

Sari Lukkari

ASSOCIATION BETWEEN
PERINATAL AND
CHILDHOOD RISK FACTORS
WITH MENTAL DISORDERS
IN ADOLESCENCE

UNIVERSITY OF OULU GRADUATE SCHOOL;
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SARI LUKKARI

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Abstract

Many adult diseases have their origins in early life events. Much remains unrevealed in this field, especially concerning associations between perinatal complications and early manifestation of psychiatric disorders. The aim of this work is to assess the association of early adverse life events and later psychiatric disorders in adolescence.

This study sample consists of 508 adolescent inpatients aged 13-17 years in need of acute psychiatric hospitalization in an adolescent psychiatric ward of Unit 70 in Oulu University Hospital between years 2001-2006. A diagnostic semi-structured interview, the Schedule for Affective Disorder and Schizophrenia for School-Age Children Present and Lifetime (K-SADS-PL), was carried out to assess psychiatric disorders according to DSM-IV criteria. The information on obstetric complications was obtained simultaneously. Birth measures data were derived from the Medical Birth Register. Diagnoses of epilepsy and other convulsions and child psychiatric diagnoses based on hospital treatment on the child psychiatric ward were obtained from the Finnish Care Register of Health Care.

Delivery complications, especially section, increased the likelihood for conduct disorders among adolescent boys. The adolescent boys were shorter and had higher ponderal index at birth compared to healthy controls. In boys high ponderal index was associated with internalizing disorders in adolescence. Febrile and other convulsions and epilepsy in childhood associated with suicide attempts among adolescent boys. The likelihood for personality disorder was 14-fold among adolescents with febrile or other convulsions in childhood and three-fold among those with childhood epilepsy.

Previous child psychiatric care associated with self-mutilative behaviour and child welfare placement in adolescence. Among boys, a history of child psychiatric care was related to anxiety and conduct disorders in adolescence, and among girls, mother's unemployment, psychiatric problems and family malfunction quantified as a low GARF.

These findings imply that especially boys with adverse biological perinatal and early childhood adversities are at risk for mental disorders in adolescence. Girls, on the other hand, in the light of this study, seem to be vulnerable especially to adverse environmental circumstances like family malfunction and maternal problems.

Keywords: adolescent psychiatry, birth measures, child psychiatry, childhood epilepsy, febrile seizures, obstetric complications, psychiatric disorders

Lukkari, Sari, Perinataalivaiheen ja lapsuusiän riskitekijöiden yhteys mielen-terveyshäiriöihin nuoruudessa.

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Tiivistelmä

Varhaiset terveydelle epäsuotuisat tekijät altistavat sairauksille aikuisena. Etenkin perinataalivaiheen ongelmien ja alaikäisenä puhjenneiden psykiatristen häiriöiden välisestä yhteydestä tiedetään kuitenkin vähän. Tämän työn tarkoitus on tutkia varhaisten epäsuotuisien tapahtumien yhteyttä nuoruusiässä puhjenneisiin psykiatrisiin häiriöihin.

Tutkimusaineisto koostuu 508:sta, iältään 13–17-vuotiaista nuoresta, jotka on otettu Oulun yliopistollisen sairaalan nuorisopsykiatrian akuuttiosastolle (osasto 70) hoitoon vuosina 2001–2006. Osastojakson aikana nuoret tutkittiin käyttäen puolistrukturoitua K-SADS-PL-haastattelua, jolla arvioitiin psykiatrisia häiriöitä DSM-IV-tautiluokituksen mukaisesti. Samalla saatiin tieto nuoren syntymään liittyneistä obstetrisista komplikaatioista. Syntymämitat selvitettiin syntyneiden lasten rekisteristä ja tiedot lapsuusiän kuume- ja muista kouristuksista, lapsuusiän epilepsioista ja lastenpsykiatrisista hoitajaksoista poimittiin sairaaloiden hoitoilmoitusrekisteristä.

Synnytykskomplikaatiot, etenkin sektio, lisäsivät poikien käytöshäiriöiden riskiä nuoruudessa. Tutkimusaineiston pojille oli tyypillisempää lyhyt syntymäpituus ja iso ponderaalimitta verrattuna samanikäisiin terveisiin kontrolleihin. Pojilla suuri ponderaalimitta lisäsi erityisesti internalisoivien häiriöiden riskiä nuoruudessa. Lapsuusiän kuume- ja muut kouristukset sekä epilepsia assosioituivat poikien itsemurhayrityksiin nuoruudessa. Kuume- ja muut kouristukset suurensivat persoonallisuushäiriön riskiä nuoruudessa 14-kertaisesti, epilepsia kolminkertaisesti. Aiempi lastenpsykiatrinen osastohoito oli yhteydessä nuorten itsensä vahingoittamiseen esimerkiksi viiltelemällä sekä sijoitukseen kodin ulkopuolelle. Lisäksi aiempi lastenpsykiatrinen hoito liittyi pojilla ahdistus- ja käytöshäiriöihin nuoruudessa ja tytöillä äidin työttömyyteen, äidin psykiatrisiin ongelmiin ja perheen huonoon toimintakykyyn GARF- mittarin perusteella arvioituna.

Nämä tulokset viittaavat siihen, että etenkin pojat sairastuvat herkemmin psykiatriseen häiriöön nuoruudessa varhaisvaiheiden epäsuotuisien tekijöiden seurauksena. Toisaalta tämän tutkimuksen valossa tyttöjen psykiatriseen sairastumiseen jo lapsuudessa vaikuttivat erityisesti epäsuotuisat ympäristötekijät, jotka liittyvät etenkin perheeseen ja äitiin.

Asiasanat: kuumekouristukset, lapsuusiän epilepsia, lastenpsykiatria, mielen-terveyshäiriöt, nuorisopsykiatria, obstetriset komplikaatiot, syntymämitat

Perheelleni

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26.11.2020

Sari Lukkari

Abbreviations

ADHD	Attention-Deficit hyperactivity disorder
APSY	only adolescent psychiatric care (no previous child psychiatric care)
CPSY	Adolescent having child psychiatry care before admission to psychiatric inpatient adolescent care
CGAS	Children's Global Assessment Scale
DSM-III-TR	Diagnostic and Statistical Manual of Mental Disorders, 3. edition, revision
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4. edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5. edition
EuropASI	European Addiction Severity Index
FCRHC	The Finnish Care Register for Healthcare?
GARF	The Global Assessment of Relational Functioning
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10. revision
ILAE	International League Against Epilepsy
K-SADS-PL	Kiddie Schedule for Affective Disorder and Schizophrenia for School-Age Children, Present and Lifetime
N	Number of participants
ODD	Oppositional Defiant Disorder
OCD	Obsessive-Compulsive Disorder
PI	Ponderal index
WHO	World Health Organization

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals I-IV:

- I Lukkari S, Hakko H, Herva A, Pouta A, Riala K, Räsänen P. (2012). Exposure to Obstetric Complications in Relation to Subsequent Psychiatric Disorders of Adolescent Inpatients: Specific Focus on Gender Differences. *Psychopathology*, 45(5), 317-326
- II Lukkari S, Hakko H, Taanila A, Räsänen P, Riala K, Herva A. (2014). Body size at birth and psychiatric disorders among adolescents: A clinical study of 310 under-age inpatient adolescents in Northern Finland. *Comprehensive Psychiatry*, 55(3), 414-421.
- III Lukkari S, Hakko H, Kantojärvi L, Riala K, Riipinen P, Ansakorpi H. Childhood seizures and adolescent psychiatric disorders: a population-based study of adolescent psychiatric inpatients in Finland. *Manuscript*.
- IV Lukkari SH, Hakko HH, Partanen MA, Riala KR, Riipinen PK. (2019). Characteristics of Adolescent Psychiatric Inpatients in Relation to Their History of Preceding Child Psychiatric Inpatient Care. *Journal of Nervous and Mental Diseases*, 207(7), 569-574.

Contents

Abstract

Tiivistelmä

Acknowledgements 9

Abbreviations 11

List of original publications 13

Contents 15

1 Introduction 19

2 Reference of the literature 21

2.1 Obstetric complications and psychiatric disorders in adolescence..... 22

2.1.1 Pregnancy complications..... 22

2.1.2 Delivery complications..... 23

2.1.3 Perinatal complications 25

2.2 Birth measures and later psychiatric disorders in adolescence 26

2.2.1 Birth weight..... 26

2.2.2 Birth length..... 27

2.2.3 Ponderal index 27

2.3 Family risk factors of psychiatric disorders in adolescence 28

2.3.1 Parental age at the time of birth..... 28

2.3.2 Parity 31

2.3.3 Birth order 31

2.3.4 Family structure..... 32

2.3.5 Sociodemographic factors 35

2.3.6 Parental psychopathology..... 36

2.4 Seizures in childhood 38

2.4.1 Febrile and other convulsions in childhood..... 39

2.4.2 Epilepsy in childhood..... 39

2.4.3 Association of febrile and other convulsions and epilepsy
in childhood with later psychiatric disorders..... 40

2.5 Psychiatric disorders in childhood and adolescence 43

2.5.1 Epidemiology 43

2.5.2 Continuity of psychiatric disorders from childhood to
adolescence..... 44

2.5.3 Childhood psychiatric disorders and suicidality in
adolescence..... 47

3	Aims of the study	53
4	Material and methods	55
4.1	Study population	55
4.1.1	Patient sample (I-IV)	55
4.1.2	Control population (II).....	55
4.2	Research instruments	56
4.2.1	K-SADS-PL (I-IV)	56
4.2.2	EuropASI (I-IV)	56
4.2.3	Register-based data (II-IV).....	56
4.2.4	Admission form (IV)	57
4.3	Variables.....	57
4.3.1	Obstetric complications (I).....	57
4.3.2	Birth measures (II).....	59
4.3.3	Epilepsy and febrile or other convulsions (III).....	59
4.3.4	Psychiatric disorders (I-IV)	59
4.3.5	Suicidality (III).....	62
4.3.6	Reason for admission, Children’s Global Assessment Scale (CGAS), The Global Assessment of Relational Functioning (GARF) (IV).....	62
4.3.7	Mortality (IV)	63
4.3.8	Background characteristics (I-IV)	63
4.4	Statistical methods	65
4.5	Ethical considerations and personal contribution.....	65
5	Results	67
5.1	Obstetric complications.....	67
5.1.1	Mother’s self-reported obstetric complications (I)	67
5.1.2	Register-based obstetric data (II).....	68
5.2	Childhood epilepsy and other febrile or other convulsions (III)	70
5.3	Previous child psychiatric inpatient care (IV).....	72
5.4	Socio-demographic and familiar risk factors (I, II, III, IV).....	73
6	Discussion	79
6.1	Overview of the results	79
6.2	Discussion of the results.....	80
6.2.1	The association of obstetric complications and psychiatric disorders	80
6.2.2	The association of birth measures and psychiatric disorders	81

6.2.3	Epilepsy, febrile and other convulsions in childhood and psychiatric disorders.....	82
6.2.4	The association of child psychiatric care and psychiatric disorders in adolescence.....	84
6.2.5	The association of child psychiatric care and suicidality in adolescence.....	86
6.2.6	The association of family characteristics and psychiatric disorders	86
6.3	Strengths and limitations.....	87
6.3.1	Strengths of the study	87
6.3.2	Limitations of the study.....	89
7	Conclusions	91
7.1	Main conclusions	91
7.2	Implications for further research.....	91
7.3	Clinical implications	92
	References	93
	List of original publication	117

1 Introduction

Theories on the origins of psychiatric disorders have existed since early in the human history. Long before the Common Era, mental disorders were thought to be caused by demons and evil spirits. This conception persisted until the times of Ancient Greece (around 400BC) when it was replaced by the theory of humoralism, which represented a more physiologic base of the origins of mental diseases. Humoralism explained diseases as an unbalance of body fluids (Harris, 2012). Many terms used in psychiatry have their origins in that era, like mania, melancholy and hysteria. The term psychiatry was coined by a German doctor, Christian Reil (1759-1813). His conception of psychiatric disorders was holistic and he emphasized the continuity of mind and body (Kaplan, 2012). In many ways he was considered to be ahead of his time, because in general, in the 1800s psychiatric disorders were considered to be due to both external and internal causes. The former were the focus of treatment practices; the latter were thought to be beyond actions of treatment.

Since that, fortunately, the theory of foetal origins of adult disease' has brought to light the importance of the prenatal circumstances in the development of diseases in adulthood, like cardiovascular disease, diabetes and neurological disorders through dysfunction of the nervous system (Barker, Eriksson, Forsén & Osmond, 2002; Barker, 2004; Lawlor, Ben-Shomo & Leon, 2004; Harding JE, 2001). Lilienfield and colleagues (1955) stated that perinatal complications produce 'a continuum of reproductive casualty' extending from foetal deaths through a descending gradient of brain damage manifested in neuropsychiatric disorders. Especially those pregnancy, delivery and infancy complications that included anoxia or non-mechanical foetal injury like toxemia and hypertension, were considered as most crucial for the development of offspring neuropsychiatric disorders. Since early findings of Lilienfield and colleagues in 1950s, a growing body of studies have reinforced the knowledge of the association between perinatal adverse circumstances and later psychiatric disorders of the offspring in childhood, adolescence and adulthood. The continuity of childhood mental disturbances and later psychiatric disorders is well recognized (Rutter, 1984). Already in 1800s a German doctor and writer, Heinrich Hoffman (1809-1894), also known as the writer of the famous children's book, *Shock-headed Pete*, built the first special ward for children with mental disorders in the city mental asylum in Frankfurt am Main (Asylum for Lunatics and Epileptics) in 1864.

2 Reference of the literature

Adolescence is defined as a developmental phase between childhood and adulthood. The definition of timing varies widely. According to the Finnish Medical Society Duodecim adolescence dates between ages 13 to 22 years (Aalto-Setälä & Marttunen, 2007). Adolescence is a time of rapid biological, social and psychological changes, and is also the period when identity formation occurs (Christie & Viner, 2005). It is also characterized by mood swings, which are normal at a certain level. Still, only three decades ago, for example, depression was seen mainly as an adult disorder (Maughan, Collishaw & Stringars, 2013).

Many adult diseases have their origins in prenatal circumstances (Barker et al., 2002; Barker, 2004). Literature on obstetric complications in psychiatry has traditionally focused on the association with schizophrenia, and the association is well established (Geddes & Lawrie, 1995; Cannon, Jones & Murray, 2002). A neurodevelopmental hypothesis of schizophrenia proposes that schizophrenia is associated with subtle brain lesions caused by a combination of genetic and environmental factors that interact with the normal maturational processes of the brain. A growing body of literature on the association between obstetric complications and schizophrenia support this theory.

Since these early findings of the association between obstetric complications and schizophrenia, obstetric complications have been found to associate with many other psychiatric disorders in adulthood, for example neuropsychiatric disorders like Attention Deficit and Hyperactivity Disorder (ADHD) (Halmøy, Klungsøyr, Skærven & Haavik, 2012), affective disorders (Gale & Martyn, 2004; Guth, Jones & Murray, 1993), conduct disorders (Raine, 2002), anxiety disorders (Freed et al., 2014), and eating disorders (Tenconi, Santonastaso, Monaco & Favaro, 2015).

The elevated risk for psychiatric disorders of the offspring has been found to associate with both pregnancy complications, such as maternal infection during pregnancy (Mednick, Huttunen, Machón, 1994; Machón, Mednick & Huttunen, 1997), heavy bleeding during pregnancy (Hirshfeld-Becker et al., 2004), pre-eclampsia (Dalman, Allebeck, Cullberg, Grunewald & Köster, 1999) and maternal diabetes (Wegelius et al., 2011; Van Lieshout & Voruganti, 2008); delivery complications such as asphyxia at birth and caesarean section (Dalman et al., 2001; Byrne et al., 2000) and perinatal complications, such as neonatal jaundice (Dalman & Cullberg, 1999).

2.1 Obstetric complications and psychiatric disorders in adolescence

The association between obstetric complications and psychotic disorders have been found already in childhood among a study population of children with childhood psychosis (Moreno et al., 2009). In a study of children aged 8-13 years (average age 12.4 years), obstetric complications elevated the risk of schizophrenia 3.5 times when compared to controls with anxiety disorder, matched for age and sex (Matsumoto, Takei, Saito, Kachi & Mori, 1999). A greater association was seen between obstetric complications and schizophrenia among boys than among girls. This finding was repeated in another study in which obstetric complications associated with early age at onset of schizophrenia, especially among boys compared to among girls (Dalman, Allebeck, Cullberg, Grunewald & Köster, 1999). Of obstetric complications, especially pre-eclampsia increased the risk of schizophrenia. Some studies have found that obstetric complications associate with earlier onset of schizophrenia (Verdoux et al., 1997; Byrne et al., 2000; Kelly et al., 2004). In the meta-analysis of Verdoux and colleagues (1997), the earlier the age of schizophrenia onset, the more likely was the history of obstetric complications. Associations with other psychiatric disorders have also been found among adults, as well as among children and adolescents, such as ADHD (Millberger, Biederman, Faraone, Guite & Tsuang, 1997), conduct disorders (Allen, Lewinsohn & Seeley, 1998; Pharoah, Stevenson, Cooke & Stevenson, 1994; Martini, Knappe, Beesdo-Baum, Liebb & Wittchen, 2010), anxiety disorders (Geller et al., 2008; Hirshfeld-Becker et al., 2004; Johnsco et al., 2016) and depressive disorders (Patton, Coffrey, Carlin, Olsson & Morley, 2004). A study by Geller and colleagues (2008) found that obstetric complications associate with earlier occurrence of obsessive-compulsive disorder (OCD).

The following three chapters focus on studies reporting the results on the association of pregnancy, delivery and perinatal complications with psychiatric disorders in late childhood and adolescence.

2.1.1 Pregnancy complications

Pregnancy complications refers to obstetric complications during pregnancy. They include, for example, heavy bleeding during pregnancy, hyperemesis, infection during pregnancy, pre-eclampsia or gestational diabetes. Several studies have been

published focusing on whether pregnancy complications relate to psychiatric disorders.

In a study among adolescent inpatients, bleeding during pregnancy occurred among 12.7% of adolescents with first episode psychosis, whereas only 2.1% of healthy controls had a history of bleeding during pregnancy (Moreno et al., 2009).

Pregnancy complications have also been linked to ADHD among 6-17-year-old boys (Millberger, Biederman, Faraone, Guite & Tsuang, 1997). In this study of 140 study subjects with ADHD, the study subjects had significantly more pregnancy complications than their 120 normal controls. Especially chronic exposures, such as maternal bleeding and substance use (smoking and illicit drug use) accounted for this association. Another study also has found an association between maternal smoking and ADHD among adolescents (Langley et al., 2007).

Maternal smoking during pregnancy is a well-recognized risk factor for later psychiatric disorders in adolescence. It has been linked to internalizing and especially externalizing conduct and oppositional disorders in childhood and adolescence (Hill, Lowers, Locke-Wellman & Shen, 2000).

Allen and colleagues (1998) studied the association between maternal health during pregnancy, obstetric complications and infant health during the first year of life on the psychopathology of 579 adolescent offspring. They found many associations between prenatal- and perinatal risk factors and later psychopathology of offspring in adolescence. Poor maternal prenatal physical health associated with disruptive behaviour disorder among adolescent offspring, but only among girls.

A study examined children with high risk for anxiety disorders according to parental anxiety disorder in comparison to groups with parental major depression and with parents without any mood or anxiety disorders (Hirshfeld-Becker et al., 2004). A dose-response relationship indicated that children with multiple (two or more) anxiety disorders had been 1.6 times more often exposed to gestational problems, namely heavy bleeding during pregnancy requiring bed-rest, hypertension and illness requiring medical attention. Most study subjects were aged 12 years or younger. The association was independent of parental diagnosis.

2.1.2 Delivery complications

Delivery complications occur during labour or delivery and include, for example breech delivery, protracted labour, forceps delivery, caesarean section and preterm birth.

The association between delivery complications and schizophrenia is well-established. A meta-analysis of 12 case-control studies found that of delivery complications, premature rupture of membranes elevated the risk of schizophrenia three-fold, and both gestational age shorter than 37 weeks and use of resuscitation or incubator elevated the risk of schizophrenia two-fold (Geddes et al., 1999). In this meta-analysis, no sex difference was found between obstetric complications and onset of schizophrenia. In a Finnish 1955 Helsinki birth cohort study examining a wide range of obstetric complications in association with schizophrenia in offspring found that only birth asphyxia significantly increased the risk of early-onset schizophrenia but not later-onset schizophrenia (Rosso et al., 2000). There was also a dose-dependent relationship indicating that the risk of early-onset schizophrenia was elevated two-fold per hypoxia-associated complication, but three or more such obstetric complications increased the risk 10-fold when compared with no complication. In a meta-analysis by Verdoux and colleagues (1997), those with early-onset schizophrenia (under the age of 22) had a 10-time higher likelihood of having experienced a complicated caesarean section and a 2.5-time higher likelihood of being born as breech or other abnormal presentation at birth than those with later-onset of schizophrenia. This meta-analysis found no associated gender difference.

The following studies represent the association between delivery complications and psychiatric disorders among adolescents other than psychotic disorders. A study by Allen and colleagues (1998) found that, in addition to pregnancy complications, also delivery complications, namely acute anoxia/hypoxia, elevated the risk of disruptive behaviour disorder three-fold in adolescence. A study of a population with genetic risk factors for psychopathology found that obstetric complications, and especially delivery complications, increased risk of offspring anxiety disorders, even after controlling for parental lifetime anxiety disorders (Freed et al., 2014). The age among study subjects varied between 4-33 years with a mean age of 14 years. A study of children and adolescents with OCD found that children with OCD had experienced more birth difficulties including forceps delivery, nuchal cord or prolonged labour, than normal controls (Geller et al., 2008). Moreover, adverse perinatal experiences associated with earlier age at onset of OCD, increased OCD severity, and increased risk for comorbidity with ADHD, chronic tic disorder, anxiety disorder and major depressive disorder.

Gestational age is a measure of the duration of a pregnancy, with a normal pregnancy ranging from 38 to 42 weeks. If a baby is born before 37 weeks, the birth

is referred to as a preterm birth. Preterm birth and short gestational age have been associated with psychiatric disorders, especially ADHD, in childhood and adolescence (Lindström, Lindblad & Hjern, 2011). A meta-analysis by Geddes and colleagues (1999) found an association between gestational age shorter than 37 weeks and schizophrenia. Extremely preterm birth (born at 26 weeks of gestation) has been found to associate with a three-fold elevated risk of psychiatric disorders at the age of 11 years (Johnson et al., 2010). The risk was significantly elevated for ADHD, emotional disorders and anxiety disorders. A Swedish follow-up study from childhood to young adulthood found an increase of psychiatric hospital admissions among those born preterm (Lindström, Lindblad & Hjern, 2009). Moreover, the shorter the gestational age was, the higher was the risk for psychiatric hospital admissions, with a 1.7-fold risk among very preterm children (gestational age 22-32 weeks), 1.2-fold risk among the moderately preterm group (gestational age 33-36 weeks) and 1.1-fold risk among the early term group (gestational age 37-38 weeks). Moreover, the effect of preterm birth was greater in those families with low socioeconomic status.

2.1.3 Perinatal complications

Perinatal complications occur during the neonatal period, extending from birth to 28 completed days of life (WHO, 2020). These complications include, for example, neonatal jaundice and neonatal infection.

Among children, infants with neonatal hyperbilirubinemia were 2.5 times more likely to receive in-patient psychiatric care in childhood than controls (Dalman & Cullberg, 1999). Reasons for psychiatric care admission were classified in groups of substance abuse, personality disorders and neurosis, psychosis and other. Concerning individual psychiatric diagnoses, there was no difference between those with neonatal jaundice and controls.

Among 7-13-year-old children with anxiety disorders, higher rates of neonatal complications were seen (44% vs. 14%) and these children had more admissions to neonatal intensive care (15% vs. 8%) when compared to controls (Johnco et al., 2016).

2.2 Birth measures and later psychiatric disorders in adolescence

2.2.1 Birth weight

A vast body of literature has accumulated on the association between deviant birth weight and later psychiatric disorders. The most used categorization of birth measures in previous literature is to divide birth measures into categories, usually four or three, with the lowest birth weight category being less than 2500 grams. Especially lower birth weights have been found to be a risk factor for many psychiatric disorders in adulthood, e.g. schizophrenia (Rifkin, Lewis, Jones, Toone & Murray, 1994; Jones et al., 1998; Wahlbeck, Forsén, Osmond, Barker & Eriksson, 2001; Kunugi et al., 2001), depression (Thompson, Syddall, Robin, Osmond & Barker, 2001; Nomura et al., 2007), anxiety disorders (Vasiliadis, Buka, Martin & Gilman, 2010; Nomura et al., 2007) and conduct disorders (Latimer et al., 2012). Most of these studies were conducted in cohort populations, and only a study by Rifkin and colleagues (1994) was conducted among a patient sample. Low birth weight has also been found to associate with earlier onset of psychosis in a patient sample (Rubio-Abadal et al., 2015).

In terms of children and adolescents, low birth weight has been found to be more common among children with behavioural disorders at the age of 10 years than among their matched controls (Pharoah, Stevenson, Cooke & Stevenson, 1994). In a Norwegian study sample, especially ADHD was more common among children with low birth weight when compared to children with normal birth weight (Elgen, Sommerfelt & Markestad, 2002).

Among adolescents, studies have also found associations between low birth weight and ADHD in adolescence (Nigg & Breslau, 2007; Idrenavik et al., 2010). Among 14-year-old Norwegian adolescents, very low birth weight (< 1500g) associated with psychiatric disorders, especially anxiety disorders (Idrenavik et al., 2004, 2010).

In adolescence, low birth weight has been found to associate with depression (Costello, Worthman, Erkanli & Angold, 2007). However, the association was found only among girls. Low birth weight has also been found to increase the risk of suicide attempt in young adulthood (Niederkrotenthaler et al., 2012).

Low birth weight may also relate to a continuum of previous obstetric complications in pregnancy. For example, malnutrition and smoking during pregnancy, pre-eclampsia and diseased placenta can lead to low birth weight (Lubchenco, 1975). Maternal influenza infection has also been found to associate

with lower birthweight in offspring (Wright, Takei, Rifkin & Murray, 1995). Low birth weight may furthermore lead to other perinatal complications, such as respiratory failure, jaundice and perinatal infection.

An association between high birth weight and later psychiatric disorders has also been found, but mainly among adults (Keskinen et al., 2013; Goodman, Heshmati, Malki & Koupil, 2014; Herva et al., 2008; Wegelius et al., 2011). The latter study found the association between high birth weight and depression among girls in adulthood. Some studies have found a J-shaped association, indicating that both low and high birth weight are risk factors for psychiatric disorders, like schizophrenia in adulthood (Moilanen et al., 2010).

Among children and adolescents, macrosomia (birth weight > 4500g) has been found to associate with externalizing behaviours among preadolescents aged 10-12 years (Buschgens et al., 2009). A J-shaped association with higher risk at the lower and higher ends of the birth weight scale has been found to associate with behaviour problems in early adolescence at the age of 14 years (Alati et al., 2009). A J-shaped association has also been found between birth weight and post-traumatic stress disorder until the age of 21 years (Betts, Williams, Najman & Alati, 2011).

2.2.2 Birth length

Concerning birth length, especially short birth length has been found to associate with psychiatric disorders, like schizophrenia among adults (Wahlbeck, Forsén, Osmond, Barker & Eriksson, 2001; Gunnell et al., 2005). A J-shaped association has also been found concerning birth length, indicating that both short and long birth length increases the risk of schizophrenia in adulthood in a Finnish study (Moilanen et al., 2010).

Among children, short birth length has been associated with behavioural difficulties, hyperactivity and conduct problems at age six years (Wiles et al., 2006). In a Swedish study among young adults, short birth length elevated the risk of attempting suicide at the mean age of 17.8 years (Mittendorfer-Rutz, Rasmussen & Wasserman, 2004).

2.2.3 Ponderal index

Ponderal index is an index of weight in relation to length (weight/length³). Especially among newborn babies, it describes the nutritional status better than body mass index (weight/length²). It is also used in studies assessing the

association between deviant birth measure and later psychiatric disorders. Among adults, low ponderal index has been found to be a risk factor for schizophrenia and anxiety disorders in adulthood (Niemi, Suvisaari, Haukka & Lönnqvist, 2005; Vasiliadis, Buka, Martin & Gilman, 2010). In a Finnish study of children aged five to six years, lower ponderal index associated with behavioural symptoms of ADHD (Lahti et al., 2006). Among Swedish adolescents admitted to psychiatric hospital at the age of 15-21 years, low ponderal index associated with three-fold increased risk of schizophrenia among boys (Hultman, Sparén, Takei, Murray & Cnattingius, 1999). One study found no association between ponderal index and depression among study subjects aged 18-27 years (Vasiliadis, Gilman & Buka, 2008).

Only one study has found an association of high ponderal index and psychiatric disorders among adults: an increased risk for depression among girls with high ponderal index (Herva et al., 2008).

2.3 Family risk factors of psychiatric disorders in adolescence

2.3.1 Parental age at the time of birth

Association of parental age and psychiatric disorders of the offspring has been studied at least since the 1940s (Barry, 1945). Since, an increasing body of literature has pointed out the association of parental age and psychiatric disorders, especially schizophrenia (Brown, Bao, McKeague, Shen & Schaefer, 2002; Dalman & Allebeck, 2002; Byrne, Agerbo, Ewald, Eaton & Mortensen, 2003).

Advanced parental age

Many studies have examined the association of advanced maternal age with offspring's psychiatric disorders in adulthood (Keskinen et al., 2013, Fountoulakis et al., 2018; Byrne, Agerbo, Ewald, Eaton & Mortensen, 2003). However, one study found that the association between advanced maternal age and schizophrenia was confounded by advanced paternal age (Sipos et al., 2004). Finally, some studies have found no association between maternal age and psychiatric disorders of offspring (Brown, Bao, McKeague, Shen & Schaefer, 2002; Malaspina et al., 2001).

Among adolescents, a Swedish national cohort study found that offspring of older parents (aged over 34 years), had the highest risk for schizophrenia in youth (Ekéus, Olausson & Hjern, 2006). The highest, a two-fold risk for schizophrenia,

was seen among offspring of older mothers. Even after adjustment of confounding and mediating factors, such as parental mental disorders and paternal age, increased maternal age still remained as a risk factor for schizophrenia.

On the other hand, increasing maternal age has also been found to be a protective factor for the offspring, since advanced maternal age has been found to associate with improved health and development of the offspring (Sutcliffe, Barnes, Belsky, Gardiner & Melhuish, 2012). In this longitudinal cohort study, offspring of those with advanced maternal age had fewer social and emotional difficulties up to five years of age. The explanation of the contradictory findings that advanced maternal age may increase the risk of offspring's psychiatric disorders, may have a biological basis as well as genetic and environmental factors. Additionally, obstetric, which tend to increase with increasing maternal age, may also explain the finding (Herstad et al., 2016).

A growing body of literature has shown that advanced age of the father at childbearing associates with many mental disorders of the offspring in adulthood, including autism, psychosis, bipolar disorders, eating disorders, schizophrenia and even personality disorders (Frans et al., 2008; Miller et al., 2011; D'Onofrio et al., 2014; McGrath et al., 2014; Javaras et al., 2017). A meta-analysis of 12 studies found that the risk for schizophrenia was elevated 1.7-fold among offspring of fathers aged 50 or older compared to offspring of fathers aged 25-29 years (Miller et al., 2011). Among adolescents, the association between advanced paternal age and psychopathology has also been found. In a Swedish cohort study among male adolescents, for each 10-year increase in paternal age, there was 1.3-fold higher risk of schizophrenia of the offspring (Zammit et al., 2003). A cohort study among youths (aged 8-21 years) found that advanced parental age associated with pervasive developmental/autism spectrum disorders (Merikangas et al., 2017). Finally, advanced paternal, but also advanced maternal age has been found to associate with bipolar affective disorder among adolescents aged 16-22 years (Menezes et al., 2010).

Young parental age

Research findings have also found a clear association between young maternal age and offspring psychiatric disorders in adulthood (McGarth et al., 2014; Mok, Antonsen, Pedersen & Webb, 2017). A large Danish nationwide cohort study revealed that offspring of the youngest mothers were at highest risk for any mental disorders (McGarth et al., 2014). Offspring of mothers aged 12-19 years had 51%

increased risk of mental disorders when compared to those of mothers aged 25 to 29 years. Offspring of young mothers especially suffered from schizophrenia, behavioural and emotional disorders, neurotic and stress-related disorders and personality disorders.

Young maternal age has also been found to predispose children and adolescents to adverse mental outcomes. Among children aged five years, emotional and behavioural problems were more prominent among children of young mothers who were less than 20 years old at childbirth when compared to mothers over 20 years old (Moffit, 2002). Among the 1987 Finnish Birth Cohort population who were followed until the age of 21 years, young maternal age was one of the main risk factors for mental disorders among offspring (Paananen, Ristikari, Merikukka & Gissler, 2013). The most common diagnoses among cohort members were affective disorders (7%), neurotic, stress-related and somatoform disorders (5.6%) and behavioural and emotional disorders (3%). Also, another follow-up study from birth to 18 years of age, found that anxiety disorders were more prominent among adolescent offspring of mothers aged less than 20 years when compared to offspring of mothers aged over 30 years (Fergusson & Woodward, 1999). Offspring of young mothers also had 1.5 to 8.9-fold higher risk of educational underachievement, juvenile crime and substance misuse and overall lower socio-economic status. Young age at motherhood has also been associated with substance abuse, suicidality and psychiatric admissions of the offspring in youth or young adulthood (Niederkrotenthaler, Rasmussen & Mittendorfer-Rutz, 2012; Mittendorffer-Rutz, Rasmussen & Wasserman, 2004; Riordan, Morris, Hattie & Stark, 2012; Ekéus, Olausson & Hjern, 2006).

Young age of the father has been found to be a risk factor for psychiatric disorders like bipolar disorder and ADHD (Chudal et al., 2014; Chudal et al., 2015) and also for suicide attempts among the offspring (Niederkrotenthaler et al., 2012). One study found that both young maternal and paternal age associated with behaviour disorders and psychosis in adolescence (Merikangas et al., 2017).

Finally, an U-shaped association has also been found between parental age and offspring's mental disorders, mainly in adulthood. In a study by McGrath and colleagues (2014), both young maternal age and advanced paternal age were risk factors for many offspring psychiatric disorders. A U-shaped association has also been found between father's age and bipolar disorder among adult offspring, with the risk of bipolar disorder being higher at both ends of the age spectrum of the father (Chudal et al., 2014).

2.3.2 Parity

Grand multiparity, frequently defined as having six or more deliveries (Sipilä, von Wendt & Hartikainen-Sorri, 1990), is considered as a risk regarding pregnancy, delivery and perinatal complications (Yves, Katrien & Sanne, 2006). Maternal grand multiparity is also reported to be an independent risk factor for future offspring psychiatric disorders. In a Helsinki Birth Cohort Study with participants born between 1934-1944 and who were followed up to adulthood, offspring of grand multiparous mothers were shown to have a 1.8-fold risk of mood disorders and over three-fold risk of suicide attempts (Lahti et al., 2014). Especially female offspring were at an increased risk for any severe mental disorders, and for specific disorders such as non-psychotic substance-use disorders, schizophrenia, schizotypal and delusional disorders, mood disorders and suicide attempts in adulthood. Also, two Finnish studies among the Northern Finland 1966 Birth cohort population have found that grand multiparity associates with hospital-treated mental disorders like psychoses and schizophrenia, alcoholism and depressive disorders of the offspring by the age of 28 years (Kempainen et al., 2000; Keskinen et al., 2013). Among men from the same cohort, grand multiparity associated with suicides of the offspring (Alaräisänen et al., 2012).

Few studies have examined maternal multiparity in association with offspring psychiatric disorders developed already in adolescence. In Finland, among the Study-70 population of 508 adolescents aged 12-17 years at admission to a psychiatric inpatient ward, 17% of them came from large families (6 or more children), whereas among the general Finnish population the corresponding percentage is 3% (Kylmänen et al., 2010). In this study, girls from large families had an approximately four-fold risk of psychosis other than schizophrenia. Among young adults (with mean age of 21), maternal multiparity (four or more children) has been found to associate with offspring suicide attempts (Niederkrötenhaler et al., 2012). Another study among young adults found a linear association indicating that increasing maternal parity predicted offspring suicide risk, self-harm and psychiatric admissions, the latter being higher among families with three children or more (Riordan, Morris, Hattie & Stark, 2012).

2.3.3 Birth order

Interest in the effect of birth order on offspring mental development has origins in the 1930s, when Alfred Adler studied birth order and human personality

characteristics (Adler, 1956). For decades in the field of psychiatry, the focus has been on association of birth order and schizophrenia. For example, in the Northern Finland 1966 Birth Cohort, the risk of schizophrenia was elevated among first-born boys in adulthood and last-born girls in adulthood (Kempainen et al., 2001).

Since Alder, studies have investigated the association between birth order and other psychopathologies among offspring in adulthood, but few studies have assessed the effect of birth order on adolescent psychiatric disorders.

A sibling-comparison study was conducted among 4-13-year-old study subjects (D'Onofrio et al., 2009). In this study, the risk of offspring disruptive behaviours was most elevated among second- and third-born children. Putter (2003) also found that depressive symptoms were most common among middle-born compared to among those with a different birth order. A Swedish register study found that later-born siblings were at increased risk for hospitalization attributable to alcohol and narcotics use under the age of 20 years than first-borns (Barclay, Myrskylä, Tynelius, Berglind & Rasmussen, 2016). The higher the sibling position, the higher was the risk for hospitalization: second-born children had a 47% higher risk and third-born children had a 65% higher risk compared to first-born children. High birth order has also been associated with deliberate self-harm-associated hospitalization of adolescents, who were aged 10-19 years at the time of admission to hospital (Hu, Li, Glauert & Taylor, 2017).

Among first-born adolescents an elevated risk has been found for neuropsychiatric disorders; ADHD and Asperger's syndrome (Marin et al., 2014; Schmidt et al., 2013).

These contradictory findings that both earlier and later sibling positions associate with psychiatric disorders of the offspring may be explained by the complex associations between sibling position and biological and social factors and also psychological stressors linked to these positions.

2.3.4 Family structure

Non-intact family structure

Non-intact family structure is defined as family structure other than a two-parent family. Non-intact family structure is a risk factor for many psychiatric disorders like personality disorders, alcoholism and depression of the offspring later in adulthood (Mäkikyrö et al., 1998). It has also been found that psychiatric adolescent

inpatients in Finland lived more often in other family types than in nuclear families (Rytilä-Manninen, Haravuori, Fröjd, Marttunen & Lindberg, 2018).

Among children, a Finnish follow-up study found that children living in other than a two-parent biological family at age eight years were associated with externalizing problems later in adolescence (Sourander & Helstelä, 2005). Change in family structure independently associated with both externalizing and internalizing problems, but only among boys.

Single-parent family

Single-parent family has been associated with different psychiatric adversities among offspring. In a community-based study, single motherhood increased the risk of adolescent offspring externalizing disorders (Daryanai, Hamilton, Abramson & Alloy, 2016). In the Northern Finland 1966 study, a single-parent family has been found to associate with suicide risk among male offspring at 16-28 years of age (Sauvola et al., 2001) and later in adulthood (Alaräisänen et al., 2012). Among the 1987 Finnish Birth Cohort, parent divorce and death of a parent associated with mental disorders among the offspring until the age of 21 years (Paananen, Ristikari, Merikukka & Gissler, 2013). Especially single motherhood associated with mental disorders in childhood and adolescence. Finally, a single-parent family has been found to associate with criminality among adolescent psychiatric inpatients in Northern Finland (Ikäheimo, Laukkanen, Hakko & Räsänen, 2013).

Out-of-home placements

In Western countries, out-of-home placements by child welfare authorities are usually a consequence of parental neglect endangering a child's development and health (Thorburn, 2010). In Finland, the emphasis of the child welfare system is on preventive child welfare to support families with difficulties coping as well as to provide help and support at a sufficiently early stage, when the emergence of problems and their worsening can still be prevented (Ministry of Social Affairs and Health, 2020). Further, the role of the child welfare system is also to arrange children to live with next-of-kin, foster families or in child welfare institutions like residential units when living in the home environment is considered to be a risk to child development.

Children placed outside the home by child welfare authorities have been found to have an increased risk for mental disorders (Lehmann, Havik & Heiervang, 2013; Lehto-Salo, 2011; Ford, Vostanis, Meltzer & Goodman, 2007). The thesis by Lehto-Salo (2011), studying mental disorders among adolescents placed in residential units, found that almost nine out of ten of them had at least one psychiatric disorder, the most common being conduct disorders (76%), followed by depressive disorders (50%) and substance use disorders (40%). Suicidality occurred among 50% of adolescents in residential school. In another Finnish study, adolescents who have been placed in a residential school for behaviour disorders had a seven-fold suicide risk compared to controls (Manninen, Pankakoski, Gissler & Suvisaari, 2015). In a British study, children and adolescents who were looked after by local authorities were compared to deprived and non-deprived children who were living in private households (Ford, Vostanis, Meltzer & Goodman, 2007). The researchers found that children looked after by local authorities had the highest prevalence of most psychiatric disorders compared to those deprived or non-deprived children living in private households. Especially children living in residential placement had a high amount of emotional and conduct disorders. Another study also found that especially those adolescents who were placed in residential units had an increased risk of psychiatric disorders (McCann, James, Wilson & Dunn, 1996). In this study, 67% of adolescents placed outside home had psychiatric disorders, while in comparison, adolescents who had no contact with child welfare authorities had a 15% prevalence of psychiatric disorders. Further in this study, as many as 96% of adolescents in residential units had a psychiatric disorder, and 57% of adolescents in foster care had a psychiatric disorder. The most common psychiatric disorders (diagnosed according to the DSM-III-R) were conduct disorders (28%) followed by anxiety disorder (26%) and major depressive disorder (23%). Comorbidity was also common.

Foster placement has also been found to be a risk factor for psychiatric disorders later in life. A study conducted in Norway among 279 foster children aged 6-12 years revealed that 51% of them met the criteria for one or more psychiatric disorders according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (Lehmann et al., 2013). The most common disorders were emotional disorders (24%), behavioural disorders (22%) and ADHD (19%). In addition, comorbidity rates were high in all three groups, with every third having two out of three disorders and every eighth belonged to all three diagnostic groups. Another study assessed lifetime and past year prevalence of psychiatric disorders among 17-year-old adolescents in foster care (McMillen et al., 2005). They found

that 61% of them met the criteria for at least one psychiatric disorder during their lifetime, 15% meet the criteria for more than one disorder and 10% for both internalizing and externalizing disorders. Finally, in Finland among a sample of 13-17-year-old adolescent psychiatric inpatients, foster care placement was more common than among gender-matched adolescents from the community (Rytilä-Manninen, Haravuori, Fröjd, Marttunen & Lindberg, 2018).

2.3.5 Sociodemographic factors

The distribution of social class and family status indicators may vary remarkably from one country to another; therefore the focus of this chapter is on Finnish Birth Cohorts. In a Finnish nationwide follow-up study of children born in 1987 and followed to 2008 by health registers, 13% of these 21-year-old young adults had a mental disorder diagnosed in specialized psychiatric care during the follow-up (Paananen, Ristikari, Merikukka & Gissler, 2013). Both families receiving social assistance and parental short education increased the odds over four-fold for mental disorder of the offspring. Among them, parental short education and low socioeconomic status (SES) were also prominent determinants for use of specialized psychiatric care (Paananen, Ristikari, Merikukka & Gissler, 2013). Especially among female offspring, parental low SES and short education associated with use of psychiatric care before the age of 13 years. The effect of low socioeconomic status extends to adolescence, since the association has also been found among Finnish adolescent psychiatric inpatients aged 13-17 years (Rytilä-Manninen, Haravuori, Fröjd, Marttunen & Lindberg, 2018).

Among study subjects of both the Northern Finland Birth Cohort 1966 (NFBC 1966) and the Northern Finland Birth Cohort 1986 (NFBC 1986), maternal low education and low socioeconomic status have also been found to associate with intellectual disability of the offspring within 20 years of follow-up (Heikura et al., 2008). Among study subjects of the NFBC 1986, a family's low SES has been found to associate with learning difficulties in school-age children (Taanila, Yliherva, Kaakinen, Moilanen & Ebeling, 2011). Among the NFBC 1966 population, low SES associated with mortality according to registers until the end of the year 2011 (Rautio et al., 2017).

2.3.6 Parental psychopathology

Parental psychopathology is a well-known risk factor for psychiatric disorders of offspring later in life (Weissman et al., 2006; Apter, Bobin, Genet, Gratier & Devouche, 2017). A study among the NFBC 1966 and NFBC 1986 investigated early risk factors for later psychotic disorders in young adulthood (Filatova et al., 2017). Among both cohorts, parental psychosis was found to be the only risk factor for later psychiatric disorders in offspring.

Due to the fact that many cumulative confounding factors affect offspring during the period between birth and later at first onset of psychiatric disorder, direct conclusions cannot be drawn without caution regarding the association between parental psychopathology and offspring psychiatric disorders. These confounding factors may be either contributory or protective concerning development of later psychiatric disorder of offspring.

The following two chapters focus on the association between parental psychiatric disorders and offspring psychiatric disorders in adolescence.

Parental psychiatric disorders

Among subjects of the 1987 Finnish Birth Cohort, having a parent treated in specialized psychiatric care increased the risk of offspring mental disorders during the follow-up to young adulthood (Paananen, Ristikari, Merikukka & Gissler, 2013). A previously mentioned study found the same likelihood of adolescent offspring depression independent of whether only one or both parents were affected by parental major depression (Lieb, Isensee, Höfler, Pfister & Wittchen, 2002). The risk was also the same for male and female offspring. Increased risk was seen also for substance use disorder and anxiety disorders of the offspring. Those adolescents affected by parental depression had also earlier onset and worse prognosis of depressive disorders than those not affected. An ongoing follow-up study of 151 offspring of depressed parents found that the risk of offspring psychopathology is three times more likely among those with depressed parents than non-depressed parents (Weissman et al., 2006). The highest incidence of major depressive disorder in offspring was between the age of 15 to 20 years and most of them were girls.

A study among children aged six to 13 years with or without first- and second-degree relatives with a lifetime history of mood disorder were followed for six years (Williamson, Birhamer, Axelson, Ryan & Dahl, 2004). The study revealed that those children with first- and second-degree relatives with mood disorder had an

approximately three-fold increased risk for developing first-onset mood disorder when compared with those without familial mood disorder. The mean age of first-onset mood disorder was 14-17 years.

Finally, parental psychopathology often associates with lower socio-economic status, lower education, unemployment and lower income of the parents. Maternal serious mental illness has also been found to increase the risk of involvement in the child welfare system or out of home placement of a child (Park, Solomon & Mandell, 2006).

Maternal psychiatric disorders

Some studies have found an association between solely psychiatric disorders of a mother during pregnancy, and later psychiatric disorders among the offspring of these pregnancies. Allen and colleagues (1998) studied a wide range of prenatal and perinatal risk factors for psychopathology in adolescence. They found that maternal emotional problems during pregnancy associated with both depression and disruptive behaviour of the offspring in adolescence. In addition, maternal substance use during pregnancy associated with offspring substance use disorder in adolescence. Antenatal depression has been found to elevate the risk of depression of the offspring in adolescence almost five-fold when compared to offspring not exposed to maternal depression during pregnancy (Pawlby, Hay, Sharp, Waters & O'Keane, 2009). It is noteworthy that each of the depressed adolescents had been exposed to maternal depression during pregnancy.

Maternal postnatal mental disorders have also been found to associate with psychiatric disorders of offspring. One study found that 41.5% of those adolescents exposed to maternal postnatal depression had experienced depression by the age of 16 years, whereas the cumulative prevalence of depression was only 12.5% among controls not exposed to maternal postnatal depression (Murray et al., 2011). Another study found that maternal postnatal depression increased the risk of adolescent offspring depression only if there had been later episodes of maternal depression (Halligan, Murray, Martins & Cooper, 2007). In contrast, maternal postnatal depression predicted offspring anxiety disorders independently of later episodes. One study found that offspring exposed to maternal depression during the first 10 years of their lives were twice as likely to have depression in adolescence when compared to those adolescents of never-depressed mothers (Hammen & Brennan, 2003). Especially severity, rather than chronicity of the mother's depression, accounted for the association.

Some studies have found that both pre- and postnatal maternal psychiatric disorders increase the risk for offspring psychiatric disorders. One study found that maternal pre- and postnatal anxiety associated with risk of conduct disorder among adolescent offspring especially among boys (Glasheen et al., 2013). Another study found that the lifetime maternal anxiety disorders associated with anxiety disorders of the offspring in early adolescence (Martini, Knappe, Beesdo-Baum, Lieblich & Wittchen, 2010).

A study assessing both ante- and postpartum depression, found the association only between postpartum depression and offspring emotional disorders and disruptive behaviour disorders in adolescence (Hay, Pawlby, Waters & Sharp, 2008). No associations were found related to antepartum depression. Controversially, one study found that antenatal maternal depression was an independent risk factor for adolescent offspring depression, whereas the effect of postnatal depression was moderated by maternal education (Pearson et al., 2013).

Paternal psychiatric disorders

Less studied is the association between paternal psychiatric disorders and later psychiatric disorders in their children. Depression among fathers in the postnatal period (eight weeks postnatal) has been associated with psychiatric disorders among their children at the age of seven years, especially with oppositional-defiant (ODD) and conduct disorders (Ramchandani, O'Connor, Heron, Murray & Evans, 2008). A study assessing parental major depression found an independent risk for offspring depression and other mental disorders in adolescence having either a father or mother with depression (Lieblich, Isensee, Höfler, Pfister & Wittchen, 2002).

2.4 Seizures in childhood

Seizures constitute the most common neurological problem in childhood as most epilepsies have their onset in childhood (Hauser, 1995). It has been estimated that the lifetime risk for a seizure of any kind is about 8% and the lifetime risk for epilepsy is about 1% (Hauser et al., 1994). According to the latest review on seizures and epilepsy in childhood, almost all studies have found approximately the same incidence in boys and girls (Camfield & Camfield, 2015). Some studies have implicated that the incidence of epilepsy is higher among boys than girls (Hauser, 1993; Wirrell, Grossardt, Wong-Kissel & Nickels, 2011). A population-based study conducted between years 1980-2004 and assessing children aged from 1 month to

17 years of age with a newly diagnosed epilepsy, found that the incidence was higher among boys than girls almost in all age groups (Wirrell, Grossardt, Wong-Kisiel & Nickels, 2011). They also suggested that the incidence among boys showed an increasing trend.

The following three chapters focus on febrile and other convulsions in childhood, epilepsy in childhood and their psychiatric consequences.

2.4.1 Febrile and other convulsions in childhood

There are many types of convulsions in childhood. These include seizures due to acute metabolic or neurologic insults (Hauser, 1994). However, of all convulsions in childhood, febrile seizure is the most common, and according to review of Seinfeld & Pellock (2013) febrile seizures affect 2-5% of children under five years.

Febrile seizure is defined by the International League against Epilepsy (ILAE) as an epileptic seizure occurring in childhood after one month of age and during febrile illness that is not due to an infection of the central nervous system, usually with a body temperature exceeding 38°C (Seinfeld & Pellock, 2013). Febrile seizures are classified as simple when they are symmetrical, lasting less than 10 minutes, and they occur only once in a 24-hour period (Wairuru & Appleton, 2004). 70% of all FS are simple. In complex FS, convulsions are multiple, lasting more than 10-15 minutes.

The cumulative incidence of febrile seizures until the age of five years in a Finnish population-based sample was 6.9% (Sillanpää et al., 2008). There was a slight predominance in girls, whereas male overrepresentation has also been found previously (Forsgren, Sidenvall, Blomquist & Heijbel, 1990). The overall prognosis of simple febrile seizures is considered good, but complex febrile seizures carry an increased risk for later epilepsy (Verity, Greenwood & Golding, 1998). It has been estimated that 2-4% of children with febrile seizures develop subsequent epilepsy (Seinfeld & Pellock, 2013).

2.4.2 Epilepsy in childhood

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. According to the ILAE, epilepsy is a disease of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition (Fisher et al., 2014). A diagnosis of

epilepsy is based on at least two unprovoked seizures more than 24 hours apart. A seizure that is provoked by a transient factor, for example psychoactive substances, acting on an otherwise normal brain to temporarily lower the seizure threshold, is not considered as epilepsy (Fisher et al., 2014).

The incidence of epilepsy is highest in childhood and particularly in the first few years of life (Camfield & Camfield, 2015). It has been estimated that children comprise 25% of all new cases of epilepsy (Camfield, Camfield, Gordon, Wirrell & Dooley, 1996). In Finland, during 2008-2012, the incidence of new epilepsy cases among children under one year was 116.7/100 000 (Saarinen, Sillanpää, Schmidt & Virta, 2016). The incidence declined remarkably among older age groups, being 62.9/100 000 among children aged 1-5 years, and 59.1/100 000 among children 6-10 years. In all age groups, there were more boys among new cases than girls. A similar gender difference has been previously found in another Finnish nationwide study of epilepsy in all age groups and in all observation years (Sillanpää, Kälviäinen, Klaukka, Helenius & Shinnar, 2006).

2.4.3 Association of febrile and other convulsions and epilepsy in childhood with later psychiatric disorders

There is little evidence of the association between febrile/other seizures and psychiatric disorders. In adulthood, an association has been found between febrile seizures and later schizophrenia in adulthood (Vestegaard et al., 2005).

The association between epilepsy in adulthood and psychiatric disorders like psychosis, depression, anxiety and suicidality, is well established (Mainio et al., 2007; Rai et al., 2012; Gandy et al., 2013). Fewer are the studies examining the association between childhood epilepsy and psychiatric disorders in childhood and adolescence. For example, in a meta-analysis assessing prevalence of psychosis in epilepsy, only three studies out of 58 were conducted among child and adolescent subjects (Clancy, Clarke, Connor, Cannon & Cotter, 2014). However, according to this meta-analysis, the prevalence of psychosis among children and adolescents with epilepsy was 5.4%, which was in line with the prevalence among epileptic adults (5.6%).

The following chapters focus on the association between febrile, other convulsions and epilepsy in childhood and later psychiatric disorders in childhood and adolescence.

Febrile and other convulsions and psychiatric disorders in childhood and adolescence

A Swedish twin study among 492 children found a significant association between febrile seizures and autism spectrum disorder, developmental coordination disorder and intellectual disability (Gillberg, Lundström, Fernell, Nilsson & Neville, 2017). Nevertheless, the association may not be direct since both seizures and later disorders may share common aetiological factors, genetic or others. Among children with seizures, the risk of behavioural problems has been found to be higher than among controls or even among controls with other chronic conditions like cardiac problems (McDermott, Mani & Krishnaswami, 1995). Another study found that behaviour problems were more common among children already at the time of the first recognized seizure when compared to their siblings (Austin et al., 2011). In one study, children aged six to nine years with a history of febrile seizures had more severe symptoms in overall behavioural (22%), internal (fear, withdrawal and depression) and especially external deficits (delinquent, antisocial and aggressive behaviour), than the healthy controls (Köflen et al., 1998). Nevertheless, some studies have found no difference in behavioural outcome among school-aged children with or without a history of febrile seizures (Verity, Greenwood & Golding, 1998; Chang, Guo, Huang, Wang & Tsai, 2000).

A novel nationwide cohort study in Denmark found that those children with both febrile seizures and epilepsy in childhood had higher risk for psychiatric disorder in adolescence and early adulthood when compared to those either with only febrile seizures or only epilepsy in childhood (Dreier, Pedersen, Cotsapas & Christensen, 2019). However, the association was reinforced with recurrent hospitalizations due to febrile seizures or when accompanied by later-onset epilepsy. An elevated risk was found across the range of psychiatric disorders, especially schizophrenia, but also anxiety disorders and affective disorders. A history of both febrile seizures and epilepsy in childhood has been found to elevate the risk for ADHD more than with only epilepsy in childhood until the age of 22 years (Bertelsen, Larsen, Petersen Christensen & Dalgaard, 2016).

Epilepsy in childhood and psychiatric disorders in adolescence

Long-term prognosis of epilepsy in childhood is considered good; more than half of children with epilepsy achieve complete remission during a follow-up to 21 years (Berg & Rychlik, 2015). However, children with active epilepsy are more

likely to suffer from considerable cognitive impairments and attention deficits compared to normal peers (Dunn & Kronenberger, 2005). Symptoms of depression and anxiety are more common among epileptic children than controls, especially in puberty (Dunn, Austin & Huster, 1999; Oguz, Kurul, Dirik & Eylül, 2002; Vega et al., 2011).

Among children with epilepsy aged 5-17 years, as many as 56% fulfilled diagnostic criteria of psychiatric diagnosis, whereas among controls 13% had psychiatric diagnosis (Caplan et al., 2004). Among children with epilepsy, disruptive disorders, namely attention deficit disorder, oppositional defiant disorder or conduct disorder, was diagnosed among 17% of them, whereas only 6% among controls had the same disorder. Of children with epilepsy, 14% had affective or anxiety disorder (versus 3% among controls) and 23% had comorbid disorder (versus 3% among controls).

In a British nationwide study among 5-15-year-old children suffering from epilepsy, 37% of them had a psychiatric disorder, whereas the percentages were 11% and 9% among children with diabetes and healthy controls, respectively (Davies, Heyman & Goodman, 2003). This was later supported by a comprehensive review by Otero (2009). Later, as many as 62% of children with epilepsy have been found to meet criteria for psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-IV-TR) (Reilly et al., 2014).

A gender difference was found in a Norwegian study among children with epilepsy at ages between 10-19 years. Of the children, 44% met diagnostic criteria for any psychiatric disorder, the most prevalent being ADHD (32% of all participants) and anxiety (24% of all participants) (Alfstad et al., 2016). Boys had more frequently psychiatric diagnoses versus girls (57% vs. 31%) and boys also more often had more than two psychiatric diagnoses (37% vs. 17%).

Epilepsy in childhood and adolescence has been found to associate with internalizing disorders (Davies, Heyman & Goodman, 2003; Caplan et al., 2005). In the latter study, among 5-16-year-old study subjects with epilepsy, as many as 33% of children with epilepsy suffered from affective and anxiety disorders and 20% of them had suicidal ideation.

Association between childhood epilepsy and externalizing disorders also exists (Davies, Heyman & Goodman, 2003; Dunn, Austin & Perkins, 2009). In the latter study, the age among study subjects varied between 9-14 years. When study subjects were assessed as a one group, an elevated risk was found for ADHD, oppositional defiant disorder and dysthymic disorder. When children (9-12 years)

and adolescents (aged 13-14 years) were assessed separately, among children epilepsy associated with conduct disorder and Asperger's disorder, whereas among adolescents epilepsy associated with anxiety disorders and antisocial personality.

A Swedish study found an almost three-fold increased risk for ADHD among study subjects by the age of 22 years (Bertelsen, Larsen, Petersen Christensen & Dalsgaard, 2016). Finally, a recent study found that neurodevelopmental comorbidities were common already at the time of first recognized seizure, and this risk was increased further among those with recurrent seizures (Åndell et al., 2015).

2.5 Psychiatric disorders in childhood and adolescence

Mental illnesses have their origins in juvenile psychiatric history (Rutter, 1984). Approximately half of the adults with mental disorders had their first episode before the age of 14 and three quarters before the age of 24 (Kessler et al., 2005). According to a study by Kim-Cohen and colleagues (2003), among young adults with a psychiatric disorder, 78% of them had received a diagnosis before the age of 18 and 58% before the age of 15. These longitudinal data support the notion that most adults with mental disorders have mental state abnormalities that can be traced back to childhood and adolescence. In addition, early onset of psychiatric disorders, as early as in childhood, have been found to have the worst prognosis (Newman et al., 1996; Kim-Cohen et al., 2003; Lauronen et al., 2007).

2.5.1 Epidemiology

A study looked at Finnish children born in 1996 and their specialized psychiatric care use for any psychiatric or neurodevelopmental disorder by the age of 14 (Gyllenberg et al., 2014). In 2010, the cumulative incidence among these children was 12.9%. This means every eighth child in Finland has used specialized services for psychiatric or neurodevelopmental disorders between birth and the age of 14. The cumulative incidence for treatment in a child and adolescent unit was 5.3% and 1.6% treatment as inpatients. The highest cumulative incidence among them was learning and coordination disorders (5.5%) followed by anxiety disorders (2.2%), hyperkinetic disorders (2.0%), conduct disorders (1.7%), depression (1.4%), autism spectrum disorders (1.0%) and stress and adjustment disorders (0.7%). Moreover, boys had more learning and coordination, hyperkinetic and autism spectrum disorders than girls. Also conduct disorders, including oppositional-defiant disorder (ODD), were more prevalent among boys but were

seldom diagnosed before school-age. Depressive, anxiety and stress and adjustment disorders had similar distributions in both sexes.

Among the Finnish 1987 Birth Cohort children, followed from birth to 21 years of age, 12.7% of them had a diagnosed mental disorder (Paananen, Ristikari, Merikukka & Gissler, 2013). More girls (14.4%) than boys (11.4%) had a psychiatric disorder. The most prevalent diagnoses were affective disorders (7%), anxiety disorders (5.6%) and behavioural and emotional disorders (3%).

Psychiatric hospital treatment becomes more common in adolescence (Pottick, Hansell, Gutterman & White, 1995). In a Finnish 1981 birth cohort study, 6.2% of boys and 4.1% of girls had been admitted for psychiatric hospital treatment between the ages of 13 to 24 years (Gyllenberg et al., 2010). The most common reason for admission was substance-related disorders (1.8%) among boys and non-psychotic mood disorders (1.9%) among girls.

According to Finnish statistics of specialized psychiatric care during 2006-2015, the most prevalent diagnosis among children under the age of 13 was behavioural and emotional disorders (Psychiatric specialized health care, 2016, the National Institute for Health and Welfare). In child psychiatric inpatient care there were more male patients than girls, whereas in adolescence (ages between 13-22 years), there were more female inpatients in psychiatric care. The most common reason for specialized psychiatric care in adolescence was depression and diagnoses classified as other anxiety disorders, for example panic disorders and generalized anxiety disorders. Especially, anxiety disorders accounted for the gender difference.

In conclusion, there is no sex difference in the prevalence of anxiety and depressive disorders in childhood, but in the prepubertal period, the amount of these disorders rapidly increases among girls (Suvisaari, 2013). Compared to girls, male conduct disorders and ODD are four times more likely in childhood and twice more likely in adolescence (Frick & Dickens, 2006). Moreover, conduct disorders with onset in childhood persisting to adolescence have been found to have a worse prognosis than when the first onset of a disorder occurs in adolescence (Odgers et al., 2007).

2.5.2 Continuity of psychiatric disorders from childhood to adolescence

A classification to homotypic and heterotypic continuity of childhood psychiatric disorders to later in life is often seen in the literature. It is noteworthy to distinguish

the concept of continuity from comorbidity. Comorbidity means that two or more different psychiatric disorders occur simultaneously in an individual. For example, comorbidity is typically seen in affective and anxiety disorders. A homotypic continuity means that the same diagnosis recurs in different assessments, for example earlier depression predicting later depression. Heterotypic continuity means that a psychiatric disorder continues but in a different diagnosis, for example early attention-deficit disorder predicting later depression.

Homotypic continuity

Homotypic continuity is typically seen in the case of depression. In a follow-up study in the United States (U.S.) children with pre-school onset depression (3-6 years of age) had an almost three-fold risk of depression in later life at the age of 6-13 years (Luby, Gaffrey, Tillman, April & Belden, 2014). This means that 52% of children with pre-school depression continued to have depression after the six-year follow-up. A study among Spanish adolescents diagnosed with major depression at the age of 18 years found that every third of them had been diagnosed with the same disorder between ages 12 to 14 years and as many as 80% had had depressive symptoms (Canals, Domènech-Llaberia, Fernández-Ballart & Marti-Henneberg, 2002). A study by Costello and colleagues (1999) among 300 children in the U.S. found that emotional disorders at the age of seven to 11 years among girls predicted the same disorder in adolescence. Homotypic continuity in depression seems to continue to young adulthood. In a birth cohort study in the U.S. among 21-year-old young adults with depression, the history of mood disorder (45%) was more likely than a history of any other kind of psychiatric disorder (27%) or no previous psychiatric disorder at all (28%) (Newman et al., 1996). However, in this study, the history of psychiatric disorders reached only to the age of 11 and therefore psychiatric disorders before that were not considered.

Anxiety disorders have also been found to follow the homotypic path. In a study by Newman and colleagues (1996), as many as 62% of cases with anxiety disorder at the age of 21 had a history of anxiety disorder in childhood and adolescence. Only 19% of them suffered previously from a different kind of psychiatric disorder (i.e. heterotypic continuity) and 20% had no previous psychiatric disorder, at least from the age of 11 onwards. Also, according to a review by Wehry and colleagues (2015), current data suggest a homotypic continuity path for anxiety disorders from childhood to later in life.

Schizophrenia is considered as quite consistent and this also concerns continuity. Although schizophrenia is relatively rare in childhood, still one study conducted in the U.S. found that as many as 61% of children diagnosed with schizophrenia in childhood continue to have the same disorder in adolescence (Asarnow, Tompson & Goldstein, 1994). As many as 22% of children showed remarkable recovery and remission, but 44% showed worse or only minimal improvement. In the same study population, as many as 89% continued to have schizophrenia spectrum disorders in adolescence (Asarnow & Tompson, 1999).

A Canadian community sample of children aged four to 12 years revealed that the greatest stability of psychiatric disorders from childhood to adolescence was seen in conduct disorders (Offord et al., 1992). In a study by Costello and colleagues (1999) behavioural disorders at the age of seven to 11 years also had homotypic continuity to adolescence. The continuity was more pronounced in boys. The stability of antisocial behaviour from childhood to adulthood has also been found somewhat greater among boys than girls (Meier, Slutske, Heath & Martin, 2011).

A study conducted in the U.S. assessing the continuity of several psychiatric disorders, namely depression, anxiety, ADHD, ODD and conduct disorder among boys from childhood up to the age of 18 years found that the homotypic continuity was rule in each disorder (Burke, Loeber, Lahey & Rathouz, 2005). A large U.S. community sample of children aged nine to 13 years were assessed until they were 16 years of age (Costello, Mustillo, Erkanli, Keeler & Angold, 2003). Homotypic continuity was significant for all disorders except specific phobias.

In a sample of UK children with ADHD at the age of six to 13 years, 70% of them continued to meet the full criteria for ADHD also in adolescence (Langley et al., 2010). 22% of them developed also conduct disorder during the follow-up.

Finally, in a large Danish follow-up study among children and adolescents aged 6-16 years and followed to early adulthood, found that affective, eating, neurodevelopmental, obsessive-compulsive and psychotic disorders showed the strongest continuity (Castagnini, Foldager, Caffo & Thomsen, 2016). However, in the same study, also heterotypic transitions were seen in affective, eating, neurodevelopmental, personality and substance use disorders.

Heterotypic continuity

Childhood anxiety typically has heterotypic continuity, often preceding depression in adolescence (Wittchen, Kessler, Pfister & Lieb, 2000; Burke, Loeber, Lahey &

Rathouz, 2005; Costello, Mustillo, Erkanli, Keeler & Angold, 2003). Reverse causality has also been observed, for example, childhood depression predicting anxiety in adolescence (Costello, Mustillo, Erkanli, Keeler & Angold, 2003; Luby, Gaffrey, Tillman, April & Belden, 2014).). In the latter study, preschool depression was also found to be a risk factor for ADHD in later school age (Luby, Gaffrey, Tillman, April & Belden, 2014). In a study by Burke and colleagues (2005), although homotypic continuity was the rule, also some heterotypic continuity traits were seen. ADHD among boys in childhood was the only disorder predicting ODD in adolescence, whereas ODD in childhood predicted conduct disorder, anxiety and depression in adolescence. In the study by Costello and colleagues (2003), heterotypic continuity was seen between ADHD in childhood and ODD in adolescence. Interestingly, in this study, heterotypic continuity was much stronger among girls than boys. Overall, children, and especially girls, who developed a psychiatric disorder in childhood, seemed to be at higher risk for continuing to have one, or developing another disorder after the remission than their unaffected peers.

Conduct disorder in preschool (3-6 years of age) has been found to associate with depression later until the age of 13 (Luby, Gaffrey, Tillman, April & Belden, 2014). However, this association was partially mediated by maternal non-support. In a U.S. study assessing ODD in late childhood and adolescence, it was found that among boys ODD was a strong risk factor, especially for conduct disorder. Conversely, among girls ODD did not predict later conduct disorder, but either continued as ODD or developed into depression or anxiety disorder (Rowe, Maughan, Pickles, Costello & Angold, 2002).

In a previously mentioned birth cohort study by Newman and colleagues (1996), substance use disorder in young adulthood showed a heterotypic continuity with preceding diagnoses of conduct disorder, depression and anxiety disorders. On the other hand, anxiety and conduct disorder have also been found to have heterotypic continuity to substance abuse from childhood to adolescence (Costello, Mustillo, Erkanli, Keeler & Angold, 2003).

2.5.3 Childhood psychiatric disorders and suicidality in adolescence

Suicide is the second leading cause of death after injuries among adolescents in most Western countries (Lerner & Steinberg, 2004). Suicidality is not a psychiatric disorder, but especially among adolescents with either suicidal ideation, suicide attempts and among those with completed suicide, concurrent psychiatric disorders are common (Fergusson, Horwood, Ridder & Beautrais, 2005; Marttunen, Aro,

Henriksson & Lönnqvist, 1991; Gould et al., 1998; Brent et al., 1993). These psychiatric disorders especially included affective, anxiety, conduct and substance use disorders, as well as personality disorders, especially borderline personality disorder. Psychiatric disorders, like affective disorders, substance use disorders and personality disorders have also been associated with deliberate self-harm (Olfson, Gameroff, Marcus, Greenberg & Shaffer, 2005; Haw, Hawton, Houston & Townsend, 2001). Other risk factors for suicidality include, for example, family background and adverse childhood experiences (Rytilä-Manninen, Haravuori, Fröjd, Marttunen & Lindberg, 2018; Santana et al., 2015). In the latter study assessing the association between parental psychopathology and later suicidality of offspring through their lifespan, the link was most evident during adolescence (Santana et al., 2015).

Suicidal ideation means that one has thoughts of actions which aim to end one's life (Rytilä-Manninen, Haravuori, Fröjd, Marttunen & Lindberg, 2018). Among U.S. adolescents, the lifetime prevalence of suicide ideation has been estimated to have a prevalence of 12.1% (Nock et al., 2013). Past suicidal ideation with a plan has been found to have at least as high risk for completed suicide as a past attempt (Brent et al., 1993; Wichstrøm, 2000).

Suicide attempt, according to the Diagnostic and Statistical Manual of Mental disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013), is a behaviour that the individual has undertaken with at least some intent to die. Approximately 25-30% of those who attempt suicide will go on to make more attempts (DSM-5). Among adolescents in a nationally representative study in the U.S., 4.1% of adolescents had attempted a suicide (Nock et al., 2013). In community setting studies, most adolescents who have attempted suicide have a psychiatric disorder (Marttunen et al., 1991; Gould et al., 1998). Studies examining whether there is any association between early childhood psychiatric disorders and later suicide attempts requiring medical care in hospital and completed suicides remain scarce. In a study of a Finnish 1981 Birth Cohort Study, of 24 deaths among boys, 13 were suicides, whereas among the 16 deaths among girls, only two of them were considered as suicide (Sourander et al., 2009). Most of those boys with either completed suicide or with a serious suicide attempt in adolescence or in early adulthood had psychiatric problems before the age of 8. The risk was highest when comorbid conduct and internalizing problems co-existed. A similar association between previous psychiatric symptoms and later suicidality was not found among girls.

In another Finnish study of adolescents of an average age of 15 with behaviour disorder and placed in residential schools, the suicide mortality rate was elevated seven-fold compared to controls when assessing a period of 22 years ahead from the baseline (Manninen, Pankakoski, Gissler & Suvisaari, 2015). Of those adolescents from residential school, 8.1% of boys and 2.2% of girls had died during the 22-year follow-up.

Concerning committed suicide, paradoxically, although girls have more suicidal ideation and attempts than boys, boys are more likely at risk of dying by suicide (Gould et al., 2003). The male-female disparity in rates of completed suicide follows a universal pattern throughout Western countries, rates being higher among boys than girls (Wasserman, Cheng & Jiang, 2005). According to suicide rate statistics (per 100,000 population) among 15-19-year-old boys and girls separately, suicide death rate was 20.2 among boys and 5.5 among girls in year 2011 (European Detailed Mortality Database, 2014). Finland is one of the leading countries concerning death rates among male adolescents, girls largely following a similar situation. Psychiatric disorders are strongly associated with completed suicide (Brent et al., 1993; Marttunen et al., 1991; Shaffer et al., 1996).

Self-injurious behaviour, also known as deliberate self-harm, refers to a broad class of behaviours in which an individual indirectly and deliberately causes harm to her- or himself (Nock, Joiner, Gordon, Lloyd-Richardson & Prinstein, 2006). It may include non-suicidal self-injury which is repetitive, deliberate and planned destruction of body tissue not resulting from suicidal intent and not as part of socially sanctioned practices (e.g. body piercings, tattoos or other acts associated with religious or cultural traditions; DSM-5). Deliberate self-harm is also one of the strongest predictors of future completed suicide (Harris & Barraclough, 1997).

In a Swedish community-based sample of adolescents, as many as a third of adolescents had intentionally harmed themselves at least once during the last year (Zetterqvist, Lundh, Dahlström & Svedin, 2013). In a large review of 128 population-based studies, mostly conducted in Western countries, revealed that 13% of adolescents had been engaged in deliberate self-harm at some point in their lives (Evans, Hawton, Rodman & Deeks, 2005). In a Finnish cohort study among 13 to 18-year-old adolescents, the lifetime prevalence of self-cutting was 11.5%, and of other self-harming behaviour 10.2% (Laukkanen et al., 2009). The prevalence of current self-cutting was 1.3%. Self-cutting occurred more among girls and in non-intact families. A previous study among Finnish 18-year-old adolescent boys revealed that the prevalence of suicide ideation of deliberate self-harm was 4.0% and of acts 2.2% during the past six months (Haavisto et al., 2005). 9.7% of those

with ideation and 16% of those with acts of deliberate self-harm had used mental health services during the past year.

In clinical samples 50% up to 70% of adolescents meet these DSM-5 criteria for non-suicidal self-injury (Wolff et al., 2013; Kaess et al., 2013; Glenn & Klonsky, 2013). Indeed, non-fatal suicidal behaviour is up to 20 times more common than fatal suicidal behaviour (WHO, 2007). Although non-suicidal self-injury can occur without any suicidal behaviour, it often occurs among adolescents who have planned or attempted suicide (Kumar et al., 2004; Nock, Joiner, Gordon, Lloyd-Richardson & Prinstein, 2006). It has been postulated that non-suicidal self-injury is one of the most robust predictors of suicide attempts in adolescents (Asarnow et al., 2011; Wilkinson, Kelvin, Roberts, Dubicka & Goodyer, 2011).

Non-suicidal self-injury is often associated with other psychiatric disorders, especially affective disorders and substance use disorders (Jacobson & Gould, 2007; Nock, Joiner, Gordon, Lloyd-Richardson & Prinstein, 2006). One must also consider that previous editions of the DSM and the current ICD-10 include self-harming only as a symptom of borderline personality disorder (ICD-10). In a study of adolescent psychiatric inpatients, as many as 88% of adolescents engaging in non-suicidal self-injury met criteria for DSM-IV Axis I psychiatric disorder, including externalizing (63%), internalizing (52%) and substance use disorders (60%) (Nock, Joiner, Gordon, Lloyd-Richardson & Prinstein, 2006). Most of them also met criteria for an Axis II personality disorders. In a recent study of adolescent psychiatric inpatients using DSM-5 criteria for assessment of psychopathology, found that 39% of them met DSM-5 criteria for non-suicidal self-injury, and as many as 51% showed self-inflicted injuries generally (Sevecke, Bock, Fenzel, Gander & Fuchs, 2017). In this study, NSSI associated especially with borderline personality disorder, but also with affective disorders and substance use disorders. Non-suicidal self-injury had a strong association with suicidality (suicidal ideation, history of suicide attempt) in this study. In a Finnish sample of self-cutting adolescents, mental disorders, especially depressive disorder, anxiety disorder and eating disorders, were more common among self-cutting girls than among controls (Hintikka et al., 2009). None of the self-cutting boys had a diagnosis of mental disorder, but due to the small size of this group ($n = 3$), further conclusions cannot be made. Also in some other studies, to a minor extent, non-suicidal self-injury was not associated with psychopathology (Jacobson & Gould, 2007; Nock, Joiner, Gordon, Lloyd-Richardson & Prinstein, 2006). In an internet-based survey among university students aged at least 18 years, as many as 44% of those with non-

suicidal self-injury had no specific psychiatric disorder (Gollust, Esisenberg & Golberstein, 2008).

3 Aims of the study

The main purpose of this work was to study how obstetric complications, birth measures, epileptic convulsions and epilepsy in childhood and psychiatric disorders in childhood affect psychiatric disorders in adolescence among under-age adolescent psychiatric inpatients. The more specific aims were:

- I To assess the association of pregnancy, delivery and perinatal complications and psychiatric disorders in adolescence;
- II to examine the association of birth measures and psychiatric disorders in adolescence;
- III to study whether there is an association between epilepsy, febrile and other convulsions in childhood and psychiatric disorders in adolescence;
- IV to investigate the relationship between psychiatric care in childhood and later psychiatric inpatient care in adolescence.

4 Material and methods

4.1 Study population

4.1.1 Patient sample (I-IV)

This is part of the Study-70 project. The study population consists of 508 adolescent inpatients (300 girls, 208 boys) aged 13 to 17 years (with a mean age of 15.5 years, SD 1.3) admitted to the Department of Psychiatry of Oulu University Hospital in Finland between April 2001 and March 2006. The catchment area of Unit 70 covers the districts of Oulu and Lapland which account for 43% of the area of Finland. All adolescents from this area who need acute psychiatric hospitalization in a closed ward are initially treated in Unit 70. A majority of the adolescents (71%) were from the province of Oulu, 22% were from the City of Oulu, 20% were from province of Lapland and 9% from other provinces in Finland. A majority of the adolescents were Caucasians (98%). The exclusion criteria were age over 18 years ($n = 1$), intellectual disability ($n = 26$) and organic brain disorder ($n = 3$). The eligible 607 subjects and their parents participated in the study with informed, voluntary and written consent and those who refused to do so were excluded ($n = 77$). Also, those with such a short hospitalization period that interviews could not be completed were excluded as well ($n = 22$). Therefore, 508 adolescents (83.7% of eligible patients) participated in the research project (Luukkonen, 2010).

4.1.2 Control population (II)

In Study II, the sample of controls was derived from the NFBC 1986. All NFBC 1986 cohort members were surveyed for ADHD symptoms (Smalley et al., 2007). Of all 6622 respondents to the ADHD survey, 487 cases and 315 age-, sex- and geographical location-matched controls were invited to participate in a direct clinical assessment. A total of 464 cohort members (268 cases, 196 controls) participated in this clinical interview and the K-SADS-PL questionnaire was used to assess their psychiatric diagnoses according to the DSM-IV criteria. As a result of the K-SADS-PL interview, the mentally healthy control population comprised 264 adolescents, aged 15-16 years, without any DSM-IV-based psychiatric disorders.

4.2 Research instruments

4.2.1 K-SADS-PL (I-IV)

Study subjects were interviewed using the Schedule for Affective Disorder and Schizophrenia for School-Age Children-Present and Lifetime questionnaire (K-SADS-PL), which is a semi-structured interview for assessing psychiatric disorders according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (American Psychiatric Association, 1987) and Fourth Edition (DSM-IV) (American Psychiatric Association, 1994). K-SADS-PL has been shown to have high test-retest reliability and validity as a diagnostic instrument to assess psychiatric disorders among adolescents (Ambrosini, 2000; Kaufman et al., 1997). The interview was carried out by a trained medical student under surveillance of the treating physician. Data were based on both information from the patient and the physician's evaluation of the diagnostic interview. In case of missing or unreliable data, the patient interview was completed by interviewing the parents/guardians.

4.2.2 EuropASI (I-IV)

The European Addiction Severity Index (EuropASI) is an objective structured face-to-face interview, performed by nurses on the ward. It contains questions on the following life areas/problems: physical health, employment and financial support, illegal and criminality activity, family and social relationships, psychiatric symptoms and alcohol and drug use. EuropASI has been proven to be a reliable and valid source of information for scientific research (Kokkevi & Hartgers, 1995).

4.2.3 Register-based data (II-IV)

The Finnish Medical Birth Register from the National Institute for Health and Welfare (was used to derive birth measures information and covariates of the pregnancies; II). It includes information on all children born in Finland since 1987 (Gissler, Louhiala & Hemminki, 1997). Thus, for the purpose of this study, the information on birth measures was available for 310 adolescents (125 boys, 185 girls).

The Finnish Care Register for Healthcare, FCRHC (previously Finnish Hospital Discharge Register, FHDR) maintained by the National Institute for

Health and Welfare comprises information on the beginning and end of each inpatient stay since 1969 (Sund, 2012). It uses the ICD classification and includes the complete diagnostic code. In our study, it was used to obtain data on hospital treatments due to diagnoses of epilepsy and febrile or other convulsions in childhood (III), personality disorders in adolescence (III) and diagnoses from psychiatric inpatient treatment in childhood (IV). The diagnoses of hospital treatments at in- or outpatient units in Finland are coded in healthcare registers according to the 9th revision during 1987-1995 (Tautiluokitus, 1987) and according to the 10th Revision (ICD-10) since 1996.

The Finnish National Cause of Death Register is maintained by Statistics Finland. It contains data on all the deaths in the country or abroad of all persons domiciled in Finland at the time of death based on death certificates filled in by the physician treating a patient before the time of death. It follows the international format for death certifications issued by the WHO. The death certificate data are compared with the Population Register Centre by the means of the personal identification code of the deceased. Thus, the coverage of death certificates in Finland is excellent (Statistics Finland, 2020).

4.2.4 Admission form (IV)

A semi-structured admission form was used to gather information about reasons for psychiatric treatment in adolescence (IV). It included each patient's hospital case note. The information was obtained from the patient and/or patient's parents or guardians at the start and on the completion of treatment in Unit 70 and it was finalized by the nurse and physician.

4.3 Variables

4.3.1 Obstetric complications (I)

The information on obstetric complications reported by the mother of the adolescent were derived from background characteristics of the K-SADS-PL. The categorization of obstetric complications into three categories (pregnancy, delivery and perinatal complications) and their frequency and percentage distributions are presented in Table 1.

Table 1. The distribution of different types of obstetric complications among underage adolescents (n = 508) with DSM-IV-diagnosed psychiatric disorders (I, Table 1).

Type of complication	N	%-distribution within all obstetric complications	%-distribution within each complication subgroup
Any obstetric complication	96	100.0	-
1. Pregnancy complications	55	57.3	100.0
Bleeding during pregnancy	3	3.1	5.5
Threatened premature delivery	9	9.4	16.4
Placental insufficiency	1	1.0	1.8
Pre-eclampsia	16	16.7	29.1
Substance use by mother of the adolescent	23	24.0	41.8
Gestational diabetes	5	5.2	9.1
Maternal infection	3	3.1	5.5
2. Delivery complications	57	59.4	100.0
Caesarean section	26	27.1	45.6
Pre-term birth	19	19.8	33.3
Prolonged labour	6	6.3	10.5
Vacuum extraction/forceps delivery	4	4.2	7.0
Breech presentation	3	3.1	5.3
Blue baby	15	15.6	26.3
Nuchal cord entanglement	4	4.2	7.0
3. Perinatal complications	13	13.5	100.0
Child's infection	7	7.3	53.8
Jaundice	6	6.3	46.1

Note: A person may have several types of complications; Multiple single complications = at least two different types of single complications; Multiple complication groups = a person has complications belonging to at least two different complication groups (i.e. pregnancy, perinatal or delivery complication groups).

A person may have been exposed to several types of complications. In this study, multiple single complications means at least two different types of complications from the same complication group (i.e. pregnancy, delivery or perinatal complications). Multiple complication groups mean that a person has been exposed to complications belonging to at least two different complication groups. The categorization of obstetric complications mainly follows those most commonly used in the literature (Allen, Lewinsohn & Seeley, 1998; Kinney, Yurgelun-Todd, Tohen & Tramer, 1998; Isohanni et al., 2005).

4.3.2 Birth measures (II)

Information on birth weight (g) and length (cm) were available for 310 adolescents from the Study-70 population from the National Medical Birth Register, since that register covers the data on birth measures since 1987. In addition, the intrauterine growth pattern was assessed using ponderal index (birth weight/length³). Ponderal index is a measure of thinness and nutritional status.

The corresponding information on birth measures among mentally healthy controls from NFBC 1986 cohort members was gathered from the antenatal clinics.

Birth measures were further derived in gender-specific upper quartiles (75th percentiles) according to birth measures (weight, length, ponderal index) to indicate the extreme values of the measures. The following cut offs were used: birth weight ≥ 4020 g among boys and ≥ 3850 g among girls; birth length ≥ 53 cm among boys and ≥ 52 cm among girls; ponderal index ($1000 \cdot \text{g}/\text{cm}^3$) ≥ 28.9 among boys and \geq among girls.

4.3.3 Epilepsy and febrile or other convulsions (III)

The diagnoses of epilepsy and febrile or other convulsions were retrieved from the Finnish Care Register of Health Care (FCRHC) (III). The inclusion criteria were diagnoses of epilepsy and febrile or other convulsion under the age of 16. The exclusion criteria were predisposition of seizure (other than fever for febrile seizures) and psychiatric or other neurological disease at the time of epileptic seizure or febrile or episode of other convulsions. The diagnoses were further on confirmed by an experienced neurologist (H.A) and a resident in psychiatry (S.L) from patients' hospital medical records whenever they were available.

4.3.4 Psychiatric disorders (I-IV)

Psychiatric disorders in childhood Information on psychiatric inpatient treatment in child psychiatric care was obtained from the FCRHC (IV). It was defined as present (yes, no) according to whether a treatment episode in specialized level child psychiatric care hospital was registered on the FCRHC. The diagnoses of child psychiatric care set at the baseline according to ICD-10 were converted to diagnostic schedule DSM-IV and further-on classified hierarchically by an experienced psychiatrist in child psychiatric care (A.P), two experienced psychiatrists in adolescent and adult psychiatry (K.R, P.R) and a resident of

psychiatry (S.L). A child could have several psychiatric diagnoses, but after the validation only one main diagnosis persisted per case. Primary psychiatric diagnoses in child psychiatric care were categorized into four following major groups:

- (1) *Internalizing disorders*: depression (DSM-IV: 296.21-296.24, 296.90, 300.4, 301.13, 311) anxiety disorders (DSM-IV: 300.00, 300.02, 300.23, 300.21, 300.3, 308.3, 309.81, 313.9) and psychotic disorders (DSM-IV: 295.70, 297.1, 298.8, 298.9)
- (2) *Externalizing disorders*: depressive conduct disorder ((DSM-IV: 312.81) and conduct/oppositional deficit disorders (DSM-IV: 312.89).
- (3) *Neuropsychiatric disorders* (DSM-IV: 299.80, 307.23, 314.9, 315.4)
- (4) *Other psychiatric disorders*: substance use disorders (DSM-IV: 304.30), personality disorders (DSM-IV: 301.9), eating disorders (DSM-IV: 307.1), adjustment disorders (DSM-IV: 309.9) and disorders usually first diagnosed in infancy, childhood, or adolescence (DSM-IV: 313.89, 313.9).

Psychiatric diagnoses of adolescents during the index hospitalization period (I-IV) were obtained from the K-SADS-PL interview and were based on DSM-IV criteria. They were categorized into five major groups: 1) substance-related disorders, 2) anxiety disorders, 3) affective disorders 4) conduct or oppositional defiant disorders and 5) psychotic disorders. Multiple diagnoses for each subject were possible and 53% of adolescents belonged to at least two diagnostic groups. The exact DSM-IV codes and distribution of disorders among adolescents can be seen in Table 2.

Table 2. All psychiatric diagnoses among adolescent psychiatric inpatients categorized into five main groups (I-IV, Table 2).

Psychiatric diagnoses	Total	Boys	Girls
Substance-related disorders: DSM-IV: 303.9,304.0-304.5, 304.8-304.9, 305.2-305.7, 305.9	195	87	108
Anxiety disorders: DSM-IV: 300.00-300.02, 300.21-300.23, 300.29, 300.3, 309.81	117	29	88
Affective disorders: DSM-IV: 296.2-296.3, 300.4, 311	251	76	175
Conduct or oppositional defiant disorders: DSM-IV: 312.8-312.9, 313.81, 314.00-314.01, 314.9, 299.80	225	122	103
Psychotic disorders: DSM-IV: 295, 296.0, 296.4-296.9, 297.1-297.3, 298.8-298.9, 301.13, 301.22	70	30	40

In Study II, psychiatric disorders in adolescence were further on grouped to two major groups: 1) internalizing (affective, anxiety and psychotic) and 2) externalizing (substance-related, conduct and oppositional defiant) disorders.

In Study IV, validation of psychiatric diagnoses in adolescence so that only one main diagnose persisted, was run by two experienced psychiatrists in adolescent and adult psychiatry (K.R, P.R) to enable comparison between childhood and adolescence psychiatric diagnoses.

Personality disorders. In Study III, personality disorders (PDs) diagnosed up to young adulthood was also included in the analyses. PDs tend to appear in late childhood or adolescence and continue to be manifest into adulthood. Therefore, the diagnosis for PD is unlikely appropriate until the age of 16 years. In the present study adolescents were considered to have PD only if it was diagnosed at 16 years or older. If the diagnosis of PD was set before the age of 18 years, the associated features must have been present for at least one year, as stated in DSM-IV criteria for PD. All diagnoses of PD (primary and additional diagnoses, ICD-10 codes F21, 60-60.9; DSM-IV-TR codes 301.00, 301.20-301.9) were extracted from the FCRHC data on the study subjects. ICD-diagnoses were retrieved by senior researcher (L.K) using DSM-IV-TR criteria. DSM-IV-TR was used because DSM-IV was not in use at the time the study was conducted. The mean age of first out- or inpatient treatment for PD in the study population was 20.7 years (sd 2.7).

4.3.5 Suicidality (III)

Suicidality information (suicide ideation, suicide attempts and non-suicidal self-injury) was obtained from the screening caesarean section for depressive disorders of the K-SADS-PL interview (Kaufman et al., 1997). Suicide ideation criteria were fulfilled when recurrent thoughts of suicide existed and the adolescent had planned the method of suicide. Suicide attempts were evaluated by their seriousness and the medical lethality of the intent. If the threshold of either seriousness (definite suicide attempt) or medical lethality (e.g., took 10 seconds and suffered a brief period of unconsciousness) reached the threshold level, the criteria for a suicide attempt were fulfilled (for more detail, see Luukkonen, 2010). Non-suicidal self-injury was defined as non-suicidal physical self-injury acts without any intent to kill themselves, which reached the threshold in terms of frequency (4 or more times a year) or seriousness of injury (e.g. a burn with scarring, a broken bone).

4.3.6 Reason for admission, Children's Global Assessment Scale (CGAS), The Global Assessment of Relational Functioning (GARF) (IV)

Information on reason for admission, CGAS and GARF were all obtained from the reason for admission form.

Reasons for psychiatric admission were gathered from the open-text field on a reason for admission form. Reasons for admission were classified into eight groups: 1) depressive mood, 2) suicidality (including both suicidal ideation and behaviour), 3) non-suicidal self-injury 4) psychotic symptoms, 5) anxiety symptoms, 6) substance use, 7) behavioural problems and 8) aggression.

CGAS was used to measure the level of functioning of adolescents at both admission and discharge from Unit 70. The CGAS is a numeric (1-100) rating scale used by mental health professionals and doctors to evaluate mental health in a continuum from psychological and psychiatric sickness to full health in a specified time period among children and adolescents under the age of 18 years (Schorre & Vandvik, 2004). Ratings on a CGAS scale are independent of specific mental health diagnoses. CGAS 100 reflects the best functioning of mental health and the worst possible functional level.

GARF was used to evaluate the functioning of the family among adolescents. It is a brief, clinician-rated instrument used to assess family functioning and is included in DSM-IV-TR (Denton, Nakonezny & Burwell, 2010). The overall

GARF assessment is based on a family's ability to meet needs in three areas: problem solving, organization and emotional climate. The GARF rating is a continuum between 1 (lowest level) and 100 (highest level).

4.3.7 Mortality (IV)

Mortality information until May 2016 among the study population was obtained from the Finnish Cause of Death register. The data included the exact time of death, the primary cause of death and diagnoses associated with the basic cause of death (the immediate, intermediary and complementary cause of death).

4.3.8 Background characteristics (I-IV)

Table 3 presents socio-demographic and clinical background characteristics based on EuropASI, except family type and sibling position, which were obtained from K-SADS-PL (I). In addition, in Study III we also assessed sibling characteristics (substance use and psychiatric problems), also derived from the EuropASI questionnaire.

Family type information was based on the K-SADS-PL interview and, as Table 3 presents, was categorized in either six (1. two biological parents, 2. blended family, 3. single parent, 4. foster family, 5. child welfare placement, 6. other) (I) or four (1. two biological parents, 2. one biological parent, including blended family or single parent family, 3. child welfare placement and 4. other, including foster family or other type of home environment) (IV).

In Study II, covariates of pregnancies among mothers of Study-70 subjects were collected from the Medical Birth Register from the Finnish National Institute for Health and Welfare (II). The following covariates were used: gestational age (under 37 weeks, 37 to 42 weeks, over 42 weeks), mother's age (under 20, 20-35, 36 or over), parity (none, 1-2 previous deliveries, 3 or more previous deliveries) and maternal smoking (non-smoker, quit smoking in first trimester, kept smoking during pregnancy). The corresponding information among the healthy controls was obtained from the collected data on pregnancy, delivery and children's survival by the antenatal clinics.

Table 3. Background characteristics among adolescents with obstetric complications (n = 96) as total and separately among boys and girls (I, Table 3).

Variables	Total (N = 96) n (%)	Boys (N = 46) n (%)	Girls (N = 50) n (%)
<i>Family type</i>			
Two biological parents	29 (30)	12(26)	17(34)
Blended family	10 (10)	6 (13)	4 (8)
Single parent	20 (21)	10 (22)	10(20)
Foster family	9 (9)	4 (9)	5 (10)
Child welfare placement	19 (20)	11(24)	8 (16)
Other	9 (9)	3 (7)	6 (12)
<i>Sibling position</i>			
Only child	23 (24)	13(28)	10 (20)
Oldest child	27 (28)	16 (35)	11 (22)
Middle child	22 (23)	10(22)	12 (24)
Youngest child	24 (25)	7 (15)	17 (34)
<i>Number of children in family</i>			
1-5 children	82 (85)	39(87)	43(86)
6 or more (multiparity)	13 (14)	6 (13)	7 (14)
<i>Characteristics of the mother</i>			
<i>Mother's education</i>			
No	11 (11)	4 (11)	7 (16)
Courses, etc.	19 (20)	9 (24)	10 (23)
Vocational education	31(32)	16 (42)	15 (35)
College/University degree	20 (21)	9 (24)	11 (26)
Mother working (full-time/part time)	56 (58)	29(63)	27 (54)
Mother's substance use problems	24 (25)	8 (17)	16(32)
Mother's psychiatric problems	13 (14)	4 (9)	9 (18)
<i>Characteristics of the father</i>			
<i>Father's education</i>			
No	11 (11)	6 (16)	5 (13)
Courses, etc.	14 (15)	9 (24)	5 (13)
Vocational education	33 (34)	16 (43)	17 (45)
College/ University degree	17 (18)	6 (16)	11 (29)
Father working (all day/part time)	53 (55)	21 (46)	32 (64)
Father's substance use problems	28 (29)	10 (22)	18 (36)
Father's psychiatric problems	6 (6)	3 (7)	3 (6)

4.4 Statistical methods

Cross-tabulation, chi-square test, X² test or Fisher's exact test and in continuous variables with Student's t test or Mann-Whitney U test were used to assess statistical significance of differences between variables of two groups. All tests were two-tailed and the limit for statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS for Windows, version 13-22. The specific statistical analyses used in each study are presented below.

Study 1. The statistical significance of the associations of obstetric complications and psychiatric disorders were assessed in binary logistic regression analyses after adjusting for the study subject's age, gender and background characteristics.

Study 2. A binary logistic regression model was used to examine the difference between study sample and healthy controls in birth measures (birth weight, length and ponderal index) and externalizing and internalizing disorders of the adolescent after controlling for the adolescent's age, gestational age (in weeks), age of mother (in years) at the time of the child's birth, maternal smoking during pregnancy (non-smoker, quit smoking during pregnancy) and number of previous pregnancies.

Study 3. Each case with epilepsy or febrile or other convulsion ($n = 28$) was matched with four controls by age (± 1 year), gender and family type from the Study-70 population without any neurological disease ($n = 112$). Binary logistic regression analysis was used to examine the statistical significance of the association between epilepsy and psychiatric disorders and separately the association of febrile or other convulsions and psychiatric disorders, after adjusting for the study subject's age, gender and background characteristics.

Study 4. The association of age, family-related factors and clinical characteristics (suicidal ideation and attempts, non-suicidal self-injury, psychiatric disorders) with child psychiatric inpatient care before admission to adolescent psychiatric care was examined using a binary logistic regression analysis.

4.5 Ethical considerations and personal contribution

Ethical considerations. The study plan for the Study-70 project, which the present research is part of, was approved by the Ethics Committee of the University of Oulu Faculty of Medicine. The NFBC 1986 study protocol was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. The permission to the

use of healthcare registers (Birth register, FCRHC, Cause of Death Register) was obtained from the National Institute for Health and Welfare.

The study subjects were given a complete description of the research and were informed that refusal to participate in the research would not affect their treatment in any way. Signed, informed consent was obtained from both the adolescent and at least one parent (or guardian) before enrolment in the study.

Personal contribution. I, the author of this thesis, extracted the information on obstetric complications from the K-SADS-PL interviews and participated in categorization of obstetric complications into three main groups (pregnancy, delivery and perinatal complications) according to previous literature under the surveillance of senior paediatricians (A.P). I also participated in checking all the diagnoses of epilepsy and febrile or other convulsions from hospital medical records under the surveillance of a senior neurologist (H.A). I made a major contribution to all the original studies and I am named as the first author and the corresponding author in each study, except for the first and third study. I participated in study design and data analyses and interpreted the results in consultation with co-authors. I wrote the first draft of each manuscript and was responsible for the final form of each study as it was submitted.

5 Results

5.1 Obstetric complications

5.1.1 Mother's self-reported obstetric complications (I)

According to data obtained from the K-SADS-PL interview of the mother's recall of obstetric complications, 19% (n = 96) of 508 adolescents had been exposed to some obstetric complication. Of them, 57% had suffered from pregnancy complications, 59% from delivery complications and 14% from perinatal complications. Figure 1 presents the gender-specific distribution of obstetric complications divided to three main groups (pregnancy, delivery and perinatal complications) and separated into specific complications. A marginally significant finding was that boys had been exposed more often to delivery complications than girls (14% vs. 9%, $p = 0.057$). When assessing gender-specific prevalence, boys had more often suffered from multiple complications (12% vs. 5%, $p = 0.006$) and more commonly belonged to a group with more than one type of complications (9% vs. 3%, $p = 0.005$) than girls.

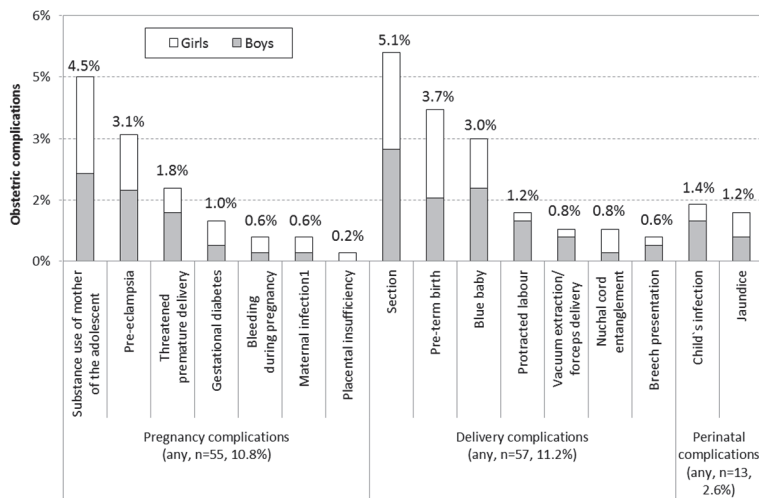


Fig. 1. Gender-specific prevalence of obstetric complications divided to three main complication groups (pregnancy, delivery and perinatal complications) and to specific complications.

Table 4 presents the distribution of obstetric complications within five major psychiatric disorder groups by gender. Boys with affective, anxiety, conduct or substance-related disorders had been more often exposed to multiple single complications and more often belonged to multiple complication groups than girls with corresponding disorders. Boys with conduct disorders had had more delivery complications than girls with conduct disorder (16% vs. 5%, $p = 0.006$). At marginal significance, boys with anxiety disorder had had more delivery complications than girls (21% vs. 8%, $p = 0.085$).

When assessing conduct disorder group more closely, especially caesarean section delivery emerged as a significant risk factor for conduct disorder among boys compared to girls (7% vs. 1%, $p = 0.023$).

In addition, the prevalence of specific obstetric complications was analysed in relation to psychiatric disorder in adolescence. After adjusting for age, gender and background characteristics of the adolescents, only blue baby, of all the specific obstetric complications, emerged as a significant risk factor for conduct disorder in adolescence (OR 7.9, 95% CI = 1.0-62.5, $p = 0.049$).

5.1.2 Register-based obstetric data (II)

Based on the National Birth Register of birth measures data, boys with psychiatric disorders had lower birth length (50.7 vs. 51.3, $p = 0.021$) and higher ponderal index (28.0 vs. 27.5, $p = 0.04$) compared to healthy controls. Table 5 shows the association of birth measures with internalizing disorders, by gender. High ponderal index associated especially with internalizing disorders among boys (OR 2.4, 95% CI 1.1-5.5, $p = 0.039$). No association between birth measures and externalizing disorders was found.

Table 4. Type of complication in different psychiatric diagnostic groups by gender.

Type of complication	Total (n = 508) n (%)	Boys (n = 208) n (%)	Girls (n = 300) n (%)	p - value
<i>Affective disorders (N = 251)</i>				
Any obstetric complication	46 (18.3)	17 (22.4)	29 (16.6)	0.275
Pregnancy complications	26 (10.4)	10 (13.2)	16 (9.1)	0.337
Delivery complications	26 (10.4)	10 (13.2)	16 (9.1)	0.337
Perinatal complications	7 (2.8)	4 (5.3)	3 (1.7)	0.204
Multiple single complications	16 (6.4)	9 (11.8)	7 (4.0)	0.026
Multiple complication groups	12 (4.8)	7 (9.2)	5 (2.9)	0.048
<i>Anxiety disorders (N = 117)</i>				
Any obstetric complication	20 (17.1)	7 (24.1)	13 (14.8)	0.263
Pregnancy complications	19 (8.5)	4 (13.8)	6 (6.8)	0.262
Delivery complications	13 (11.1)	6 (20.7)	7 (8.0)	0.085
Perinatal complications	4 (3.4)	2 (6.9)	2 (2.3)	0.256
Multiple single complications	9 (7.7)	5 (17.2)	4 (4.5)	0.041
Multiple complication groups	7 (6.0)	5 (17.2)	2 (2.3)	0.010
<i>Conduct disorders (N = 225)</i>				
Any obstetric complication	43 (19.1)	28 (23.0)	15 (14.6)	0.111
Pregnancy complications	26 (11.6)	15 (12.3)	11 (10.7)	0.706
Delivery complications	25 (11.1)	20 (16.4)	5 (4.9)	0.006
Perinatal complications	6 (2.7)	4 (3.3)	2 (1.9)	0.690
Multiple single complications	20 (8.9)	16 (13.1)	4 (3.9)	0.015
Multiple complication groups	13 (5.8)	11 (9.0)	2 (1.9)	0.023
<i>Substance-related disorders (N=195)</i>				
Any obstetric complication	37 (19.0)	21 (24.1)	16 (14.8)	0.099
Pregnancy complications	20 (10.3)	11(12.6)	9 (8.3)	0.324
Delivery complications	22 (11.3)	13 (14.9)	9 (8.3)	0.147
Perinatal complications	8 (4.1)	6 (6.9)	2 (1.9)	0.142
Multiple single complications	17 (8.7)	12 (13.8)	5 (4.6)	0.024
Multiple complication groups	12 (6.2)	9 (10.3)	3 (2.8)	0.029
<i>Psychotic disorders (N=70)</i>				
Any obstetric complication	10 (14.3)	5 (16.7)	5 (12.5)	0.735
Pregnancy complications	4 (5.7)	3 (10.0)	1 (2.5)	0.307
Delivery complications	7 (10.0)	3 (10.0)	4 (10.0)	1.000
Perinatal complications	0	0	0	ne
Multiple single complications	2 (2.9)	1 (3.3)	1 (2.5)	1.000
Multiple complication groups	1 (1.4)	1 (3.3)	0	0.429

Note: Multiple single complications = at least two different types of single complications; Multiple complication groups = a person has complications belonging to at least two different complication groups (i.e. pregnancy, perinatal or delivery complication groups).

Table 5. Association of birth measures to internalizing disorders of the adolescents.

Birth measure	Internalizing disorder			Likelihood for internalizing disorder ¹	
	Patient sample mean (sd)	Healthy controls mean (sd)	p - value	OR (95%CI)	p - value
Adolescent boys					
Birth weight (gr)	3647.1 (504.5)	3695.9 (524.0)	0.605	0.8 (0.3-2.2)	0.716
Birth length (cm)	50.6 (1.9)	51.3 (2.1)	0.055	0.4 (0.1-1.3)	0.141
Ponderal index	28.1 (2.2)	27.5 (2.1)	0.099	2.40 (1.1-5.5)	0.039
Adolescent girls					
Birth weight (g)	3397.1 (618.8)	3506.8 (530.4)	0.192	0.9 (0.4-1.9)	0.821
Birth length (cm)	49.4 (2.7)	49.9 (2.2)	0.162	0.8 (0.4-1.9)	0.661
Ponderal index	27.8 (2.4)	28.2 (2.6)	0.396	0.6 (0.3-1.3)	0.196

Note: ORs are adjusted for age of adolescents, gestational age (weeks), age of mother (in years) at time of birth, maternal smoking during pregnancy (non-smokers, quit during first trimester, smoker during pregnancy) and number of previous pregnancies. Adolescents without any psychiatric disorder form the reference group in binary logistic regression analysis.

¹High birth measure upper quartile (75th percentile) means birth weight ≥ 4020 gr in boys and ≥ 3850 gr in girls; birth length ≥ 53 cm in boys and ≥ 52 cm in girls; ponderal index > 28.9 in boys and ≥ 29.8 in girls.

5.2 Childhood epilepsy and other febrile or other convulsions (III)

Table 6 presents prevalence of psychiatric disorders and suicidal behaviour (suicide ideation, suicide attempts, non-suicidal self-injury) among the study group (epilepsy, febrile and other convulsions) and controls by gender. Of specific psychiatric disorders, personality disorders were more common among boys with febrile or other convulsions compared to controls without any neurologic disorder (67% v. 10%, p-value = 0.014). This was only marginally true among female study subjects with febrile or other convulsions (33% vs. 7%, p-value = 0.09). Suicide attempts were more common among boys with epilepsy (40% vs. 8%, p-value 0.02) and febrile or other convulsions (67% vs. 8%, p-value = 0.03).

Table 6. Psychiatric disorders and suicidal behaviour (suicide ideation, suicide attempts, self-harm) of study subjects (epilepsy group, febrile and other convulsions group and controls) by gender.

Psychiatric disorders and suicidal behavior	Study groups			Difference between study groups p – value
	Epilepsy n (%)	Febrile and other convulsions n (%)	Controls n (%)	
<i>Adolescent boys</i>	<i>(n = 10)</i>	<i>(n = 3)</i>	<i>(n = 52)</i>	
Affective disorder	3 (30)	2 (66)	16 (31)	0.507
Anxiety disorder	1 (10)	0	7 (14)	1.000
Psychotic disorder	1 (10)	0	7 (14)	1.000
Substance use disorder	3 (30)	2 (67)	25 (48)	0.482
Conduct disorder	5 (50)	3 (100)	31 (60)	0.425
Personality disorder	3 (30)	2 (67)	5 (10)	0.014
Suicide ideation	3 (30)	2 (67)	10 (19)	0.148
Suicide attempts	4 (40)	2 (67)	4 (8)	0.003
Non-suicidal self-injury	1 (10)	1 (33)	5 (10)	0.347
<i>Adolescent girls</i>	<i>(n = 9)</i>	<i>(n = 6)</i>	<i>(n = 60)</i>	
Affective disorder	5 (56)	2 (33)	38 (63)	0.310
Anxiety disorder	1 (11)	2 (33)	19 (32)	0.467
Psychotic disorder	1 (11)	0	3 (5)	0.599
Substance use disorder	2 (22)	2 (33)	21 (35)	0.900
Conduct disorder	2 (22)	2 (33)	24 (40)	0.682
Personality disorder	1 (11)	2 (33)	4 (7)	0.085
Suicide ideation	4 (44)	2 (33)	29 (48)	0.836
Suicide attempts	3 (33)	1 (17)	16 (27)	0.795
Self-harm	3 (33)	3 (50)	23 (38)	0.824

Note: Psychiatric diagnoses are assessed at index hospitalization, except personality disorders. Personality disorders are defined after index hospitalization when age for personality disorder diagnosis was reached (18 years old).

In binary logistic regression analysis (see Table 7) the risk of personality disorder was 14-fold among adolescents with febrile or other convulsions. A marginally significant finding was that the risk of suicide attempts was three-fold higher among adolescents with epilepsy when both groups were separately compared to their matched controls.

Table 8 shows that of specific psychiatric disorders, conduct disorders were more common among CPSY boys compared to APSY boys ($p = 0.001$). NNSI at index hospitalization was more common among both CPSY boys ($p = 0.01$) and

CPSY girls ($p = 0.004$) compared to APSY ones. At the discharge, CGAS was lower among CPSY girls compared to APSY girls (49 vs. 54, $p = 0.002$).

Table 7. Association of epilepsy and febrile and other convulsions to psychiatric disorder and suicidal behaviour of study subjects.

Outcome variables	Epilepsy (n = 19)		Febrile and other convulsions (n = 9)	
	OR (95%CI) ¹	p-value	OR (95%CI)	p-value
Affective disorder	0.8 (0.3-2.2)	0.664	0.8 (0.2-3.3)	0.743
Anxiety disorder	0.3 (0.1-1.7)	0.175	1.1 (0.2-6.1)	0.912
Psychotic disorder	1.2 (0.2-5.9)	0.858	ne	
Substance use disorder	0.4 (0.1-1.3)	0.117	1.9 (0.4-8.6)	0.414
Conduct disorder	0.6 (0.2-1.6)	0.265	1.5 (0.4-6.0)	0.595
Personality disorder	2.9 (0.8-10.8)	0.116	14.2 (2.7-73.5)	0.002
Suicide ideation	1.1 (0.4-3.2)	0.835	1.5 (0.4-6.2)	0.579
Suicide attempts	2.8 (1.0-8.2)	0.063	2.4 (0.5-10.7)	0.259
Self-harm	0.9 (0.3-3.0)	0.809	2.2 (0.5-9.6)	0.299

¹ Odds Ratios (ORs) are adjusted by age and gender of adolescents.

5.3 Previous child psychiatric inpatient care (IV)

In total, 18% ($n = 89$) of the adolescents, every fourth ($n = 57$) boy and every tenth ($n = 32$) girl had previously been in child psychiatric inpatient care (CPSY) before admission to adolescent psychiatric inpatient care (APSY). CPSY adolescents were younger at admission to adolescent psychiatric inpatient care than APSY (14.9 vs. 15.6 years, $p = 0.001$).

After analysis using the binary logistic regression model, the risk of anxiety disorders in adolescence at index hospitalization was 2.7-fold higher among CPSY boys than among APSY boys ($p = 0.05$) and the risk of conduct disorder in adolescence at index hospitalization was 2.8-fold higher among CPSY boys than among APSY boys ($p = 0.010$). Among girls, non-suicidal self-injury was three-fold higher among CPSY girls when compared to APSY girls ($p = 0.009$).

In addition, the mortality until May 2016 was assessed separately among CPSY and APSY study subjects. During the follow-up, a total of 15 (7.2%) boys had died, six (10.5%) of them in the CPSY group and nine (6.0%) in the APSY group. Suicides accounted for 60% ($n = 9$) of deaths, 33.3% ($n = 2$) among CPSY boys and 77.8% ($n = 7$) among APSY boys.

In girls, a total of five (1.7%) adolescents had died, all in the APSY group (1.9% of all APSY). Suicides covered 60% (n = 3) of all deaths among APSY girls.

Table 9 presents the change of psychiatric disorders from childhood to adolescence. A homotypic continuity from childhood to adolescence was seen among the total population in all psychiatric disorders except anxiety disorder. 40% of children with anxiety disorder shifted to the group of conduct /oppositional deficit disorders in adolescence. Boys showed mainly homotypic continuity of psychiatric disorders throughout disorders, except in neuropsychiatric disorder, of which 50% of children shifted to the externalizing disorder group in adolescence. Girls showed more heterotypic continuity, for example those with externalizing disorders in childhood shifted to the group of internalizing disorders in adolescence.

Figure 2 illustrates the change in four major groups (internalizing, externalizing, neuropsychiatric and others). The proportion of internalizing disorders increased from childhood to adolescence in both genders.

5.4 Socio-demographic and familial risk factors (I, II, III, IV)

Mother's young age at the time of birth was more common among boys with psychiatric disorders compared to healthy controls (27.1 vs. 28.5 years, $p = 0.041$) (II). When adolescent boys and girls were compared with each other in terms of background characteristics, the mother's current substance use problems reported by adolescents were more common among girls with obstetric complications (32% yes, 14% no, $p = 0.002$) compared to boys (17% yes vs. 9% no, $p=0.089$) (I). Among girls, being middle-born (56 vs. 22%, $p = 0.045$) and multiparity of a mother (44 v. 10%, $p = 0.021$) associated with childhood epilepsy when compared to controls (III).

In terms of measures of level of functioning, the family GARF was weaker among CPSY girls compared to APSY girls (38 vs. 56, $p < 0.001$) (IV). Having a mother with a psychiatric disorder was more common among both CPSY girls (28 vs. 13%, $p = 0.033$, OR 4.8) and CPSY boys (14 vs. 7.9%, $p = 0.018$, OR 4.0). Child welfare placement was more common among CPSY compared to APSY in both girls (34 vs. 10%, $p < 0.001$, OR 6.7) and boys (39 vs. 20, $p = 0.005$, OR 2.8). Among CPSY girls, having a mother not at work was more common than among APSY girls (60 vs. 37%, $p = 0.014$, OR 2.7), whereas CPSY boys were less likely to have a father with substance-related problems when compared to APSY boys (12 vs. 26%, $p = 0.036$, OR 0.2).

Table 8. Clinical characteristics (suicidal ideation and attempts, non-suicidal self-injury, psychiatric disorders and CGAS) assessed at index hospitalization during adolescent psychiatric inpatient care.

Clinical characteristics	Adolescent boys			Adolescent girls		
	CPSY (n = 57) n (%)	APSY (n = 151) n (%)	p- value	CPSY (n = 32) n (%)	APSY (n = 268) n (%)	p- value
Suicidality at index hospitalization						
Suicide ideation	11 (19)	42 (28)	0.209	17 (53)	134 (50)	0.738
Suicide attempts	4 (7)	22 (15)	0.142	11 (34)	67 (25)	0.253
Non-suicidal self-injury	13 (23)	14 (9)	0.010	20 (63)	97 (36)	0.004
Psychiatric disorders						
Affective disorders	18 (32)	58 (38)	0.361	21 (66)	154 (58)	0.376
Anxiety disorders	10 (18)	18 (12)	0.289	12 (38)	74 (28)	0.242
Psychotic disorders	4 (7)	26 (17)	0.062	4 (13)	36 (13)	0.883
Substance use-related disorders	20 (35)	67 (44)	0.226	12 (38)	96 (36)	0.852
Conduct and oppositional defiant disorders	44 (77)	78 (52)	0.001	16 (50)	87 (33)	0.048
CGAS ¹ , mean (sd)						
At admission	42 (9)	43 (10)	0.726	39 (6)	42 (9)	0.063
At discharge	54 (9)	53 (10)	0.583	49 (10)	54 (9)	0.002

CPSY = adolescent having child psychiatry care before admission to psychiatric inpatient adolescent care

APSY = only adolescent psychiatric care (no previous child psychiatric care)

¹ CGAS at admission and at discharge is missing for 6 boys and 8 girls

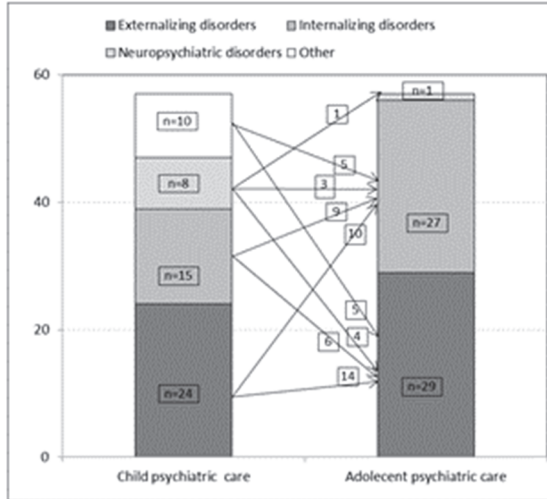
Table 9. Change in psychiatric disorders (primary diagnosis) from child psychiatric care to adolescent psychiatric care.

Psychiatric diagnoses set during child psychiatric care	Total number of subjects	Internalizing disorders in adolescence		Externalizing disorders in adolescence		Neuropsychiatric disorders in adolescence	Comorbid substance use-related diagnosis in adolescence ¹
		Affective disorders	Anxiety disorder	Psychotic disorders	Conduct/oppositional deficit disorders		
Total data (N = 89)	89						
Depression	21	11 (52.4)	1 (12.5)	2 (9.5)	5 (23.8)	2 (9.5)	5 (23.8)
Int Anxiety disorder	5	1 (20.0)	1 (20.0)	1 (20.0)	2 (40.0)		0
Psychotic disorders	5	1 (20.0)		3 (60.0)	1 (20.0)		3 (60.0)
Depressive conduct	22	8 (36.4)	2 (9.1)	1 (4.5)	11 (50.0)		11 (50.0)
Ext disorder							
Conduct/oppositional deficit disorder	8	1 (12.5)	1 (12.5)	1 (12.5)	5 (62.5)		3 (37.5)
Neuropsychiatric disorders	8	2 (25.0)		1 (12.5)	4 (50.0)	1 (12.5)	1 (12.5)
Other psychiatric disorders	20	12 (60.0)	3 (15.0)		5 (25.0)		7 (35.0)
Adolescent boys	57						
Depression	10	4 (40.0)		1 (10.0)	3 (30.0)	2 (10.0)	3 (30.0)
Int Anxiety disorder	2	1 (50.0)			1 (50.0)		0
Psychotic disorders	3	1 (33.3)		3 (60.0)			2 (66.7)
Depressive conduct	17	6 (35.3)	2 (11.8)		9 (52.9)		7 (41.2)
Ext disorder							
Conduct/oppositional deficit disorder	7		1 (14.3)	1 (14.3)	5 (71.4)		3 (42.9)
Neuropsychiatric disorders	8	2 (25.0)		1 (12.5)	4 (50.0)	1 (12.5)	1 (12.5)

Psychiatric diagnoses set during child psychiatric care	Total number of subjects	Internalizing disorders in adolescence		Externalizing disorders in adolescence		Neuropsychiatric disorders in adolescence	Comorbid substance use-related diagnosis in adolescence ¹
		Affective disorders	Anxiety disorder	Psychotic disorders	Conduct/oppositional deficit disorders		
Other psychiatric disorders	10	3 (30.0)	2 (20.0)		5 (50.0)		2 (20.0)
Adolescent girls	32						
Depression	11	7 (63.6)	1 (9.1)	1 (9.1)	2 (18.2)		2 (18.2)
Int Anxiety disorder	3	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)		0
Psychotic disorders	2			1 (50.0)	1 (50.0)		1 (50.0)
Depressive conduct	5	2 (40.0)		1 (20.0)	2 (40.0)		4 (80.0)
Ext disorder							
Conduct/oppositional deficit disorder	8	1 (100.0)					0
Neuropsychiatric disorders	0						0
Other psychiatric disorders	10	9 (90.0)	1 (10.0)				5 (50.0)

¹ Total number of subjects does not include the number of cases of comorbid substance use related disorders, because those are also counted in the group of substance use-related disorders.

a) Adolescent boys



b) Adolescent girls

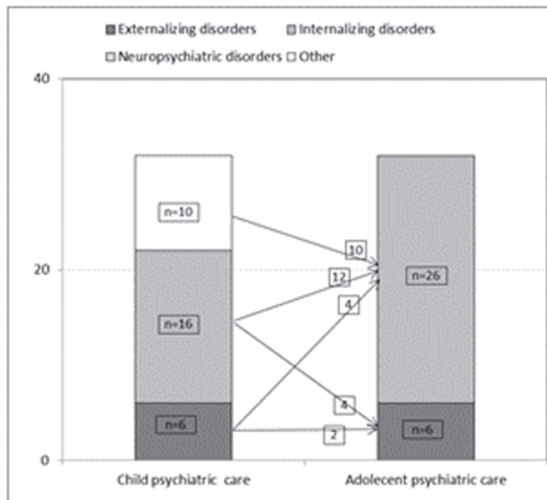


Fig. 2. Change in psychiatric diagnosis between child and adolescent psychiatric inpatient care among adolescents having a history of child psychiatric inpatient care.

6 Discussion

6.1 Overview of the results

Among this population of under-aged adolescent psychiatric inpatients, 19 of them had been exposed to obstetric complication. Of obstetric complications, previous delivery complications and especially caesarean section delivery associated with conduct disorders among boys. There was also a trend of a similar association between delivery complications and anxiety disorders among boys. Mother's substance use problems associated with obstetric complications among girls. Of specific obstetric complications, the only association that reached a statistical significance was being a blue baby at the time of birth and later conduct disorder in adolescence (I).

In comparison to healthy controls, psychiatric inpatient adolescents had lower birth length and higher ponderal index. High ponderal index associated especially with internalizing disorders among boys (II).

Febrile and other convulsions in childhood associated with later personality disorders in adolescence among boys. Febrile and other convulsions and epilepsy in childhood associated with later suicide attempts among boys in adolescence. Among girls, being middle-born and multiparity of the mother associated with childhood epilepsy (III).

Every fourth of boys and every tenth of girls in this study population had experienced previous child psychiatric care. Childhood psychiatric care associated with both anxiety and conduct disorders in adolescence among boys. Non-suicidal self-injury in adolescence was more common among both boys and girls with previous child psychiatric care when compared to those adolescents without previous child psychiatric care (IV).

Having a mother with unemployment, with a psychiatric disorder and malfunctioning of the family in terms of family GARF score associated with child psychiatric care among girls. Among both girls and boys, child welfare placement was more common among those adolescents with previous child psychiatric care than those without previous child psychiatric care. Among boys, the father's substance-related problems decreased the risk of previous child psychiatric care (IV).

6.2 Discussion of the results

6.2.1 The association of obstetric complications and psychiatric disorders

The association of obstetric complications and conduct disorders

This study revealed that boys with conduct disorder had more often experienced delivery complications than girls with conduct disorder. Already in 1956, Pasamanick and colleagues stated that prenatal and perinatal records showed significantly more complications of pregnancy, delivery and prematurity among children with behaviour disorders than among their matched controls.

Our results are in line with a previous study which found that especially birth complications associated with disruptive behaviour disorders among adolescents (Allen, Lewinsohn & Seeley, 1998). In their study, especially acute anoxia or hypoxia accounted for this association, with a three-fold risk. In our study, the only specific obstetric complication which associated with psychiatric disorders in adolescence was blue baby, which was a significant risk factor for conduct disorders among these adolescents. In addition, in this study, especially caesarean section associated with conduct disorders among boys. Caesarean section may associate with anoxia or hypoxia; if a baby is suffering from anoxia or hypoxia, an emergency caesarean section may be required.

An interesting study has found that maternal distress during pregnancy elevates the risk of caesarean section and the likelihood of early childhood disorders, including conduct disorder (Martini, Knappe, Beesdo-Baum, Liebb & Wittchen, 2010). In their study, like in the present study, the information about obstetric complications was based on the recall of a mother. Offspring mental disorders were diagnosed according to DSM-IV criteria.

The association of obstetric complications and anxiety disorders

This study showed a trend between delivery complications and anxiety disorders among boys. This is in line with previous studies in which delivery complications increased the risk for offspring anxiety disorders (Geller et al., 2008; Brander et al., 2016; Freed et al., 2014). In the latter study, offspring were four to 33 years of age, with a mean age of 13.6 years. They also found a link between maternal anxiety

disorder and obstetric complications. In fact, path analyses suggested that delivery complications mediated the relationship between maternal anxiety disorder and offspring anxiety disorder. This outlines a shared vulnerability of offspring anxiety disorder of both genetic and early environmental pathways. A large Swedish population-based cohort study found that delivery complications and also caesarean section elevated the risk of obsessive-compulsive disorder among offspring (Brander et al., 2016). The mean age at the first diagnosis of OCD was 23.4 years.

Other studies have also found the association between obstetric complications, also pregnancy complications and offspring anxiety disorders in childhood and adolescence (Hirshfeld-Becker et al., 2004; Geller et al., 2008).

6.2.2 The association of birth measures and psychiatric disorders

The association of birth measures and schizophrenia

In the present study, adolescents with psychiatric disorders had more likely small birth length than controls without any psychiatric disorders. In the Helsinki High-Risk (HR) Study, especially girls treated for schizophrenia spectrum disorder at adolescence or early adulthood were shorter at birth than controls (Niemi, Suvisaari, Haukka & Lönnqvist, 2005). Association between shortness at birth and schizophrenia in adulthood has also been found in several studies (Wahlbeck, Forsén, Osmond, Barker & Eriksson, 2001; Gunnell et al., 2005; Moilanen et al., 2010).

The association of birth measures and externalizing disorders

Short birth length has been associated with behavioural problems, especially hyperactivity and conduct problems at the age of seven (Wiles et al., 2006). They postulated an interesting explanation for why birth length rather than birth weight associated with psychiatric problems. The length increases more rapidly in the first two trimesters, as does the timing of the most critical period for brain development. Disturbances in this period may therefore affect both length and the development of psychiatric illness. On the contrary, the most rapid weight gain time is in the final trimester. Low ponderal index has also been associated with behavioural symptoms of ADHD at the age of six (Lahti et al., 2006).

The association of birth measures and internalizing disorders

In this study, high ponderal index associated with psychiatric disorders and especially with internalizing disorders, namely depression, anxiety or psychotic disorders, among boys. To my knowledge, the association of high ponderal index and internalizing disorders in adolescence is a novel finding. Previous studies have found an association between high ponderal index and internalizing disorders in adulthood. Herva and colleagues (2008) found that high ponderal index associated with depression in adulthood, but only among girls. Also low ponderal index has been associated with schizophrenia in adolescence or early adulthood (Niemi, Suvisaari, Haukka & Lönnqvist, 2005) and anxiety disorders in adulthood (Vasiliadis, Buka, Martin & Gilman, 2010). However, these studies assessing internalizing disorders found the association mostly with adulthood psychiatric disorders, whereas we study the association in adolescence. Also, we studied boys and girls separately, which may bring out new associations. Finally, many confounding, both contributory or protective factors, may contribute to the association between early birth measures and later psychiatric disorders.

6.2.3 *Epilepsy, febrile and other convulsions in childhood and psychiatric disorders*

Epilepsy, febrile and other convulsions in childhood and suicidality in adolescence

Both epilepsy in childhood, febrile and other convulsions associated with suicide attempts among adolescent boys in this study. Previously, children and adolescents with epilepsy have been found to have more suicidal ideation than children without epilepsy (Caplan et al., 2005). However, none of them had made a suicide attempt. The explanation for why in our study sample it was especially suicide attempts that differed between children with convulsive disease and controls, could be that our patient sample was older, as all participants were adolescents at the time of evaluation of suicidality. On the contrary, in the study by Caplan and colleagues, the age among the patient sample varied between 5-16 years. However, in their study, even 37% of the patients had suicidal plans. Perhaps if there would have been a longer follow-up period, suicide attempts may have also occurred. Finally, in the study by Caplan and colleagues, especially children with epilepsy who had a

combined disruptive and affective/ anxiety disorder were 12 times more likely to have suicidal ideation than those without a psychiatric diagnosis.

One previous study has found a trend towards the association between male epileptic patients and suicidality (Kalinin & Polyanskiy, 2005). When they assessed suicidal attempts separately, they found a statistically significant difference between boys when compared with the joint group which comprised both boys and girls. The risk of suicide attempts among patients with epilepsy has been found to be increased even before the onset of epilepsy (Hesdorffer et al., 2016).

However, to my knowledge, no previous study has found an association between febrile and other convulsions and later suicidality in adolescence.

Epilepsy, febrile and other convulsions in childhood and personality disorders in adolescence and young adulthood

We found that febrile and other convulsions in childhood associated with personality disorders in adolescence among boys. Previous studies have found associations between epilepsy and personality disorders among adults (Machanda et al., 1996; Perini et al., 1996) and in childhood (Dunn, Austin & Perkins, 2009). In the latter study, children suffering from epilepsy were 9-14 years old at the time of psychopathology evaluation. Childhood epilepsy associated with antisocial personality, especially among a subgroup of 13-14-year-old children. In our study, adolescents were older, 13-17 years old at the time of index hospitalization, prior to personality disorder development. The mean age among study subjects at the time of diagnosis for personality disorder was 20.3 years among boys and 19.2 years among girls. A review of the association between epilepsy and suicide concluded that one of the main risk factors for suicide among epileptic patients was psychiatric comorbidity, including personality disorders (Verrotti et al., 2008). Another study found that borderline personality disorder significantly predicted prospective suicide attempts (Yen et al., 2003). In our study, personality disorders may also counterpart the association between childhood febrile and other convulsions and suicide attempts among adolescent boys. Most of the personality disorder cases in this study were borderline personality disorders.

Birth order, maternal parity among children with epilepsy and psychiatric disorders in adolescence

Finally, this study revealed that in the study group of girls with previous childhood epilepsy, being middle-born and maternal multiparity were more common than among controls of the same study population without childhood epilepsy. A previous study among this same study population, Study-70, revealed that girls from large families had a four-fold increased risk for psychosis other than schizophrenia (Kylmänen et al., 2010). In another study, higher maternal parity increased the risk of psychiatric admissions, suicide and self-harm of adolescent offspring (Riordan, Morris, Hattie & Stark, 2012). Being middle children in the birth order has been previously associated with later depression in adolescence and higher birth order (≥ 2) has been also linked to more deliberate self-harm in adolescence (Putter, 2003; Hu et al., 2017). The association of being middle-born and multiparity with epilepsy among girls with later psychiatric disorders found in this study, is complex and requires an advanced approach, taking into account more widely potential confounding factors and biological, social and psychological aspects.

6.2.4 The association of child psychiatric care and psychiatric disorders in adolescence

Of all study subjects, 18% had previous child psychiatric care before admission to adolescent psychiatric inpatient care. Previous child psychiatric care was more common among boys than girls, with every fourth of the boys having previous child psychiatric care versus only every tenth of the girls. This finding is supported by nationwide statistics in Finland, revealing that there is an excess of adolescent boys in psychiatric treatment in childhood (The National Institute for Health and Welfare, 2016).

In this study, a history of child psychiatric care associated with anxiety or conduct disorders among boys in adolescence. The continuity of psychiatric problems and disorders from childhood to adolescence is supported by previous studies (Costello, Angold & Keeler, 1999; Costello, Mustillo, Erkanli, Keeler & Angold, 2003; Mesman & Koot, 2001; Goodwin, Fergusson & Horwood, 2014). Children with a history of psychiatric disorder have been found to have a three times greater likelihood to have a later psychiatric diagnosis in adolescence than those with no previous disorder (Costello, Mustillo, Erkanli, Keeler & Angold,

2003). A study of 300 children aged 7-11 years with psychiatric disorders found a considerable continuity of psychopathology in adolescence (Costello, Angold & Keeler, 1999). Among boys, especially behavioural disorders showed continuity to adolescence, whereas among girls, emotional disorders were strongly predictive only among girls.

Psychiatric problems, even as early as in 2-3 years of age, have been found to predict psychiatric disorders eight years later (Mesman & Koot, 2001). Also, a Finnish study assessing psychiatric problems at the age of three found that especially externalizing problems predicted both externalizing and internalizing problems later at the age of 12 years (Pihlakoski et al., 2006). The study by Mesman and Koot (2001) found internalizing and externalizing problems have relatively homotypic continuity. In the present study, psychiatric disorders from childhood to adolescence also seemed to have homotypic continuity, except concerning anxiety disorders. Costello and colleagues (2003) found also that homotypic continuity was significant for all disorders except specific phobias, which are included in the category of anxiety disorders. They also found that all the heterotypic continuity which occurred was seen among girls. In this present study also, especially homotypic continuity was more common among boys than girls.

A study extending from childhood through adolescence to adulthood found that 26% of the study population of 1000 adult psychiatric inpatients had had former child and adolescent inpatient care (Fuchs et al., 2016). Both homotypic and heterotypic continuity was seen from childhood to adulthood. Another study also found that only 16.5% of cases with psychiatric disorder had their first diagnosis as adults (Newman et al., 1996).

Especially children with combined conduct and internalizing problems at the age of eight years have been found to have worse long-term outcomes when compared to those with only conduct problems without internalizing problems or when compared to children with attention problems (Sourander et al., 2007). Children with combined conduct and internalizing problems more often had subsequent psychiatric disorders, criminal offenses and self-reported problems later in adolescence and young adulthood. Another study found that children with a diagnosis of oppositional defiance, and especially those with major depression, were more likely to be readmitted to psychiatric inpatients (Foster, 1999). In this thesis, boys with anxiety or conduct disorders were more likely to have a history of child psychiatric care.

In this thesis, at discharge from adolescent inpatient care, the CGAS points measuring the level of functioning were lower among girls with a history of child

psychiatric care than among those girls without a history of child psychiatric care. Previous studies have indicated that those with a previous history of psychiatric disorder in childhood and adolescence have a greater likelihood of worse prognosis and more often comorbid diagnoses (Newman et al., 1996; Kovacs, 1996; Kim-Cohen et al., 2003; Lauronen et al., 2007). Finally, in a follow-up study among children and adolescents with depression, female gender associated with a worse longitudinal course (Birhamer et al., 2004).

6.2.5 The association of child psychiatric care and suicidality in adolescence

This study showed that adolescents with previous child psychiatric care had more often non-suicidal self-injury in adolescence than those without. Previous literature supports this finding (Haavisto et al., 2005; Mitrou, Gaudie, Silburn, Stanley & Zubrick, 2010). A Finnish study among boys revealed that self-reported depressive symptoms at eight predicted suicide ideation and acts of deliberate self-harm at the age of 18 years (Haavisto et al., 2005). Especially, anxious or depressed symptoms and aggressive behaviour associated with later suicidal tendency. Mitrou and colleagues (2010) also found that emotional and behavioural problems at the age of 4-16 years associated with deliberate self-ham later in adolescence and adulthood. In the present study we had information on psychiatric diagnoses according to diagnostic schedules, which reinforces these previous findings. Other studies have also shown that previous psychiatric disorders, like mood disorder, as well as previous suicidality, associate with suicidality in adolescence (Shaffer et al., 1996; Brent et al., 1993).

6.2.6 The association of family characteristics and psychiatric disorders

This study revealed that child welfare placement was more common among those adolescents with a history of child psychiatric care than among adolescents without previous psychiatric care in childhood. A large study population among children and adolescents looked after by local authorities found a higher level of psychopathology among them (46.4%) when compared to a disadvantaged private household sample (14.6%) and from the private household sample (8.5%) (Ford, Vostanis, Meltzer & Goodman, 2007). A variation in prevalence of psychiatric disorder according to where a child or adolescent is placed has been found. Among

a study population of children in foster care, every second of them met the criteria for one or more DSM-IVC disorders (Lehmann et al., 2013). Moreover, over half of them had comorbid diagnoses of the main diagnostic groups. When another study analysed psychiatric disorders among adolescents in the foster care system, they found an even higher occurrence, with 61% having at least one psychiatric disorder during their lifetime (McMillen et al., 2005). Among adolescents placed in residential units, the prevalence of psychiatric disorders has been found to be even higher; as much as 96% of them had a psychiatric disorder. Also, Ford and colleagues (2007) found the highest prevalence of psychiatric disorders (71%) among children living in residential care. The present study reinforces the association between placement outside the primary family and psychiatric disorders.

In the present study, disadvantaged family characteristics had the greatest impact on girls who had previous child psychiatric care. These disadvantages included child welfare placement, but among girls also maternal unemployment, maternal psychiatric disorders and lower family GARF points were of significance. Neither parental disadvantage nor maternal disadvantages among boys was found. Maternal psychopathology clearly associates with psychiatric disorders of the offspring in childhood and adolescence (Apter, Bobin, Genet, Gratier & Devouche, 2017; Pawlby, Hay, Sharp, Waters & O'Keane, 2009; Glasheen et al., 2013; Pearson et al., 2013). Maternal mental illness has been associated with higher risk of involvement in the child welfare system (Park, Solomon & Mandell, 2006; Kohl et al., 2011). Considering that parental psychopathology also often leads to unemployment, the accumulation of adverse family characteristics is understandable. So, why are girls more sensitive to these risk factors, indicated by the fact that they were in need of earlier psychiatric care in childhood? One theoretical approach to explaining this is that the aetiology of psychiatric disorders among boys is more genetic, while among girls environmental factors play a greater role.

6.3 Strengths and limitations

6.3.1 Strengths of the study

The main strength in this study is accurate and valid psychiatric diagnosis derived from a semi-structured diagnostic interview K-SADS-PL made by a specialist

which minimizes the likelihood for subjective bias. K-SADS-PL itself has been found to be a reliable instrument to evaluate DSM-IV-based diagnoses among adolescents (Ambrosini et al., 2000; Kaufman et al., 1999; Kim et al., 2004).

The second strength of this work is that the study comprised a large sample of adolescents in need of psychiatric closed-ward treatment in the catchment area. This area comprises a geographically large area in Northern Finland, which covers about 45% of Finland's whole geographic area. All adolescents who are in need for acute psychiatric inpatient care are treated in Unit 70. Thus, the study population represents the most serious cases of adolescents with psychiatric disorders in this area. Considering that the participation percent was relatively high, with 84% of all those eligible participating in this study, this study is highly representative in this population. In addition, in the second work (II), a strength was the case-control setting where both cases and controls have the same catchment area, are comparable in terms of age, gender and time of birth.

The third strength in this study is the diverse use of national registers. Birth measures were based on the Medical Birth Register (II), whereas information on childhood seizure, epilepsy, personality disorders and childhood psychiatric disorders (III, IV) were gathered from the Finnish Care Register for Health care (FCRHC), with both datasets held by the National Institute for Health and Welfare. The validity of personality disorders was excellent, since it was based on reliable register data of hospital discharge registers and the inclusion criteria was 18 years of age or older.

The information on mortality (IV) was based on the National Register of Causes of Death, held by Statistics Finland. These registers provide specific, verified and accurate diagnoses of these childhood diseases and personality disorders in adolescence and early adulthood. They are found to be a reliable source of information (Miettunen, Suvisaari, Haukka & Isohanni, 2011; Lahti & Penttilä 2001).

All cases with childhood seizures and epilepsy were further verified by a clinician under the supervision of an expert in a field of neurology (H.A). This process also enabled the exclusion of those patients with a psychiatric disorder prior to convulsion or epilepsy, or those with provoked seizures due to such factors as substance use or central nervous system infection. Childhood psychiatric disorders were hierarchically classified by an expert in the field of childhood psychiatry (A.P) and in (IV) also psychiatric disorders among adolescents were classified hierarchically by two experts (K.R, P.R).

Finally, all information on family-related factors except family type and sibling position was gathered using the EuropASI questionnaire, which is a reliable and valid source of information among substance using populations (Kokkevi & Hartgers, 1995).

6.3.2 Limitations of the study

The main limitation in this study is that this is a clinical study among adolescents with the most severe form of psychiatric disorders, and thus the generalization of these study findings to the general population should be done with caution.

Due to the relatively small sample size, especially in some subgroup analyses, may have caused type II error, which means that some findings may not have reached statistical significance. Many statistical comparisons may have caused type I error, leading to chance findings. Small sample size also enabled assessment of the association between such variables as birth measures and specific psychiatric disorders like depression or conduct disorder. Instead, associations were found in larger main groups, internalizing and externalizing disorders groups (II). In particular, this was a limitation in the III work, with a small number of cases with febrile and other seizures in childhood and epilepsy. Therefore, the evaluations of the association between specific epilepsy type or certain type of antiepileptic medication and psychiatric disorders were impossible.

The lack of inter-rater agreement between researchers and clinicians who conducted the K-SADS-PL interview may be considered as a limitation of this study. This thought was abandoned because the additional interviews would not be inappropriate due to the young age of the participants, the severity of psychiatric disorders among them and the short length of their stay in psychiatric care (Luukkonen, 2010).

In the first work (I), a limitation is that the information about obstetric complications was obtained retrospectively by interviewing the adolescent's mother. This may cause a recall bias. However, maternal self-reports of obstetric complications are found to be objective (O'Callaghan, Lerkin & Waddington, 1990).

Another important limitation is the lack of accurate, register-based information about parental psychopathology. Instead, it was based on a EuropASI questionnaire and the information was obtained from adolescents and is therefore a subject of subjective bias. On the other hand, for parental characteristics, adolescents' self-reports have been found to be as reliable as data sources (Pisinger, Bloomfield &

Tolstrup, 2016). Also, maternal substance use during pregnancy was self-reported and may be underestimated since mothers tend to underreport this kind of behaviour.

Finally, a limitation in this study is that K-SADS-PL (version 1.0, Oct 1996) does not include autism spectrum disorders as does the newer version of the K-SADS-PL-interview. This would have been important information, especially in IV work assessing childhood psychiatric disorders.

7 Conclusions

7.1 Main conclusions

This thesis showed that boys encountered many adverse effects during the perinatal and early childhood period, such as delivery complications, deviant birth measures, childhood epilepsy, febrile and other convulsions and later psychiatric disorders in adolescence. Delivery complications, and especially caesarean section, increased the risk for conduct disorders, and to a lower extent, for anxiety disorders in adolescence among boys. At the time of birth, high ponderal index associated with internalizing disorders in adolescence among boys, and finally in childhood, epilepsy, febrile or other convulsions increased the risk for suicide attempts in adolescence and personality disorders in adolescence and young adulthood. These findings may indicate that boys are more vulnerable to adverse biological effects in early development.

Among girls, the accumulation of many adverse family-related factors was evident, especially among those with early-onset psychiatric disorders already in childhood. These included maternal psychiatric disorders, maternal unemployment and family malfunctioning. This may indicate that girls are more vulnerable to maladaptive environmental circumstances, rather than biological effects.

Finally, among both genders, child welfare placement was more common among adolescents with psychiatric disorders as early as in childhood. The need for child welfare placement often presents complex problems associated with the individual, the family involved and their surroundings.

7.2 Implications for further research

Future research on the association between obstetric complications and psychiatric disorders among adolescent psychiatric inpatients is needed with more accurate, register-based information on obstetric complications. Studies with larger study populations may also bring out more precise associations between birth measures and specific psychiatric disorders. Also, studies that consider potential biological effects, namely genetic factors and parental psychopathology, are important targets for future studies. For example, one such area of further study could be uncovering how childhood epilepsy and other convulsions and perinatal factors counterpart

each other among psychiatric adolescent patients. Studies involving neuroimaging may also enlighten the association.

7.3 Clinical implications

Children and adolescents with a history of obstetric complications and deviant birth measures should be prioritized for targeted preventative actions. Especially children with a history of febrile or other convulsions and childhood epilepsy should be identified and have more accurate psychiatric evaluations. It has been estimated that among children and adolescents with epilepsy, 60% of them meet criteria for DSM-IV psychiatric disorders, but only 33% of them receive appropriate psychiatric treatment (Ott et al., 2003). In this light, consultation and liaison psychiatry is needed in the interface between child neurology and child psychiatry. A study assessing psychiatric diagnoses after epilepsy diagnosis found that the highest risk for occurrence of psychiatric disorder was the first year after epilepsy diagnosis (Chang, Liao, Hu, Shen & Chen, 2013). Therefore, concerning psychiatric effects, sufficient surveillance is crucial following epilepsy diagnosis. Longitudinal surveillance among children with psychiatric disorders should be ensured and continue to adolescent psychiatric care when needed.

Finally, targeted family interventions should be addressed to children, and according to this study, especially to girls in child psychiatric care. Psychosocial support should be focused to families already in the child health centre at the time of pregnancy and after the child is born. For families with already identified problems, more active supportive and preventive actions should be applied such as social work and family interventions. Especially families with parental psychiatric problems should be ensured sufficient support.

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- III Lukkari S, Hakko H, Kantojärvi L, Riala K, Riipinen P, Ansakorpi H. Childhood seizures and adolescent psychiatric disorders: a population-based study of adolescent psychiatric inpatients in Finland. *Manuscript*.
- IV Lukkari SH, Hakko HH, Partanen MA, Riala KR, Riipinen PK. (2019). Characteristics of Adolescent Psychiatric Inpatients in Relation to Their History of Preceding Child Psychiatric Inpatient Care. *Journal of Nervous and Mental Diseases*, 207(7), 569-574.

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