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INCIDENCE OF DEPRESSION, PRENATAL AND PERINATAL RISK FACTORS ASSOCIATED WITH DEPRESSION AND REACTIVE ATTACHMENT DISORDER IN CHILDREN

A nationwide register-based study

Subina Upadhyaya

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ABSTRACT

Prenatal and perinatal risk factors are associated with development of mental disorders in the offspring. Studying these risk factors in a prospective population-based design helps to understand more on the etiology and development of depression and reactive attachment disorder (RAD). The aim of the thesis was to study the prenatal and perinatal risk factors associated with depression and RAD among children in a nationwide register-based, nested case-control study.

The cases for the study included all individuals born singleton in Finland and diagnosed with depression or RAD according to the Care Register for Health Care (CRHC). The study identified 37,682 cases of depression born between January 1987 and December 2007 and diagnosed before December 2012 and 148,795 controls. There were 614 cases for RAD born between January 1996 and December 2012 and diagnosed before December 2012 and 2,423 controls. Conditional logistic regression models were used to examine the associations between risk factors and depression/RAD.

The mean age at diagnosis of depression was 16 years (standard deviation (SD): 3.5 years, range: 5-25 years). The incidence of diagnosed depression increased from 1.8% to 2.9% in females and 1.0% to 1.6% in males when compared with those born in 1987–1993 with those born 1994–2000. In the adjusted analyses, a U-shaped distribution of odds ratio was observed for the association between parental age and depression. Preterm birth was associated with increased odds of depression. The mean age at diagnosis of RAD was 7.36 years (SD: 3.0 years, range: 0-16 years). In the multivariate analyses, parental psychopathology was strongly associated with offspring RAD. Other parental risk factors including maternal smoking during pregnancy, single motherhood and advanced paternal age were also associated with offspring RAD. Preterm birth, low birth weight, admission to neonatal intensive care unit and induced labour were associated with increased odds of RAD.

These findings highlight variation among pre- and perinatal risk factors between depression and RAD. It also emphasizes the need for early identification of at-risk population and facilitates targeted interventions as early as the antenatal period.

KEYWORDS: risk factors, prenatal, perinatal, incidence, epidemiology, nested case-control, register-based, depression, reactive attachment disorder

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Lastenpsykiatrian oppiaine
SUBINA UPADHYAYA: Lasten masennuksen ja reaktiivisen kiintymyssuhdehäiriön esiintyvyys ja niihin liittyvät pre- ja perinataaliset riskitekijät: kansallinen rekisteripohjainen tutkimus
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TIIVISTELMÄ

Lasten mielenterveyshäiriöiden kehittymiseen liittyy pre- ja perinataalisia riskitekijöitä, joiden tutkiminen prospektiivisella väestöpohjaisella mallilla auttaa ymmärtämään häiriöiden syitä ja kehitystä. Väitöskirjatyön tavoite oli tutkia tällaisia lasten masennukseen ja reaktiiviseen kiintymyssuhdehäiriöön liittyviä riskitekijöitä kansallisella rekisteripohjaisella, pesitetyllä tapaus-verrokkitutkimuksella.

Tutkimuksessa olivat mukana kaikki yksisikiöisestä raskaudesta Suomessa syntyneet yksilöt, joilta löytyi diagnosoitu masennus tai reaktiivinen kiintymyssuhdehäiriö hoitoilmoitusrekisteristä. Vuosina 1987–2007 syntyneitä, ennen joulukuuta 2012 diagnosoituja masennustapauksia oli yhteensä 37 682 ja verrokkeja 148 795. Vuosina 1996–2012 syntyneitä ja ennen joulukuuta 2012 diagnosoituja reaktiivisen kiintymyssuhdehäiriön tapauksia oli 614 ja verrokkeja 2423. Riskitekijöiden ja häiriöiden välisiä suhteita tutkittiin käyttäen ehdollisia logistisia regressiomalleja.

Masennusdiagnoosi saatiin keskimäärin 16 vuoden iässä (keskihajonta (SD): 3,5 vuotta, vaihteluväli: 5–25 vuotta). Diagnosoitujen tapausten esiintyvyys nousi 1,8%–2,9% naispuolisilla ja 1,0%–1,6% miespuolisilla tutkittavilla verrattaessa vuosina 1987–1993 ja 1994–2000 syntyneitä. Vanhempien iän ja lapsen masennusdiagnoosin välillä oli U:n muotoinen yhteys. Ennenaikainen synnytys oli yhteydessä masennuksen kohonneeseen todennäköisyyteen. Reaktiivisen kiintymyssuhdehäiriön diagnoosi saatiin keskimäärin 7,36 vuoden iässä (SD: 3,0 vuotta, vaihteluväli: 0–16 vuotta). Monimuuttuja-analyyseissa vanhempien psykopatologia liittyi vahvasti lapsen reaktiiviseen kiintymyssuhdehäiriöön, samoin kuin esimerkiksi raskaudenaikainen tupakointi, äidin yksinhuoltajuus sekä isän korkea ikä. Myös ennenaikainen synnytys, alhainen syntymäpaino, vastasyntyneen tehohoito ja synnytyksen käynnistäminen lisäsivät diagnoosin todennäköisyyttä.

Löydökset näyttävät pre- ja perinataaliriskitekijöiden vaihtelevan masennuksessa ja reaktiivisessa kiintymyssuhdehäiriössä. Ne osoittavat myös riskiryhmien varhaisen tunnistamisen ja helposti saavutettavan kohdennetun hoidon tarpeen.

AVAINSANAT: riskitekijät, prenataalinen, perinataalinen, esiintyvyys, epidemiologia, pesitetyllä tapaus-verrokkitutkimus, rekisteripohjainen, masennus, reaktiivinen kiintymyssuhdehäiriö

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Abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aPR	Adjusted probability ratio
aRR	Adjusted risk ratio
CI	Confidence interval
CRHC	Care Register for Health Care
DNA	Deoxyribonucleic Acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
FMBR	Finnish Medical Birth Register
FPRC	Finnish Population Register Centre
FHDR	Finnish Hospital Discharge Register
HPA	Hypothalamic-pituitary-adrenal axis
ICD	International Classification of Diseases
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
pH	Potential of Hydrogen
RAD	Reactive attachment disorder
SD	Standard Deviation
SE	Standard Error
SES	Socio-economic status
SGA	Small for gestational age
SSP	Strange Situation Procedure
WGA	Weight for gestational age
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Filatova S, Upadhyaya S, Kronström K, Suominen A, Chudal R, Luntamo T, Sourander A, Gyllenberg D. Time trends in the incidence of diagnosed depression among people aged 5–25 years living in Finland 1995–2012. *Nord J Psychiatry,* 2019;23:1–7. doi: 10.1080/08039488.2019.1652342.

II Filatova S*, Upadhyaya S*, Luntamo T, Sourander A, Chudal R. Parental age and risk of depression: a nationwide, population-based case-control study. *J Affect Disord,* 2020;282:322–328. doi: 10.1016/j.jad.2020.12.197.

III Upadhyaya S, Sourander A, Luntamo T, Matinolli H-M, Chudal R, Hinkka-Yli-Salomäki S, Filatova S, Cheslack-Postava K, Sucksdorff M, Gissler M, Brown AS, Lehtonen L. Preterm birth is associated with depression diagnosed in specialized services. *J Am Acad Child Adolesc Psychiatry,* 2020;S0890-8567(20)31983-3. doi: 10.1016/j.jaac.2020.09.020.

IV Upadhyaya S, Chudal R, Luntamo T, Sinkkonen J, Hinkka-Yli-Salomäki S, Kaneko H, Sourander A. Parental Risk Factors among Children with Reactive Attachment Disorder Referred to Specialized Services: A Nationwide Population-Based Study. *Child Psychiatry Hum Dev,* 2019;50(4):546–556. doi: 10.1007/s10578-018-00861-6.

V Upadhyaya S, Chudal R, Luntamo T, Hinkka-Yli-Salomäki S, Sucksdorff M, Lehtonen L, Sourander A. Perinatal risk factors and reactive attachment disorder: a nationwide population-based study. *Acta Paediatrica, 2020.* doi: 10.1111/apa.15156.

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1 Introduction

Intrauterine exposure to environmental insults is associated with increased morbidity and mortality at the perinatal period but also at later stages of lifespan. Prenatal and perinatal insults are the stresses experienced by a developing fetus e.g., maternal stress, smoking, nutritional deficiency, obstetric complications, poor fetal growth and preterm birth. The early prenatal insults may impair infant's overall health, affecting general indices of growth and development, in turn predisposing the child to ill health later in life (Susser, Brown and Matte, 1999).

The Dutch famine study is one of the earliest epidemiological studies supporting the findings of prenatal insults and later onset mental illnesses (Susser *et al.,* 1996). The Dutch Hunger Winter of 1944–1945, with a sharp decline in food intake in western region by less than 1000 kcal per person per day demonstrated a twofold higher risk of developing schizophrenia and increased risk of affective disorders in adulthood when exposed to severe famine in early gestation. Moreover, a Finnish cohort study reported significantly higher rate of schizophrenia diagnosis among individuals exposed to influenza epidemic during second trimester of pregnancy (Mednick *et al.,* 1988). The study based on the Avon Longitudinal Study of Parents and Children cohort, consisting of 14,062 pregnant women delivering between 1991 to 1992 and their offspring, followed up for 20 years has contributed largely to understanding child psychiatric epidemiology. They hypothesized that exposure to stress in utero would affect the development of the hypothalamic-pituitary-adrenal (HPA) axis and alter the stress response, increasing the vulnerability to offspring mental disorders. They found that offspring of mothers exposed to stressful life events during early pregnancy were at increased risk of depression and elevated depressive symptoms in adolescence, even when the chronic stressors such as low socioeconomic status, maternal depression, and stressful life events in the postnatal period were adjusted. They observed a linear dose-response relationship between prenatal exposure to stressful life events and offspring depressive symptoms in adolescence (Kingsbury *et al.,* 2016).

The fetal programming hypothesis also suggests that the early perinatal adversities predispose the fetus to certain postnatal diseases through metabolic programming or other specific mechanisms (Barker, 1998). The insult *in utero* may

cause developmental adaptations that produce structural, physiological and metabolic changes in particular brain regions and neurotransmitters (Kwon and Kim, 2017). The programmed changes during this critical period may contribute to poor stress management and reduced resiliency, increasing vulnerability to mental illness.

Major depressive disorder is a leading cause of disability worldwide, causing impairment in social and occupational functioning and a major public health concern (World Health Organization, 2020). Depression is a major contributor of global burden of diseases affecting almost 4.4% of world's population and is the third leading cause of all-age years lived with disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; World Health Organization, 2020). The etiology of depression is multifactorial and increasing research has suggested the possible heritability and environmental risk factors in the development of depression. Many associated familial risk factors have been investigated for depression, including maternal depression, smoking during pregnancy, parental psychopathology, socio-economic status during pregnancy (Taylor *et al.,* 2017; Thapar *et al.,* 2012). Previous studies that examined the association between prenatal and perinatal risk factors including parental age, preterm birth, poor fetal growth and offspring depression, were primarily based on clinical populations, and have produced inconclusive findings. The inconsistencies of the findings may be due to differences in population sample, diagnostic tools for depression, covariates and age at diagnosis of depression.

Reactive attachment disorder (RAD) is a rather rare childhood disorder of social functioning. The prevalence of RAD was estimated to be 0.9% (95% CI 0.1–3.4) in 1.5-year-olds in a Copenhagen child cohort study (Skovgaard *et al.,* 2007). Higher prevalence is reported in high-risk populations; 1.40% in a population survey of a UK city with high levels of deprivation (Minnis *et al.,* 2013), 19.4% among children in foster care (Lehmann *et al.,* 2013), 38-40% of maltreated toddlers (Zeanah *et al.,* 2004). Children with RAD are subjected to either repeated changes of caregivers and/or abuse or neglect in the early years of life. Most of the studies on RAD have been conducted on high-risk populations and it has been rarely studied in children outside institutions (Rutter *et al.,* 2010). These studies have focused on the prevalence, phenotypic characteristics, course of treatment, and comorbidities of the disorder. The children with RAD have been associated with other psychiatric and developmental symptoms including learning difficulties (Gleason *et al.,* 2011), later social difficulties including victimization and bullying behavior (Raaska *et al.,* 2012) and increased risk of comorbidity including emotional and behavioral disorders (Lehmann *et al.,* 2013). To date, only two studies have examined the prenatal risk factors for RAD: a clinical study of maltreated toddlers (Zeanah *et al.,* 2004) and a Danish register-based study (Nilsson *et al.,* 2017). No previous study has examined perinatal risk factors in relation to offspring RAD. The complications arising during

perinatal period may affect the maternal-fetal attachment and early postpartum bonding. The pregnancy-specific complications influence mother's recovery that may alter the conducive environment for mother-infant attachment and bonding. Higher prevalence of depressive symptoms has been observed in women with severe obstetric complications (including severe bleeding, maternal hypertension and preeclampsia) (Alder *et al.,* 2007). These complications are associated with long term maternal morbidity (Neiger, 2017), thereby affecting the maternal-child interactions.

Early life experiences are associated with the increased risk of several psychopathology, including depression and RAD. The presence of "insufficient caregiving" such as social neglect or deprivation, repeated changes in caregivers or rearing in institutions, is necessary to diagnose RAD in children (Boris *et al.,* 2004; Zeanah *et al.,* 2004), which is also an important risk factor for depression (Gilbert *et al.,* 2009; Sheridan *et al.,* 2018). Children with disrupted attachment are at increased risk for developmental and behavioural difficulties, emotional regulation, peer/social relationships, and low self-esteem (Lehmann *et al.,* 2013; Raaska *et al.,* 2012). The clinical phenotypes of depression and RAD share some features including reduced or absent positive affect, difficulties in emotional regulation and social withdrawal (Zeanah *et al.,* 2016). In a Bucharest Early Intervention Project, children with RAD showed associations between signs of RAD and depression, when examined during 22 months to 54 months, but most children with depression did not meet the criteria for RAD at 54 months (Gleason *et al.,* 2011).The comorbidity could result from a shared aetiology or as a cause or consequence of a disorder. It is important to understand if these early risk factors contribute equally to both disorders, or have specificity as an etiological factor for some mental disorders.

The present thesis uses several national registers to examine the prenatal and perinatal risk factors associated with depression among 5-25 years old and RAD in children. These large epidemiological studies on prenatal and perinatal risk factors associated with depression and RAD can contribute to understanding their etiology, social context and their outcomes. The possibility of studying similar risk factors among two distinct offspring psychiatric disorders in a population-based sample addresses the question of specificity of mental disorders, i.e., whether the studied risk factors influence the risk of developing depression or RAD differently. The epidemiological research has implications for public health, in development of the overall framework for policy, support for the planning of specialized services and designing interventions for pregnant women visiting maternity clinics and specific programmes for mental health promotion.

2 Review of the Literature

2.1 Depression

2.1.1 Diagnostic classification

The International Classification of diseases (ICD) and Diagnostic Statistical Manual of Mental Disorders (DSM) are two widely used diagnostic systems that diagnose depression according to number of symptoms criteria. Although some heterogeneity exists between two different criteria, previous study comparing ICD-10 and DSM-4 showed similar results in diagnosing severe or moderate depressive episodes (Saito *et al.,* 2010). In Finland, mental disorders in health care systems are diagnosed based on ICD classifications. **Table 1** shows the ICD-10 diagnostic criteria for depression.

Table 1. ICD-10 diagnostic criteria for depression. Modified and reproduced with the permission from WHO 2020.

CODES	DESCRIPTION
F32	**Depressive episode** Depressive episodes lasting for at least 2 weeks. No hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30.-) at any time in the individual's life. Somatic syndrome: Four of the following should be met. (1) marked loss of interest or pleasure in activities that are normally pleasurable; (2) lack of emotional reactions to events or activities that normally produce an emotional response; (3) waking in the morning 2 hours or more before the usual time; (4) depression worse in the morning; (5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people); (6) marked loss of appetite; (7) weight loss (5% or more of body weight in the past month); (8) marked loss of libido. Exclusion: Not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00–F09).
F32.0	*Mild depressive episode* The general criteria of depressive episodes are met (F32). Two of the three criteria (A) are met (1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks; (2) loss of interest or pleasure in activities that are normally pleasurable; (3) decreased energy or increased fatiguability. Additional symptom or symptoms from following list should be present (1) loss of confidence and self-esteem; (2) unreasonable feelings of self-reproach or excessive and inappropriate guilt; (3) recurrent thoughts of death or suicide, or any suicidal behaviour;

CODES	DESCRIPTION
	(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation; (5) change in psychomotor activity, with agitation or retardation (either subjective or objective); (6) sleep disturbance of any type; (7) change in appetite (decrease or increase) with corresponding weight change). Presence of absence of somatic syndrome described in depressive episode.
F32.1	*Moderate depressive episode* The general criteria of depressive episodes are met (F32). Two of the three criteria (A) are met. Additional symptoms mentioned in F32.0 are met to give a total of 6 symptoms. Presence of absence of somatic syndrome described in depressive episode.
F32.2	*Severe depressive episode without psychotic symptoms* The general criteria of depressive episodes are met (F32). Two of the three criteria (A) are met. Additional symptoms mentioned in F32.0 are met to give a total of 8 symptoms. No hallucinations, delusions, or depressive stupor.
F32.3	*Severe depressive episode with psychotic symptoms* Meets the criteria given for F32.2 above and in which delusions, hallucinations, or depressive stupor are present. The criteria for schizophrenia (F20.-) or schizoaffective disorder, depressive type (F25.1) are not met.
F32.8	*Other depressive episodes* Includes episodes which do not fit the descriptions given for depressive episodes described in F32.0-F32.3, but for which the overall diagnostic impression indicates that they are depressive in nature.
F32.9	*Depressive episode, unspecified* Includes: depression NOS, depressive disorder NOS
F33	**Recurrent depressive disorder** At least one previous episode of mild (F32.0), moderate (F32.1), or severe (F32.2 or F32.3), lasting a minimum of 2 weeks and separated from the current episode by at least 2 months without significant mood symptoms. Exclusion: not attributable to psychoactive substance use (F1) or any organic mental disorder (F0).
F33.0	*Recurrent depressive disorder, current episode, mild* The general criteria for recurrent depressive disorder (F33) are met and the current episode meets the criteria for depressive episode, mild severity (F32.0). Presence or absence of somatic syndrome.
F33.1	*Recurrent depressive disorder, current episode moderate* The general criteria for recurrent depressive disorder (F33) are met and the current episode meets the criteria for depressive episode, mild severity (F32.1). Presence or absence of somatic syndrome.
F33.2	*Recurrent depressive disorder, current episode severe without psychotic symptoms* The general criteria for recurrent depressive disorder (F33) are met and the current episode meets the criteria for depressive episode, mild severity (F32.2).
F33.3	*Recurrent depressive disorder, current episode severe with psychotic symptoms* The general criteria for recurrent depressive disorder (F33) are met and the current episode meets the criteria for depressive episode, mild severity (F32.3).
F33.4	*Recurrent depressive disorder, currently in remission* The general criteria for recurrent depressive disorder (F33) have been met in the past. The current state does not meet the criteria for a depressive episode (F32.-) of any severity, or for any other disorder in F33 (the patient may receive treatment to reduce the risk of further episodes).
F33.8	*Other recurrent depressive disorders*
F33.9	*Recurrent depressive disorder, unspecified* Includes: monopolar depression NOS

2.1.2 Incidence and prevalence

Depression is a common mental disorder, affecting almost 4.4% of world's population, and is a major contributor of global burden of diseases (World Health Organization, 2020). The lifetime prevalence of depression is 15–18% and is episodic over the life course (Bromet *et al.,* 2011). The lifetime prevalence of depression varies across countries, with higher prevalence reported in high-income countries compared to low- and middle-income countries (Kessler and Bromet, 2013). Depression is comparatively rare during childhood, and the reported point prevalence of depressive disorders in preschool and prepubertal children is 1–2% and in adolescents is 3–8% (Costello *et al.,* 2003; Whalen, Sylvester and Luby, 2017). The lifetime prevalence by the end of adolescence is around 20% (Lewinsohn, Rohde and Seeley, 1998).

During childhood, there is little difference overall among genders in depressive disorders with slightly higher rates reported among boys (Twenge and Nolen-Hoeksema, 2002). However, the gender differences change after puberty (Angold and Costello, 2006; Hankin *et al.,* 1998; Hayward and Sanborn, 2002), and females are twice more likely to experience depressive disorders than males (Kessler and Bromet, 2013).

The global incidence and prevalence of depression is increasing over the years. The total estimated number of people living with depression worldwide increased by 12.6% between 2007 and 2017 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). In Nordics, two register-based studies have reported the time trend of incidence or cumulative incidence of diagnosed depression in children and adolescence. The Danish study of 4–29-year-olds during the time-period 1995–2010 reported a 6.7–7.5% annual increase in incidence of diagnosed depression, using a broad definition of depression including dysthymia (Jensen and Steinhausen, 2016). In Finland, the register-based study of 1987 and 1997 birth cohorts showed that the cumulative incidence of depression have increased among adolescents during the study period; 4.2–7.4% among girls and 1.7–2.5% in boys (Gyllenberg *et al.,* 2018). The higher incidence of depression among girls may be related to pubertal timing and status effects. The maturation of female HPA system may be responsible for inducing and maintaining a substantial proportion of depressive states among girls (Angold and Costello, 2006). The prevalence of self-reported depression slightly increased from 2000 to 2011 in Finnish adolescents. Severe depression was reported by 4% of girls and 2.1% of boys in 2000–2001 and by 4.7% of girls and 2.2% of boys in 2010–2011 (Torikka *et al.,* 2014). The rise in diagnoses of depression may also be attributed to the changes in lifestyle (Hidaka, 2012), and increase in service use over time (Ma, Lee and Stafford, 2005; Mojtabai, Olfson and Han, 2016).

2.1.3 Prenatal risk factors

The etiology of depression is multifactorial, suggesting gene-environment interaction in the development of this disorder (Kendler *et al.,* 2018). The heritability of depression is estimated to be 30 to 40% (Sullivan, Neale and Kendler, 2000). The prenatal risk factors identified for depression include parental depression, parental divorce, parental age, low maternal socio-economic status (SES), and maternal smoking during pregnancy (Taylor *et al.,* 2017; Thapar *et al.,* 2012).

2.1.3.1 Parental age

Extensive epidemiological research suggests parental age at birth in the etiology of offspring mental disorders. Advanced parental age has been associated with offspring schizophrenia (Malaspina, 2001) and autism spectrum disorder (Lampi *et al.,* 2013; Sandin *et al.,* 2016). While advanced paternal age has been associated with bipolar disorders (Frans *et al.,* 2008), cognitive deficits (Saha *et al.,* 2009b) and ADHD (Saha *et al.,* 2009a), advanced maternal age has been associated with OCD (Chudal *et al.,* 2017). Younger parental age has also been associated with increased risk of schizophrenia (Miller 2011), bipolar disorders (Chudal *et al.,* 2014) and ADHD (Chudal *et al.,* 2015). Younger maternal age at birth is associated with behavioural disorders including ADHD (Chudal *et al.,* 2015) and substance use (McGrath *et al.,* 2014). Moreover, nonlinear associations were reported between maternal or paternal age and offspring psychopathology. The U-shaped association have been found between parental age and bipolar disorder (Chudal *et al.,* 2014), schizophrenia (McGrath *et al.,* 2014), and major depressive disorder (Buizer-Voskamp *et al.,* 2011).

2.1.3.2 Previous studies

Seven previous studies have examined the association between parental age and offspring depression. Among them, two were based on nationwide population-based registers from Nordic countries (Laursen *et al.,* 2007; McGrath *et al.,* 2014) and two were population-based studies from the Netherlands (Buizer-Voskamp *et al.,* 2011) and Australia (Tearne *et al.,* 2016). The remaining studies were longitudinal birth cohort study from New Zealand (Fergusson and Woodward, 1999), community-based sample from USA (Merikangas *et al.,* 2017) and a small clinical study from Greece (Fountoulakis *et al.,* 2019). Five of the studies were based on cohort design whereas two were case-control studies (Buizer-Voskamp *et al.,* 2011; Fountoulakis *et al.,* 2019). The number of depression cases included in the study varied from 68 (Fountoulakis *et al.,* 2019) to 69,142 (McGrath *et al.,* 2014). Two studies showed increased odds of depression with young maternal age (Fergusson and Woodward,

1999; McGrath *et al.,* 2014) and one with advanced maternal age (Tearne *et al.,* 2016). Three studies showed increased odds with both young and advanced paternal age (Buizer-Voskamp *et al.,* 2011; Fountoulakis *et al.,* 2019; McGrath *et al.,* 2014) However, two studies did not report any associations (Laursen *et al.,* 2007; Merikangas *et al.,* 2017). Previous studies on the associations between parental age and offspring depression are shown in **Table 2**.

Table 2. Studies on parental age and depression.

	AUTHOR	N	STUDY DESIGN	EXPOSURE	DIAGNOSTIC CRITERIA	COVARIATES	RESULTS
1	Tearne et al. 2016 Australia	1,220	Pregnancy cohort (The Raine Study)	Maternal age <20, 20–24, 25–29, 30–34, ≥35 Paternal age <20, 20–24, 25–29, 30–34, 35–39, ≥40	Depression Anxiety Stress Scale-21 at age 20 years	Age of other parent, maternal smoking in pregnancy, maternal education, total family income, maternal experience of stressful life events, and maternal gestational hypertension	Maternal age ≥35 aRR 1.51 (95% CI 1.05–2.16). Paternal age was not associated.
2	McGrath et al. 2014 Denmark	69,142	Register-based Cohort from 1955 through 2006 followed up from 1995 through 2011	Maternal age and paternal age 12–19, 20–24, 30–34, 35–39, 40–44, ≥45	ICD-10 diagnoses F30–F39	Age and sex of offspring, calendar year and other parent's age	Maternal age 12–19, 20–24 years was associated with mood disorders in offspring Paternal age: all age groups had increased risk of mood disorders, but highest aOR was in youngest and oldest group, aOR 1.20 (95% CI: 1.13–1.27) and aOR 1.25 (95% CI: 1.18–1.32), respectively
3	Buizer-Voskamp et al. 2011 Middle-Netherlands	8,284 cases, 33,136 controls	Case-control Psychiatric Case Registry Jan 1999 and December 2008	Paternal age <20, 20–24, 25–29, 30–34, 35–39, ≥40	DSM-IV-TR (296.20–296.26, 296.30–296.36 or 311.00-depressive disorder NOS)	Average income of neighbourhood, difference in age between the father and the mother and the ethnic background	Paternal age <20, 20–24, 35–39, ≥40 is associated with depression with highest aOR 1.65 (95% CI: 1.33–2.05) for youngest fathers and aOR 1.22 (95% CI: 1.09–1.36) for oldest fathers
4	Laursen et al. 2007 Denmark	31,752	Register-based cohort Jan 1995 and July 1987	Paternal age ≤20, 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, ≥56	ICD-8: 296.09, 296.29, 296.99, 298.09, 300.49 dysthymia or 300.19; ICD 10: F32 or F33	Age, calendar time, gender, family history of psychiatric admission, and maternal age	No significant association

	AUTHOR	N	STUDY DESIGN	EXPOSURE	DIAGNOSTIC CRITERIA	COVARIATES	RESULTS
5	Fergusson & Woodward 1999 New Zealand	1,025	Christchurch Health and Development cohort Study	Maternal age <20, 20–24, 25–29, 30+	DSM-IV major depression at age 18 years	Maternal educational qualifications, SES, family type, maternal ethnicity, pregnancy planning, firstborn child, maternal smoking during pregnancy, maternal history of parental changes, maternal relationships with own mother unhappy childhood	Youngest mothers (<20) rates of major depression (30.4% p<0.05)
6	Merikangas et al. 2017 United States of America	8,725	Community cohort	Continuous and categorical Maternal age <20, 20–24, 25–29, 30–34, 35–39, ≥40 Paternal age <20, 20–24, 25–29, 30–34, 35–39, 40–44, ≥45	Depression and mania Measured by: Genetic Epidemiology Research Branch Kiddie-Schedule for Affective Disorders and Schizophrenia Family Study Interview for structured evaluation of psychopathology domains	Sex, age, binary race, SES,	Younger maternal age on mood disorders (aOR=0.982; p=.008). No association when adjusting for comorbidity. No association between paternal age and mood disorders.
7	Fountoulakis et al. 2019, Greece	68 cases, 204 controls	Case-control	Maternal age >20, >22, >26 and >35. Paternal age >20, >25, >30 and >40.	DSM-IV-TR criteria on the basis of a semi structured interview based on the Schedules for Clinical Assessment in Neuropsychiatry version 2.0	None	Maternal age >22: OR 2.23 (95% CI: 1.13–4.40) Paternal age >25: OR 4.06 (95% CI: 1.90–8.64) Paternal age >30: OR 2.51 (95% CI: 1.43–4.39)

OR odds ratio; aOR adjusted odds ratio; aRR adjusted risk ratio; CI confidence interval; ICD International Classification of Diseases; DSM Diagnostic and Statistical Manual of Mental Disorders; SES socio-economic status.

2.1.4 Perinatal risk factors

2.1.4.1 Preterm birth

Preterm birth is a public health concern and refers to those that occur before 37 weeks of gestational age. It occurs in 5% to 18% of all births and is a leading cause of mortality among children under 5 years of age (World Health Organization, 2018). Although an increasing number of preterm infants survive, they are at increased risk of neurodevelopmental disorders, behavioural problems and functional impairments (Saigal and Doyle, 2008).

2.1.4.2 Birth weight for gestational age

Low birth weight is defined by the World Health Organization (WHO) as a birthweight of an infant below 2,500 grams (World Health Organization, 1992), and is based on epidemiological studies that infants weighing less than 2,500 g at birth are 20-times more likely to die than babies weighing more than 2500 g at birth (Kramer, 1987). Low birth weight for gestational age is an indicator of poor fetal growth and is calculated according to national gender-specific birth weight distribution standards at a given gestational age for singletons (Sankilampi *et al.,* 2013). Poor fetal growth is associated with increased risk of mortality and morbidity including, neurodevelopmental problems, ADHD and other psychiatric illnesses (Chudal, Sourander *et al.,* 2014; Glasson *et al.,* 2004; Gregory *et al.,* 2013; Lampi, K. M. *et al.,* 2012; Loret de Mola *et al.,* 2014; Polo-Kantola *et al.,* 2014; Sucksdorff *et al.,* 2015).

2.1.4.3 Previous Studies

Twelve previous studies have examined the association between preterm birth and/or poor fetal growth and diagnosed depression. Among them, six were population-based studies (Gudmundsson *et al.,* 2011; Inskip *et al.,* 2008; Laursen *et al.,* 2007; Loret de Mola *et al.,* 2015; Nosarti *et al.,* 2012; Wang *et al.,* 2015), including two Nordic register-based studies (Laursen *et al.,* 2007; Nosarti *et al.,* 2012). All the studies were based on a cohort design. The cases of depression in the study varied from 63 (Patton *et al.,* 2004) to 31752 (Laursen *et al.,* 2007). Five studies have reported that preterm birth was associated with an increased risk of depression (Farooqi *et al.,* 2007; Gudmundsson *et al.,* 2011; Nosarti *et al.,* 2012; Patton *et al.,* 2004; Räikkönen *et al.,* 2007), while some did not report any associations (Inskip *et al.,* 2008; Loret de Mola *et al.,* 2015; Vasiliadis, Gilman and Buka, 2008; Wang *et al.,* 2015). Most of these studies focused on very preterm infants, born before 32

weeks of gestation. Only two (Vasiliadis, Gilman and Buka, 2008; Wang *et al.,* 2015) examined the risk of depression among post-term infants, born after 42 weeks of gestation, but the findings were not significant. Three studies reported significant associations between poor fetal growth and depression (Colman *et al.,* 2012; Laursen *et al.,* 2007; Rice, Harold and Thapar, 2006), and others did not report any associations (Loret de Mola *et al.,* 2015; Nosarti *et al.,* 2012; Vasiliadis, Gilman and Buka, 2008). Previous studies on preterm birth and weight for gestational age with depression is shown in **Table 3**.

Table 3. Studies on preterm birth, fetal growth and depression.

SN	AUTHOR	N	STUDY DESIGN	EXPOSURE	DIAGNOSTIC CRITERIA	COVARIATES	RESULTS
	Population-based/register-based studies						
1	Nosarti et al. 2012 Sweden	2333	Register based, 1973 and 1985	Preterm birth (gestation) Birth weight, Weight for gestational age: <-2 SD, -2 to 2 SD, > 2SD	ICD 8: 300.4, 296.0, 296.2, ICD 9: 296 C-D, 300E, 311, ICD 10: F32-F33 except F32.3 and F33.3	Sex, parity, mother's age at delivery, mother's educational level, and maternal psychiatric family history	32 to 36 weeks' gestation and depression: aHR 1.3 (95% CI: 1.1–1.7) <32 weeks and depression: aHR 2.9 (95% CI: 1.8–4.6) <-2 SD and depression: aHR 1.1 (95% CI: 0.9–1.4)
2	Loret De Mola et al. 2015 Brazil	live births (n= 5914)	Birth Cohort	SGA: <-1.28 SD Gestational age: ≤37, >37 weeks Birth weight <2500, 2500–3000, 3000–3500, >3500	Outcome: Mini International Neuropsychiatric Interview, Beck Depression Inventory-II	skin color, mother's age, schooling, previous gestations, pregnancy risk factors, C-section, smoking and income at birth, assets index, mother 'nerve' problems, father live together and history of psychiatric illness, parent's alcoholism and breastfeeding.	≤37 weeks and depression: aPR 1.22 (95% CI: 0.72–2.07) SGA and depression: aPR 0.87 (95% CI:0.64–1.19) SGA and stunted and depression: aPR 1.87 (95% CI: 1.06–3.29) SGA and Beck Depression Inventory-II aOR 2.18 (95% CI: 1.34–3.53).
3	Gudmundsson et al. 2011 Sweden	at baseline cohort n=1381	Prospective population study of women 1968–1969, reexamined in 1974, 1980, 1992, and 2000.	Birth weight ≤3500 g gestational time in weeks: within 1.5 SDs (greater than 35.2 and less than 44.9 weeks)	DSM-III-R in 1968, 1974, 1980, and 1992 and 2000. History of previous depression: Medical records, Psychopathological Rating Scale	Birth weight, gestational time, birth length, and head circumference. Parental occupation, maternal age, maternal parity and the participant's birth location and twin status.	Birth weights ≤3500 g and depression: aOR 1.72 (95% CI 1.29–2.28) and shorter gestational time and depression: aOR 1.13 (95% CI 1.04–1.24).
4	Laursen et al. 2007 Denmark	n=31752 (depression)	Register based 1.1.1955–1.6.1987, follow up between 1.1.1973–30.6.2005	SGA and depression SGA: lower 10% of birth weight	ICD 8: 296.09, 296.29, 296.99, 298.09, 300.49, 300.19. ICD 10: F 32 or F33.	Family history of psychiatric disorders, place of birth, loss of parent, maternal age, paternal age.	SGA and depression: Lower 10% before week 37: aRR 2.23 (95% CI: 1.68–2.95).

SN	AUTHOR	N	STUDY DESIGN	EXPOSURE	DIAGNOSTIC CRITERIA	COVARIATES	RESULTS
5	Wang et al. 2015 Hongkong	n=5795 (depression)	Birth cohort 49 Maternal and Child Health Centers in Hong Kong	(<34, 34–36, 37–38, 39–40, 41, ≥42)	Patient Health Questionnaire-9	Sex, age, socio-economic position, mother's birthplace, birth order, second-hand smoke exposure and parents' age at birth.	No association between gestational age and depression.
6	Inskip et al. 2008 United Kingdom (Southampton)	n=5150 (gestational age)/ 5830 (birth weight)	Retrospective (Women)	early, late or at term	General health questionnaire, Self-reported for treatment	Age, education, social class, perceived financial strain, and low income	No relationship was found between birth weight, duration of gestation and depressive symptoms
	Clinical studies						
7	Räikkönen et al. 2007 Finland	n=1371, included in the study	Helsinki birth cohort born 1934–1944	length of gestation: Continuous (days) Birth weight: Continuous (kg) and <2.5 kg or >2.5 kg	Beck Depression Inventory, Center for Epidemiologic Studies - Depression Scale	Birth records: date of birth, weight, length, head circumference, mothers, father's occupation. Offspring (height and weight, age, education).	Depressive symptoms increased by 0.8–0.9% per day decrease in length of gestation. No interaction by sex (P>0.15)
8	Farooqi et al. 2007 Sweden	n= 86 born before 26 completed weeks of gestation and controls	National birth cohort born between 1990 and 1992	Gestational age (extreme immaturity)	Child behavior checklist (parents), Teacher report form, Depression self-rating scale at age 11 years Traced children (11 years) and parents, sent questionnaires	Social risk score, family function, gender, maternal mental health risk score, and presence of a chronic medical condition.	Parents report (anxious/depressed): aOR 2.56 (95% CI: 1.06–6.18) Teachers report (anxious/ depressed): aOR 3.54 (95% CI: 1.39–9.03) Depression Symptoms According to Children's Self-Reports: aOR 1.27 (95% CI: 0.46–3.54).
9	Colman et al. 2012 Canada	3732 children assessed	Prospective cohort study 0 to 11 years old, followed every 2 years	SGA, AGA, LGA	Symptoms of depression and anxiety: Child behavior checklist—Total score grouped into 4 categories	Acute and chronic stressors	SGA and depression: aOR 1.50 (95% CI: 1.08–2.08) SGA and depression (Males): aOR 1.64 (955 CI: 1.06–2.53) (Females) aOR 1.35 (95% CI: 0.90–2.02).

SN	AUTHOR	N	STUDY DESIGN	EXPOSURE	DIAGNOSTIC CRITERIA	COVARIATES	RESULTS
10	Vasiliadis et al. 2008 United States	n=1101 (depression)	Prospective cohort study	[<2.5, 2.5–3.0, >3.0–3.5 (reference), >3.5]; [≤2.0, >2.0 (reference)] preterm (≤37), term (38–41, reference), post-term (≥42); SGA: below 10th percentile of weight	Diagnostic Interview Schedule	Mother's age marital status, parental psychiatry, parental employment, subject's race and age at interview, pregnancy, delivery complications, potential learning disability	No significant difference in risk of depression across birth weight categories
11	Patton et al. 2004 Australia	depression =63; no depression =112	Cohort 1992–1995	<2.5 kg, ≥2.5 kg; Premature: 53 weeks prior to term (maternal report)	Computerized revised Clinical Interview Schedule revised Parental telephone interview: Composite International Diagnostic Interview	Parenting style, negative life events, previous depression/ anxiety, gender, parental education, parental separation, parental history of depressive disorder, maternal smoking in pregnancy, maternal age at birth and serious illness in the first year of life.	Prematurity and depression: aOR 5.7; (95% CI: 1.4–23) low birthweight and depression: aOR 2.9 (95% CI: 0.6–14)
12	Rice et al. 2006/ United Kingdom (England)	n=934 twin pairs	Twin study	WGA: ≤10th percentile	Mood and Feelings Questionnaire	Sex, maternal smoking during pregnancy, social class and maternal age at birth, maternal depression.	Association between small birth weight for gestation and depression during child and adolescence (*b* -0.001, SE 0.001, P 0.015, 95% CI: -0.003 to -0.0003)

aOR adjusted odds ratio; aRR adjusted risk ratio; aHR adjusted hazard ratio; aPR adjusted prevalence ratio; CI confidence interval; SD standard deviation; SGA small for gestational age; AGA appropriate for gestational age; LGA large for gestational age; ICD International Classification of Diseases; DSM Diagnostic and Statistical Manual of Mental Disorders

2.2 Reactive attachment disorder

2.2.1 Diagnostic classification

Reactive attachment disorder is a complex disorder characterized by ambivalence about seeking comfort from caregiver, emotionally withdrawn, lack of social approach, reduced positive affect and unexplained fearfulness or irritability. RAD is described in both diagnostic systems: ICD-10 and DSM-5. While ICD-10 separates RAD from disinhibited attachment disorder, DSM-4 included both inhibited and disinhibited subtypes of attachment disorder into RAD. DSM-5 separated these subtypes into RAD and disinhibited social engagement disorder based on the research in last decades that explained their differences in phenotypic characteristics, correlates, courses and responses to interventions (Zeanah *et al.,* 2016). **Table 4** shows the ICD-10 diagnostic criteria for RAD.

Table 4. ICD-10 diagnostic criteria for RAD. Modified and reproduced with the permission from WHO 2020.

CODE	DESCRIPTION
F94.1	**Reactive attachment disorder**
	A. Onset before the age of five years.
	B. Strongly contradictory or ambivalent social responses that extend across social situations (but which may show variability from relationship to relationship).
	C. Emotional disturbance as shown by lack of emotional responsiveness, withdrawal reactions, aggressive responses to one's own or other's distress and/or fearful hypervigilance.
	D. Evidence of capacity for social reciprocity and responsiveness as shown by elements of normal social relatedness in interactions with appropriately responsive non-deviant adults.
	E. Does not meet criteria for pervasive developmental disorders (F84).

2.2.2 Attachment concept

John Bowlby's work on "44 juvenile thieves" describing the role of early separation from the mother in the development of an 'Affectionless Character', a personality trait mainly evident in chronic offenders, is one of his earliest contributions to attachment theory (Bowlby, 1944). Bowlby, well known as the father of attachment theory has published a trilogy, Attachment (Bowlby, 1973b), Separation (Bowlby, 1973a) and Loss (Bowlby, 1980). Bowlby describes attachment as "a profound, reciprocal, physical and emotional relationship between a parent and a child that endures and sets the stage for all future intimate and trusting relationships" (Bowlby, 1973). Infants develop attachment with their primary caregiver and seek proximity during distress or under threatening conditions (Bowlby, 1969). The infant is

dependent on the primary caregiver for nutrition, protection, socialization and survival. The need of physical proximity and dependency ensures the infant's protection and survival. Bowlby collaborated with James Robertson to research about separation of mother and child. Robertson investigated children separated from their parents in a residential care and carried out attachment theory from academic arena to the professions, policy makers and to the general community (Alsop-Shields and Mohay, 2001). The attachment theory was empirically tested by Mary Ainsworth, who developed the Strange Situation Procedure (SSP). SSP is a test involving separation and reunion from a primary attachment figure and a stranger. It is an observational assessment designed to test individual differences in attachment behaviour, and were categorized as secure, insecure/avoidant, and insecure/resistant (Ainsworth *et al.,* 1978). Ainsworth also described an unclassifiable attachment behaviour, which was later identified as disorganized attachment (Main and Solomon,1986).

Attachment patterns are developmental psychology-based classifications that represent levels of protective vs risk factors and are not in and of themselves forms of psychopathology. Attachment begins in infancy that proceeds through various stages in life and can be disrupted when an infant's basic needs are consistently not met. The quality of caregiving affects the child's social, emotional and cognitive development (Thapar *et al.,* 2015). The quality of attachment influences the child's risk for social problems and mental disorders (Green and Goldwyn, 2002; Zeanah, Berlin and Boris, 2011). Secure attachment may act as a protective factor, whereas, insecure and in particular disorganized attachments are associated with higher risk for psychopathology (Green and Goldwyn, 2002).

2.2.3 Incidence and prevalence

RAD has been considered to be a rather rare disorder although there have been no careful epidemiological studies reporting their prevalence in the community sample. In a Danish cohort study (n=211), the prevalence of RAD in 1.5 years old was 0.9% (95% CI 0.1–3.4) (Skovgaard *et al.,* 2007). Most of the studies on RAD have been conducted on extreme populations and it has been much less noted and studied in children outside institutions (Rutter *et al.,* 2010). The prevalence in these high-risk populations is subsequently higher: 1.40% in a deprived population of UK (Minnis *et al.,* 2013), 19.4% in foster care (Lehmann *et al.,* 2013), 38–40% of maltreated toddlers in foster care (Zeanah *et al.,* 2004). Most of the literature focuses on RAD in early childhood. The long-term sequel of RAD is not clearly understood. A recent study found prevalence of 9% in a high-risk group of adolescents (Seim *et al.,* 2019). Children experiencing severe deprivation, neglect or insufficient caregiving are at increased risk of RAD (Boris *et al.,* 2004; Zeanah *et al.,* 2004). RAD is a complex

disorder, and children with RAD have an inceased risk of comorbidity including emotional problems, learning difficulties and poor social skills (Pritchett, Pritchett *et al.,* 2013; Raaska *et al.,* 2012).

2.2.4 Early caregiving and RAD

The Bucharest Early Intervention Project is the first randomized control trial that included 136 children abandoned at or near birth and cared for in institutions in Bucharest, Romania (Zeanah *et al.,* 2003). Children were assessed at baseline for signs of reactive attachment disorder through structured interviews with their caregivers. The authors observed significantly more signs of reactive attachment disorder among institutionalized children without any history of institutional rearing (Zeanah *et al.,* 2005). Following baseline assessment, children were randomly assigned to either care as usual or to removal from institutions and placement in foster (Smyke *et al.,* 2009). When the signs of reactive attachment disorder were examined at ages 30, 42, 54 months and 12 years, children demonstrated early and substantial decrease in signs of RAD with access to enhanced caregiving (Humphreys *et al.,* 2017; Smyke *et al.,* 2012).

2.2.5 Prenatal risk factors

2.2.5.1 Parental psychiatric diagnoses

RAD has been mostly studied in at-risk populations including maltreated samples, orphan-samples, adopted child populations, psychiatrically impaired and substance abusing parent samples, describing its nosology and clinical treatment practices (Boris *et al.,* 2004; Minnis *et al.,* 2013; Pritchett, Rochat *et al.,* 2013; Raaska *et al.,* 2012; Zeanah *et al.,* 2004; Zeanah *et al.,* 2016; Zeanah *et al.,* 2005). Only one previous study of maltreated toddlers in foster care examined maternal risk factors including, education, teen parent, partner violence, criminal history, depressed mood, maltreatment as a child, psychiatric history and substance abuse history and offspring RAD. Only maternal psychiatric history was associated with the risk of offspring RAD. The risk was 2.3-fold higher when mother had any history of psychiatric illness compared to mothers without any history of psychiatric illness (Zeanah *et al.,* 2004). However, the study included both inhibited and disinhibited subtypes.

2.2.5.2 Socio-demographic and lifestyle factors

A Danish register-based cohort study showed increased risk for attachment disorder when both parents had a history of homelessness. The risk was significant even after adjusting for both maternal and paternal psychopathology (Nilsson *et al.,* 2017). Moreover, a clinical study on maltreated toddlers in foster care did not report significant findings for maternal education, teen pregnancy and RAD (Zeanah *et al.,* 2004). Both of these studies however, included both subtypes of attachment disorder, and findings are not specific to only RAD.

2.2.6 Perinatal risk factors

2.2.6.1 Preterm birth and low birth weight

Premature birth or infants with low birth weight are at increased risk of psychiatric illnesses. The interaction between mother and preterm infant is interrupted due to mother-infant separation. Parents of premature infant may find difficulty in understanding their need for proximity and closeness as infants born preterm are less alert and responsive compared to their full-term counterparts (Muller-Nix *et al.,* 2004). Mothers of preterm infants experience increased level of psychological distress during neonatal period including emotional disorders, anxiety, depression and post-traumatic stress disorder (Kersting *et al.,* 2004). The separation due to monitoring in NICU, may disturb the development of the attachment relationship between preterm infant and the parents. There are no previous clinical or population-based studies that have examined preterm birth or low birth weight as risk factors for RAD.

2.2.6.2 Obstetric complications

Mode of delivery. Vaginal delivery is the common and in majority of cases the safest mode of delivery (Ray Chaudhuri Bhatta and Keriakos, 2011), however operative deliveries are increasing rapidly due to advances in medical technology. Operative delivery can be either operative vaginal delivery or caesarean delivery. Operative vaginal delivery, also known as assisted delivery, uses vacuum or forceps in the delivery. The vacuum and forceps use may incur maternal and neonatal injuries if not operated properly. Caesarean delivery is a surgical procedure of delivering a fetus, placenta and membranes through abdominal and uterine incision. The rate of caesarean delivery is increasing, as the indications for caesarean section has changed, including maternal anxiety about the delivery, or even the mother's wish to have a caesarean section in the absence of any medical indication. The WHO global survey

reported that caesarean sections are associated with an increase in risks for both mother and infant compared to vaginal delivery and should therefore be performed only when medically indicated (Souza *et al.,* 2010).

Breech presentation. Breech presentation occurs when the fetus is in the longitude presentation where buttocks, foot or feet are adjacent to the maternal pelvis. The incidence of breech presentation at birth is estimated to be between 2–4%. Preterm birth is the most common reason for breech presentation. The prevalence of breech presentation in preterm birth is 22%, compared to 4% in at term birth (Hickok *et al.,* 1992). Prematurity, fetal growth restriction, advanced maternal age, maternal smoking, gestational hypertension, and gestational diabetes have been identified as risk factor for breech presentation (Cammu *et al.,* 2014; Toijonen *et al.,* 2020), and furthermore are associated with increased risk for adverse perinatal outcomes (Macharey *et al.,* 2017).

Obstetric haemorrhage. Obstetric haemorrhage is the leading cause of maternal morbidity and severe mortality and accounts for 27% of all maternal deaths worldwide (Say *et al.,* 2014). The blood loss greater than 500 ml or greater than 1000 mL is considered as moderate and severe obstetric haemorrhage respectively (Abdul-Kadir *et al.,* 2014). Obstetric haemorrhage is associated with adverse maternal and neonatal outcomes (Sheldon *et al.,* 2014).

Hypertensive disorders. Hypertensive disorders are common medical complications during pregnancy and occur in 5–10% of pregnancies (Vest and Cho, 2014). Hypertension in pregnancy is defined as a blood pressure of ≥ 140 mm Hg systolic or ≥90 mm Hg diastolic on at least two measurements, separated by resting period. Gestational hypertension is first identified in pregnancy after 20 weeks of gestation in absence of diagnostic criteria for preeclampsia (Brown *et al.,* 2018). Approximately 15–25% of women with gestational hypertension will develop preeclampsia (Saudan *et al.,* 1998). Preeclampsia is hypertension during pregnancy after 20 weeks of gestation accompanied by protein in the urine or evidence of end-organ dysfunction (Brown *et al.,* 2018). Eclampsia is the occurrence of seizures in a woman with preeclampsia without other identifiable cause. Pre-eclampsia and eclampsia are associated with increased risk of offspring neurodevelopmental diseases (Sun *et al.,* 2020).

Umbilical cord artery pH. The umbilical cord blood pH is important in monitoring the obstetrical quality and neonatal condition at birth. The American College of Obstetricians and Gynecologists recommend the arterial pH <7.00 as a clinical cut-off value for the identification of high-risk neonates (American College of Obstetricians and Gynecologists, 2014). However, the reference values may vary by gestational age and sex of the fetus (Skiöld *et al.,* 2017; Zaigham, Källén and Olofsson, 2019). A low umbilical blood pH usually is the consequence of

intrauterine hypoxemia. Low umbilical cord pH has been associated with adverse neonatal outcomes (Malin, Morris and Khan, 2010; Victory *et al.,* 2004).

Induced labour. Induction of labour is the artificial stimulation of labour before its spontaneous onset in order to achieve vaginal delivery. Oxytocin or prostaglandins is administered to the pregnant woman or induced through manually rupturing the amniotic membranes (World Health Organization, 2011). The incidence of induction of labour has increased in past decades. In Finland, induction of labour increased from 18.6% to 30.5% of all pregnancies between 2010 and 2018 (Finnish Institute for Health and Welfare, 2019). The indications for induced labour include gestational age of 41 completed weeks or more, pre-labour rupture of amniotic membranes, hypertensive disorders, maternal medical complications, fetal death, fetal growth restriction, chorioamnionitis, multiple pregnancy, vaginal bleeding and other complications. The elective induction of labour is not recommended as it affects the natural process of pregnancy and labour and may increase the risk of complications, including bleeding, caesarean section, uterine hyper stimulation and rupture and other adverse outcomes (World Health Organization, 2011).

Apgar score. Apgar score is a method developed by Dr. Virginia Apgar in 1952 to assess newborn's adjustment to extrauterine life and to manage complications (Apgar, 1953). Five items, color, heart rate, reflex irritability, muscle tone, respiration are evaluated 1 minute after birth and again after 5 minutes. These items are scored as 0, 1 or 2 with total of 10 Apgar score. A score lower than 7 suggests newborn needing medical assistance (American Academy of Pediatrics Committee on Fetus and Newborn and American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2015). Low Apgar score is associated with later neurodevelopmental and cognitive outcomes (Ehrenstein *et al.,* 2009).

Intensive care. High-risk newborns with extreme prematurity, severely inappropriate growth for gestational age, respiratory distress, metabolic abnormalities, or major congenital malformations and life-threatening birth defects are taken to NICU for early evaluation and treatment. These newborns are provided with intravenous lines and nasogastric tubes for nutrition, ventilators for maintaining oxygen, and incubators for maintaining the body temperature. They are also exposed to fluorescent lights for proper vision and also to sounds of varying intensities, including human voices and other noises. All these medical procedures prepare the newborn to cope to the new environment (Goldson, 1999). The time trend analyses in United States showed increased incidence of NICU admission from 2007 to 2012. They reported a relative increase of 23% (64.0 to 77.9 per 1000 live births) in six years, even after controlling for infant and maternal risk factors likely to influence a newborn's chance for NICU admission (Harrison and Goodman, 2015).

2.3 Gaps in previous research

Early risk factors play an important role in the development of mental disorders. There are limited studies on prenatal and perinatal risk factors associated with depression or RAD. Previous studies that examined the association between prenatal and perinatal risk factors including parental age, preterm birth, poor fetal growth and offspring depression, were primarily based on clinical samples, and have produced inconclusive findings. The epidemiological studies on RAD are limited and mostly conducted on high-risk populations and it has been rarely studied in children outside institutions (Rutter *et al.,* 2010). These studies have focused on the prevalence, phenotypic characteristics, course of treatment, and comorbidities of the disorder. To date, only two studies have examined the prenatal risk factors for RAD: a clinical study of maltreated toddlers (Zeanah *et al.,* 2004) and a Danish register-based study (Nilsson *et al.,* 2017). No previous study has examined perinatal risk factors in relation to offspring RAD.

3 Aims

The main objective of this thesis was to explore the prenatal and perinatal risk factors associated with depression among 5–25 years old and RAD in children and adolescents. A summary of the operational framework of the overall study is illustrated below (**Figure 1**). The specific aims of the study included:

1. To report the time trends of the age-specific and gender-specific incidence and cumulative incidence of diagnosed depression (Study I). The study hypothesis was that there is an increase in the incidence and cumulative incidence of diagnosed depression over time.
2. To examine the association between preterm birth, prematurity and depression (Study II). The study hypothesis was that the association between preterm birth, poor fetal growth and depression is in an exposure-response manner. In addition, the associations between preterm birth and depression differ by sex and the age of depression diagnosis.
3. To study the association between parental age and offspring depression (Study III). The study hypothesis was that there is an association between both young and advanced parental age and offspring depression.
4. To explore the association between several parental risk factors and offspring RAD (Study IV). The study hypothesis was that parental risk factors are strongly associated with offspring RAD.
5. To examine the association between perinatal risk factors and offspring RAD (Study V). The study hypothesis was that perinatal risk factors are associated with RAD diagnoses.

4 Materials and Methods

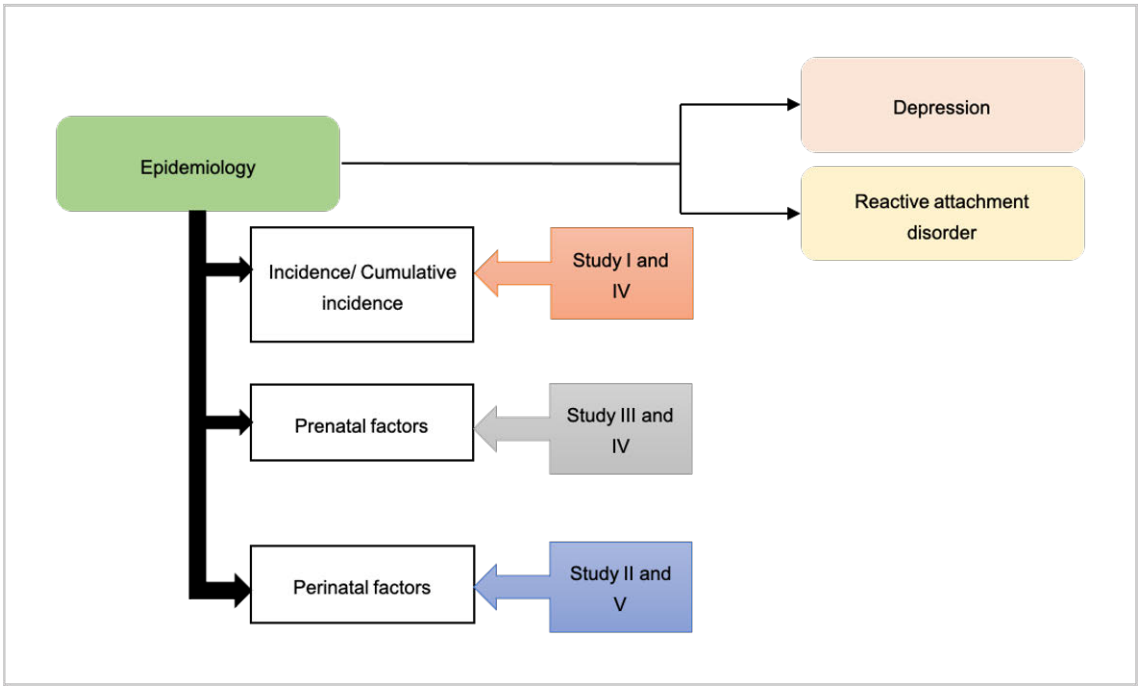

Figure 1. Operational framework of the study.

4.1 Study population

The study used Finnish national registers to identify cases, controls, their parents and other background information. **Figure 2** shows the detailed information on the usage of registers, source population, identification of cases and controls for depression and RAD.

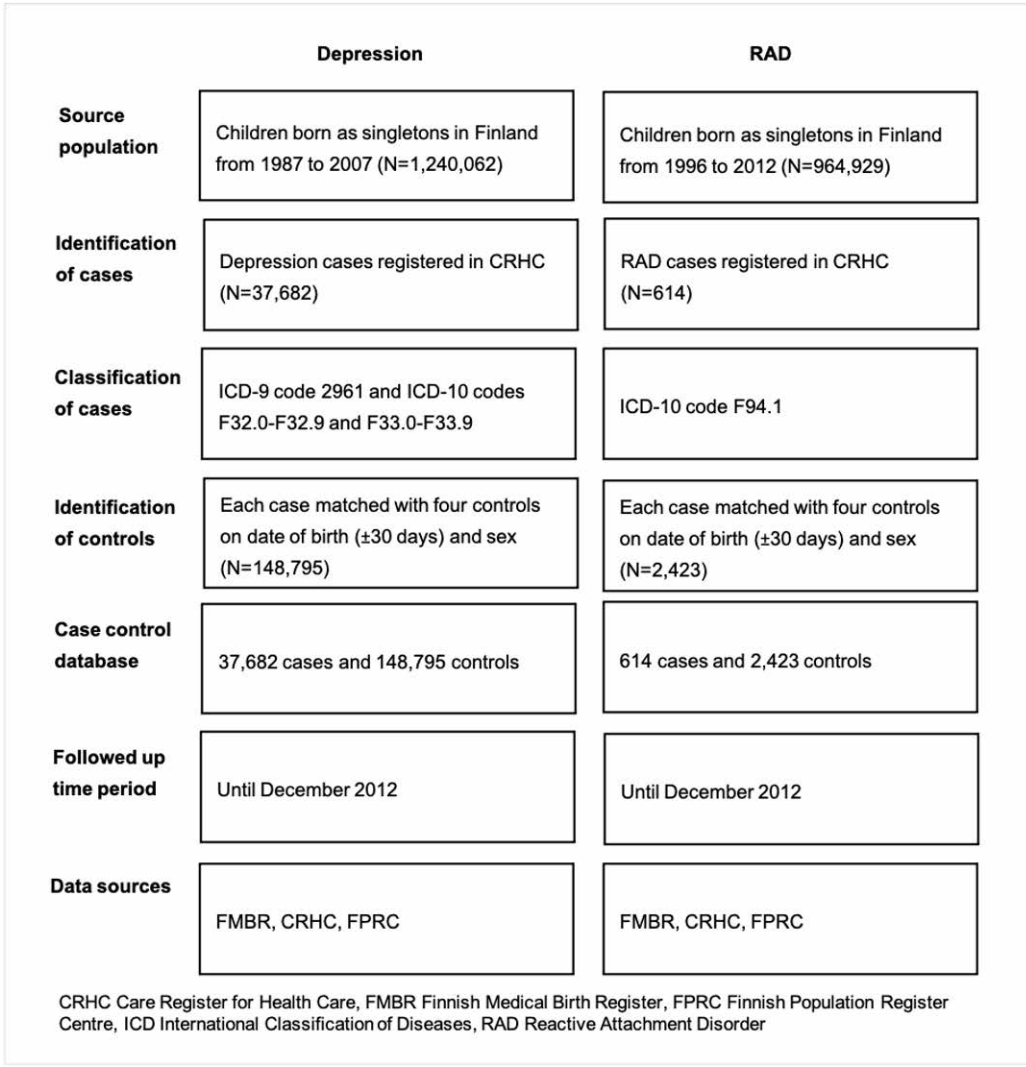

Figure 2. Study description of depression and RAD.

4.2 Study design

The study was based on a nested case-control study design. The nested case-control study design involves a well-defined study cohort and subsequent selection of cases and controls from the cohort. The cases are identified based on the occurrence of particular outcome during the time period. The controls are selected from the remaining cohort without the occurrence of particular outcome during the same time period. The controls are matched with cases by time (e.g., age, date of entry to cohort,

length of time in cohort or their combinations). Following four steps are involved while designing a nested case-control study (Essebag *et al.,* 2003).

1. **Cohort time axis.** A cohort is selected for the study based on eligibility, and defined entry and exit time period. Individuals enter into a cohort at the same predefined zero-time, which may be a calendar time, time from a particular event or onset of a disease, or a certain age. The exit time is determined on the basis of followed-up time period, such as occurrence of disease or particular event, calendar time, specific age, death, or loss to follow up. In the study, two initial cohorts were selected separately for depression and RAD. Two separate cohorts were selected for depression and RAD because the defined entry and exit time period were different for these disorders. For example, the initial cohort of depression included all singleton children born during 1987 to 2007 and were followed up until December 2012 (N=1,240,062). The initial cohort for RAD included all singleton children born during 1996 and 2012 and were followed up until December 2012 (N=964,929).
2. **Case identification.** A case is selected on the basis of occurrence of a particular event or outcome at a defined time period. In the study, cases of depression (n=37,682) and RAD (n=614) were selected when they were registered in CRHC during their predefined cohort time period.
3. **Risk set definition.** Risk sets refer to all the non-cases present in the cohort when the cases become a case. All individuals in the risk set are matched to the case according to the defined time axis.
4. **Control selection.** The controls are selected randomly from the risk sets matched to the case. In the study, four controls were selected from the remaining cohort for each case, matched by sex and date of birth (±30 days). The case control ratio of 1:4 improves the power of the study, and beyond 1:4, there is a little power improvement with increasing the number of controls (Grimes and Schulz, 2005). The controls had to be alive and living in Finland when the case (depression, RAD) was diagnosed.

4.3 Data sources

4.3.1 Care Register for Health Care

The Care Register for Health Care (CRHC), formerly known as the Finnish hospital discharge register (FHDR) is maintained by the Finnish Institute for Health and Welfare. It was established in 1967 and since 1969, it includes complete

computerized data of all medical diagnoses. The register initially included information on patients discharged from inpatient care in hospitals, and since 1994 the register also includes specialized outpatient care. CRHC contains the information on the personal identity code, the date of birth, sex, the dates of any medical admissions and discharges and any primary diagnoses at discharge. All diagnoses are recorded according to the International Classification of Diseases (ICD): ICD-8 from 1969 to 1986, ICD-9 from 1987 to 1995 and ICD-10 since 1996. The quality of CHRC data has been shown to be good. A systematic review on the quality of CHRC data showed that the positive predictive value of common diagnoses was between 75 and 99%, and the completeness and accuracy of register varied from satisfactory to very good (Sund, 2012). When the medical records of the patients were examined, 98% of the main diagnoses of mental disorders at the 3-digit ICD code level had been correctly reported in the CRHC (Keskimäki and Aro, 1991). Previous register-based studies have shown good accuracy and validity of specific psychiatric diagnoses including schizophrenia and bipolar disorder (Arajärvi *et al.,* 2005; Pihlajamaa *et al.,* 2008), autism (Lampi *et al.,* 2010), Tourette syndrome (Leivonen *et al.,* 2014), and attention-deficit/hyperactivity disorder (Joelsson *et al.,* 2015). In this study, CRHC has been used to extract the information on the cases of depression and RAD, and other parental psychiatric diagnoses. The data from CRHC has been linked with data from other registers to build a comprehensive research database. The detail explanation on the linkages of registers are provided below.

4.3.2 Finnish Maternal Birth Register

The Finnish Maternal Birth Register (FMBR) is also maintained by the Finnish Institute for Health and Welfare. It was established in 1987 to collect data on maternity care, obstetrical services and neonates. The register includes detail information on the mother: personal information of mother, previous pregnancies and deliveries, present pregnancy and its monitoring, delivery, and infant: data on personal identity code, birth characteristics, data at discharge or by the age of 7 days. In this study, FMBR was used to extract the information on mothers' regarding the place of birth, the mother's marital status, maternal smoking during pregnancy, maternal SES, parity, obstetric complications, and infants' birth characteristics including birth weight, gestational age, neonatal monitoring, Apgar score, mode of delivery and umbilical artery pH value.

4.3.3 Finnish Population Register Centre

The Finnish Population Register Centre (FPRC) is a Finnish government agency, established in 1969 along with local register offices that are responsible for

maintaining the data in the population information system. The Finnish population information system is a digitalized national register that contains basic information about Finnish citizens and foreign citizens in Finland residing either on a permanent or temporary basis. It includes their name, personal identity code, address, citizenship, native language, date of birth and date of death, if applicable. In this study, FPRC was used to obtain information on parents of cases and controls, identification of controls and identification of place of birth of cases and controls.

4.3.4 Statistics Finland

Statistics Finland is the Finnish public authority established in 1865 for information service and to provide statistics and expertise in the statistical sciences. In this study, statistics Finland was used to obtain information on the source population of the study sample.

4.3.5 Data linkages in registers

The linkage of information from the national Finnish registers mentioned above is performed through the personal identity code. The personal identity code was introduced to Finland in the 1960s and is based on the date of birth and gender. It consists of 11 characters, with a control number, which is unique to each person. It is issued to a person who is registered in Finland's population information system. The issued personal identity code is permanent, which can only be changed if the date of birth or gender were incorrect, or if a person has been legally confirmed to have changed. Moreover, new identity codes could be issued to protect the person, in case of threat to their life or safety and the person's original code have been misused by another person.

4.3.6 Description of study variables and covariates

4.3.6.1 Prenatal variables

Prenatal variables were derived from Finnish national registers including FMBR, CRHC or FCPR. Maternal SES was categorized into four categories based on the national Finnish classification on occupations and socio-economic groups: upper white-collar workers, lower white-collar, blue collar workers and other workers. Upper white-collar workers included employees such as managers, experts in their field and teachers. Lower white-collar workers included employees such as people doing office work and do not fall into earlier category. Blue collar workers included manual workers and others included people involved in unclassifiable work such as

entrepreneurs, students, homemakers and unemployed people. Women were classified according to educational background into upper white-collar workers if they graduated from university and lower white-collar workers if they had a vocational degree, which is lower than a university degree. Maternal smoking during pregnancy was dichotomized as yes or no. Number of previous births was divided into none and one or more. Marital status was dichotomized as being single or married/ in a relationship.

Maternal and paternal immigration status was dichotomized as immigrants and non-immigrants. Immigrant parents were defined as those not born in Finland and/or whose native language was not Finnish. Parental age was treated as a continuous variable in study II and categorized into several categories in Study III, IV and V. Maternal and paternal psychopathology were defined as having a history of any psychiatric disorder, registered in the CRHC by ICD codes (ICD-10: F10-99, ICD-9: 291-316 and ICD-8: 291-308). Maternal and paternal psychopathology were dichotomized as yes or no. Parental depression was defined by ICD codes (ICD-10: F32, F33, ICD-9: 2961, ICD-8: 296.00, 298.00, 300.40, 300.41), and was categorized as yes or no. Maternal substance use was defined by ICD codes (ICD-10: F10-F19, ICD-9: 291, 292, 303, 304, 305, ICD-8: 291, 303, 304), and was categorized as yes or no.

4.3.6.2 Perinatal and obstetric variables

All the perinatal and obstetric variables were derived from FMBR. Region of birth was categorized as southern (region 1), western (region 2), eastern (region 3) and northern (region 4) (**Figure 3**), based on information obtained from Statistics Finland (Statistics Finland, 2004). In the study, region 5 was combined with region 2. Place of birth was categorized as urban, semi-urban and rural. Gestational age was calculated based on mothers' last menstrual period, which has been verified and corrected by a first trimester ultrasound since the late 1980s (Pihkala *et al.,* 1989). Birth weight for gestational age was calculated according to the national sex-specific birth weight distribution standards at a given gestational age for singletons (Sankilampi *et al.,* 2013).

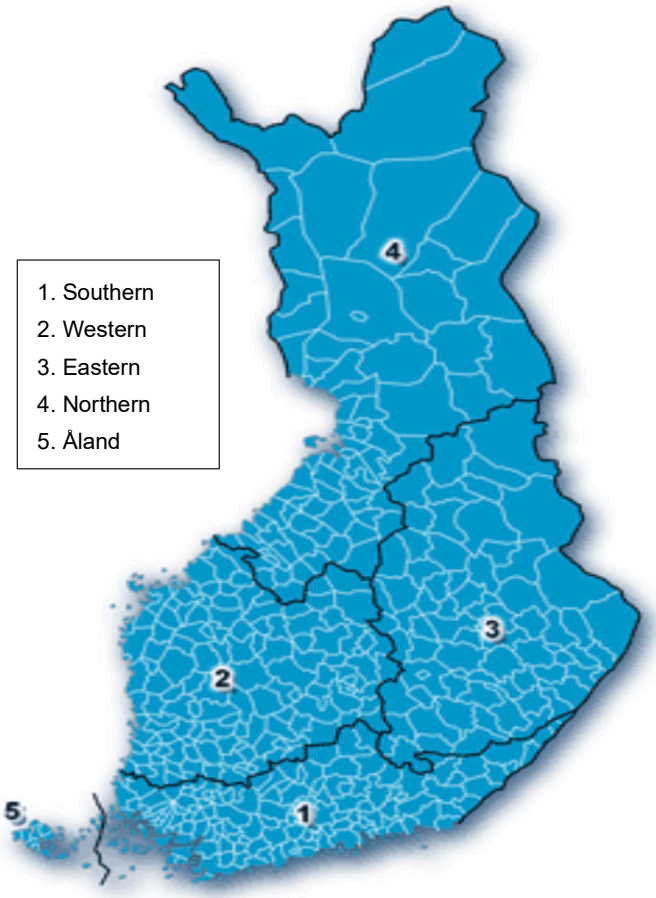

Figure 3. Map of Finland showing major regions. Figure adapted from Statistics Finland (Statistics Finland, 2004).

The Apgar score at one minute was classified as less than 7, 7-8 and 9-10. Neonatal monitoring was classified as either normal follow up or admission to NICU. Birth presentation was classified as cephalic, breech, or other. Birth type was classified as vaginal cephalic, vacuum extractor or forceps, or vaginal breech, planned Caesarean section, other Caesarean section including urgent and emergency Caesarean section, and unknown. Uterine bleeding that required hospitalization, induced labour and maternal hypertension that required hospitalization were all dichotomized as yes or no. Maternal high blood pressure included both pre-eclampsia and pregnancy induced hypertension. The diagnosis of maternal hypertension was based on ICD codes registered in FMBR and CRHC, which has been previously described in detail (Lahti-Pulkkinen *et al.,* 2020). Umbilical artery pH was analysed as a continuous variable.

The summary of study variables and covariates used in the studies (I-V), their categorization and data sources used to extract these variables is given in **Table 5**.

Table 5. Summary of study variables, covariates and data sources used in the study.

STUDY	STUDY VARIABLES AND COVARIATES	CATEGORIZATION	DATA SOURCES
DEMOGRAPHIC DATA			
II–V	Maternal age	<20, 20–24, 25–29, 30–34, 35–39, ≥40 years. Continuous <29, ≥29	FPRC
II–V	Paternal age	<20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50 years. Continuous <31, ≥31	FPRC
II–V	Parental psychiatric history	Yes, no Only mothers, only fathers, both, none	CRHC
II	Parental depression	Yes, no	CRHC
III	Parental immigration status	Immigrants, non-immigrants	FPRC
II, IV, V	Marital status	Married or in a relationship, single	FMBR
I–V	Maternal SES	Upper-collar, lower-collar, blue-collar, others.	FMBR
II, V	Number of previous births	0, ≥1	FMBR
DATA ON PREGNANCY			
II–V	Maternal smoking during pregnancy	Yes, no	FMBR
V	Maternal hypertension	Yes, no	FMBR, CRHC
V	Uterine bleeding	Yes, no	FMBR
V	Induced labour	Yes, no	FMBR
DATA ON THE INFANT			
I–IV	Child's place of birth	Urban, semi-urban and rural	FPRC
II, III	Birth weight for gestational age	Small for gestational age, appropriate for gestational age, large for gestational age Nine categories according to z score, below -2.0 to above 2.0.	FMBR
III, V	Gestational age	Each week Less than 28 weeks, 28–32 weeks, 32–36 weeks, 37–41 weeks and 42 weeks or more. <32 weeks, 32–36, 37–41 (reference), 42 weeks or more.	FMBR
V	Birth weight	Under 2,500 grams, 2,500–3,999 (reference), 4,000–4,499 and 4,500 grams or more.	FMBR
V	Apgar score	7, 7–8, 9–10 (reference)	FMBR
V	Neonatal treatment	Normal, NICU	FMBR
V	Birth type	Vaginal cephalic (reference), vacuum extractor or forceps, or vaginal breech, planned Caesarean section, other Caesarean section including urgent and emergency Caesarean section, unknown.	FMBR
V	Umbilical artery pH	Continuous	FMBR

4.4 Depression

Figure 2 shows the detailed information on the study design and study population of depression. The study population comprised of 1,240,062 singleton children born alive in Finland between 1 January 1987 and 31 December 2007.

The cases were born during the same time period and diagnosed with a depressive episode or recurrent depression in the CRHC before December 2012, when they were at least five years old. The diagnoses of depression were based on ICD-9 code 2961 and ICD-10 codes F32.0-F32.9 and F33.0-F33.9. Each case was matched with four controls, without depression, by their date of birth (±30 days), sex, birthplace and where they lived when the case was diagnosed. The exclusion criteria for cases and controls included: severe or profound mental disabilities - with ICD-9 codes 3181 and 3182 and ICD-10 codes F72 and F73 as these conditions make it hard to diagnose depression. The study included 37,682 cases and 148,795 controls.

4.4.1 Incidence of depression (Study I)

The incidence and cumulative incidence of depression were estimated according to the age at diagnosis in three cohorts, 1987–1993 (aged 5 to 25 years), 1994–2000 (aged 5 to 18 years) and 2001–2007 (aged 5 to 11 years) and stratified by sex. The information on numerator, depression cases by sex in three cohorts was obtained from CRHC and the denominator, total population was obtained from Statistics Finland. The information on maternal SES, place of birth and region of birth was obtained from FMBR.

4.4.2 Prenatal factors (Study II)

Information on parental age was obtained from FPRC. The prenatal factors included in this study are maternal and paternal age. The covariates in the study include parental psychopathology, parental depression, maternal SES, place of birth, marital status, maternal smoking during pregnancy, number of previous births and birth weight for gestational age. The categorization of maternal and paternal age and covariates used in the study is presented in **Table 5**.

4.4.3 Perinatal factors (study III)

The perinatal factors included in this study are gestational age and birth weight for gestational age, and the information was obtained from FMBR. Gestational age was studied by each gestational week and stratified by sex. Similarly, gestational age was also studied in five categories <28 weeks, 28 to 32 weeks, 32–36 weeks, 37 to 41

weeks, and ≥42 weeks, and stratified by sex and age at diagnosis of depression. Birth weight for gestational age was calculated according to national gender-specific birth weight distribution standards at a given gestational age for singletons (Sankilampi *et al.,* 2013). The covariates in the study include parental age, parental psychopathology, parental depression, parental immigration status, maternal substance use, number of previous births, marital status, maternal SES, smoking during pregnancy and place of birth. The categorization of perinatal factors and covariates used in the study is presented in **Table 5**.

4.5 Reactive attachment disorder

Figure 2 shows the detailed information on the study design and study population of RAD. The study population for this study comprised of 964,929 singleton children born alive in Finland between 1 January 1996 and 31 December 2012.

The cases were born during the same time period and diagnosed with RAD with ICD-10 code F94.1 in the CRHC. The children with severe or profound intellectual disability (F72 and/or F73) or pervasive developmental disorders (F84) were excluded from the study. The controls were also born during the same time period without any diagnosis of RAD, severe or profound intellectual disability, pervasive developmental disorders, or anxiety disorders (F 40–42 and/or F93). Each case was matched with four controls, without RAD, by their date of birth (±30 days), sex, birthplace and where they lived when the case was diagnosed. The final study cohort included 614 cases and 2,423 controls.

The children with severe or profound intellectual disability were excluded from the cases and controls as the severity of these conditions make it difficult to assess RAD symptoms. Moreover, pervasive developmental disorder was an exclusion criterion for diagnosing RAD, according to ICD-10 classification. Therefore, they were excluded from cases and controls to increase the reliability of the RAD diagnoses as children with pervasive developmental disorders display similar characteristics to RAD and they could be misdiagnosed as RAD during infancy or early childhood. The diagnosis of anxiety among controls were excluded because this study was a sub-study of a larger anxiety and trauma related study. Therefore, anxiety disorders were excluded in the initial sample. The categorization of prenatal factors used in the study is presented in **Table 5**.

4.5.1 Cumulative incidence of RAD (Study IV)

The cumulative incidence of RAD was estimated according to the number of cases of RAD during the study period (1 January 1996 and 31 December 2012) and divided by total population during the same study period. The cumulative incidence is

expressed per 10,000 population and stratified by sex. The information on numerator, RAD cases, and by sex was obtained from CRHC and the denominator, total population was obtained from Statistics Finland.

4.5.2 Prenatal factors (Study IV)

The prenatal risk factors used in the study were parental psychopathology, maternal smoking, maternal age, paternal age, maternal SES, marital status and residence.

The specific diagnostic categories of maternal and paternal psychopathology including schizophrenia and schizoaffective disorders, other psychoses, bipolar disorders, depression, anxiety disorders, personality disorders and alcohol and drug addiction/abuse were also studied. Parents with schizophrenia and or schizoaffective groups were not assigned to other groups due to the severe, chronic and pervasive nature of the disorder. The parents could be assigned to all other groups in case of comorbidity. Similar categorization has been used in previous studies of parental psychopathology and ADHD (Joelsson *et al.,* 2017) and Tourette Syndrome/Tic disorders (Leivonen *et al.,* 2017). In addition, different combinations of maternal and paternal psychopathology were also studied.

RAD cases were further stratified into RAD with or without any comorbid psychiatric diagnoses (at least one comorbid psychiatric disorder). Cases were examined for following comorbidities: attention deficit hyperactivity disorder (F90), emotional disorders with onset specific to childhood (F93), learning and coordination disorders (F80-F83), conduct and oppositional disorders (F91–F92), tic disorders (F95), elective mutism (F94.0), disinhibited attachment disorder of childhood (F94.2), depression (F32, F33, F34, F38, F39), obsessive compulsive disorder (F42) and reaction to severe stress and adjustment disorders (F43). The covariates included in the study were parental psychopathology, maternal smoking during pregnancy, maternal SES, marital status, residence and parental age. The categorization of prenatal factors and covariates used in the study is presented in **Table 5**.

4.5.3 Perinatal factors (Study V)

The covariates in the study included parental age, maternal SES, maternal smoking, marital status, previous births and parental psychopathology. The perinatal factors included in the study were uterine bleeding that required hospitalization, induced labour, maternal hypertension that required hospitalization, birth presentation, birth type, gestational age, birth weight, umbilical artery pH, Apgar score and neonatal treatment. The categorization of covariates and perinatal factors used in the study is presented in **Table 5**.

4.5.4 Validation of RAD (Study V)

The patient medical record of the Hospital District of Southwest Finland was reviewed for the validation of RAD cases. A total of 40 children born between January 1996 and December 2011, diagnosed with ICD-10 diagnosis code of F94.1 by December 2012 were selected for the review. Two independent reviewers (a registered nurse and a 5th year medical student) studied the medical records for all 40 cases. The reviewing process was supervised by Professor in child psychiatry and a specialist in child psychiatry. The medical records were studied according to the ICD-10 criteria for RAD diagnoses as shown in Table 2. The medical records were also studied if they reported any insufficient care including psychological abuse or neglect, harsh punishment, persistent failure to respond to the child's overtures, or grossly inept parenting), or physical abuse or neglect (persistent disregard of the child's basic physical needs, repeated deliberate injury, or inadequate provision of nutrition). The final case status was determined by comparing the recordings of both reviewers and additional review by the specialist in child psychiatry.

4.6 Statistical methods

In Study I, two separate time-to-event analyses were performed to estimate yearly the incidence and cumulative incidence of diagnosed depression. The incidences of diagnosed depression were estimated in three cohorts 1987–1993 (aged 5 to 25 years), 1994–2000 (aged 5 to 18 years) and 2001–2007 (aged 5 to 11 years) for males and females per 100 persons at risk. The numerator for incidence was calculated as the yearly number of new diagnosed depression cases in the three cohorts. The numerator for yearly cumulative incidence was calculated, separately for males and females, as the added number of new diagnosed depression cases starting from age 5 until age 25 for cohort 1987–1993, age 18 for cohort 1994–2000 and age 11 for cohort 2001–2007 per 100 persons at risk. The denominator for both incidences was the Finnish born population at risk (alive and living in Finland) in three cohorts 1987–1992 (aged 5 to 25 years), 1994–2000 (aged 5 to 18 years) and 2001–2007 (aged 5 to 11 years). Confidence intervals (95% CI) for cumulative incidence were estimated.

In study II, III and V, bivariate analyses were conducted to test the significance of association between covariates and outcomes (depression and RAD) as well as covariates and exposure variables among controls. Conditional logistic regression was used to examine the associations between exposure variables and outcomes. The unadjusted odds ratio and 95% confidence intervals were estimated for exposure variables and outcomes. The adjustment for potential confounding variables was made and estimated adjusted odds ratio and 95% confidence interval. A two-sided p value of <0.05 was considered statistically significant.

In Study IV, univariate analyses were conducted using conditional logistic regression to examine the associations between prenatal risk factors, including parental psychopathology, maternal smoking, maternal age, paternal age, maternal SES, marital status and residence and offspring RAD. The variables were selected for multivariate analyses with the limit of significance of $p<0.1$. The association between offspring RAD to the exposure was reported as an odds ratio (OR) and two-sided 95% confidence interval (95% CI). The level of significance was $p<0.05$.

The association between maternal and paternal adulthood-onset psychiatric disorder, including schizophrenia and schizoaffective disorders, other psychoses, bipolar disorders, depression, anxiety disorders, personality disorders and alcohol and drug addiction/abuse, were examined for offspring RAD. The adjustments were made for risk factors that were shown to be significantly associated with offspring RAD in the univariate analysis ($p<0.1$). Conditional logistic regression analyses were used, and the associations were reported as odds ratios (OR) and two-sided 95% confidence intervals (95% CI). The level of significance was $p<0.05$.

The frequencies of different combinations of maternal and paternal adulthood-onset psychiatric diagnoses among the cases and controls were examined and were reported as percentages. In addition, the comorbid psychiatric diagnoses of RAD were studied and reported as percentages.

All the statistical analyses in the study were performed with SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC, USA). The statistical analyses used in different studies are summarized in **Table 6**.

Table 6. Summary of statistical methods in different studies.

STUDY	EXPOSURE	STRENGTH OF ASSOCIATION	COVARIATES	STATISTICAL METHODS
DEPRESSION				
I	..	Incidence and cumulative incidence, 95% CI	..	Cumulative incidence, time to event analyses
II	Parental age	OR (unadjusted, adjusted), 95% CI	Parental psychopathology, parental depression, maternal SES, place of residence, marital status, maternal smoking during pregnancy, number of previous births and birth weight for gestational age	Conditional logistic regression analyses
III	Gestational age, birth weight for gestational age	OR (unadjusted, adjusted), 95% CI	Parental age, parental psychopathology, parental depression, parental immigrant status, maternal substance abuse, number of previous births, marital status, maternal SES, smoking during pregnancy and place of birth.	Conditional logistic regression analyses
RAD				
IV	Parental psychopathology, maternal smoking during pregnancy, maternal SES, marital status, residence and parental age	OR (univariate, multivariate), 95% CI	Parental psychopathology, maternal smoking during pregnancy, maternal SES, marital status, residence and parental age	Conditional logistic regression analyses
V	Gestational age, birth weight, Apgar score, neonatal monitoring, birth presentation, birth type, uterine bleeding, induced labour and maternal hypertension	OR (unadjusted, adjusted), 95% CI	Parental age, maternal SES, maternal smoking, marital status, previous births and parental psychopathology	Conditional logistic regression analyses

4.7 Ethical considerations

The study was approved by the Ministry of Social Affairs of Health and the National Institute of Health and Welfare and ethical approval was provided by the Ethics Committee of the Hospital District of Southwest Finland. The approval for this validation study was provided by the ethics committee of the Hospital District of Southwest Finland and Turku Clinical Research Centre. The Finnish Data Protection Board approved the utilization of the health registers data and their linkage using personal identity code and maintaining the anonymity of subjects for the register-based study.

5 Results

5.1 Depression

5.1.1 Characteristics of the sample and incidence of depression (Study I)

There were 37,682 cases of depression and 148,795 controls in the study. The mean age at diagnosis of depression was 16 years, with a standard deviation (SD) of 3.5 years and range of 5–25 years. Of the cases of depression, 65.5% were females and 34.5% were males.

Figure 4 shows the incidence of diagnosed depression cases for males and females by birth years 1987–1993, 1994–2000 and 2001–2007. In the youngest cohort, the incidence among males increased at 8 years, but at 10 years in females. In the oldest cohort, the incidence increased steadily over the age span 8–20 years in males, but it increased rapidly at age 11–12 to 15–16 years in females. The incidence decreased among females but remained relatively stable among males. The peak incidence was 16 years among females born 1987–1993 but at 15 years among females born in 1994–2000.

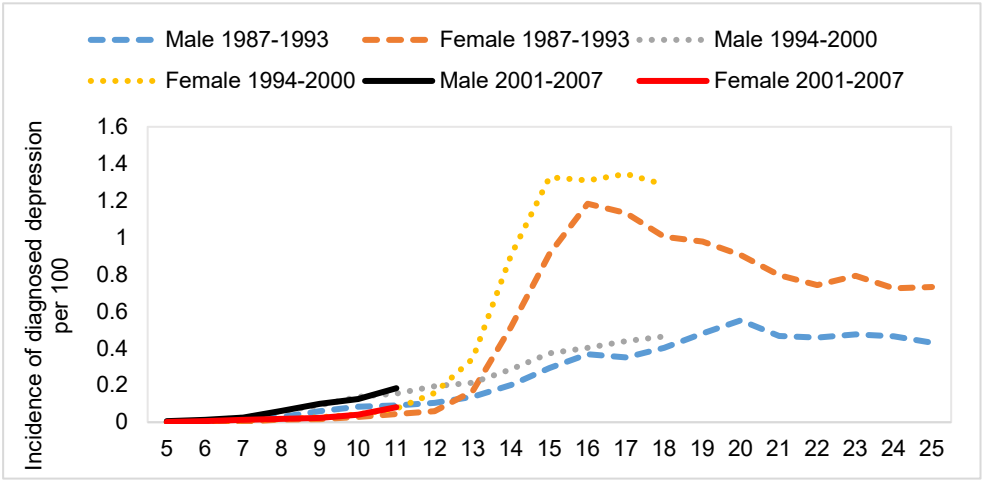

Figure 4. Incidence of diagnosed depression by sex and birth years. Modified from Filatova et al. 2019, study I.

Figure 5 shows the cumulative incidence of diagnosed depression cases for males and females by birth years 1987–1993, 1994–2000 and 2001–2007. The three cohorts were followed up until the age of 25 years, 18 years and 11 years. The cumulative incidence of diagnosed depression by the age 25 years was 5.5% (95% CI 5.4–5.7) among males and 10.4% (95% CI 10.3–10.6) among females in the first cohort.

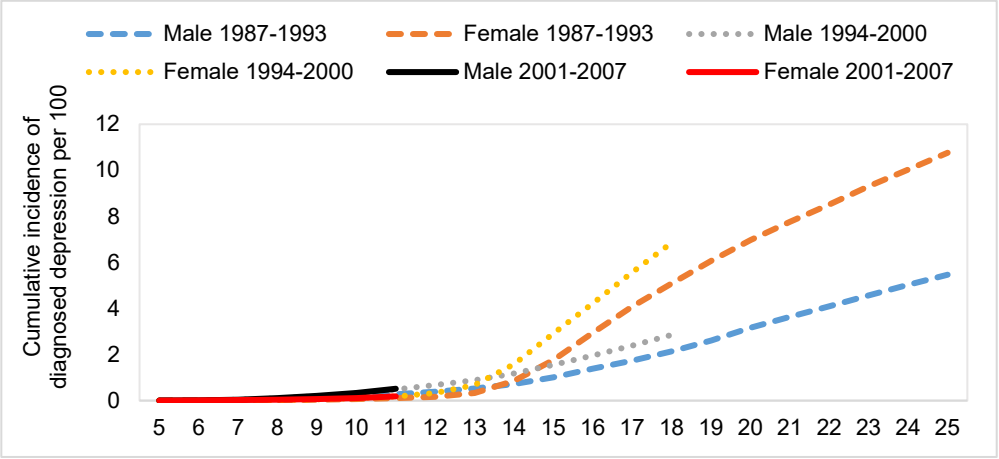

Figure 5. Cumulative incidence of diagnosed depression by sex and birth years. Modified from Filatova et al. 2019, study I.

5.1.2 Prenatal factors (Study II)

Maternal and paternal age were examined as risk factors for depression. The distribution of maternal and paternal age among cases and controls are shown in **Figure 6**.

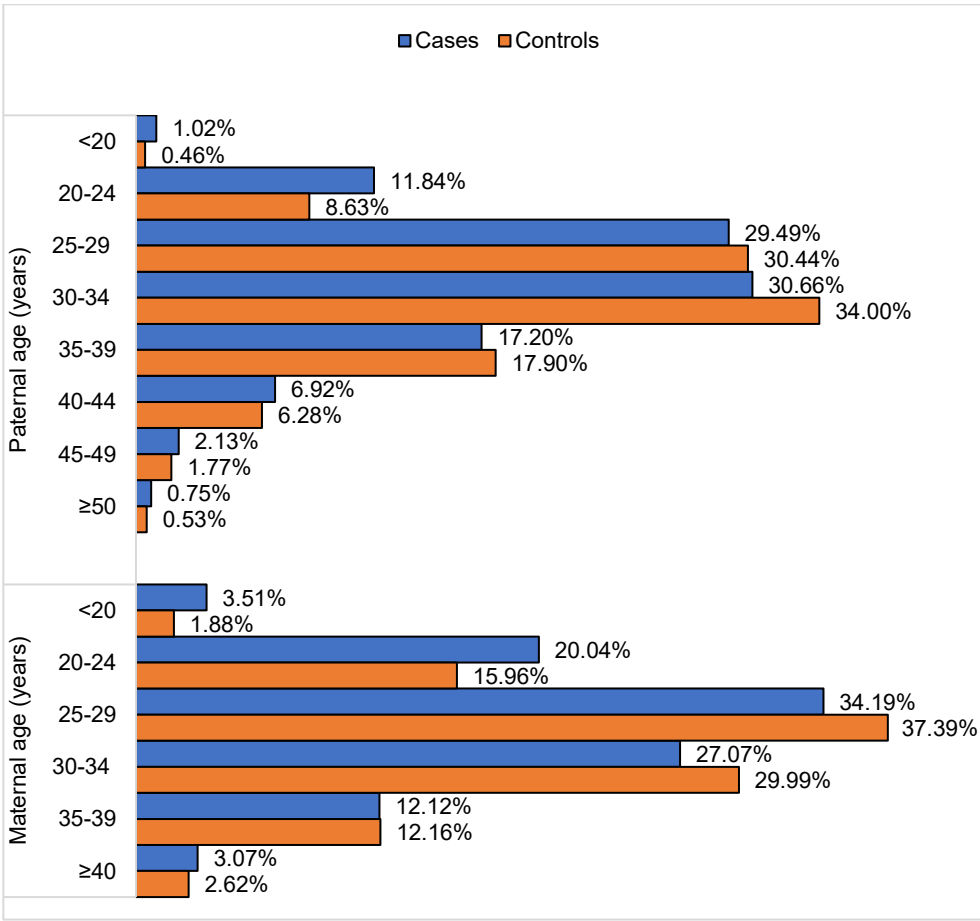

Figure 6. Distribution of paternal and maternal age among depression cases and controls.

In the adjusted models, both younger and older parental age were associated with increased odds of offspring depression (Figure 6). The odds of depression was increased in maternal age categories <20, 20–24, ≥ 40 years, and in paternal age categories <20, 20–24, 35–39, 40–44, 45–49 and ≥ 50 years. The highest odds of offspring depression was observed for advanced paternal age ≥50 years (aOR 1.56, 95% CI 1.29–1.90) and young maternal age <20 years (aOR 1.47, 95% CI 1.33–1.62) (**Figure 7**).

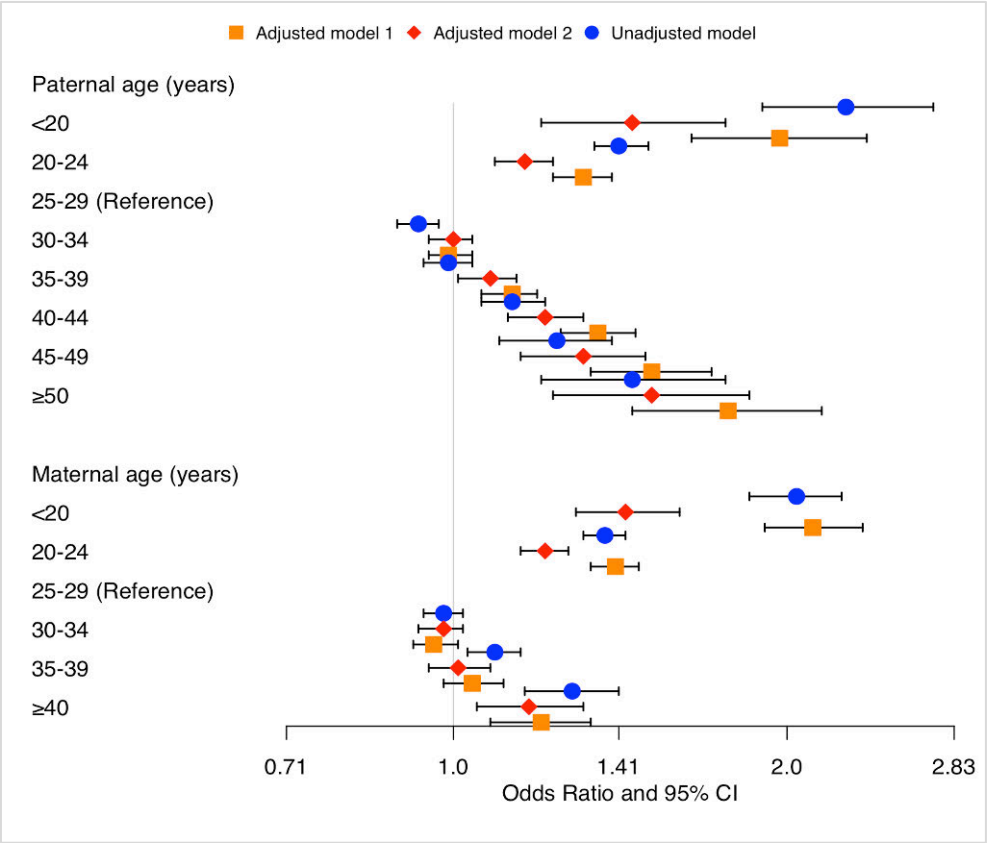

Figure 7. Odds ratio and 95% confidence interval of the association between parental age and offspring depression.

5.1.3 Perinatal factors (Study III)

Preterm birth and fetal growth were examined as a risk factor for depression. The distribution of gestational age in weeks and weight for gestational age (z-scores) among depression cases and controls are shown in **Figure 8** and **Figure 9** respectively.

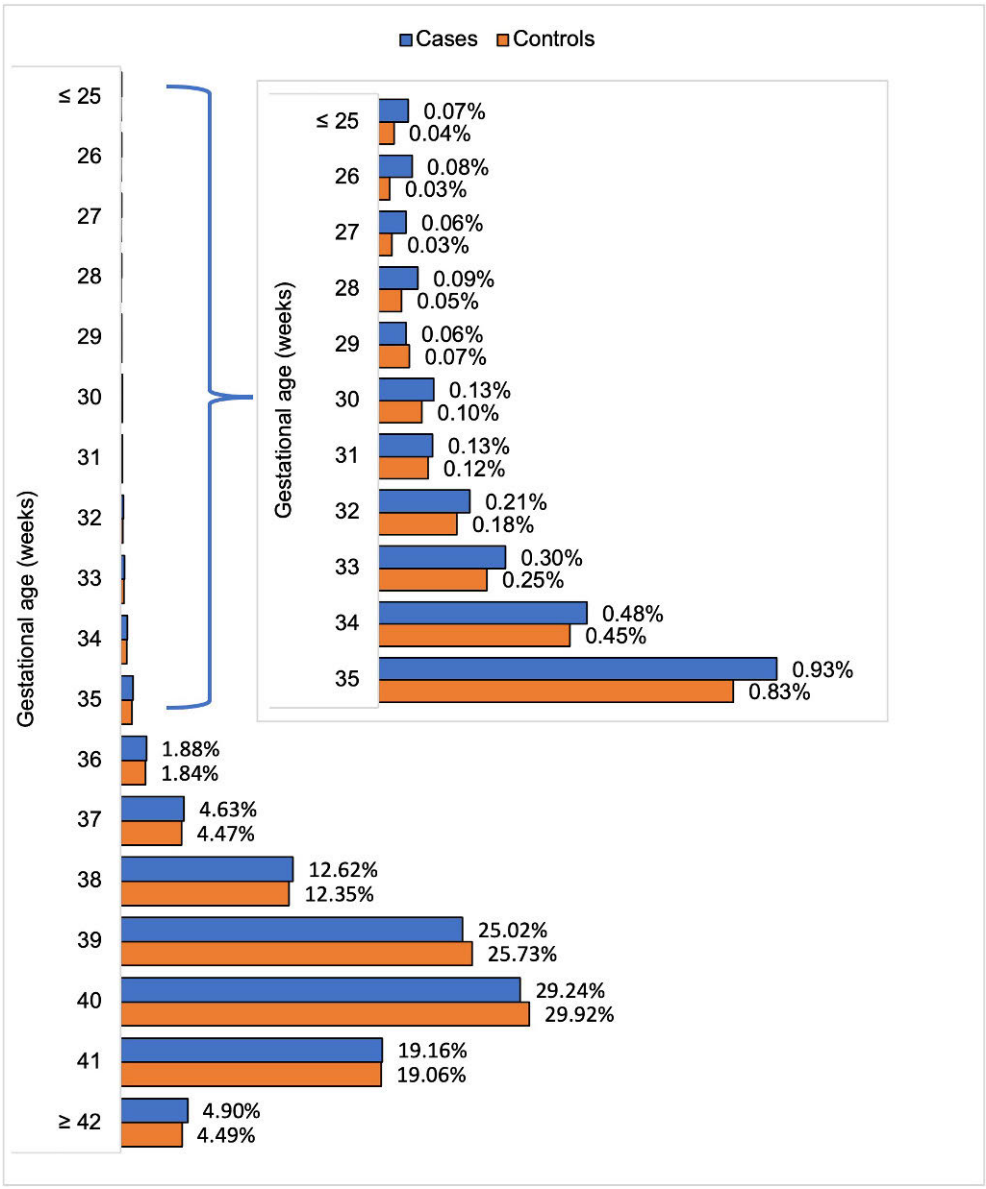

Figure 8. Distribution of gestational age in weeks among cases and controls.

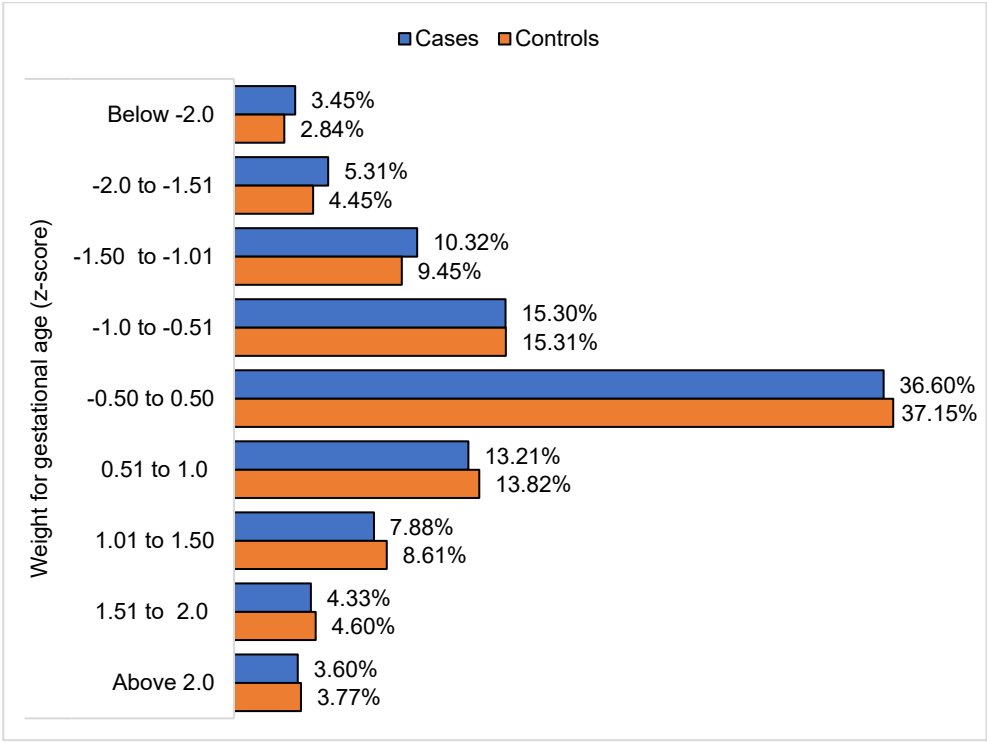

Figure 9. Distribution of weight for gestational age (z-score) among cases and controls.

In the adjusted models, the increased odds of depression was observed in children born ≤25 gestational weeks (aOR 1.89, 95% CI 1.08–3.31, p=0.02), at 26 gestational weeks (aOR 2.62, 95% CI 1.49–4.61, p <0.001), at 27 gestational weeks (aOR 1.93, 95% CI 1.05–3.53, p=0.03) and ≥42 gestational weeks (aOR 1.11, 95% CI 1.05–1.19, p=<0.001). Moderate or late preterm birth was not associated with increased odds of depression (**Figure 10**).

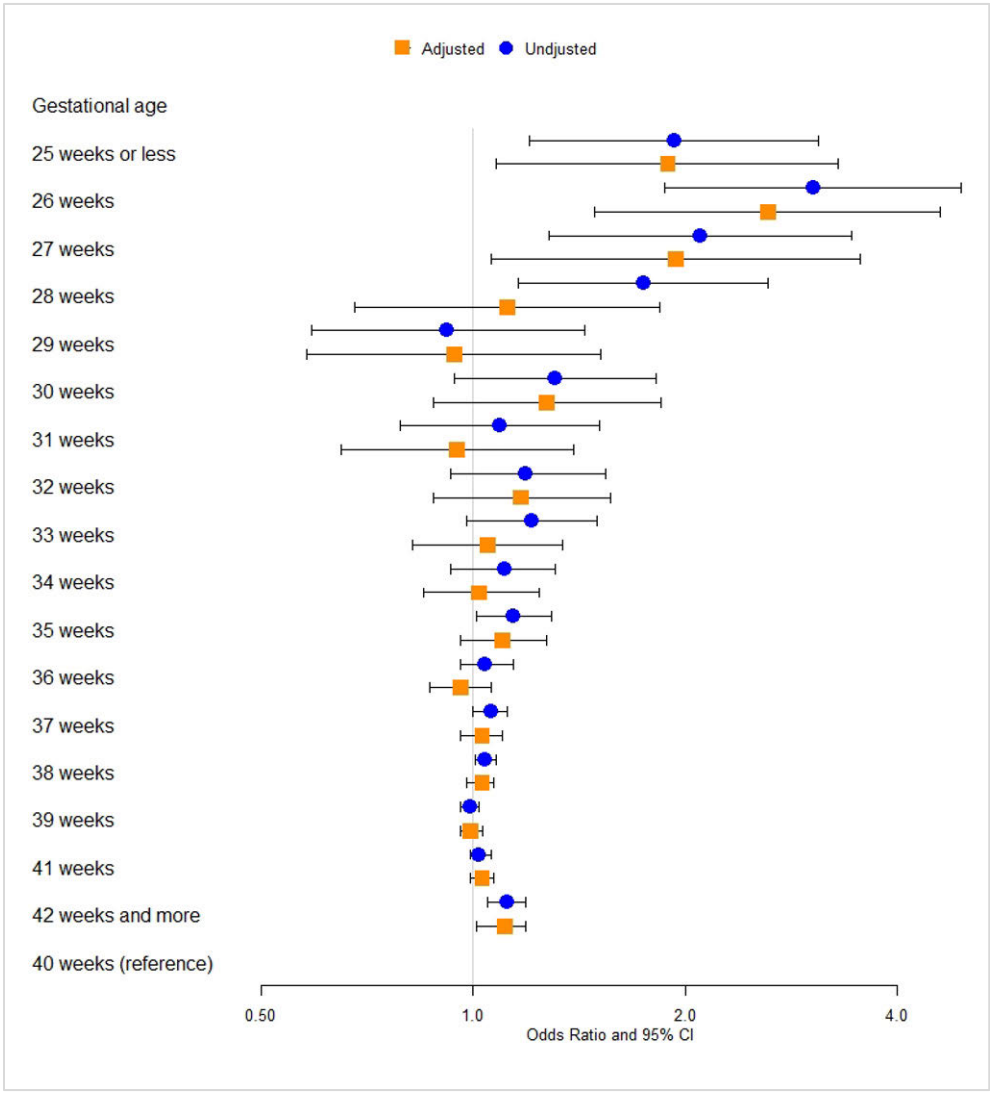

Figure 10. Odds ratio and 95% confidence interval of the association between gestational age in weeks and depression.

There was a significant interaction by sex and gestational age with depression (p=0.002). Preterm birth was associated with depression in females, whereas post-term birth was associated with depression in both males and females. In females, increased odds of depression were observed in children born at or below 25 gestation weeks aOR 2.27 (95% CI 1.19–4.32, p=0.01), 26 gestational weeks aOR 3.22 (95% CI 1.66–6.24, p <0.001), 27 gestational weeks aOR 3.00 (95% CI 1.46–6.15, p=0.002) and at or after 42 gestational weeks aOR 1.09 (95% CI 1.01–1.19, p=0.01).

In males, the increased odds of depression were observed in children born post-term aOR 1.15 (95% CI 1.03–1.28, p=0.009).

The additional analyses were conducted stratifying the children according to the age at the diagnosis of depression and sex. In females, extreme preterm birth (below 28 gestational weeks) was associated with depression diagnosed between 5 to 12 years of age (aOR 2.70, 95% CI 1.83-3.98, p=<0.001) and 13 to 18 years (aOR 2.97, 95% CI 1.84–4.78, p <0.001). In males, post term birth (≥42 weeks) was associated with depression diagnosed between 19 to 25 years (aOR 1.28, 95% CI 1.07–1.54, p=0.006).

Small birth weight for gestational age was associated with increased odds of depression. The risk for depression increased as the z-scores decreased, with ORs ranging from 1.1 to 1.23 in the unadjusted analyses. In the adjusted models, the aORs for a z-score below -2.0 was 1.07 (95% CI 0.99–1.15, p=0.07), for z-score -2.0 to -1.5 was 1.06 (95% CI 1.00–1.13, p=0.05), and for a z-score of -1.5 to -1.0 was 1.05 (95% CI 1.008–1.10, p=0.02) (**Figure 11**). The associations between birth weight z- score and depression diminished when analysed separately for both sexes.

The associations were also examined between combined prematurity and fetal growth categories and depression. In the adjusted model, the significant association was observed for extremely preterm infants with normal fetal growth (aOR 2.99, 95% CI 1.87–4.78), p <0.001), full term infants with poor fetal growth (aOR 1.06, 95% CI 1.03–1.10, p <0.001), post-term infants with poor fetal growth (aOR 1.24, 95% CI 1.08–1.43, p=0.002) and post-term infants with normal fetal growth (aOR 1.09, 95% CI 1.02–1.18, p=0.01).

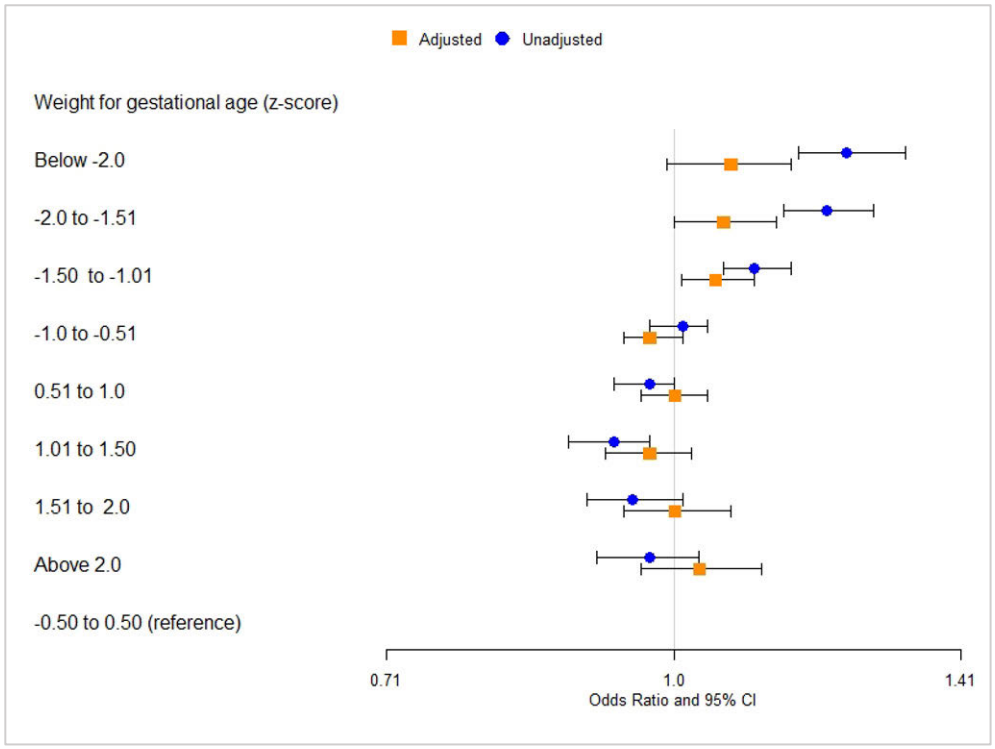

Figure 11. Odds ratio and 95% confidence interval of the association between birth weight for gestational age (z-scores) and depression.

5.2 Reactive attachment disorder

5.2.1 Characteristics of the sample and cumulative incidence of RAD (Study IV)

The mean age at diagnosis of RAD was 7.36 years (SD:3.0 years, range of 0–16 years). Among total of 614 cases, 61% were male. The cumulative incidence of RAD cases treated in specialized health care services over the 16-year period (1996–2012) was 6.38/10,000 births: 7.38/10,000 among males and 4.92/10,000 among females.

5.2.2 Validation of RAD (Study V)

For the validation of RAD, 40 cases were selected from the patient medical record of the Hospital District of Southwest Finland. Among them, three cases were excluded from the review due to having incomplete information. Out of 37 reviewed cases, two cases did not fulfil the diagnostic criteria. The full ICD-10 criteria were

met in 35 out of 37 cases (94.5%). The psychological and/or physical abuse or neglect were present in all the examined cases.

5.2.3 Prenatal factors (Study IV)

Parental psychiatric diagnoses, maternal smoking during pregnancy, maternal SES, marital status, residence, maternal age and paternal age were examined as risk factors for RAD. The distribution of parental factors among RAD cases and controls are shown in **Figure 12**.

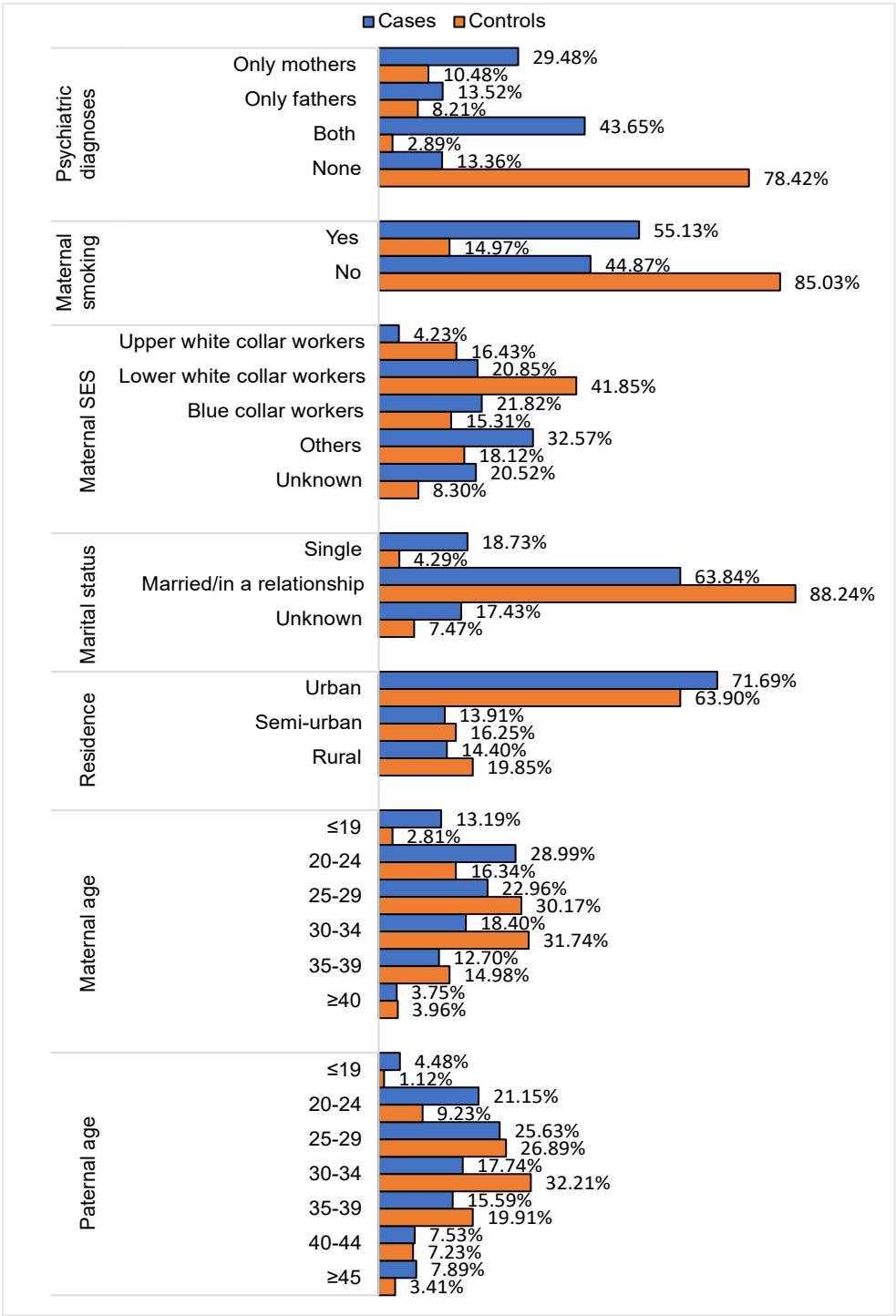

Figure 12. Distribution of prenatal risk factors among RAD cases and controls.

In the multivariate models, increased odds for RAD were associated with a maternal psychopathology (OR 8.82, 95% CI 5.87–13.26) and paternal psychopathology (OR 5.60, 95% CI 3.56–8.82). Similarly, the odds significantly increased when both parents had a diagnosis of psychiatric illness (OR 51.47, 95% CI 31.50–84.11) when compared to only mothers ($p<0.001$) or only fathers ($p<0.001$). The association was also significant with maternal smoking during pregnancy (OR 2.34, 95% CI 1.67–3.28), single motherhood (OR 2.18, 95% CI 1.29–3.66) and advanced paternal age (OR 2.85, 95% CI 1.32–6.14) (**Figure 13** and **Figure 14**).

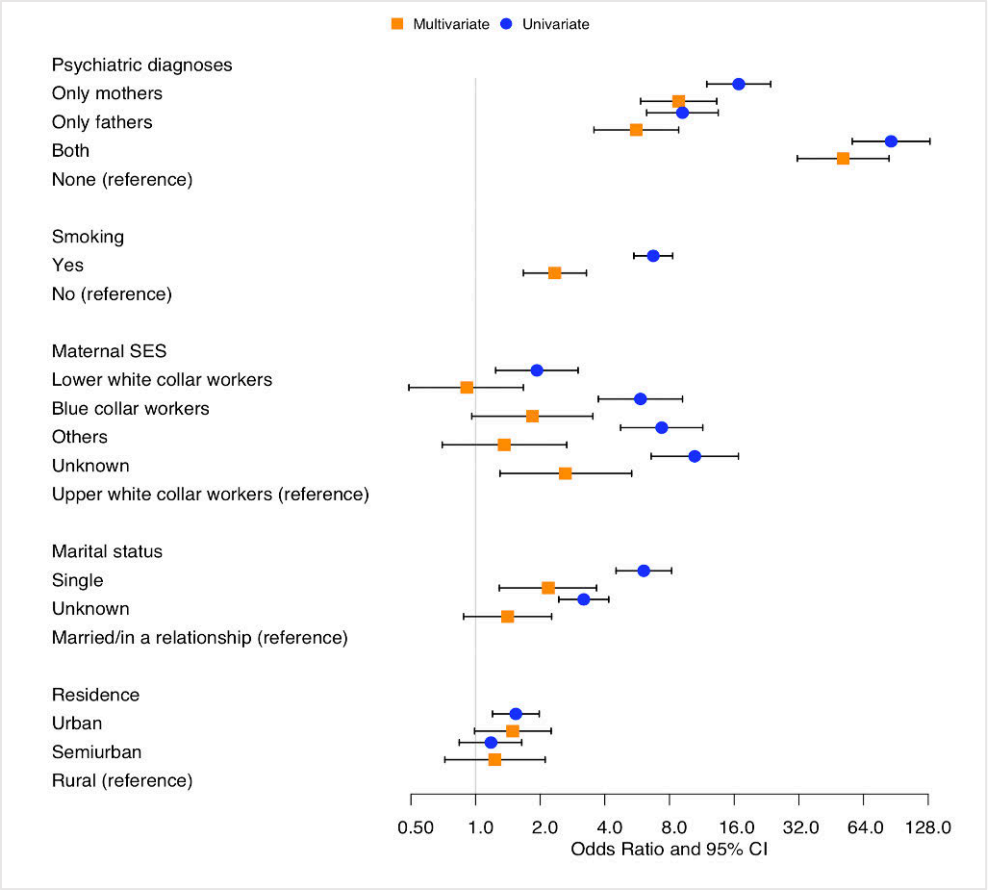

Figure 13. Odds ratio and 95% confidence interval of the association between prenatal risk factors and RAD (excluding parental age).

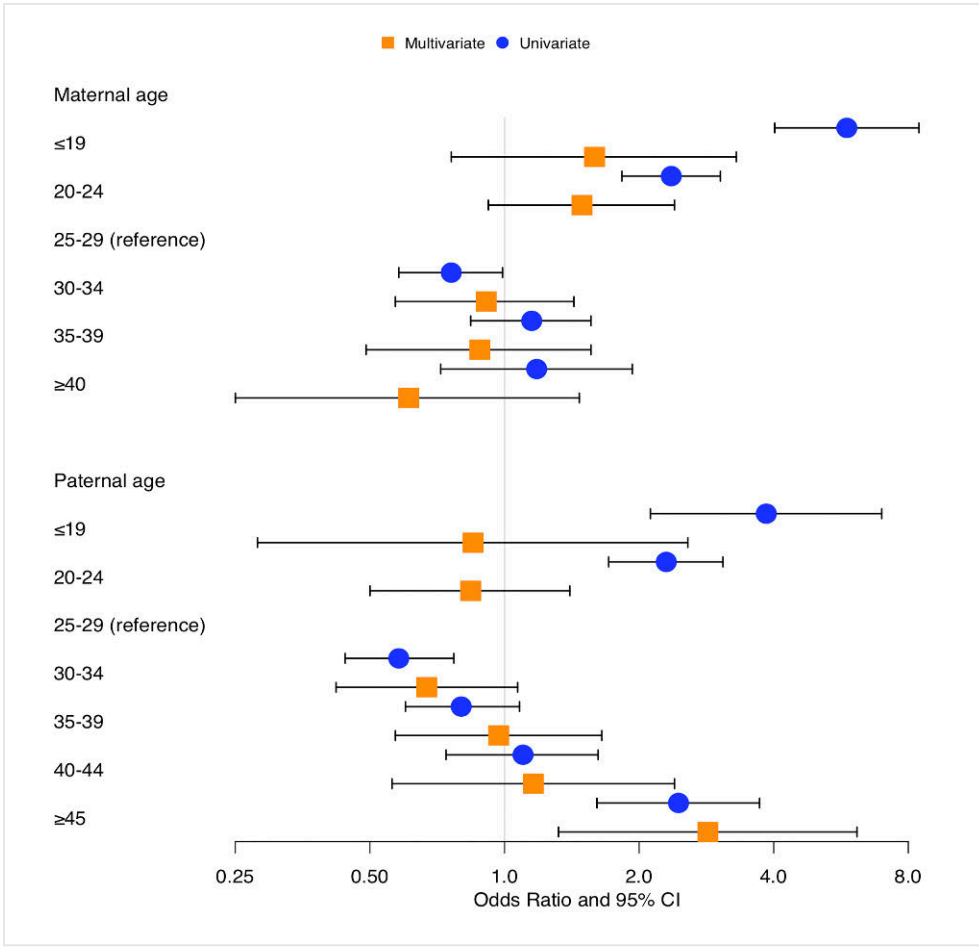

Figure 14. Odds ratio and 95% confidence interval of the association between parental age and RAD.

The parental specific psychiatric diagnoses including schizophrenia and schizoaffective disorders, psychoses, bipolar disorder, depression, anxiety disorder, personality disorder and alcohol and drug addiction/abuse were examined for the association with offspring RAD. In both unadjusted and adjusted models, all the psychiatric disorders in both mothers and fathers remained significant for offspring RAD (**Figure 15**).

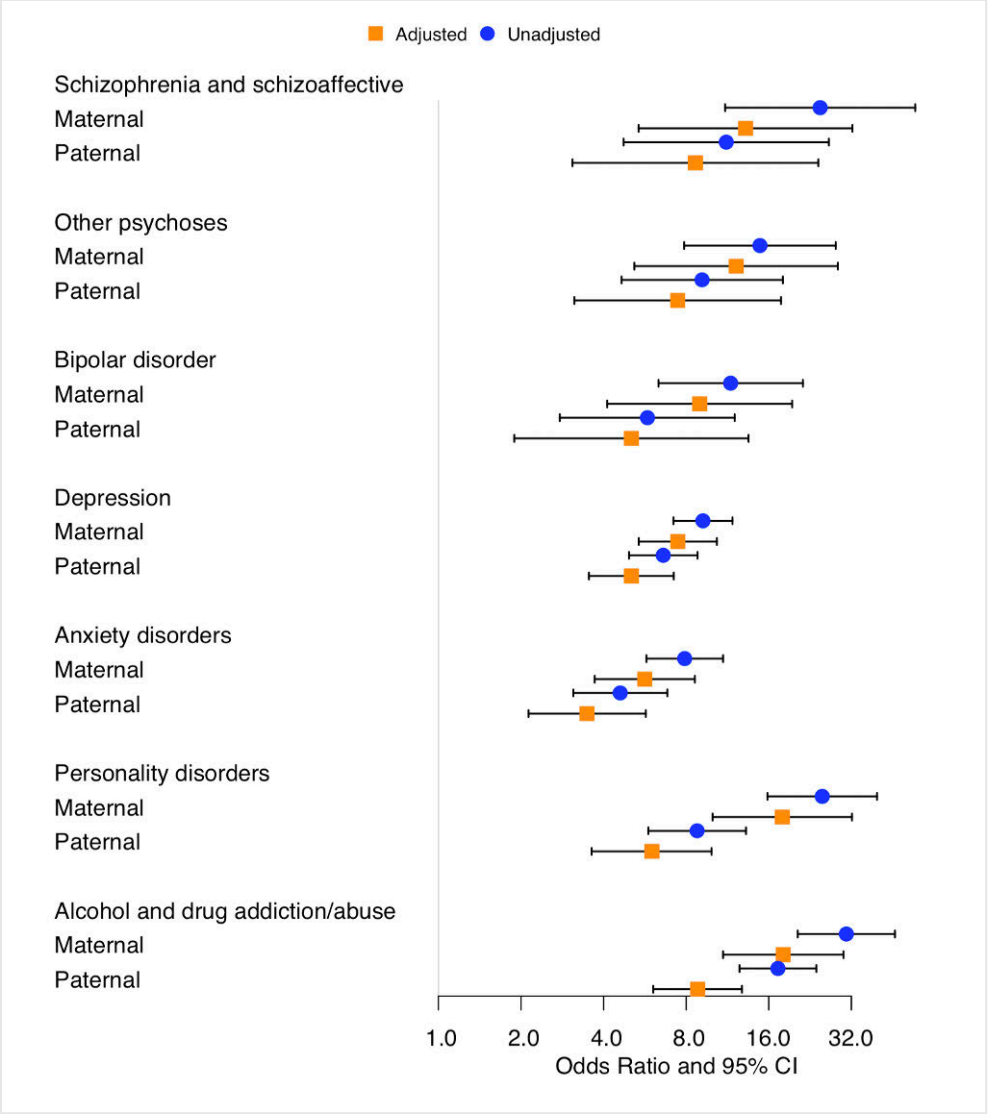

Figure 15. Odds ratio and 95% confidence interval of the association between parental specific psychiatric diagnoses and offspring RAD.

The combinations of several maternal and paternal psychopathology were examined for children diagnosed with RAD. The three most common combinations were: both parents diagnosed with alcohol and drug addiction/abuse (cases 20.03%, controls 0.25%), mothers diagnosed with depression and fathers with alcohol and drug addiction/abuse (cases 17.43%, controls 0.66%) and both parents diagnosed with depression (cases 10.75%, controls 0.83%).

At least one comorbid psychiatric diagnosis was present in 484 (78.82%) of total 614 RAD cases. The conduct and oppositional disorders (35.34%) were the most common comorbid diagnoses, followed by learning and coordination disorders (29.64%), attention deficit hyperactivity disorder (23.94%), emotional disorders with onset specific to childhood (21.66%), reaction to severe stress and adjustment disorders (15.80%) and depression (10.75%) (**Figure 16**).

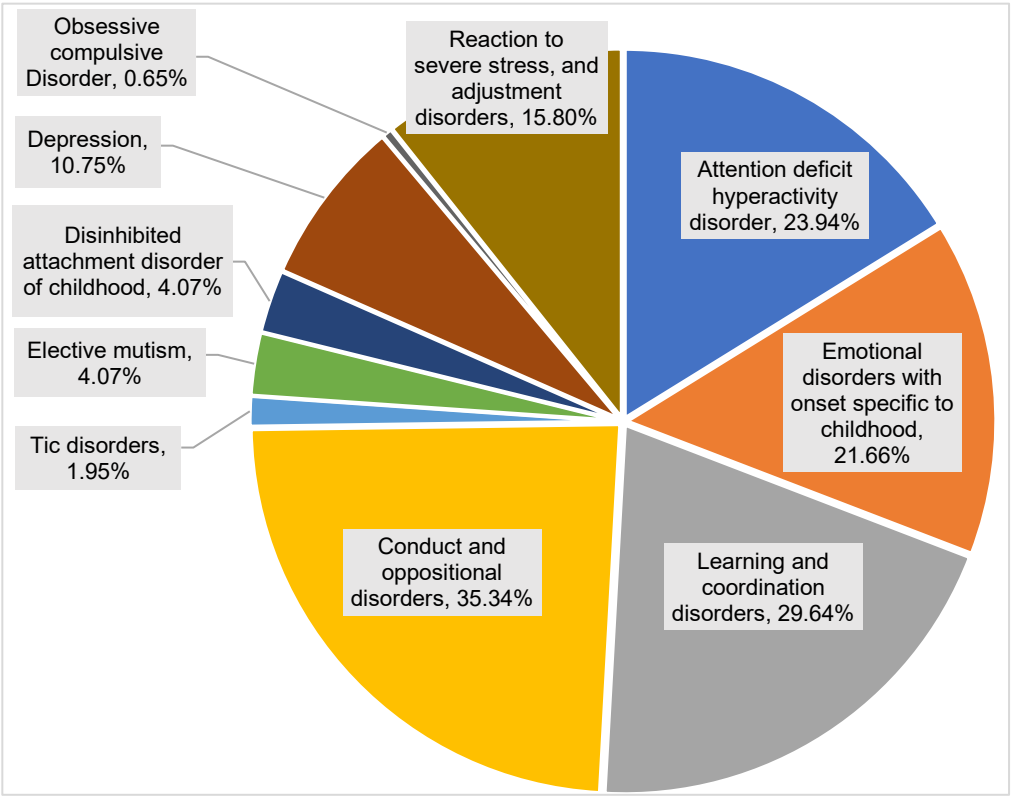

Figure 16. Frequency of comorbid psychiatric diagnoses with RAD.

5.2.4 Perinatal factors (Study V)

The distribution of perinatal factors among RAD cases and controls are shown in **Figure 17**.

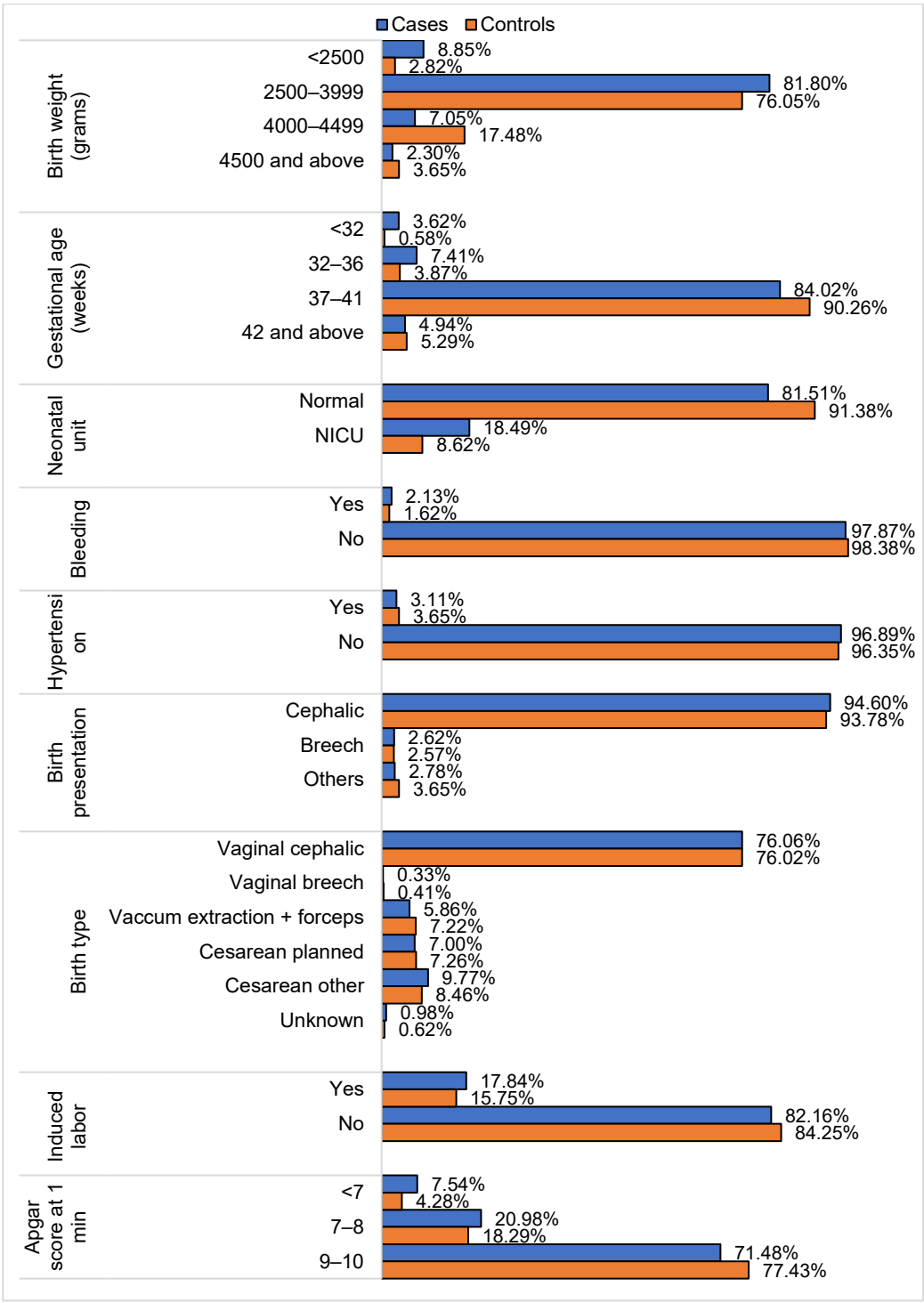

Figure 17. Distribution of perinatal risk factors among RAD cases and controls.

In the adjusted analyses, the perinatal risk factors associated with RAD were, a low birthweight of less than 2,500 grams OR 1.96 (95% CI 1.17, 3.30), a high birthweight of 4,000–4,499 grams OR 0.49 (95% CI 0.31, 0.75), a low gestational age of less than 32 weeks OR 3.72 (95% CI 1.52, 9.10), induced labour OR 1.34 (95% CI 1.03, 1.75) and admission to a NICU OR 1.67 (95% CI 1.09, 2.55) (**Figure 18**).

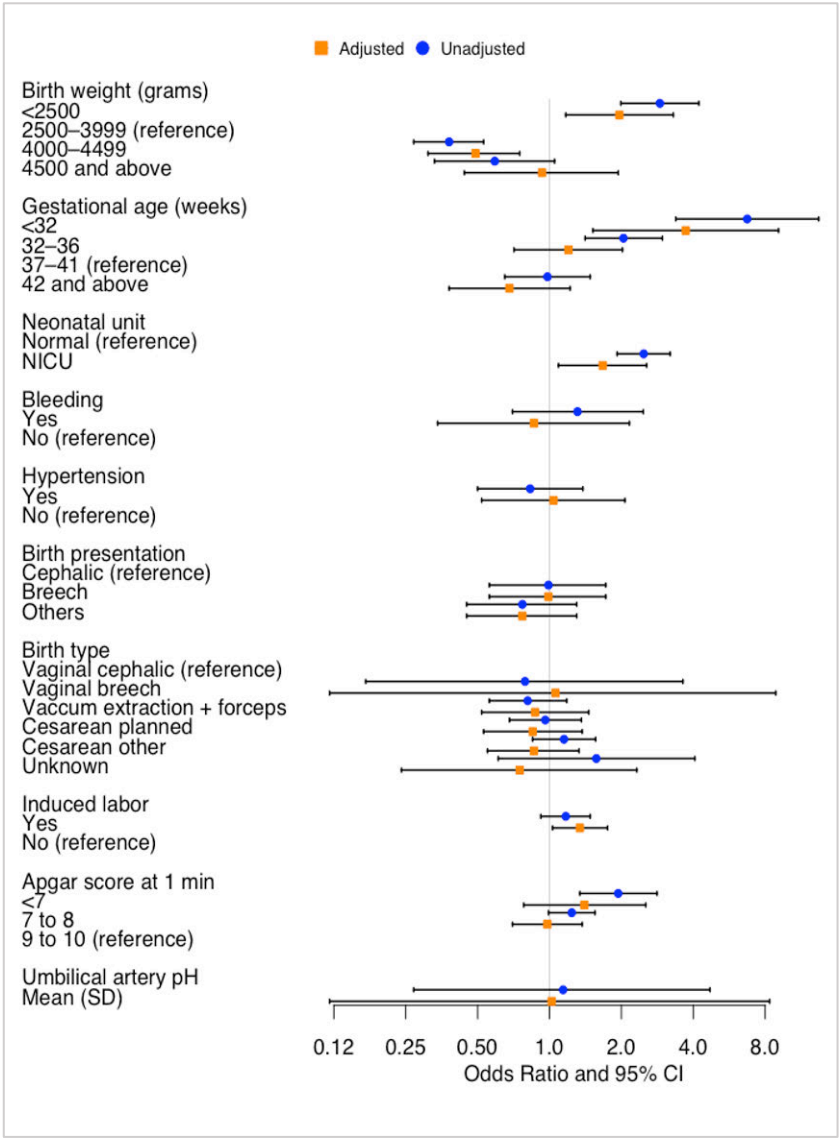

Figure 18. Odds ratio and 95% confidence interval of the association between perinatal and obstetric factors and RAD.

6 Discussion

6.1 Main findings

The study was based on the Finnish nationwide registers, and we examined prenatal and perinatal risk factors associated with depression among 5–25 years old and RAD in children and adolescents. The main findings of this study are:

I. The diagnosis of depression among population younger than 26 was higher in females than males.

II. Offspring of both young and advanced parents had increased odds of depression.

III. Extremely preterm and post-term birth were both risk factors for depression. In females, extremely preterm birth was associated with depression, whereas post-term birth was associated with depression in both sexes. Poor fetal growth was associated with depression and the association was stronger as the gestational weeks increased.

IV. Strong associations were observed between parental psychopathology and offspring RAD, and the odds were particularly increased when both parents had a psychiatric diagnosis. The association was also significant for smoking during pregnancy, single motherhood, and advanced paternal age and RAD.

V. Novel associations were observed between perinatal and obstetric risk factors, including low birthweight, preterm birth below 32 weeks of gestation, admission to the NICU, induced labour, and RAD.

6.2 Methodological considerations

6.2.1 Study design

The study is based on a nested case-control study design, which offers more strength over a traditional case-control study, while incorporating some benefits of a full cohort study. Unlike traditional case-control design, where cases and controls are

selected through convenience sampling, the nested case-control design minimizes the selection bias and recall bias due to selection of cases and control within an established cohort, and therefore are more representative of the population. Nested case-control studies are relatively inexpensive to perform and cost-effective compared with the full cohort design (Ernster, 1994). The disadvantages of nested case-control studies are the reduced statistical power and precision due to sampling of controls, and possible error in the sampling design (Wacholder, 2009). Moreover, all the risk factors needed for the study may not be likely to be recorded, and there could be discrepancies in accuracy and consistency in the measurement of risk factors and outcomes due to involvement of different health care professional in the health care system. Similar to other observational studies, causality cannot be inferred from a nested case-control study (Sedgwick, 2014).

6.2.2 Data sources

The Finnish nationwide registers were used to obtain the information on all the risk factors and outcomes in the study. The cases of depression and RAD included in the study are representative of Finnish nationwide population. There are several strengths to the use of nationwide registers in the epidemiological studies. They are cost-effective design with large sample size, possibility of linkage between national registers, a prospective design preventing recall bias and included extensive confounding factors adjusted in the models.

The register-based study design has several limitations that should be considered while interpreting the findings. First, the data in the registers were primarily collected for administrative purposes and not for research. The statistical information in the registers is utilized for planning and organization of health care. Therefore, the information may not be recorded with same accuracy and consistency throughout the study period. In addition, the variables relevant for the study may not be available from the registers alone. For example, registers do not include the information on several important psychological risk factors and protective factors. However, register-based research is cost-effective and a feasible way to examine various risk factors with nationally representative data. Although the registers used in the study are nationwide, there are limitations to the coverage. The cases were identified during the follow-up period of the study and cover specialized outpatient services at public hospitals, but its coverage is not consistent throughout the country. Moreover, in Finland, the outpatient diagnosis was only included from 1998 onwards. The registers only cover the cases that used specialized services, and there may have been the more severe cases, and we might have also missed milder cases that were diagnosed by primary care or private clinics. Therefore, a number of undiagnosed or less severe cases may not be referred to specialized services and therefore not

recorded in the CRHC. Furthermore, the diagnosis of mental disorders is only limited to the CRHC. Therefore, a person with untreated or undiagnosed cases during the follow-up period may end up as a study control, which may diminish the strength of the association.

Second, the diagnoses of mental disorders were based on clinical evaluation by psychiatrists in a specialized service, and there might be a significant delay in getting a diagnosis. For instance, the mean age of RAD diagnosis was 7.5 years. This was in line with previous register-based study that showed a delay of several years in getting a diagnosis of autism spectrum disorder (Hinkka-Yli-Salomäki *et al.,* 2014). Furthermore, the validity of diagnosis of depression in CRHC has not been specifically studied. However, CRHC has demonstrated good accuracy for diagnosing mental disorders in general (Sund, 2012). The accuracy and validation of specific psychiatric diagnoses in the CRHC has been shown to be of good quality by previous register-based studies including schizophrenia and bipolar disorder (Arajärvi *et al.,* 2005; Pihlajamaa *et al.,* 2008), autism (Lampi *et al.,* 2010), Tourette syndrome (Leivonen *et al.,* 2014), and attention-deficit/hyperactivity disorder (Joelsson *et al.,* 2015). Moreover, well validated diagnostic tool and standardized interviews or scales designed for diagnosing RAD would be more reliable than the diagnoses that are registered in the health register. Nevertheless, validation study of RAD cases in study V showed that 94.5% of cases met full ICD-10 criteria.

Third, there were limited confounders related to child abuse and early psychosocial issues in the study, which are key concerns for diagnosing RAD in children. The information regarding insufficient childcare, child abuse or neglect, institutional placements and child custody were not available for the study III and IV. The availability of these variables in the study along with their severity and chronicity would provide clear perspective in understanding the role of parental adversities associated with increased risk of offspring RAD. This information is important as children with severe deprivation or living in adverse caregiving environments are more likely to get RAD diagnosis (Boris *et al.,* 2004). Children are more likely to be placed in early and long-term custody when parents were alcohol and/or substance abusers (Sarkola *et al.,* 2007). Furthermore, study III and V did not include important data on the infant's morbidity during perinatal and neonatal period, including the need of resuscitation (asphyxia), antibiotic use, phototherapy and diagnoses during the first 7 days of life. This may cause heterogeneity in study population in terms of causes of admissions to NICU.

Fourth, the data on maternal smoking was based on maternal self-report during health care visits and the amounts of tobacco smoked during the pregnancy were not known. The subjective measure of smoking may underestimate the actual smoking exposure. In addition, the information on the alcohol or substance abuse during pregnancy and information on postnatal smoking was not available in the FMBR.

Fifth, the study focused on the diagnosis of depression before the age of 26, so the results are not generalizable to depression diagnosis at later age. In study IV and V, the diagnosis of anxiety among controls were excluded as this study was a sub-study of a larger anxiety and trauma related study. Therefore, anxiety disorders were not included in the initial sample, which may cause selection bias. However, when the anxiety disorders were also excluded from cases of RAD, the examined association remained significant.

6.3 Discussion of main findings and possible mechanisms

6.3.1 Depression (Study I–III)

6.3.1.1 Incidence, cumulative incidence and time trend of depression

The study showed that 10% of the females and 5% of the males were diagnosed with depression in specialized services by the age of 25 years. The incidence increased from 1.8% to 2.9% in females and 1.0% to 1.6% in males when compared with those born in 1987–1993 with those born in 1994–2000. In females, the peak age of depression diagnosis shifted earlier in the 1994–2000 cohort compared to the 1987–1993 cohort.

The cumulative incidence of diagnosed depression by age 20 years was 7% in females and 3% in males, which was considerably higher compared to a Danish register-based study with similar depression definition, 4% in females and 2% in males (Wesselhoeft *et al.,* 2015). The yearly incidence of diagnosed depression in Finland was higher among all age groups i.e., 5–12, 13–18, and 19–25 years, compared to Denmark. In the present study, incidence rates of diagnosed depression peaked during adolescence and then declined in early adulthood, which contradicted with another Danish register-based study during 1995-2010 period that reported higher incidence rates of depression in early adulthood than in adolescence (Jensen and Steinhausen, 2016). Despite of the similar follow-up years and use of national registers, there were considerable variations in incidence and cumulative incidence estimates between Finland and Denmark. These might be affected by differences in definitions included in studies and by different diagnostic practices and access to specialized care in Denmark and Finland, especially among children and adolescents. Moreover, interview-based Dunedin cohort study of 11–19 years old adolescents (Hankin *et al.,* 1998) reported higher incidence of depression in the community, 7% in males and 15% in females, and United States national survey of 12–17 years old adolescents (Breslau *et al.,* 2017) reported cumulative incidence to

be 14% in males and 36% in females. However, it should be noted that in register-based studies, the reported incidence rates were based on individuals who came into contact with the public health care system.

The increase in incidence and cumulative incidence of treated depression over time during childhood and adulthood was in line with earlier studies (Gyllenberg *et al.,* 2018; Jensen and Steinhausen, 2016). However, we also observed slight decrease in incidence rates after age 16 years in females. The UK study of 3–18 years old during 1995–2009, observed first increase and later decrease in incidence rates of diagnosed depression (Wijlaars, Nazareth and Petersen, 2012). The authors speculated that the changes in diagnostic practices and prescription pattern might reduce the later depression. In the present study, the increase in incidence of diagnosed depression could be due to changes in depressive symptoms, increased awareness and reduced stigma associated with the disorder and the health care service system.

In Finland, increase in emotional problems has been observed in both girls and female adolescents, while among males it was not pronounced (Mishina *et al.,* 2018; Sourander, Lempinen and Brunstein Klomek, 2016; Torikka *et al.,* 2014). This may for some part explain the increased incidence among female adolescents during the study period. In addition, a number of factors related to changes in the service system should be considered. For instance, in Finland, between 1994 to 2008, the outpatient visits to child psychiatric services and inpatient visits to adolescent psychiatric services increased by almost three and four times respectively (Paananen *et al.,* 2013). Similar service use trends were also observed in many countries (Atladottir *et al.,* 2015; Collishaw, 2015; Ma, Lee and Stafford, 2005; Mojtabai, Olfson and Han, 2016). Furthermore, better recognition of psychiatric problems and reduced stigma (Collishaw, 2015; Jensen and Steinhausen, 2016; Lindfors, Solantaus and Rimpelä, 2012), and other environmental changes during the study period such as increased help seeking behaviour and perceived stress may explain the increase in the incidence of diagnosed depression. For instance, changes in emotional factors including increased peer victimization (Sourander *et al.,* 2009), school burnout (Salmela-Aro, Savolainen and Holopainen, 2009; West and Sweeting, 2003), fears regarding health, death, loneliness and relationships (Lindfors, Solantaus and Rimpelä, 2012), childhood recurrent health complaints including pain, sleep problems and fatigue (Luntamo *et al.,* 2012) were observed. In addition, changes in background factors such as decrease in sleep time (Matricciani, Olds and Petkov, 2012), increase in parental depression (Thapar *et al.,* 2012)and social inequalities (Langton *et al.,* 2011; Torikka *et al.,* 2014) were found over time. Moreover, earlier identification of depression may also be attributed to early onset of puberty, both in males and females (Lee and Styne, 2013).

6.3.1.2 Parental age and depression

The study showed significant associations between both young and advanced maternal and paternal age and offspring depression. The highest odds of offspring depression were observed with advanced paternal age (≥50 years) and young maternal age (<20 years).

A U-shaped distribution of odds ratio was observed for the association between paternal age and depression, which was in line with two register-based studies (Buizer-Voskamp *et al.,* 2011; McGrath *et al.,* 2014) and a case-control study (Fountoulakis *et al.,* 2019). However, studies from Denmark (Laursen *et al.,* 2007), United States (Merikangas *et al.,* 2017) and Australia (Tearne *et al.,* 2016) did not find any significant associations with paternal age. The study from United States used the diagnostic interview (Kiddie-Schedule for Affective Disorders) and Australian study used questionnaires (the Depression Anxiety Stress Scales), but only included female offspring. The differences in the findings may be attributed to the target populations in terms of clinical diagnoses, population size and measurement scales. Moreover, the association may be confounded by residual factors which are not available in the register-based studies.

Both young (<20 years and 20–24 years) and advanced maternal age (≥40 years) were associated with increased odds of depression diagnosis, which was in line with previous studies (Fergusson and Woodward, 1999; McGrath *et al.,* 2014; Merikangas *et al.,* 2017; Tearne *et al.,* 2016). A Danish register-based study showed that younger maternal age (12–19 and 20–24 years) was associated with mood disorders in offspring (McGrath *et al.,* 2014). However, that study included a broad range of depression diagnoses (ICD-10 F30–F39, excluding bipolar) compared to the present study, where only diagnoses of depressive episodes or recurrent depression were studied (ICD-10 F32 and F33 and ICD-9 2961). Moreover, studies from New Zealand (Fergusson and Woodward, 1999) and the United States (Merikangas *et al.,* 2017) reported significant association between young maternal age and offspring depression. A Western Australian study reported significant association with advanced maternal age (≥ 35 years) (Tearne *et al.,* 2016).

The possible mechanisms for the association between young parental age and increased odds of offspring depression may be explained by the socio-economic disadvantage and personality traits of younger parents. Young parents often come from economically disadvantaged and less educated families (Fergusson and Woodward, 1999; Kiernan, 1997). Childhood victimization and psychiatric diagnoses may increase the subsequent risk of teenage pregnancy (Lehti *et al.,* 2011). The early life adversities and economic hardship may continue to next generation, increasing the risk of depression in the offspring. Moreover, young parents are more likely to have low impulse control and high risk-taking behaviour, involving alcohol and illicit drug abuse and smoking (Merikangas *et al.,* 2017) and less likely to use

prenatal care (D'Ascoli *et al.,* 1997; Kiernan, 1997; Lehti *et al.,* 2015). The children exposed to these environmental stressors are likely to have structural and functional impairment in brain development, leading to deficits in affective and cognitive functioning that contributes to the progression of mental illness including mood disorders (Gunnar and Quevedo, 2007; Pechtel and Pizzagalli, 2011).

The association between advanced parenthood and offspring depression may be explained by several potential mechanisms. The link between advanced paternal age and offspring depression may be related to an increase in de novo mutations in the male germ line with advancing age due to repeated cell divisions occurring during normal development of sperm (Crow, 2003; Flatscher-Bader *et al.,* 2011; Malaspina, 2001). The exposure to various environmental toxins over time may induce genomic and epigenetic alterations in the germ cells of older parents. These toxins can result in DNA damage, germline mutations and global hypermethylation in germ cells, which might have long-term negative effects on the offspring (Williams and Ross, 2007; Yauk *et al.,* 2008). The additive effect of shared pathways involving genetic, epigenetic, hormonal and environmental factors, may increase the risk of offspring depression (Buizer-Voskamp *et al.,* 2011; Shelton, Tancredi and Hertz-Picciotto, 2010). Moreover, the personality traits of some parents causing difficulty in building relationships may lead to delayed age at parenthood (Zammit *et al.,* 2003). In addition, history of prior divorce and a desire for children with a new partner later in life may also lead to parenthood at an advanced age. These factors could also be related to advanced maternal age. Mothers delivering at older age are at increased risk of obstetric and perinatal complications that are linked with offspring depression (Batstra *et al.,* 2006; Tarín, Brines and Cano, 1998). Increasing maternal age also affects endocrine and hormonal factors, leading to offspring depression due to maternal stress (Weinstock, 2010). Furthermore, the generational differences between parents and their children may arouse tension in parent-offspring relationship, especially during adolescence (Tearne *et al.,* 2016). Older parents are at higher risk of chronic illnesses including cancer, heart disease and chronic respiratory diseases, which might induce stress in children (Merikukka *et al.,* 2020; Osborn, 2007).

6.3.1.3 Perinatal factors and depression

The present study (study III) was the first population-based study to examine the association between gestational age and depression by each gestational week. We found that the odds of depression diagnosis increased with declining gestational age. Extremely preterm birth and post-term birth were associated with depression among children and young adults. Upon stratification by sex, extremely preterm birth was associated with depression among females, whereas post-term birth was associated

with depression in both sexes. Poor fetal growth was associated with depression in full-term infants and post-term infants.

The association between extremely preterm birth and depression was consistent with a Swedish register-based study of 2,333 young adults. However, that study also reported a significant association with moderately preterm birth at 32–36 weeks, which was not observed in our study (Nosarti *et al.,* 2012). We adjusted for more extensive parental background factors than the Swedish study (Nosarti *et al.,* 2012), which might explain the different findings. Associations between preterm birth and depression have also been shown by other smaller studies (Farooqi *et al.,* 2007; Gudmundsson *et al.,* 2011; Patton *et al.,* 2004; Räikkönen *et al.,* 2007), while some reported that preterm birth was not a risk factor (Inskip *et al.,* 2008; Loret de Mola *et al.,* 2015; Vasiliadis, Gilman and Buka, 2008; Wang *et al.,* 2015).

There have also been inconsistencies in previous findings for the associations between fetal growth and depression. A register-based study from Denmark showed a significant association between being born small for gestational age (SGA) and depression (Laursen *et al.,* 2007), but others did not report any associations (Loret de Mola *et al.,* 2015; Nosarti *et al.,* 2012; Vasiliadis, Gilman and Buka, 2008). Räikkönen and colleagues found that poor fetal growth was a larger underlying factor for depression than prematurity (Räikkönen *et al.,* 2007). However, our study found stronger association between extreme prematurity and depression than poor fetal growth and depression. In our study, the full-term and post-term infants with poor fetal growth were at increased odds of depression diagnosis. Poor fetal growth did not increase the risk of depression in extremely preterm infants, but the risk was highest in extremely preterm infants with normal growth. Previous nationwide population-based studies that have reported associations between gestational age, fetal growth and depression were limited by lack of adjustment for parental depression, parental psychiatric illness and maternal substance abuse, which are important risk factors for depression.

The potential mechanisms underlying depression in preterm-born children and adolescents may be related to the causes of preterm birth, such as physiological and psychosocial stress, intrauterine infections and poor nutritional status (Goldenberg *et al.,* 2008). The normal labor process may be activated early due to glucocorticoid-induced programming of the HPA axis (Goldenberg *et al.,* 2008; Kapoor *et al.,* 2006), which is a key component in tuning the symbiotic relationship between the mother and her developing fetus (Alcántara-Alonso *et al.,* 2017).

Preterm birth affects the microstructural changes in the brain, including delayed maturation of oligodendroglial lineage and cortical connectivity. This altered brain development may be due to abnormal fetal development when the cortical subplate and neocortex are formed during the second trimester (Ment, Hirtz and Hüppi, 2009). Other potential underlying factors include a genetic predisposition and the effects of

a non-physiological environment after birth on the development of cortical connectivity (Gui *et al.,* 2019). It is possible that these differences in brain development play a role in predisposing preterm-born infants to later depression (Whittle *et al.,* 2014). It is also possible that the stressful experiences during long hospital stays alter the infant's HPA axis (Provenzi *et al.,* 2016), and potentially leads to the pathways to depression. The alteration in the function of the HPA axis are seen with increased cortisol reactivity in infancy, childhood and adulthood in preterm born individuals (Mörelius, He and Shorey, 2016; Sullivan, M. C. *et al.,* 2017). Elevated cortisol levels have been associated with depression (Morris, Rao and Garber, 2012).

The long neonatal intensive care needed for children born extremely preterm affects the development of the parent-infant relationship and attachment in preterm infants (Korja *et al.,* 2008). Parents of preterm infants have been shown to have a higher rate of depression than parents of term infants (Pace *et al.,* 2016). Parental depression is associated with increased risk of depression in children (Weissman *et al.,* 2016). Individuals born preterm are also more likely to suffer from somatic diseases, psychosocial challenges, bullying and psychiatric symptoms and are less likely to have romantic partners and become parents (Mendonça, Bilgin and Wolke, 2019; Pyhälä *et al.,* 2010; Wolke *et al.,* 2015).

The mechanisms behind poor fetal growth and subsequent depression may be related to the causes of poor fetal growth, such as chronic stress before birth, suboptimal maternal conditions and placental insufficiency (Tolsa *et al.,* 2004). Exposure to stress in utero may increase vulnerability to stress and impair the functions of the HPA axis, leading to subsequent poor stress management and reduced resiliency (Lester, Conradt and Marsit, 2013), which may predispose them to increased risk of depression later in life.

Sex-specific differences were observed for the associations between gestational age and depression. Extreme prematurity was associated with depression among females, whereas post-term birth was associated with depression among both sexes. Our sex-specific findings contradicted a previous Finnish cohort study that tested for the interaction by sex (Räikkönen *et al.,* 2007). However, that study only examined depression among older adults aged 57-71 years, using a structured questionnaire, and that could have led to the higher estimates on the rate of depression. The cases in our study were clinically diagnosed by healthcare professionals in a specialized services and cases may have had more severe and complex diagnosis than the questionnaire study (Räikkönen *et al.,* 2007). As depression is more common in females, especially during adolescence, it was important to investigate if preterm birth was associated with an increased risk of depression differently in different age groups. Extremely preterm birth was associated with increased odds of depression

in females with onset before 19 years of age. No associations were observed between depression and prematurity in any age groups in males.

The sex-specific programming of the HPA axis may explain the sex-specific differences in the associations between preterm birth and depression (McGowan and Matthews, 2018; Seckl, 2004). In primates, longer course of prenatal glucocorticoids exposure reduced plasma cortisol levels in males. However, similar exposure in the female fetus led to high plasma cortisol levels in adulthood (McCormick *et al.,* 1995; Uno *et al.,* 1994; Weinstock *et al.,* 1992). Puberty and sex hormones play important roles in adolescent psychiatric morbidity (Paus, Keshavan and Giedd, 2008), as females undergo puberty earlier than males. Studies suggest that depression is more common among females and that their lifetime prevalence of depression is two times higher than among males (Kuehner, 2017). However, previous studies have also shown sex-specific help-seeking behavior. For example, females are more likely to seek help for depression than males (Doblyte and Jiménez-Mejías, 2017; Seidler *et al.,* 2016).

Several remedies for maternal depression after preterm birth have been developed. For instance, single family rooms provide the opportunity to increase parent-infant bonding and skin-to-skin contact (Raiskila *et al.,* 2017) reducing parental stress and accelerating the infants' overall development (Ahlqvist-Björkroth *et al.,* 2017). Moreover, parenting interventions supporting parent-infant closeness developed in neonatal units decrease parental depression (Ahlqvist-Björkroth *et al.,* 2019), that in turn may reduce psychiatric problems, including depression among children born preterm.

6.3.2 Reactive attachment disorder (Study IV–V)

6.3.2.1 Cumulative incidence of RAD

RAD is considered a rather rare disorder. There is limited literature on the population-based incidence or prevalence of RAD. In a Danish cohort study (n=211), the prevalence of RAD in 1.5 years old was 0.9% (95% CI 0.1–3.4) (Skovgaard *et al.,* 2007). However, the study of 350 Romanian preschool children recruited from paediatric waiting room found no cases of RAD (Gleason, Zamfirescu *et al.,* 2011). In a deprived urban community of UK, where child maltreatment was more common, the prevalence of RAD was 1.40% (Minnis *et al.,* 2013). The prevalence of RAD is particularly high in high-risk samples, 19.4% in foster care (Lehmann *et al.,* 2013), 38–40% of maltreated toddlers in foster care (Zeanah *et al.,* 2004). However, these previous studies were based on interview data to apply DSM-IV (Zeanah *et al.,* 2004), semi-structured parent-report interview, such as the Child and Adolescent Psychiatric Assessment, RAD Module (Minnis *et al.,* 2013; Pritchett *et al.,* 2013),

Developmental and Well-Being Assessment-RAD (Lehmann *et al.,* 2013), and Preschool Age Psychiatric Assessment (Gleason *et al.,* 2011) and did not differentiate the inhibited and disinhibited type of attachment disorders.

6.3.2.2 Prenatal risk factors and RAD

The prenatal factors associated with RAD, after adjusting for a wide range of possible confounders, were parental psychopathology, maternal smoking, single motherhood, and advanced parental age.

Maternal and paternal psychiatric diagnoses were associated with increased odds of offspring RAD. When both parents were diagnosed with psychiatric diagnoses, the odds of offspring RAD was particularly high. The findings are similar to previous clinical observation in a study with maltreated samples, that reported association of maternal psychiatric illness with offspring RAD (Zeanah *et al.,* 2004). It is important for parents to be sensitive and predictive to their child's need for secure attachment behaviour (McGoron *et al.,* 2012). When parent themselves are suffering from a psychiatric disorder, they may not be readily available for their child's needs, which may induce insecure attachment in children. The parental absence may be profound depending on the severity of a psychiatric disorder. For example, parental depression has been associated with withdrawn and intrusive parental behavior (Goodman, S. H. and Gotlib, 1999). These negative effects may get stronger when both parents have psychiatric disorders than when a single parent has a psychiatric disorder, as the other parent can compensate for the unwell partner's difficulties. In addition, assortative mating or spousal resemblance for psychiatric conditions have suggested an increased likelihood that a mother with a particular psychiatric illness will have a spouse with a psychiatric illness or a family history of psychiatric illness (Nordsletten *et al.,* 2016). The present study showed that the most common psychiatric diagnosis in parents with children with RAD were alcohol and drug addiction/abuse and depression. Parental substance abuse may affect the infants' development, either through direct exposure in utero (Shankaran *et al.,* 2007), less breast-feeding (Wachman, Byun and Philipp, 2010), harsh parenting behavior, abuse and/or neglectful caregiving environment (Miller, Smyth and Mudar, 1999). Studies have shown that the children of parents who abuse substances are more likely to experience physical and sexual abuse (Walsh, MacMillan and Jamieson, 2003) and likely to end up in the foster care and institutional rearing with repeated changes in caregiver. RAD is more likely to be detected among children living in adverse caregiving environments or with severe deprivation (Boris *et al.,* 2004; Zeanah *et al.,* 2004). Moreover, parental psychiatric disorders may influence the parental-infant relationship, which is important for optimal development of infants.

Maternal smoking during pregnancy had an independent effect on offspring RAD. No previous study has examined this association. Maternal smoking during pregnancy is associated with adverse infant outcomes including fetal growth restriction, reduced brain size and alterations in brain functions (Banderali *et al.,* 2015), lower maternal-fetal attachment (Magee *et al.,* 2014), and reduced breastfeeding practices (Banderali *et al.,* 2015). It is also likely that these mothers lack motivation to regulate the smoking behaviour. A Finnish study reported that the children of mothers who smoke during pregnancy were more likely to end up in foster care compared to the children of mothers who did not smoke (Kalland *et al.,* 2006). The association of maternal smoking and RAD might also be possibly due to the likelihood that the parents' psychopathology is associated with higher rates of smoking. Although we adjusted maternal smoking for maternal psychopathology, it is likely that less severe psychopathology could be undiagnosed and may contribute to the findings. The specific contribution of nicotine or other smoking by-product toxin exposure nevertheless remains unknown relative to the contribution of parental psychopathology associated with higher rates of smoking.

The association between advanced paternal age and RAD has not been reported previously. There are few hypotheses related to de novo germline mutation (Malaspina, 2001) and epigenetic alterations (Perrin, Brown and Malaspina, 2007) with advancing paternal age that may lead to the development of psychiatric disorders in the offspring. Moreover, the personality traits of some parents causing difficulty in building relationships may lead to delayed parenthood (Zammit *et al.,* 2003). In addition, history of prior divorce and a desire for children with a new partner later in life may also lead to parenthood at an advanced age. It is likely that the similar mechanisms may play a role in development of RAD. It is important for future studies to examine the association between parental age and offspring RAD.

6.3.2.3 Perinatal risk factors and RAD

The present study (study V) was the first population-based study to show that neonatal and obstetric risk factors, including low birthweight, low gestational age, admission to the NICU and induced labour, were associated with RAD. They have been identified as risk factors for other mental disorders including depression, bipolar disorder, attention deficit hyperactivity disorder and Tourette syndrome (Chudal *et al.,* 2014; Glasson *et al.,* 2004; Gregory *et al.,* 2013; Lampi *et al.,* 2012; Loret de Mola *et al.,* 2014; Polo-Kantola *et al.,* 2014; Sucksdorff *et al.,* 2015). The associations between perinatal risk factors and RAD may be explained by several possible mechanisms.

The developing brain of a preterm infant is affected by their physical and psychosocial environment. Preterm infants are born too soon leaving the adaptive

environment of mothers' uterus early exposing them to medical procedures that could potentially cause stress or trauma. Perinatal adversity is associated with poor stress management and reduced resiliency later in life (Lester, Conradt and Marsit, 2013). Moreover, maternal mental representation of a baby may be different when a baby is born preterm (Spinelli *et al.,* 2016). Mother of premature infant may find difficulty in understanding the preterm infants' need for proximity and closeness as infants born preterm are less alert and responsive compared to their full-term counterparts (Muller-Nix *et al.,* 2004). Parents of preterm infants experience increased level of psychological distress during neonatal period including emotional disorders, anxiety, depression and post-traumatic stress disorder (Kersting *et al.,* 2004). This elevated level of distress may persist over several months after discharge from NICU (Holditch-Davis *et al.,* 2015; Kersting *et al.,* 2004) and disrupt parent's ability to respond sensitively to their newborn (Forcada-Guex *et al.,* 2006). The combination of stressful environment, brain immaturity and maternal separation at NICU causes disturbances in preterm infants' cortisol (Buss *et al.,* 2012). These factors coupled with physician's emphasis of life saving measures for infants might result in parent being more withdrawn from their children. These infants thus may miss out on much needed emotional care and nurture leading to an increased risk of RAD.

The NICU admission was independently associated with RAD. Parent-infant separation for a long period of time is still common during neonatal intensive care and may disturb normal parental-infant attachment and bonding (Raiskila *et al.,* 2017). Family centered care promotes parent-infant closeness and bonding. Furthermore, new infrastructure with availability of parents to stay overnight may increase parents' presence and the duration of parent-infant skin-to-skin contact (Raiskila *et al.,* 2017). Increased maternal and newborn contact lowers stress and improves cortisol reactivity (Mörelius *et al.,* 2015). Maternal proximity promotes maternal sensitivity and bonding, increasing oxytocin production in mother and child, and improving infant neuro-behavioral (Feldman *et al.,* 2002). The potential role of sensitive and enhanced caregiving for the development of attachment relationship has been shown by a randomized control trail study in the institutionalized children (Smyke et al., 2012) and also in animal studies (van Ijzendoorn *et al.,* 2009). Therefore, it is important for future studies to examine whether being admitted to a NICU would continue be a risk factor for RAD during the era of family centered care and single-family rooms. However, the development of RAD involves complex interplay of nature and nurture, and advancement in NICU care may partly address the risks involved.

There may be other underlying reasons for risk of developing RAD when infants are born preterm or low birth weight. Numerous studies have suggested several biological pathways involving maternal depression and smoking during pregnancy

affecting intrauterine fetal growth (Goldenberg *et al.,* 2008). Especially mothers with substance abuse and/or depression are more likely to receive less antenatal care and experience more complications during pregnancy (Dennis and Chung-Lee, 2006; Goodman, J. H., 2009; Terplan, McNamara and Chisolm, 2012). The study IV included in the thesis suggested increased risk of offspring RAD with parental psychopathology, maternal smoking during pregnancy and single motherhood (Upadhyaya *et al.,* 2019). These maternal adversities coupled with maternal-infant separation might influence maternal-infant attachment and bonding.

Induced labour was associated with increased risk of RAD. To date, no previous studies have examined the association between obstetric risk factors and RAD. However, associations have been reported between obstetric factors and attention deficit hyperactivity disorder and autism spectrum disorder (Glasson *et al.,* 2004; Gregory *et al.,* 2013; Sucksdorff *et al.,* 2018). The association between induced labour and RAD may be explained by the mechanism related to exposure to exogenous oxytocin and vasopressin, as oxytocin signaling play important role in the regulation of affiliative behaviours including bonding, parenting behaviour and attachment (Bartz and Hollander, 2006). Future studies with larger sample sizes should examine these factors in relation to offspring RAD.

6.3.3 Depression and RAD (Study IV)

The present study (study IV) found that 10.75% of children with RAD also had a diagnosis of depression. The comorbidity of RAD with depression has also been reported by previous studies on institutional samples (Gleason *et al.,* 2011). Depression is a common mental disorder and earlier studies have demonstrated that the children with RAD have internalizing problems (Pritchett *et al.,* 2013). The long course of RAD is not yet clear and therefore, it would be interesting to know how the comorbidity of RAD with depression would persist over long term and if they would share the similar etiological factors.

7 Summary/Conclusions

The thesis produced several relevant findings for planning early prevention and interventions in infant and child mental health. Furthermore, despite differences in risk factors profile, there were some overlap in the examined risk factors for depression and RAD. Both young and advanced parental age were associated with increased odds of offspring depression while advanced paternal age was only associated with increased odds of offspring RAD. Moreover, preterm birth was associated with increased odds of both depression and RAD, but the magnitude of odds ratio was higher in RAD.

First, the cumulative incidence of diagnosed depression increased in 1994-2000 cohort compared to 1987-1993 cohort, especially in females. The proportion of young people diagnosed with depression increased over time, which may be due to a better recognition and reduced stigmatization of mental illness, and increased availability of health services. The study highlights a need for timely and effective prevention strategies for depression in children and adolescents.

Second, the association between parental age and offspring depression showed U-shaped distribution. Both younger and older parental age were associated with increased odds of offspring depression. The findings suggest that the age of a parent plays a role in the etiology of depression in their offspring, but further studies are required before we can understand the biological, psychological and social mechanisms underlying those effects. These findings are highly relevant to the global changes in the ages at which men and women become parents. This can contribute to increased awareness about the effect of parental age on offspring depression and identification of individual at risk of depression at an earlier age.

Third, the children born preterm were at increased risk of depression. Depression is a common mental health disorder and preventive interventions are needed, especially those that target children born preterm. Essential support should be provided to parents, especially parental mental health during pregnancy and during neonatal care, in case of extremely preterm infants and growth retarded full term infants. The high-risk infants, including their parents should be followed-up for the screening of depression and the provision of appropriate mental health support should be provided.

Fourth, there were several novel findings on parental adversities and offspring RAD. Parental psychopathology was strongly associated with offspring RAD, and the odds were extremely higher when both parents had a psychiatric disorder. The genetic predisposition, adversities related to parenting and parental risk behavior exposing the fetal brain to substance use may explain the possible mechanisms. These factors may interact with each other and strengthen the associated risk. The findings on other parental risk factors, including maternal smoking, single parenthood and advanced parental age also point towards their role in the development of RAD. Moreover, they may be proxy indicators for wide range of factors such as poor parenting behavior, abuse or neglect which could not be studied, as health registers did not have their information. Secure attachment with a primary caregiver is important for a sound mental health later in life. It is important to identify children at risk and also identify and help parents with mental health problems to develop a positive environment as early as antenatal period. The findings have important implications for prevention and interventions in infant mental health.

Lastly, low birth weight, low gestational age and NICU admission were associated with RAD. The findings may be explained by the biological factors related to neonatal immaturity and potentially aggravated by psychosocial effects of parent-infant separation in early life. In the present era of family centered care, it is important to study if new NICU treatment approaches have decreased this association between NICU and RAD. Health professionals working with premature infants should be aware of the risk of RAD in children. These findings highlight the need for interventions that promote parental-infant attachment during the neonatal period.

7.1 Implications for future research

The existing knowledge on the associations between prenatal and perinatal risk factors for depression and RAD is limited. The present findings are important for setting aims for future studies that can potentially identify causal pathways for depression and RAD. For example, future studies are needed to understand the complex effects of social, biological, psychological and environmental risk factors. Moreover, future studies that utilize prospective biomarkers of prenatal exposures and detailed data on prenatal and perinatal experiences are warranted. It is also important for future studies to investigate whether several psychiatric disorders have a common prenatal risk profile or specific profiles.

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