

Milla Toivonen

Emotional and behavioral problems of adolescents born preterm

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TOIVONEN MILLA: Emotional and behavioral problems of adolescents born preterm

Maailman terveysjärjestö (WHO) määrittelee keskoseksi vastasyntyneet, jotka ovat syntyneet ennen raskausviikkoa 37. Nuorilla, jotka ovat syntyneet keskosena, on kirjallisuuden mukaan enemmän tunne-elämän ongelmia ja käytösoireita kuin täysiaikaisena syntyneillä. Tämän opinnäytetyön kirjallisuuskatsaus käsittelee nuoruusiän tyypillisimpiä mielenterveyden häiriöitä keskosilla ja verrokeilla.

Opinnäytetyön tutkimusosuudessa on tutkittu suomalaisten keskosena syntyneiden nuorten käyttäytymisen ja tunne-elämän ongelmia 17 vuoden iässä verrattuna täysiaikaisena syntyneisiin. Opinnäytetyön aineisto on kerätty osana PIPARI (Pienipainoiset Riskilapset) -tutkimusta, joka on Turun yliopistollisen keskussairaalan lastenkliniikalla vuonna 2001 käynnistetty pitkäaikaisseurantatutkimus. Tutkimuksessa on seurattu kuuden vuoden aikana syntyneitä keskosia heidän syntymästään lähtien nyt jo täysi-ikäisyyden kynnykselle. Tässä opinnäytetyössä on tarkasteltu kahden ensimmäisen vuosikohortin itse raportoimia käyttäytymisen ja tunne-elämän ongelmia.

Tutkittavat täyttivät CBCL (Child Behaviour Checklist) -itsearviointilomakkeet, joissa on tunne-elämään, käyttäytymiseen ja sosiaalisiin vaikeuksiin liittyviä kysymyksiä. Oirekokonaisuuksia ovat ahdistuneisuus/masentuneisuus, vetäytyneisyys/masentuneisuus, somaattinen oireilu, sosiaaliset vaikeudet, ajattelun vaikeudet, tarkkaavuuden ongelmat, sääntöjä rikkova käyttäytyminen ja aggressiivinen käyttäytyminen. Opinnäytetyössä vertailtiin keskosena ja täysiaikaisena syntyneiden nuorten käyttäytymisen ja tunne-elämän ongelmia CBCL-YSR -lomakkeiden avulla. Vertailu tehtiin myös tyttöjen ja poikien välillä.

Keskosena syntyneet nuoret raportoivat verrokkeja vähemmän eksternalisoivia eli ulospäin suuntautuvia oireita. Suurempi osa keskosena syntyneistä nuorista ylitti kliinisen rajan internalisoiville eli sisäänpäin suuntautuille oireille verrattuna verrokkeihin. Sosiaalinen kompetenssi oli verrokeilla parempi kuin keskosilla. Tutkimuksen tulokset olivat osittain samansuuntaisia aiempien kansainvälisten keskostutkimusten kanssa. Otokoko työssä oli pieni, joten lisätutkimusta aiheesta tarvitaan.

Asiasanat: keskonen, käytöshäiriöt, tunne-elämän ongelmat, internalisoivat oireet, eksternalisoivat oireet

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1 Introduction

The psychological development of a child begins with the development of the brain already during the fetal period and it continues throughout the life. This long developmental time frame is especially vulnerable for mental disturbances. The development is especially rapid from the fetal period to the adolescence. Any factors causing long term stress to an individual during the first years of life e.g. being born premature, may affect the brain development and thus also the psychological development. Other factors which may contribute to the psychological development of the child are physical development, genetic factors and environmental factors. (Kumpulainen et al. 2017.)

Adolescence is a time-period of rapid physical, psychological and social development. Mental health issues are one of the most common disorders in adolescence and approximately 20–25 % of adolescents suffer from a mental disorder in Finland. Mental disorders are one of the most common disorders in childhood and youth. (Nuorten mielenterveyshäiriöt. THL. www.thl.fi, Ranta et al. 2020) It is also notable that half of the mental disorders begin already in childhood and three quarters occur before 24 years of age. (Lasten ja nuorten mielenterveys. THL. www.thl.fi)

Prematurity is an acknowledged risk factor for neurocognitive, psychological and social problems. These adversities continue until later childhood and adolescence. (Kumpulainen et al. 2017.) An increased risk for these problems has been associated with intensive care in the hospital after birth, premature organs and parental stress. (Huhtala et al. 2014, 2012 and 2011). The quality of early interaction between the child and the parents affect the psychological development of the child. In the families with premature infants, the early interaction may be affected already in the neonatal intensive care unit (NICU). (Kumpulainen et al. 2017.) Also, the physical consequences of preterm birth, such as i.e. neonatal respiratory distress syndrome (RDS), necrotizing

enterocolitis (NEC), intraventricular hemorrhages and infections, may affect the psychological development (Heinonen and Fellman 1997).

2 Review of literature

2.1 Preterm birth

According to the definition of World Health Organization (WHO), infants born before 37 weeks of gestation are born preterm. Based on gestational age (GA) infants born extremely preterm (EPT) are born before 28 weeks of gestation. Infants born very preterm (VPT) are born between 28 and 32 weeks of gestation and infants born late preterm are born between 32 and 37 weeks of gestation. The vulnerability of infants born preterm is also described by a weight classification. A very low birth weight (VLBW) is considered as a birth weight below 1500 g and extremely low birth weight (ELBW) as birth weight below 1000 g.

Globally, about 15 million infants were born preterm in 2010, which is about 10 % of all live births. In several European countries, the prevalence of preterm birth is about 5 % in comparison to 18 % in some African countries (Blencowe et al. 2012). According to the Finnish Institute for Health and Welfare, Finland (THL), there were 47 913 live births in Finland, in 2018. Of those infants, 2772 (5.8 %) infants were born preterm. Four hundred eleven infants were born VPT, which is 0.9 % of all live births. (Perinataaltilasto-synnyttäjät ja synnytykset 2018. THL. www.thl.fi)

2.1.1 Risk factors for preterm labor

There are several risk factors for preterm labor, all of which are not excessively well understood. Indicated preterm births include about 30–35 % of all preterm births. Approximately 40–45 % of all preterm births occur because of spontaneous preterm labor and 25–30 % happen after preterm premature rupture of membranes. (Goldenberg et al. 2008.) It is also notable, that almost 60 % of twins are born prematurely (Goldenberg et al. 2008.).

The risk factors for preterm labor can be associated with the fetus, genetic factors, infections and some environmental factors such as stress and socioeconomic status of

the family (Evren et al. 2016, Zhang et al. 2017.) The causes of preterm birth differ between the ethnic groups (Goldenberg et al. 2008). Nadeau et al. (2016) showed an association between infections and preterm birth. Approximately 25–40 % of preterm births are associated with a genital tract infection of the mother. (Nadeau et al. 2016.) Infections are associated with most preterm births of 30 weeks of gestation or less, but rarely in preterm births of from 34 to 36 weeks of gestation (Goldenberg et al. 2000).

2.1.2 Prematurity-related morbidities

The lower the birth weight is, the higher is the risk for morbidity and mortality. The morbidity is associated with the immaturity of the preterm infant, which leads to a higher risk of different acute complications in different organs compared to infants born at term. (Heinonen and Fellman 1997.) In addition, there is an association between chronic morbidity and preterm birth. Survival rates of premature infants have increased but infants born preterm are still at a higher risk for chronic illnesses compared to those born term. (Saigal and Doyle 2008.)

Infants born VPT/VLBW are at risk for respiratory problems in terms of neonatal RDS and chronic lung disease (CLD). The prevalence for RDS is 78 % in infants with birth weight between 501 and 750 g and 26 % in the infants with birth weight between 1251 and 1500 g. (Lemons et al. 2001.) CLD affects 52 % and 7 % respectively (Lemons et al. 2001.) Children born preterm are at a higher risk for abnormal pulmonary function compared to term born children (Gross et al. 1998).

The immaturity of the bowel, inflammation and decreased blood circulation can lead to NEC. NEC is seen in different degrees of severity and leads to a bowel perforation in approximately 33 % of the cases. (Rajantie et al. 2016, Kafetzis et al. 2003.) Incidence of NEC in newborns is approximately 0.7 in 1000 live births and the incidence in infants born VLBW infants is about 6.6 %. (Llanos et al. 2002, Sankaran et al. 2004) The infants born preterm are also at increased risk for developing different infections due to the

immature immune system. After the birth, one third of the infants born preterm get a septic infection (Heinonen and Fellman 1997.)

Children born preterm are at an increased risk for hearing impairments, visual impairments and growth problems compared to children born at term (Hirvonen et al. 2018, Behrman and Butler 2007).

2.1.2.1 Long term neurocognitive morbidity

Preterm born infants have an immature nervous system and they are at a risk for different types of brain injuries in neonatal period i.e. germinal matrix-intraventricular hemorrhage, periventricular hemorrhagic infarction, periventricular leukomalacia and axonal injuries (Volpe 2009). Approximately 15 to 20 % of infants born before 32 weeks of gestation are affected by intraventricular hemorrhage. (Szpecht et al. 2016.) Disturbances in brain development caused by preterm birth may be associated with psychiatric and neuropsychiatric problems, learning difficulties, problems with language and cerebral palsy (CP) (Johnson and Marlow 2017).

In particular, children born <26 weeks of gestation age are at a risk for learning difficulties and intellectual disability, but this is also seen in the whole group of infants born VPT (Nyman et al. 2019, Johnson et al. 2016). Children born EPT are also at a higher risk for executive function deficits, which affect the school performance (Johnson et al. 2016). Children born VPT have more educational problems, more learning difficulties, lower classroom performance and lower academic performance at the age of 6 and 11 (Nyman et al. 2019, Pritchard et al. 2008).

Children born VPT are at a 3-fold risk for developmental coordination disorder (DCD) compared to children born term (Spittle et al. 2020). DCD is defined as motor difficulties, which are not caused by a neurological condition, visual impairment or intellectual disability (Blank et al. 2019). Preterm birth is a risk factor for epilepsy later in childhood. Intracranial hemorrhage and convulsions in the neonatal period are the

two most prominent risk factors for epilepsy in preterm born children. The incidence increases with decreasing GA. (Hirvonen et al. 2017.)

2.2 Behavioral problems in adolescence

In Finland, approximately 20 % of adolescents have a mental disorder. More specifically 12–15 % of adolescents have depression or anxiety disorder. (Ranta et al. 2020, Kumpulainen et al. 2017.) The prevalence of mental disorders is at its highest in the adolescence (de Girolamo et al. 2012). Many of the mental disorders that threaten the performance and quality of life in adulthood arise in adolescence, approximately at the age of 16 and 75 % of these disorders arise before the age of 24 (Kaivosoja 2019).

Prevalence of behavioral problems is associated with many risk factors including genetic factors, neurobiology, the temper of the individual, personality factors, social competences, parenting and the growing environment. The likelihood of developing a behavioral disorder increases when an individual has multiple risk factors. (Murray and Farrington 2010.) Among others, preterm birth is an acknowledged risk factor for behavioral problems (Johnson and Marlow 2017).

2.2.1 Terminology in behavioral problems

Behavioral problems are divided into two categories, externalizing and internalizing problems. The psychiatric morbidity can also be described in terms of symptoms, traits or diagnoses.

Internalizing problems refer to emotional disturbances which affect the individuals themselves. Psychiatric disorders such as depression, anxiety disorders, eating disorders, stress disorders and bipolar disorder are referred as internalizing disorders. Internalizing symptoms include feelings like anxiety, sadness, fear, and anhedonia. (Cutler 2014, Willner et al. 2016).

Externalizing problems refer to behavioral disturbances which affect mostly the individual's outward behavior. Psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD) are referred as externalizing disorders. Externalizing symptoms include conduct problems, aggression, hyperactivity, attention problems, and oppositionality (Cutler 2014, Willner et al. 2016.)

2.2.2 Emotional and behavioral problems of adolescents born preterm

Children born VPT/VLBW are at an elevated risk for developing emotional and behavioral problems and this can affect the quality of life of the child or their family (Hayes and Sharif 2009, Loe et al. 2011). Burnett et al. (2011) showed that preterm/low birth weight (LBW) children are at a 3.5 times higher risk of developing a psychiatric condition in childhood and adolescence compared to children born term (Burnett et al. 2011).

2.2.2.1 Depression

Depression is a mood disorder which can manifest in multiple ways. The main symptoms of depression are depressed mood, anhedonia and fatigue. Other symptoms include insomnia, low self-esteem, feeling guilty, change in weight, suicidal thoughts, concentration difficulties, and psychomotor retardation. (Kumpulainen et al. 2017, ICD-10.)

In adolescence, the manifestation of depression can be different compared to adults. In early adolescence physical symptoms, behavior disturbances and agitation may be the most prominent signs of depression. In addition, decreased school performance and increased risk taking are associated with depression in early adolescence. Later in adolescence the symptoms of depression may turn more inwards and manifest as pessimistic thinking, depressed mood, and specific suicidal thoughts. (Kumpulainen et al. 2017.)

Depression becomes more common around puberty and is one of the most common disorders in adolescence (Kumpulainen et al. 2019). In 2019, 11 % of males and 24 % of females in the 8th and 9th grade had experienced depressive symptoms over last two weeks, whereas in the first two years of high school, the prevalence was 12 % and 22 % respectively. (Kouluterveyskysely 2019.) From 5 to 10 % of Finnish adolescents have a depressive disorder (THL. Nuorten masennusoireilu ja masennustilat).

2.2.2.2 Depression in adolescents born preterm

An increased risk for emotional problems such as depression and anxiety has been reported in VLBW and ELBW children and adolescents (Johnson and Marlow 2011). Johnson et al. (2010) showed that children born EPT are four times more likely to have an emotional disorder compared to term-born peers. In the study of Chiu et al. (2019), children born preterm were at a 2.75-folded risk for depression at the age of 9 compared to children born term. Parents of adolescents between 12 and 16 years of age born ELBW have reported more depression symptoms compared to parents of term born controls (Saigal et al. 2003). Patton et al. (2004) showed a 6-fold risk for depressive disorder in adolescents born preterm compared to term born adolescents. The term born boys had a cumulative rate of 0.25 % and girls 1.8 % of depression. Respectively the rates were 1.0 % for preterm born boys and 15.2 % for preterm born girls. The mean ages in this interview study were 15.0 and 17.4. (Patton et al. 2004.) In Sweden, Nosarti et al. (2012) showed that adolescents born between 32 and 36 weeks of gestation are diagnosed with depression at 16 years of age 1.3 times more likely than adolescents born term. Adolescents with GA <32 weeks had a 2.9 times higher risk for depressive disorder at the age of 16. (Nosarti et al. 2012.)

Chiu et al. (2019) suggested that the reason for higher risk of depression in adolescents born preterm is multifactorial. They may experience poorer maternal conditions such as poor nutrition, psychological stress and infections. (Chiu et al. 2019.) Those intrauterine conditions can cause stress to the infant even before the birth (Upadhyaya et al. 2020). Intensive care after the birth also creates a stressful environment for

infants. Stress in early life may affect the hypothalamic-pituitary-adrenal axis and so make preterm infants more prone to develop depression later in life. (Chiu et al. 2019.) Neurodevelopmental impairments may influence the development of depression (Nosarti et al. 2012). Other mechanisms that are related to the higher risk for depression might be genetic (Upadhyahya et al. 2020.)

2.2.2.3 Anxiety disorders

Anxiety disorders include several types of disorders ranging from specific fear to generalized anxiety and are characterized with anxiety that affect activities of daily living and lower the quality of life. The different types of anxiety disorders include generalized anxiety disorder (GAD), panic disorder, separation anxiety, specific phobias, agoraphobia and social anxiety disorder (SAD). Typical symptoms of anxiety disorders are exaggerated worrying or fears and avoiding the causes of these worries and fears. Sometimes anxiety may cause physical symptoms such as hyperventilation, pain in different body parts or nausea or manifest mainly as anger. (Kumpulainen et al. 2017.)

The most common anxiety disorders in adolescence are SAD, agoraphobia and panic disorder. GAD typically develops in adolescence or early adulthood. (Kumpulainen et al. 2017.) Moderate to severe anxiety was experienced by 20 % of females and 6 % of males in adolescents in 8th and 9th grade. The prevalence was equal in the 1st and 2nd grade in high school in 2019. (Kouluterveyskysely 2019.) It is estimated that 4 to 10 % of adolescents in Finland suffer from an anxiety disorder making anxiety disorders one of the most common disorder categories in childhood and adolescence (Kumpulainen et al. 2017). Anxiety disorders have a lot of comorbidities such as other anxiety disorders, depression and ADHD (Kumpulainen et al. 2017).

2.2.2.4 Anxiety disorders in adolescents born preterm

Johnson et al. (2010) showed that the most common types of anxiety disorders in children at the age of 11 born EPT are GAD and separation anxiety. Hack et al. (2009) showed that the risk for GAD is higher in ELBW children at the age of 8 compared to normal birth weight children at the same age (Hack et al. 2009). Sømhovd et al. (2012) showed that VLBW children at the age of 8 have a 2.3-fold risk for anxiety symptoms compared to children born with a normal weight. Reported by mothers, adolescents born EPT have slightly more symptoms of anxiety, especially social phobia anxiety, compared to adolescents born term (Sømhovd et al. 2018). Boyle et al. (2011) showed that young adults born with ELBW aged 22 to 26 years old had an increased risk for anxiety symptoms compared to young adults born at normal birth weight.

Sømhovd et al. (2012) suggested that higher risk for anxiety disorders in preterm born adolescents is multifactorial. Preterm born babies experience more brain injuries and damage which may lead to higher prevalence of anxiety in later life. Especially damage in pre-frontal cortex might lead to more anxiety symptoms. Preterm born infants experience a lot of stress early in their life which may lead to neuroendocrine dysfunction and so make preterm born adolescents more prone to anxiety. Maternal and paternal stress might be one cause behind the higher anxiety rates in preterm born adolescents. (Huhtala et al. 2012, Sømhovd et al. 2012.)

2.2.2.5 Eating disorders

Eating disorders are characterized with physical and mental problems and disturbances in eating habits. (Kumpulainen et al. 2017). The diagnostic criteria of anorexia nervosa are body mass index below 17.5 due to self-caused weight loss, seeing oneself as obese or fear of weight gain and endocrine dysfunction (ICD-10). The diagnostic criteria of bulimia nervosa are binge eating at least twice a week over 3 months, difficulties in eating control or compulsive food and eating related thoughts and trying to avoid weight gain by vomiting, fasting or using laxatives (ICD-10). Some

more uncommon eating disorders include for example binge eating disorder and atypical eating disorders (Kumpulainen et al. 2017).

Anorexia and bulimia are the most common eating disorders in adolescence (THL. Nuorten syömishäiriöt). The incidence of anorexia in females and males is the highest between 10 and 24 years of age. In females, the most common ages to develop anorexia nervosa is from 13 to 14 years old or at 17 years old. At the age of 18 the lifetime prevalence of anorexia is 2.6 % in female adolescents. The lifetime prevalence of bulimia is 2.3 % in female adolescents (Kumpulainen et al. 2017). Syndromes that do not meet the diagnostic criteria of anorexia or bulimia but still affects the health of an individual are much more common. (THL. Nuorten syömishäiriöt.) Anorexia and bulimia are much more common in females than males. Females have a 4 to 12 times higher risk for anorexia and 18 times higher risk for bulimia compared to males (Kumpulainen et al. 2017).

2.2.2.6 Eating disorders in adolescents born preterm

The results regarding the associations between eating disorders and preterm birth are controversial. Nosarti et al. (2012) studied 16 years old adolescents using a nationwide Swedish Medical Birth Register and identifying psychiatric admissions from the National Board of Health and Welfare, Stockholm, Sweden. They showed that the risk for eating disorders in adolescents born VPT is more than 3-fold compared to their term born peers. (Nosarti et al. 2012.) This finding was supported by the results of Micali et al. (2015), who studied young adults born VPT and term at the age of 21. They showed that eating disorders are associated with obstetric complications. (Micali et al. 2015). On contrary a study of Matinolli et al. (2016) with individuals at the age of 24 showed that females born preterm have fewer eating disorder symptoms than females born term (Matinolli et al. 2016). Also, Wehkalampi et al. (2010) showed that young adults at the age of 22 born with VLBW have fewer symptoms related to body size and shape and might have a smaller risk for eating disorders (Wehkalampi et al. 2010). Matinolli et al. (2015) and Wehkalampi et al. (2010) used Eating Disorder

Inventory in their study whereas Micali et al. (2015) used Eating Disorders Examination Questionnaire (Matinolli et al. 2016, Micali et al. 2015, Wehkalampi et al. 2010).

Factors that might increase the risk for eating disorders in adolescents born preterm are neuropsychological disorders, nutrition problems early in life, neurodevelopmental disabilities and complications after birth. Eating disorders might be associated with differences in volume of grey and white matter in several brain areas. (Micali et al. 2015.) Matinolli et al. (2016) suggest that preterm birth might have a protective effect against eating disorders. They suggest that the explanation could be the parent-child relationship. Parents of preterm born children might be more protective and have a supporting parenting style which might protect from developing an eating disorder. (Matinolli et al. 2016.)

2.2.2.7 Attention deficit/hyperactivity disorder

Attention deficit/hyperactivity disorder (ADHD) is the most common developmental neuropsychiatric condition. Neuropsychiatric conditions describe states that manifest as psychiatric symptoms but have a neurological etiology. (Kumpulainen et al. 2017.) ADHD includes traits of impulsivity, inattention and hyperactivity with varying levels, combinations and effects on daily life (DSM-5). ADHD is further divided to three subtypes. The combined type is the most common and includes symptoms from all categories. Also, a primarily hyperactive/impulsive subtype and a primarily inattentive subtype are recognized. Etiology of ADHD is a combination of genetic and environmental factors but heredity is the main etiology explaining 80 % of the cases. Psychiatric comorbidities in ADHD patients are common including depression, anxiety, conduct disorder, substance use disorder and learning disabilities. (Kumpulainen et al. 2017.)

The prevalence of ADHD in 6 to 8 years old Finnish adolescents is 4 to 8 %. ADHD is more common in males than in females. Half of the children with ADHD continues to have ADHD in adolescence. Some individuals are diagnosed with ADHD in adolescence.

The prevalence of ADHD decreases when the individuals become older because the diagnostic criteria for hyperactivity are not met anymore. In addition, the symptoms may change when individuals become older. (Kumpulainen et al. 2017.)

2.2.2.8 ADHD in adolescents born preterm

A meta-analysis made in 2018 showed that children born preterm are at a higher risk of developing ADHD compared to controls (Franz et al. 2018). The prevalence of ADHD in VLBW children is from 9 % to 11 % and in ELBW children from 17 % to 20 % (Johnson and Marlow 2011). Aarnoudse-Moens et al. (2009) showed that ADHD and internalizing problems are the most prevalent behavioral problems in children born VLBW. The children born with VLBW/ELBW seem to have more inattention symptoms than hyperactivity or impulsivity (Johnson and Marlow 2011). The symptoms of inattentiveness seem to persist to adulthood in the preterm born population (Breeman et al. 2016).

Johnson and Marlow (2011) suggested that the association between ADHD and preterm birth could be explained by the impaired brain growth and cognitive impairment in preterm born children. There are significant associations between ADHD and head circumference, parenchymal lesions, intraventricular hemorrhage and/or ventricular enlargement on neonatal cranial ultrasound and later at school-age on MRI. (Johnson and Marlow 2011.) There is also an association between early acquired brain injury and ADHD which may cause preterm born children to be more prone to develop ADHD. In addition, preterm born children have alterations in brain development which may affect the neurodevelopment. (Breeman et al. 2016.) Rommel et al. (2016) showed that preterm born adolescents have more impairments in response preparation, response inhibition and executive response control. (Rommel et al. 2016.)

2.2.2.9 Autism spectrum disorder

Autism spectrum refers to a large variety of neurodevelopmental conditions that affect the way the individual socializes with other individuals and that may cause problems in communication, interaction and behavior (DSM-5.) ICD-10 defines three main symptoms for autism spectrum disorders including qualitative problems in communication and social interaction and restrictive or repetitive behavior which can manifest as specific interests (ICD-10). The spectrum has a wide range of different conditions and individuals vary a lot (DSM-5). The disturbances in communication, social interaction and cognition are seen already in first years of life in autism spectrum disorders, but especially in the high-functioning end of the spectrum, the diagnostic criteria are not met until the social interaction among peers becomes more complicated in the adolescence (Kumpulainen et al. 2017).

The estimate of prevalence of autism spectrum disorders varies from 0.1 to 0.7 % globally (Moilanen et al. 2012). The prevalence of autism is about 0.1 % in Finland. The autism spectrum disorders are from 1.8 to 6.5 times more common in males compared to females. (Kumpulainen et al. 2017.)

2.2.2.10 Autism spectrum disorder in adolescents born preterm

The prevalence of autism spectrum disorder in adolescents born with LBW (< 2000 grams) is about 5 % in the US (Pinto-Martin et al. 2011). Joseph et al. (2016) showed that the prevalence of autism spectrum disorder in children born EPT at the age of 10 is 7.1 %. Persson et al. (2020) showed in a national medical registries based cohort-study in Finland, Sweden and Norway that the risk of autism spectrum disorder decreased when the GA increased. The risk for autism spectrum disorder was 2.31-folded in preterm born children born at 22–31 weeks of GA and 1.35-folded in children born at 32–36 weeks of GA compared to term born children. (Persson et al. 2020.) This finding is supported by older studies (Joseph et al. 2016).

The risk for social competence difficulties in childhood and adolescence is higher in children born VPT compared to children born full term (FT). The problems begin already in early childhood and continue to adolescence. Most common difficulties include peer relationship problems and social withdrawal. The risk for the social problems is higher in EPT born children compared to VPT born children and males have a higher risk than females. (Ritchie et al. 2015.) Twilhaar et al. (2019) showed that there is an association between VPT birth and poorer emotion recognition in adolescence.

Recent studies have shown that EPT born children and adolescents have more social difficulties compared to FT born individuals. At the age of 13 years, teachers and parents reported more social problems in preterm born children than children born FT. Preterm children themselves did not report more social problems. Autism spectrum disorder symptoms were more reported by the parents of EPT born children than the parents of FT born children. (Twilhaar et al. 2019.)

Twilhaar et al. (2019) suggested that cognition control deficits would increase the risk for social difficulties in individuals born preterm. Preterm born children have abnormalities in different networks in brain which may lead to poor cognitive control and social impairments and so to autism spectrum disorders. It is also suggested that environmental factors such as socioeconomic background could affect the development of social impairments in preterm born children. (Twilhaar et al. 2019.)

2.2.3 Preterm behavioral phenotype

There is a wide spectrum of behavioral and emotional problems which individuals born preterm are at a risk to develop later in childhood or adolescence. The risk is higher for both internalizing and externalizing problems in preterm children. The lower the GA is the greater the risk is for the problems. (Johnson and Marlow 2011.) However, there is a commonly acknowledged “preterm behavioral phenotype”. This phenotype

highlights patterns and the profile of the behavioral and emotional problems which are common to many of adolescents born preterm. (Burnett et al. 2019).

Johnson and Marlow (2011) suggested that the preterm behavioral phenotype would be characterized by symptoms of anxiety, inattention and social difficulties.

Inattention is also a core feature of ADHD (especially inattentive subtype), and social difficulties characterize the autism spectrum disorder. The three symptoms acknowledged as preterm behavioral phenotype and the related diagnoses are the most prevalent psychiatric disorders in children born preterm. (Johnson and Marlow 2011.)

Although children born preterm may have the distinct preterm behavioral phenotype, behavioral outcomes have seen to vary. Burnett et al. (2019) showed that more than half of the EPT children had emotional symptoms, hyperactivity/inattention, peer problems and conduct problems. They estimated that 20 % of the children born EPT had preterm behavioral phenotype. Lower academic and cognitive performance was associated with more severe behavioral problems. (Burnett et al. 2019.)

3 Materials and methods

3.1 Subjects

Participants of the PIPARI (Pienipainoiset riskilapset) study were born at Turku University Hospital between 2001 and 2006. All VLBW infants born in Turku University Hospital and living in the hospital catchment area were eligible. From the beginning of 2004, the inclusion criteria were expanded to include all infants born before 32 weeks of gestation, regardless of birthweight. The sample consisted of families speaking Finnish and/or Swedish. Exclusion criteria were severe congenital anomalies or diagnosed syndromes that affect the development.

The control group consisted of FT infants born between 2001 and 2004. Also, the families of these FT infants spoke Finnish and/or Swedish. FT infants were not admitted to NICU and were born at or above 37 weeks of gestation. Infants with congenital anomalies or syndromes, who were small for gestational age (SGA) or whose mothers self-reported use of illicit drugs or alcohol during pregnancy were excluded.

This present study included participants of the PIPARI study, both preterm and control group, born in 2001 and 2002 who were invited to participate for a follow-up at the age of 17.

3.2 CBCL-YSR

Child Behavior Checklist (CBCL) Youth Self-Report (YSR) is a widely used tool to measure psychopathology in adolescents aged 11 to 18 years. CBCL-YSR is answered by the adolescent. The questionnaire has eight different empirically based syndrome scales including anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule breaking behavior and aggressive behavior. The questionnaire has also six DSM-oriented scales including depressive problems, anxiety problems, somatic problems, attention

deficit/hyperactivity problems, oppositional defiant problems and conduct problems. The questionnaire also has scales for internalizing and externalizing problems, total problems and total competence. Higher scores mean more problems in all scales except in total competence scale where a higher score means better total competence. The scores below 82nd percentile in each scale are considered normal. The scores from 82nd to 90th percentile are considered as borderline and the scores over 90th percentile are in clinical range. (Helstelä and Sourander 2001 ; Child's Behavioral Check List-Youth Self Report, Achenbach 1991.)

3.3 Statistics

Statistical analyses were performed with Excel and JMP Pro (version 15). The group wise comparisons between adolescents born VPT and controls were done with median scores of all scales. In addition, syndrome scale and DSM-oriented scale points were compared between preterm and term born girls, and also between preterm and term born boys. Descriptive statistics is shown with medians and lower and upper quartile (Q1, Q3). Normal distribution was checked visually together with Shapiro Wilk's test and none of the data was normally distributed, thus Wilcoxon rank-sum test was used in comparison. P-values <0.05 were considered statistically significant.

4 Results

A total of 52 adolescents born premature (25 boys and 27 girls) took part in this present study. The control group consisted of 40 adolescents born FT (14 boys and 26 girls). The background characteristics of adolescents born preterm are presented in Table 1. All the controls were born FT and healthy. The median T-scores and the count of individuals exceeding 82nd and 90th cut-off points for internalizing, externalizing and total problems and total competence for preterm and control group are shown in Table 2. More adolescents exceeded the clinical range in internalizing problems in preterm group compared to control group.

The scores for externalizing problems, total competence and somatic complaints were higher in the control group ($p < 0.04$, $p < 0.02$, $p = 0.01$, respectively). This referred to more externalizing problems and somatic complaints but higher total competence in the controls compared to the adolescents born preterm (Table 3 and 4).

There were no significant differences between preterm and FT girls or preterm and FT boys in the scores of the syndrome scales except for total competence. The girls of the control group had significantly higher scores in total competence scale compared to the girls of premature group ($p = 0.01$). A higher score represents less problems in social/total competence. (Table 5 and 6).

There were significant differences in the scores of somatic problems and oppositional defiant problems, between the preterm and the control group ($p < 0.05$, $p = 0.001$, respectively). The controls adolescents reported more somatic and oppositional defiant problems than the adolescents born preterm. (Table 7).

There was a significant difference between the scores of girls born preterm and control girls in oppositional defiant problems scale ($p < 0.01$). The controls reported more oppositional defiant problems than the girls born prematurely. (Table 8).

Table 1. Background variables of preterm born adolescents

Background variables	Preterm
Gestational age in weeks Mean, (SD), [min, max]	29.4, (2.4), [24.9, 37]
Birthweight in grams Mean, (SD), [min, max]	1119, (243), [580, 1500]
Male n (%)	25 (48)
Female n (%)	27 (52)
SGA status (less than z score -2) (%)	20 (38)
Multiple birth n (%)	13 (25)
Cerebral palsy n (%)	4 (8)

SGA= Small for gestational age

Table 2. CBCL-YSR median T-scores and count of individuals (percentage) exceeding the cut-off points for borderline (82nd percentile) and clinical symptom range (90th percentile) for preterm and control group

	Preterm n=52			Control n=40		
	Median (Q1, Q3)	82nd percentile	90th percentile	Median (Q1, Q3)	82nd percentile	90th percentile
Total problems	51.5 (41, 56)	4 (7.7 %)	3 (5.8 %)	51 (44.25, 58)	4 (10 %)	2 (5.0 %)
Externalizing problems	46 (39.25, 53)	1 (1.9 %)	1 (1.9 %)	50 (45.25, 55)	0 (0 %)	2 (5.0 %)
Internalizing problems	50 (43.25, 59)	3 (5.8 %)	8 (15.4 %)	53 (47, 60)	11 (27.5 %)	2 (5.0 %)
Total competence	36 (32, 42)	0 (0 %)	1 (1.9 %)	43 (35, 49.75)	0 (0.0 %)	1 (2.5 %)

Q1=lower quartile, Q3=upper quartile

Table 3. Comparison of the median T-scores of total problems, externalizing problems, internalizing problems and total competence in preterm and control group

	Preterm group n=52	Control group n=40	Preterm vs control
	Median (Q1, Q3)	Median (Q1, Q3)	P
Total problems	51.5 (41, 56)	51 (44.25, 58)	0.203
Externalizing	46 (39.25, 53)	50 (45.25, 55)	0.038
Internalizing	50 (43.25, 59)	53 (47, 60)	0.266
Total competence	36 (32, 42)	43 (35, 49.75)	0.018

Q1=lower quartile, Q3=upper quartile
Significant differences are bolded.

Table 4. Comparison of the median T-scores of syndrome scales in preterm and control group

Syndrome scales	Preterm group n=52	Control group n=40	Preterm vs control
	Median (Q1, Q3)	Median (Q1, Q3)	P
Withdrawn	52 (50, 57)	53 (50.25, 56.5)	0.876
Somatic complaints	51.5 (50, 57.5)	55.5 (52, 60)	0.010
Anxious-depressive	51 (50, 58.75)	52 (50, 58.75)	0.802
Social problems	52 (50,56)	52 (50, 59)	0.600
Thought	54 (51, 58)	54 (50, 61.25)	0.857
Attention	52.5 (50, 58.75)	52 (51, 55)	0.291
Delinquency	51 (50, 55.75)	51 (50.25, 56)	0.222
Aggressivity	50 (50, 52)	51 (50, 54.5)	0.055

Q1=lower quartile, Q3=upper quartile
Significant differences are bolded.

Table 5. Comparison of the median T-scores of total problems, externalizing problems, internalizing problems and total competence between preterm boys and control boys, and between preterm girls and control girls

	Boys			Girls		
	Preterm n=25 Median (Q1, Q3)	Control n=14 Median (Q1, Q3)	P	Preterm n=27 Median (Q1, Q3)	Control n=26 Median (Q1, Q3)	P
Total problems	48 (41, 55.5)	50.5 (43.75, 58.5)	0.187	53 (41, 58)	52,5 (44.75, 56.5)	0.824
Externalizing	45 (40, 51)	49 (45.75, 57.25)	0.134	46 (39, 53)	50 (44, 53.5)	0.198
Internalizing	47 (41, 55)	49.5 (43.25, 61.25)	0.191	58 (47, 63)	54.5 (48.5, 60)	0.702
Total competence	36 (31.75, 43.25)	37.5 (29.5, 44)	0.922	37 (30.5, 42)	43.5 (37.75, 51)	0.010

Q1=lower quartile, Q3=upper quartile
Significant difference is bolded.

Table 6. Comparison of the median T-scores of syndromes scales between preterm boys and control boys, and between preterm girls and control girls

Syndrome scales	Boys			Girls		
	Preterm n=25 Median (Q1, Q3)	Control n=14 Median (Q1, Q3)	P	Preterm n=27 Median (Q1, Q3)	Control n=26 Median (Q1, Q3)	P
Withdrawn	51 (50, 56)	55 (50, 62)	0.132	55 (50, 61)	52 (50.75, 55)	0.206
Somatic complaints	51 (50, 54.5)	54.5 (50.75, 59)	0.079	52 (50, 60)	56.5 (52, 60.75)	0.106
Anxious-depressive	51 (50, 53)	50.5 (50, 58.5)	0.707	57 (50, 62)	53.5 (50, 59)	0.425
Social problem	50 (50, 53)	50 (50, 60.75)	0.685	52 (50, 59)	52 (50, 59)	0.898
Thought	51 (51,55)	53 (50, 62)	0.988	54 (50, 58)	54 (50.75, 59)	0.856
Attention	54 (51, 59)	51.5 (51, 56)	0.374	52 (50, 58)	52 (50, 55)	0.651
Delinquency	51 (50, 54)	52 (50, 61)	0.490	51 (50, 57)	51 (50.75, 56)	0.404
Aggressivity	50 (50, 52)	51 (50, 53)	0.164	50 (50, 52)	52 (50, 55)	0.206

Q1=lower quartile, Q3=upper quartile

Table 7. Comparison of the median T-scores of DSM-oriented scales in preterm and control group

DSM-oriented scales	Preterm group n=52	Control group n=40	Preterm vs control
	Median (Q1, Q3)	Median (Q1, Q3)	P
Depressive	56 (50.25, 60)	56.5 (50, 62)	0.936
Anxiety	50 (50, 55)	51 (50, 57)	0.529
Somatic problems	51 (50,55)	55 (50, 59.75)	0.049
Attention deficit/hyperactivity problems	51.5 (50, 56.5)	51 (50, 55)	0.868
Oppositional defiant problems	50 (50, 53)	53 (50.25, 56.75)	0.001
Conduct problems	50 (50, 51)	50 (50, 53.75)	0.477

Q1=lower quartile, Q3=upper quartile
Significant differences are bolded.

Table 8. Comparison of the median T-scores of DSM-oriented scales in preterm boys and control boys, and preterm girls and control girls

DSM-oriented scales	Boys			Girls		
	Preterm n=25 Median (Q1, Q3)	Control n=14 Median (Q1, Q3)	P	Preterm n=27 Median (Q1, Q3)	Control n=26 Median (Q1, Q3)	P
Depressive	54 (50, 57)	52 (50, 63.25)	0.904	58 (51, 65)	58 (50, 62)	0.494
Anxiety	50 (50, 51)	50 (50, 58)	0.814	51 (50, 60)	51 (50, 57)	0.941
Somatic problems	50 (50, 51)	51 (50, 60)	0.071	51 (50, 59)	55 (50, 60)	0.360
Attention deficit/hyperactivity problems	53 (50, 57)	51 (50, 57.75)	0.916	51 (50, 55)	51.5 (50.75, 55)	0.636
Oppositional defiant problems	50 (50, 52)	52 (50, 54)	0.067	50 (50, 53)	53 (50.75, 60)	0.007
Conduct problems	50 (50, 51)	50.5 (50, 56.25)	0.300	50 (50, 51)	50 (50, 51.75)	0.928

Q1=lower quartile, Q3=upper quartile
Significant difference is bolded.

5 Discussion

The controls reported significantly more externalizing symptoms and somatic complaints compared to the prematurely born adolescents. Johnson and Marlow (2011) showed that adolescents born preterm had more externalizing problems, so the result of this present study is not in line with previous studies.

The controls reported significantly more somatic problems and oppositional defiant problems on the DSM-oriented scale. According to the previous literature, preterm born adolescents have more somatic illnesses (Heinonen and Fellman 1997). Preterm born adolescents may assume easier that different symptoms might be connected to previously diagnosed somatic illnesses. They might thereby evaluate their symptoms differently and score lower scores on this subscale compared to adolescents born at term. The term born controls had a significantly higher total competence. Also, the total competence of preterm born girls was significantly higher compared to the control girls.

Chiu. et al (2019), Patton et al. (2004) and Nosarti et al. (2012) showed that preterm born adolescents are at a higher risk for depression. Sømhovd et al. (2012) and Hack et al. (2009) showed that preterm born adolescents are at a higher risk for different anxiety disorders. In present study, preterm born adolescents had less depression, less anxiety and fewer internalizing problems compared to controls. This is not in line with previous studies. The explanation may be the rather small sample size of the present study. It is also notable that the group differences in the present study were not statistically significant.

Franz et al. (2018) and Johnson and Marlow (2011) showed that preterm born adolescents are at a higher risk for ADHD. Even though the group differences of the ADHD related scores were not significant in the present study, they are in line with the previous studies. In this study the preterm group had higher scores in attention syndrome scale and ADHD DSM-oriented scale.

Twilhaar et al. (2019) showed that adolescents born VPT have poorer emotion recognition, more deficits in cognitive control and more social problems compared to adolescents born FT (Twilhaar et al. 2019). Adolescents born preterm may have decreased competence in recognizing their own emotions and this might lead to lower self-reported scores especially in internalizing scales i.e. depression and anxiety. In the present study, only self-reports were used. A previous study has shown that parents report more behavioral problems in adolescents born preterm than the adolescents themselves (Twilhaar et al. 2019).

The data was based on a controlled follow-up study (Pipari study) which is a strength of this study. The response rate of CBCL-YSR questionnaire was high which is another strength of the present study. The limitations of the present study were a rather small study population, the use of self-reports only and that the data was not normally distributed.

The results of the present study give no reasons to believe that the mental health of the adolescents born preterm would differ from the controls. A bigger sample size and more research are needed to confirm the results of this study.

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