported a median delay of 5.5 years from first symptoms to seeking treatment for the first time. The median delay from first episode to first diagnosis was 7.8 years in the same study (Mantere *et al.* 2004). There are two possible implications of the long diagnostic delay in this study. First, the mean age at onset of BPD is earlier than the currently reported age at diagnosis. Second, many cases of BPD in the source population have not yet been identified due to either delay in treatment seeking or a delay in diagnosis.

6.3.1.1 Sex

Females accounted for 68 % of all cases. Previous nationwide population-based studies have also shown BPD to be more common among females (Laursen *et al.* 2007, Frans *et al.* 2008). A previous study from Finland showed that females account for 72% of BPD cases with age of onset of less than 18 years (Suominen *et al.* 2007). On the other hand, international epidemiological studies have not shown gender differences in BPD (Weissman *et al.* 1996). It is possible that the early onset cases of BPD are more common among females. This difference could also be due to the differences between males and females in treatment seeking behavior. It has been shown that women tend to seek

psychiatric help, in general, more often than men (Kessler *et al.* 1981). Women have been shown to be more likely than men to have a treatment contact for BPD (Wang *et al.* 2005). Parents, social health workers and clinicians in Finland dealing with young boys with symptoms suggestive of BPD should be more careful as it could be possible that young boys with BPD remain underdiagnosed.

6.3.1.1 Cumulative Incidence

The cumulative incidence of BPD at the end of the 11 years follow up period in 2008 was 11.6 per 10,000 population. The study design, with the oldest subjects aged 25 years means that the incidence figures are not comparable to the total population incidence rates of BPD. There is wide variation in the lifetime prevalence of BPD worldwide ranging from 0.3% in Taiwan to 1.5% in New Zealand when using population-based interviews (Weissman *et al.* 1996). Another cross national study found that the prevalence of BPD varied from 0.1% in India to 4.4% in the USA. (Merikangas *et al.*2011). One previous Finnish study using inpatient data from the FHDR among population aged older than 15 years showed the incidence of BPD to be 3 per 10,000 (Räsänen *et al.* 1998). The study identified BPD cases based on inpatient diagnosis from the FHDR between 1987 and 1994. The low incidence rates in that study is likely due to the information obtained only from the inpatient diagnosis, thereby missing milder cases of BPD treated in outpatient care. Although the findings are not comparable with the current study, it highlights the limitation of FHDR in identifying the BPD cases in the population. The incidence rates were highest among age group 15-19 years followed by closely among those in age groups 20-25 years. One previous study has shown that more than half of BPD II cases and more than 25% of BPD I cases are never hospitalized (Mantere *et al*. 2004). Therefore, a large proportion of cases of BPD without an inpatient diagnosis are not registered in the FHDR. The estimates of cumulative incidence of BPD are thus, likely to be an underestimation of the actual incidence in the population.

6.3.1.1 Parental educational level

Offspring of mothers with the lowest level of educational attainment, i.e. those with only comprehensive school education had an increased odd of BPD. Previous studies have shown lower socioeconomic status (Van Oort *et al.* 2011, Fryers *et al.* 2003) and lower parental education (Paananen *et al.* 2013a, 2013b) to be associated with increased risk of offspring mental disorders. Two possible explanations for the increased odds associated with lower parental SES include: different morbidity according to parental SES or differences in the access to healthcare (Paananen *et al.* 2013b). It has been shown that children from lower socioeconomic or educational backgrounds are more likely to use specialized mental health services. But there is no evidence suggesting a limited access to health care among children of parents with a higher SES. Therefore, different

level of morbidity according to parental educational level is more likely to explain the association (Paananen *et al.* 2013b).

A previous study showed that offspring of parents (both father and mother) with the highest educational level had an increased risk of BPD (Tsuchiya *et al.* 2004). Both fathers and mothers with at least a bachelor degree had an increased risk of BPD in offspring. The association was stronger for mother's educational level as compared to fathers. It should be noted that Tsuchiya *et al.* (2004) adjusted for the potential confounding due to covariates including parental age and psychiatric history. However, the findings of our study are based only on univariate analyses and likely to be confounded by other risk factors, e.g. parental age and psychiatric history.

6.3.1.1 Birth region

Children born in Eastern and Southern Finland had increased odds of BPD whereas the odds decreased among those born in Northern and Western Finland. These findings on the regional differences of risk of BPD are in line with previous studies. They have shown the prevalence of psychiatric disorders (Perälä *et al.* 2008, Lehtinen *et al.* 1990) and psychiatric inpatient rates (Korkeila *et al.* 1998) to be the greatest in Southern and Eastern Finland. The Mini Finland Health Survey assessed over 8000 individuals aged more than 30 years using health interviews and health examination. The psychiatric cases identified based on General Health Questionnaire (GHQ) were most frequent in Eastern Finland and least frequent in Southwest and Southern Finland. Clinically assessed mental disorders were most common in Southern Finland and least common in Southwest Finland (Lehtinen *et al.* 1990). Korkeila *et al.* (1998) used the FHDR to obtain information on all psychiatric hospital discharges in 1993. The use of psychiatric hospital beds was highest in Southern and Eastern Finland. Eastern Finland also had the highest rate of new inpatients with psychosis and affective disorders. The Health 2000 Survey (Aromaa & Koskinen 2004) included a population of more than 8000 people aged over 30 years and consisted of interview, health examination and questionnaires. Among them, cases with psychotic disorders were screened using Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.* 2001). Being born in Eastern Finland was associated with increased odds of any psychosis (Perälä *et al.* 2008).

This association between regional variation in birthplace and BPD suggests the role of area related risk factors i.e. genetic, environmental or both as shown with schizophrenia (Haukka *et al.* 2001). A relatively stable regional population isolate was formed in Eastern Finland out of the founder families in the 17th century. This high clustering of genes predisposing to development of psychotic disorders could explain the increased odds in Eastern Finland (Varilo *et al.* 2000, Hovatta *et al.* 1997). The Eastern and

Northern Finland used to be one of the least developed regions with higher rates of infant mortality, low birth weight and short duration of pregnancy in the 1950s (Palmgren 1964). These regions are still characterized by high migration rates, high unemployment, and lower level of education (Haukka *et al.* 2001). Thus, many environmental risk factors for psychosis influencing the pre- and perinatal stage, continuing through childhood and adolescence (Cannon *et al.* 2002) have been prevalent in these areas (Perälä *et al.* 2008). However, these factors are likely to play a lesser role in this study due to the following reasons: a weak association in general between perinatal complications and BPD; and decreased odds of BPD among those born in Northern Finland. The increased odd in Southern Finland could be due to the migration of population after the Second World War from the East and North to the urban areas in the south (Myrskylä 1978, Korkiasaari *et al.* 1994, Saarela & Finnäs 2008). The migration of the high genetic risk population to larger cities in the South could explain the higher odds in Southern Finland. The risk of BPD associated with urbanicity at birth (Mortensen *et al.* 2003) and upbringing (Pedersen & Mortensen 2006) could further contribute to the odds. These findings are based on unadjusted analyses and lack adjustment for potential confounder such as parental psychiatric history.

6.3.2 Parental age (study II)

This study examined the association between paternal and maternal age and their age difference and BPD. The association between paternal age and BPD showed a U-shaped curve of odds ratio in the unadjusted analyses. The odds for developing BPD were increased among offspring of both young and old fathers. On adjusting for confounders, the odds were attenuated for young fathers and increased for the offspring of the oldest fathers. The finding of increased odds of BPD with advanced paternal age is in line with most of the previous studies (McGrath *et al.* 2014, D'Onofrio *et al.* 2014, Menezes *et al.* 2010, Frans *et al.* 2008, Laursen *et al.* 2007). An increased odd for BPD was seen among offspring of mothers younger than 24 years in the unadjusted analysis. The findings were not significant on adjusting for paternal age, as well as on adjusting for available confounders. The findings of previous studies on maternal age have been inconsistent with two studies showing an increased risk among offspring of mothers aged 30-39 years (Frans *et al.* 2008) and younger than 20 years (McGrath *et al.* 2014) whereas, two studies did not find any association (Menezes *et al.* 2010, Brown *et al.* 2013).

McGrath *et al.* (2014) showed a 1.2-fold increased risk of BPD among offspring of fathers older than 45 years, while another study found more than 5-fold increased among fathers older than 45 years (D'Onofrio *et al.* 2014). An increased risk of BPD was observed with fathers aged 35 years or older with a 1.4-fold increased risk among those aged 40-44 years (Menezes *et al.* 2010). Frans *et al.* (2008) demonstrated an increased risk of BPD among offspring of fathers aged 30-34 years, 40-44 years and older than 55

years. The risk among the oldest fathers increased to 2.6-fold when examining cases of BPD with an early onset (less than 20 years). Lastly, Laursen *et al.* (2007) showed an increased risk among fathers aged 31-40 years and 50-55 with offspring of fathers aged 50-55 years having a 1.7-fold increased risk of BPD.

Few hypotheses have been put forward as possible explanations for the association with advanced paternal age. First, it has been hypothesized that increasing *de novo* mutations in the male germ line with advancing paternal age may lead to the development of schizophrenia (Malaspina 2001). It is likely that similar mechanisms play a role in BPD as well. The differences in the pattern of germline cell division between males and females can explain the association demonstrated only with advancing paternal and not maternal age. There are 24 cell divisions during the development of an ovum, 22 before meiosis and 2 during meiosis. The total number of chromosomal replication is 23 as only one replication occurs during the two meiotic divisions. Furthermore, all these cell divisions are completed before birth. There are no changes in the number of replications in the ovum with advancing age (Pearson *et al.* 2005). The sperm production continues throughout the reproductive life and therefore, the number of cell divisions and replications also increase with advancing age. There are 30 cell divisions in the male germline until puberty. Subsequently there is one mitotic division in the sperm every 16 days, resulting in 23 cell divisions every year at the males in the reproductive age. Thus, the sperm of a man aged 20 years has 7-fold more chromosomal replications than an ovum and the ratio increases to 25-fold times for a man aged 40 years (Crow 2000). Providing support to this hypothesis, a recent gene sequencing study showed an increase of two mutations with a year increase in paternal age at conception and estimated that the number of paternal mutations double every 16.5 years (Kong *et al.* 2012). *De novo* mutations have been shown to be an important contributor to the development of BPD (Malhotra *et al.* 2011).

Second, epigenetic dysregulation, which leads to errors in parental imprinting, has been suggested to increase susceptibility to the development of neuropsychiatric disorders (Perrin *et al.* 2007). There is evidence suggesting the possible role of advancing age along with environmental exposures in altering the epigenetic process (Bennett-Baker *et al.* 2003, Fraga *et al.* 2005). Thus, it is possible that the age related epigenetic dysregulation contributes to the association with advancing paternal age. Third, the accumulation of exposure to various environmental toxins over the lifetime could result in genomic and/or epigenetic changes in the male germ cells (Yauk *et al.* 2008). Lastly, it has been suggested that heritable traits of the parents which limit their social interaction skills, results in having children later in life. This could explain the association with advanced paternal age (Hare & Moran 1979). In this study we examined the association between age difference between parents and BPD to evaluate the possible role of parental personality traits and did not find any association. This

was based on the assumption that the lack of social interaction skills among the older fathers, results in poor interaction among their peers, and are more likely to be involved in a relationship with much younger female partners. However, one possible reason for the lack of the association seen with parental age difference could be due to the increasing rates of divorces in Finland during the study period. There has been an increase in the rate of divorces in Finland (Statistics Finland. 2013) and it is likely that rates of older man fathering children from second marriages have also increased. These fathers are less likely to have the risk seen with older first time fathers. The reduced risk among their offspring for BPD could have resulted in the overall negative association seen with parental age difference in the study.

A weaker, but significant association was observed between young paternal age and BPD. The association between young paternal age and BPD has only been reported in one previous study, when the BPD cases were limited to those with an early onset, i.e. younger than 20 years (Frans *et al.* 2008). Young parents represent a special group with higher rates of psychiatric problems. Childhood conduct problems have been associated with teenage parenthood (Lehti *et al*. 2012a, 2012b). The personality features of young parents such as impulsive behavior, influences early reproduction, and also passes the genetic risk of neurodevelopmental disorders to the offspring (Lundstöm *et al.* 2010). The increased risk for *de novo* genetic disorders among offspring of young fathers has been suggested to result from the immaturity of spermatids or impaired DNA repair or lower antioxidant enzymes activities (Malaspina 2001). Young parents are usually less educated and economically disadvantaged (Kiernan 1997) and young mothers have poor prenatal care (D'Ascoli *et al.* 1997). Inadequate prenatal care leads to adverse perinatal events (low birth weight and prematurity), which in turn have been associated with BPD (Nosarti *et al.* 2012). Lastly, young fathers are more likely to have risky health behaviors such as drug abuse, which have been linked with germline *de novo* mutations (Robbins *et al.* 2005).

It should be noted that the possible explanations for findings seen with young parental age are still unclear and do not entirely explain the findings. The association with BPD was observed only in those aged 20-24 years and not in the youngest age group of fathers i.e. younger than 20 years. The small number of cases and controls in the youngest age group and thereby a low statistical power could explain the lack of association. The association between maternal age and BPD was confounded by paternal age. It is possible that the attenuated association is due to the high correlation between paternal and maternal age, resulting in reduced precision in the estimation of the maternal age effect. Many of the biological risk factors associated with young parental age seem to affect the pregnant mother and the developing fetus, although no significant association was observed between young mothers and BPD in the adjusted analyses. The trend of increasing age at parenthood due to socioeconomic changes in the society coupled with

its association with mental disorders, including BPD, further increases the relevance of this field of research in the future.

The comparison of these findings on parental age with other psychiatric disorders makes an interesting observation. Overall, advanced paternal age is strongly associated with schizophrenia, whereas a weak/no association is observed with both young paternal and maternal age (Malaspina *et al.* 2001). Both advanced paternal and maternal age were strongly associated with ASD (Kolevzon *et al*. 2007, Hultman *et al.* 2011). BPD is thus closely related with schizophrenia in terms of association with parental age. This is relevant considering the shared genetic relationship between schizophrenia and BPD (Lichtenstein *et al.* 2009).

6.3.3 Perinatal complications (study III)

Birth by planned cesarean section was associated with an increased odd of BPD. Post-term birth i.e. gestational age of 42 weeks or more was associated with BPD in the unadjusted analyses but it did not reach statistical significance on adjusting for available confounders.

The finding of an association between birth by cesarean section and BPD has not been reported previously. There are few obstetric indications for a birth by planned cesarean section e.g. twin delivery and history of previous cesarean section (Penn & Ghaem-maghami 2001). Cesarean section can also be requested by the mother without any obvious obstetric indications (Wiklund *et al.* 2012). A study has shown that women with cesarean section as their preferred mode of delivery have a stronger fear of childbirth (Rouhe *et al.* 2009). The mothers requesting cesarean section for delivery have been shown to be anxious, depressed, have low self-esteem, lack social support and have personality traits like neuroticism (Saisto *et al.* 2001, Storksen *et al.* 2012). It could be possible that these maternal characteristics are transmitted to the offspring. The influences of these maternal characteristics on the family environment during growth and development may contribute towards development of BPD. It should be noted that this is the first study showing an association between planned cesarean delivery and BPD and the underlying mechanisms are still unclear. In addition, the FMBR lacks adequate information regarding categorization of indications for caesarean birth, i.e. either due to obstetric causes or out of fear of childbirth in the mother.

The number of births by cesarean section is increasing globally (Kuehn 2010). Cesarean section by maternal request arising out of fear of childbirth has been suggested to be one of the main reasons for the rise in the trend (Wiklund *et al.* 2007, Rouhe *et al.* 2009). Studies have shown that special focus and treatment, based on psycho-education and counselling provided to women with a fear of childbirth by specialized staff at the

maternity clinics have helped up to 86% women to accept giving birth vaginally although their initial request of birth was by cesarean section (Saisto *et al.* 2006, Nerum *et al.* 2006). It is important that these preventive measures be promoted whenever possible to reduce the rates of delivery by cesarean section in cases without a proper indication. All the other obstetric risk factors examined (maternal high blood pressure, uterine bleeding during pregnancy, birth presentation, induced labor, 1 minute Apgar scores and neonatal treatment) were not associated with BPD.

A Swedish cohort study reported preterm birth (gestational age of less than 37 weeks) to be associated with BPD, whereas no association was found with post term birth (Nosarti *et al*. 2012). Children born with gestational age of 32-36 weeks had a 2.7-fold increased risk and the risk increased to 7.4-fold among those with a gestational age of less than 32 weeks. A Danish cohort study (Laursen *et al*. 2007) demonstrated a 5-fold increased risk of BPD among preterm children born small for gestational age (i.e. lower 10 % birth weight among less than 37 weeks gestational age). However, another Danish study examining the association between birth weight, gestational age, WGA and BPD did not find any association (Øgendahl *et al.* 2006). Interestingly, studies examining the indicators of growth and development with BPD and schizophrenia grouped together have shown significant findings for both preterm birth and low birth weight (D'Onofrio *et al.* 2013, Class *et al*. 2014).

Despite the lack of association between most of the risk factors, it should be noted that many less common perinatal outcomes e.g. very low birth weight (less than 1500 grams) and preterm birth (less than 32 weeks) had very few cases. Thus, it is possible that despite having an overall large sample size, the statistical power in the study was weak to detect some associations. The oldest cases of BPD in this study were only 21 years and therefore, it is possible that the lack of findings is specific to the early onset group of BPD. Recent advances in the prenatal and neonatal care have significantly improved the survival rates of premature and low birth weight infants (Moster *et al*. 2008, Costello *et al.* 2005). Thus, with an increasing number of children surviving despite exposure to perinatal risk factors in the coming years, the examination of these putative risk factors in relation to BPD will be a more fruitful area of endeavor.

These findings provide support to the existing literature stating a weak overall association between pre- and perinatal complications and BPD. However, several indicators of fetal growth and obstetric complications have repeatedly been shown to be associated with schizophrenia (Rapoport *et al.* 2012). Based on these differences, it has been suggested that schizophrenia and BPD share some common genetic susceptibility. The subsequent exposure to obstetric complications and/or poor fetal growth and development favors the development of schizophrenia, whereas the lack of the latter factors is more likely to add the risk of BPD (Demjaha *et al.* 2012, Murray *et al.* 2004).

6.3.4 Maternal smoking during pregnancy (study IV)

Maternal smoking during pregnancy was associated with BPD in the unadjusted analyses. However, the association was not statistically significant on adjusting for available confounding factors. The categorization of information on maternal smoking in the FMBR was changed during the study period resulting in the use of two different classifications for smoking status. The classification of smoking into less than 10 or more than 10 cigarettes per day (January 1987-September 1990) enabled examining the dose-response effect of prenatal smoking exposure. Smoking more than 10 cigarettes per day was more strongly associated with BPD than smoking less than 10 per day. The subsequent classification of maternal smoking (October 1990-December 1998) was based on the timing of exposure during the pregnancy, i.e. only in the first trimester or throughout the pregnancy. The continuation of smoking during pregnancy after the first trimester shows a more chronic exposure to the deleterious effects to the developing fetus. In addition, mothers who continue smoking throughout pregnancy are more likely to have more psychosocial problems than those who quit smoking early in pregnancy. Along similar lines, the association was stronger for maternal smoking throughout the pregnancy than smoking only during the first trimester. Nevertheless, the availability of a single classification throughout the study period would have further increased the statistical power to detect an association.

This was the second study to examine the association specifically for BPD. Talati *et al.* (2013) used a cohort of children born during 1959-1966 in California, USA to study the risk for BPD associated with exposure to smoking during pregnancy. They demonstrated more than 2-fold increased risk for BPD among offspring of mothers who smoked. Ekblad *et al.* (2010) used a cohort of children born in Finland between 1987 and 1999 (n= 186, 246) identified from the FMBR to examine the risk of psychiatric morbidity associated with prenatal smoking exposure. Mothers smoking less than 10 cigarettes / day had a 1.6-fold increased risk of mood disorders (F30-F39) in their offspring. The risk increased to 1.9-fold among mothers smoking more than 10 cigarettes /day.

Prenatal exposure to maternal smoking is associated with a range of adversities. The adverse influence occurs already in the intrauterine life resulting in adverse perinatal events including low birth and even still birth (Hofhuis *et al.* 2003). Among the exposed, symptoms of inattention have been observed in infancy and disruptive behavior disorders have been observed later in childhood (Hunter *et al.* 2011, Nigg *et al.* 2007). Increased substance use and antisocial behaviors are more common among them in adolescence (Ekblad *et al.* 2010, Weissman *et al.* 1999). Another aspect that needs to be considered while interpreting the findings of risks with maternal smoking is the possible role of confounding by maternal characteristics. It has been consistently shown that mothers who continue to smoke during pregnancy have different characteristics than mothers

who never smoked and those who quit after knowledge of pregnancy (Button *et al.* 2007). Mothers who continue to smoke during pregnancy are usually younger, have shorter years of education, of a lower socioeconomic status and have less access to antenatal care and more often have a history of psychiatric illness (Matthews 2001, Ventura *et al.* 2000).

Some aspects of the study need to be considered while interpreting these findings. It could be possible that mild symptoms of BPD, which have not been diagnosed, exist among smoking mothers and this genetic risk can be transmitted to the offspring. The study sample included only BPD cases younger than 21 years and the findings are more likely to be relevant to early onset BPD. The information of maternal smoking was based on self-report, which has been shown to be prone to bias (Ford *et al.* 1997). However, inadequate relevant samples, despite moderate sample size, could have contributed to the lack of statistical power to detect significant associations.

Overall, the findings on prenatal smoking and BPD are still unclear with two existing studies showing opposing findings. One future possibility is examining biomarkers such as cotinine, a nicotine metabolite, as a documented measure of smoking exposure during pregnancy, making use of maternal biological samples.

7. CONCLUSIONS

This thesis, aimed at improving the understanding of the role of prenatal and prenatal risk factors associated with BPD demonstrated several relevant findings. First, the demographic characteristics of the BPD cases were identified. A majority of the young BPD cases in Finland identified from the FHDR were females. This could either be a true finding among young cases, or due to an increased likelihood of being diagnosed among females. The cumulative incidence of BPD was lower than the global estimates probably due to inclusion of a narrow age range and limited ascertainment of cases from the population in the FHDR. People born in Eastern Finland had the highest odds of BPD compared to other regions suggesting the role of area related risk factors i.e. genetic, environmental or a combination of them. Offspring of least educated mothers had increased odds of BPD, which is likely due to differences in psychiatric morbidity according to parental socioeconomic status.

Second, the odds ratio of the association between paternal age and BPD showed a U-shaped distribution whereas no association was observed with mother's age. *De-novo* mutations with increasing paternal age, epigenetic changes and personality traits among fathers having a child at a later age are the possible mechanisms for the association. Age difference between parents was examined, to test the role of parental personality traits as a possible explanation for the increasing odd of BPD with advanced paternal age. To our knowledge, this was the first study to test the association between parental age difference and BPD and no association was observed. These findings on parental age are highly relevant considering the trend of increasing age at parenthood in most developed countries.

Third, birth by planned cesarean section was associated with BPD. The association is most likely due to some genetic traits among mothers favoring a planned cesarean section birth, which is transmitted to the offspring and not by the actual risk of cesarean birth per se. A range of factors of growth and development and obstetric risk factors were examined for their association with BPD. The lack of association with a range of other obstetric risk factors provides support to previously suggested hypothesis that BPD and schizophrenia stem from a common genetic background. The subsequent exposure to adverse obstetric events favors development of schizophrenia whereas the lack of it results in BPD.

Lastly, there was an association between prenatal maternal smoking and BPD in the univariate analyses, which did not remain significant on adjusting for confounders. Mothers who continue to smoke despite the knowledge of their pregnancy are different than non-smokers or those who quit during pregnancy. It is possible that they have

features of BPD, although the symptoms may not meet the diagnostic threshold and are likely to transmit the genetic risk. However, with only one previous study showing a positive association and a lack of association in this study, subsequent studies would be needed to have a clearer picture. The findings of this study add to the existing literature on the prenatal risk factors for BPD and support the possibility of different prenatal risk profiles in different psychiatric disorders.

7.1 Implications for future research

The majority of studies on prenatal and perinatal risk factors and psychiatric disorders have focused on schizophrenia and ASD. The existing knowledge is limited if these results can be extended to other psychiatric disorders. It is important to further investigate whether several psychiatric disorders have a common prenatal risk profile or several specific profiles. Recently, there has been a shift in psychiatric research, from a symptoms and syndrome based approach to more dimensional neurobiological and behavioral outcomes approach. Future research on prenatal epidemiology of psychiatric disorders should aim along similar lines at examining prenatal and perinatal risk profile and dimensions of neurobiology and observable behavior. The study of some risk factors e.g. maternal smoking exposure can be improved by making use of biomarkers of smoking exposure such as cotinine, a nicotine metabolite. Finally, considering the intricate etiology of psychiatric disorders, future studies should aim at focusing on the interaction of prenatal risk factors with genetic and epigenetic factors and the role of gene environment interactions.

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Roshan Chudal

ERRATUM

1. Manuscript I

a. Page 6, paragraph 2, "Statistical analysis, Cumulative incidence of BPD"
The paragraph should have ended at line 18 after (reference 44). No odds ratios were calculated for cumulative incidence as stated erroneously there.

b. Page 6, paragraph 7, Results
The highest number of BPD subjects (cases and controls) were born in southern Finland (40.4%). It should have been total number of subjects (cases and controls).

2. Manuscript II

a. Page 625, paragraph 4, Materials and methods, study design
Ethical approval for the study was provided by the Ethics committee of the hospital district of Southwest Finland and Institutional Review Board of the New York State Psychiatric Institute and NOT by Institutional Ethical Review Board at Turku University Hospital, Turku University as stated currently.

b. Page 626. Paragraph 6, parental age
The age difference between parents was analyzed only as a categorical variable (NOT as a continuous as stated in the manuscript).

3. Manuscript III

a. Page 2, paragraph 4, Methods
Ethical approval for the study was provided by the Ethics committee of the hospital district of Southwest Finland and Institutional Review Board of the New York State Psychiatric Institute and NOT by Institutional Ethical Review Board at Turku University Hospital, Turku University as stated currently.

b. Page 4. Paragraph 1,2, Results
The values of strength of association, ORs and 95% confidence interval in the text are erroneous. The values in the results Table 1 and 2 are correct.

c. Page 5. Table 2, Results
The OR for adjusted model for maternal high blood pressure has two values: 1.89 and 1.84. The OR of 1.89 is the correct value.

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