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PRENATAL AND PERINATAL EPIDEMIOLOGY OF ANXIETY DISORDERS

Tiia Ståhlberg

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To my family

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ABSTRACT

Anxiety disorders are the most common psychiatric disorders among children and adolescents. The aetiology of anxiety disorders is known to be multi-factorial and to include genetic and environmental factors. Prenatal and perinatal factors have been associated with other mental health disorders, but there has been less research on the role they play in anxiety disorders. The aim of this thesis was to comprehensively investigate the associations between prenatal and perinatal factors and child and adolescent anxiety disorders, as well as identifying the treated incidence of anxiety disorders.

The first step was to conduct a systematic literature review of the existing literature. The following studies were part of the Finnish Prenatal Study of Anxiety disorders (FIPS-Anx), which is an ongoing nested case-control study. This nationwide birth cohort included 22,388 cases, who were born in 1992 – 2006, and diagnosed with anxiety disorders in 1998 – 2012. Each identified case was matched with four controls. The data were obtained from three national Finnish registers: the Care Register for Health Care, the Finnish Medical Birth Register and the Finnish Population Register Centre.

Maternal low socioeconomic status and mother being single at the time of birth increased the odds for offspring anxiety disorders. Preterm birth and poor foetal growth increased the odds for anxiety disorders linearly but comorbid conditions of depressive and neurodevelopmental disorders explained these associations. Birth by caesarean section increased the odds for anxiety disorders. Differences in the associations for specific anxiety disorders were observed.

The thesis demonstrates associations between prenatal and perinatal factors and child and adolescent anxiety disorders. However, these associations were impacted by comorbid conditions and possibly some residual confounding factors. The findings support the complex multifactorial aetiology model for anxiety disorders rather than major findings for just prenatal or perinatal factors.

KEYWORDS: adolescent psychiatry, anxiety disorders, cesarean section, child psychiatry, comorbidities, epidemiology, foetal growth, gestational age, prenatal, perinatal, preterm birth, registries

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Ahdistuneisuushäiriöt ovat lasten yleisimpiä mielenterveydenhäiriöitä. Ahdistuneisuushäiriöiden etiologian tiedetään olevan monitekijäinen, sekä geeneillä että ympäristötekijöillä on osuutensa. Raskauden ja synnytyksen aikana esiintyviä tekijöitä on yhdistetty joihinkin muihin mielenterveyshäiriöihin, mutta ahdistuneisuushäiriöiden osalta tieto prenataalisten ja perinataalisten tekijöiden osuudesta on ollut vielä vajavaista. Tämän väitöskirjan tavoitteena oli selvittää prenataalisten ja perinataalisten tekijöiden yhteyttä lapsuudessa ja nuoruudessa esiintyviin ahdistuneisuushäiriöihin sekä ahdistuneisuushäiriöiden esiintyvyyttä erikoisairaanhoidossa.

Ensimmäinen osatyö oli systemaattinen kirjallisuuskatsaus. Muut osatyöt olivat osa käynnissä olevaa tutkimuskokonaisuutta (the Finnish Prenatal Study of Anxiety disorders, FIPS-Anx), joka tutkii ahdistuneisuushäiriöiden prenataalisia ja perinataalisia riskitekijöitä pesiytetyn tapaus-verrokkiasetelman avulla. Maanlaajuinen syntymäkohortti sisälsi 22,388 vuosina 1992 – 2006 syntynyttä lasta ja nuorta, joilla oli diagnosoitu ahdistuneisuushäiriö vuosina 1998 – 2012, sekä jokaista tapausta kohden neljä verrokkia. Tiedot muuttujista saatiin kolmesta kansallisesta rekisteristä.

Äidin matala sosioekonominen asema ja yksinhuoltajuus syntymähetkellä, ennenaikainen syntymä ja pieni syntymäpaino viikkoihin nähden sekä syntymä sektiolla olivat yhteydessä suurentuneeseen ahdistuneisuushäiriöiden todennäköisyyteen. Eroja esiintyi eri ahdistuneisuushäiriöiden alatyyppien välillä.

Tämä väitöskirja löysi yhteyksiä prenataalisten ja perinataalisten tekijöiden ja lasten ja nuorten ahdistuneisuushäiriöiden välillä. Osa yhteyksistä selittyi kuitenkin psykiatristen komorbiditeettien avulla ja lisäksi jotkin perinataaliset jäännöstekijät voivat mahdollisesti olla osallisina havaittuihin yhteyksiin. Tutkitut prenataaliset ja perinataaliset tekijät selittänevät vain pienen osan ahdistuneisuushäiriöiden monitekijäisestä etiologiasta.

AVAINSANAT: ahdistuneisuushäiriöt, epidemiologia, keskosuus, komorbiditeetit, lastenpsykiatria, nuorisopsykiatria, prenataalinen, perinataalinen, rekisterit, syntymätapa.

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Abbreviations

ADHD = Attention deficit hyperactive disorder
AGA = Appropriate for gestational age
ALSPAC = the Avon Longitudinal Study of Parents and children
APA = American Psychiatric Association
ASD = Autism spectrum disorder
ASQ = Anxiety Symptoms Questionnaire
BMI = Body mass index
BW = Birth weight
CBCL = Child Behaviour Checklist
CCEI = the Crown Crisp Experiential Index
CI = Confidence interval
CIS-R = The Clinical Interview Schedule-Revised
CNS = Central nervous system
CRH = Corticotrophin releasing hormone
DM = Diabetes mellitus
DNA = Deoxyribonucleic acid
DSM = Diagnostic and Statistical Manual of Mental Disorders
DVV = Digi- ja väestötietovirasto (The Digital and Population Data Services Agency)
EDPS = Edinburgh Postnatal Depression Scale
FAS = Foetal alcohol syndrome
FIPS-Anx = the Finnish Prenatal Study of Anxiety Disorders
GA = Gestational age
HELLP syndrome = syndrome of pregnancy including haemolysis, elevated liver enzyme levels, low platelet levels
HIV = Human immunodeficiency virus
HPA = Hypothalamus-pituitary-adrenal
HR = Hazard ratio
ICD = International Classification of Diseases
IRR = Incidence rate ratio
K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia

LGA = Large for gestational age
NICU = Neonatal intensive care unit
ND = Neurodevelopmental disorders
NS = Not significant
OCD = Obsessive-compulsive disorder
ODD = Oppositional defiant disorder
OR = Odds ratio
PRISMA = Preferred Reporting Items of Systematic Reviews and Meta-analyses
PROSPERO = The International Prospective Register of Systematic Reviews
PTSD = Post-traumatic stress disorder
PYAR = Person years at risk
SAS = Statistical Analysis Software
SCID = Structured Clinical Interview for DSM-5
SD = Standard deviation
SES = Socio-economic status
SGA = Small for gestational age
SSNRI = Selective serotonin norepinephrine reuptake inhibitors
SSRI = Selective serotonin reuptake inhibitors
SUD = Substance use disorder
THL = Terveyden ja hyvinvoinnin laitos (The National Institute for Health and Welfare)
UK = United Kingdom
USA = United States of America
WGA = Weight for gestational age
WHO = World Health Organization
11β-HSD2 = 11β-hydroxysteroid dehydrogenase type 2

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 Prenatal and perinatal risk factors for anxiety disorders: a systematic review. Ståhlberg T, Khanal P, Chudal R, Luntamo T, Kronström K, Sourander A. Journal of Affective Disorders 2020; 277: 85–93.

II Time trends in treated incidence, sociodemographic risk factors and comorbidities: a Finnish nationwide study on anxiety disorders. Khanal, P., Ståhlberg T, Luntamo T, Gyllenberg, D., Kronström K, Suominen, A., Sourander A. BMC Psychiatry 2022; 22:144

III Preterm birth, poor foetal growth and anxiety disorders in a Finnish nationwide register sample. Ståhlberg, T., Upadhyaya, S., Khanal, P., Sucksdorf, M., Luntamo, T., Suominen, A., & Sourander, A. Acta Paediatrica 2022; 111(8): 1556–1565.

IV Associations Between Delivery Modes, Birth Outcomes and Offspring Anxiety Disorders in a Population-Based Birth Cohort of Children and Adolescents. Ståhlberg, T., Upadhyaya, S., Polo-Kantola, P., Khanal, P., Luntamo, T., Hinkka-Yli-Salomäki, S., & Sourander, A. Frontiers in psychiatry 2022; 1350.

1 Introduction

Anxiety disorders are one of the earliest psychiatric disorders to manifest and the prevalence rates in children and adolescents are high (Kessler et al., 2005). According to a meta-analysis, the global pooled prevalence of anxiety disorders in children and adolescents was 6.5% (Polanczyk et al., 2015). Less than half of the adolescents with notable anxiety are thought to receive treatment (Niermann et al., 2021). Despite the low treatment rate, the incidence of treated anxiety disorders among children and adolescents has been increasing in recent years (Ask et al., 2020; Gyllenberg et al., 2018).

The definition of anxiety disorders is that the experienced fear or anxiety is persistent or excessive, causing individuals to avoid things or situations that are frightening, and that these symptoms cause notable distress or impairment (Beesdo-Baum & Knappe, 2012; Stein, D. J. et al., 2014). Children and adolescents with anxiety disorders may have difficulties in various areas of their life (Essau et al., 2000). The whole family often has to share the burden. Including functional impairment and the severity of symptoms in the definition of anxiety disorders is of huge importance. This enables us to distinguish anxiety disorders from anxiety, which is a normal emotion that everybody experiences from time to time. There are two diagnostic classification systems used worldwide for psychiatric disorders. The Diagnostic and Statistical Manual of Mental Disorders (DSM), and International Classification of Diseases (ICD). Anxiety disorders comprise a variety of disorders, depending on the classification system.

The aetiology for anxiety disorders is not fully understood although it is known to be multifactorial. The suggested risk factors for anxiety disorders are child temperament, parental psychopathology, parenting styles, and childhood adversities (Beesdo-Baum & Knappe, 2012). Heritability for anxiety disorders is around 30 to 40 % (Hettema et al., 2001), and it is obvious that other factors than genetics have an impact on the development of these disorders.

Prenatal and perinatal factors have been associated with later susceptibility to somatic diseases. In the 1980s, epidemiologist David Barker observed that those who were born small for gestational age (SGA) had an increased risk of metabolic diseases (Barker et al., 1989). Since then, prenatal and perinatal factors have been

widely studied and associations have been found with neurodevelopmental and psychiatric outcomes, including ADHD, autism, depression and schizophrenia (Abel et al., 2010; Cannon et al., 2002; Gardener et al., 2009; Halmøy et al., 2012; Sucksdorff et al., 2015, 2018; Upadhyaya et al., 2021). These associations have been explained by multiple mechanisms. However, the amount of literature on prenatal or perinatal factors for anxiety disorders is still limited and therefore so is the knowledge. In particular, large studies have been lacking and the results in the smaller studies have been inconsistent.

Large cohort studies are laborious and costly to conduct but register data offers a way to gather large datasets with less work and fewer expenses. Nationwide registers are fairly unique, and only tend to exist in the Nordic countries. Nationwide registers are optimal for epidemiological research because they include excessive amounts of data and enable researchers to use of large sample sizes. The Finnish registers include the Care Register for Health Care, the Finnish Medical Birth Register and the Finnish Population Register Centre. Various studies have used the data from these Finnish registers. Prenatal and perinatal information is recorded in the registers as well as psychiatric outcomes and therefore these registers are ideal for prenatal and perinatal epidemiological studies.

Early risk factors may enable us to identify children at risk and therefore offer preventive and early treatment interventions for those in need. Epidemiological studies form the basis for the health care system as they provide information on how to prevent diseases and disorders, as well as the level of resources needed to prevent and treat diseases and disorders (Seletano & Szklo, 2014).

2 Review of the Literature

2.1 Definition and diagnostic classification of anxiety disorders

- Anxiety is a biological emotional response to stressful situations.
- Anxiety disorders are psychiatric disorders and described by excessive or prolonged anxiety that causes functional impairment.
- The following anxiety disorders are recognized by the two diagnostic classification systems (ICD-10/11 and DSM-5): generalized anxiety disorder, social phobia, specific phobias, panic disorder, agoraphobia, separation anxiety, selective mutism and unspecific anxiety disorders.

Anxiety is a biological emotional response to stressful situations, and is experienced by everyone from time to time. The emotion of anxiety is already present in infancy. It serves as an adaptive mechanism signalling danger and telling us to avoid it. When anxiety is excessive, prolonged, and causes functional impairment, it is becoming pathological (Beesdo et al., 2009).

Fears and anxiety are part of the normal developmental processes in children and adolescents (Beesdo-Baum & Knappe, 2012). Anxiety symptoms are very common in this age group. Anxiety symptoms and clinical anxiety disorders can represent different phases of the continuum but anxiety disorders should be separated from transient feelings of anxiety or anxiety symptoms. Anxiety disorders are psychiatric disorders, which are classified by the ICD diagnostic classification systems from the World Health Organization (WHO) and the DSM from the American Psychiatric Association (APA).

The ICD and DSM diagnostic classifications are used in different countries, but both have spread globally. Finland uses the ICD. The first known classification of diseases originates from the 18th century (Jetté et al., 2010). The WHO took over the classification in 1948 and eventually named it ICD. The 9th edition of the ICD

was established in the 1970s, with the 10th revision in 1989. ICD-11 was published in 2018 (WHO, 2021).

Since 1996, the diagnostic classification used in Finland has been ICD-10 (WHO, 1992). This thesis uses ICD-10 anxiety disorder diagnoses described in Table 1. The DSM is a widely used classification from America. The first DSM was published in 1950s and it evolved into DSM-II, DSM-III, DSM-III-R, DSM-IV and finally, DSM-5 in 2013 (APA, 2013, 2021). It is important to be familiar with the DSM as well the ICD, as research articles often use DSM-classifications. Both ICD-10 and DSM-5 acknowledge the following anxiety disorder subgroups: generalized anxiety disorder, social phobia, specific phobias, panic disorder, agoraphobia and separation anxiety. In addition, selective mutism is listed under anxiety disorders in DSM-5, whereas in ICD-10 elective mutism is under childhood onset emotional disorders. The terms for mutism are different, but the term selective mutism is widely used in the literature. In ICD-10, childhood onset anxiety disorders are under childhood onset emotional disorders.

In ICD-10 obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are under neurotic, stress-related and somatoformic disorders. In DSM-5, OCD and PTSD are classified in their own sections (Abramowitz & Jacoby, 2014; Friedman, 2013; Stein, D. J. et al., 2010, 2014). These disorders can truly be seen as having a slightly different origin. OCD is thought to have neuropsychiatric background and PTSD needs a major stressor to occur, although the susceptibility for PTSD has been found to be moderately heritable (O'Connel et al., 2018; Stein et al., 2010). Furthermore, in DSM-5 the anxiety disorders that are related to substance use or other diseases and conditions are separated from anxiety disorders.

Table 1. ICD-10 diagnoses for anxiety disorders.

ICD-10: MENTAL, BEHAVIOURAL AND NEURODEVELOPMENTAL DISORDERS F01-F99

F40-48 NEUROTISM, STRESS RELATED AND SOMATOFORMIC DISORDERS
F40 PHOBIC ANXIETY DISORDERS
F41 OTHER ANXIETY DISORDERS
F42 OBSESSIVE-COMPULSIVE DISORDER
F43 REACTION TO SEVERE STRESS AND ADJUSTMENT DISORDERS
F44 DISSOCIATIVE DISORDERS
F45 SOMATOFORM DISORDERS
F48 OTHER NEUROTIC DISORDERS

F93-94 CHILDHOOD ONSET EMOTIONAL DISORDERS
F93 EMOTIONAL DISORDERS WITH ONSET SPECIFIC TO CHILDHOOD
F94 DISORDERS OF SOCIAL FUNCTIONING WITH ONSET SPECIFIC TO CHILDHOOD AND ADOLESCENCE

DETAILED DESCRIPTION OF THE BOLDED CATEGORIES FROM ABOVE, WHICH ARE THE ANIXETY DISORDER DIAGNOSES OF INTEREST IN THIS THESIS.

F40 PHOBIC ANXIETY DISORDERS
F40.0 AGORAPHOBIA
F40.1 SOCIAL PHOBIAS
F40.2 SPECIFIC PHOBIAS
F40.8 OTHER PHOBIC ANXIETY DISORDERS
F40.9 PHOBIC ANXIETY DISORDER, UNSPECIFIED

F41 OTHER ANXIETY DISORDERS
F41.0 PANIC DISORDER
F41.1 GENERALIZED ANXIETY DISORDER
F41.2 MIXED ANXIETY AND DEPRESSIVE DISORDER
F41.3 OTHER MIXED ANXIETY DISORDERS
F41.8 OTHER SPECIFIED ANXIETY DISORDERS
F41.9 ANXIETY DISORDER UNSPECIFIED

F93 EMOTIONAL DISORDERS WITH ONSET SPECIFIC TO CHILDHOOD
F93.0 SEPARATION ANXIETY DISORDER OF CHILDHOOD
F93.1 PHOBIC ANXIETY DISORDER OF CHILDHOOD
F93.2 SOCIAL ANXIETY OF CHILDHOOD
F93.3 SIBLING RIVALRY DISORDER
F93.80 GENERALIZED ANXIETY DISORDERS OF CHILDHOOD
F93.89 OTHER CHILDHOOD EMOTIONAL DISORDERS
F93.9 CHILDHOOD EMOTIONAL DISORDER, UNSPECIFIED

F94 DISORDERS OF SOCIAL FUNCTIONING WITH ONSET SPECIFIC TO CHILDHOOD AND ADOLESCENCE
F94.0 ELECTIVE MUTISM

Although the specific diagnoses seem to be a valid way to separate these disorders, clinically unclear symptoms may lead to the need to use unspecific anxiety disorder diagnoses. Uncertainty exists concerning the relationships between different anxiety disorders. It remains undiscovered, to what extent they are separate disorders and how much they simply represent different phenotypes, owing to the same core vulnerability factor. It is possible, that some of these disorders share the same aetiology and are indeed more or less manifestations of the same core problem. However, some of them represent different disorders with different aetiological factors. (Wittchen et al., 2000)

Despite the specific anxiety disorder diagnoses in the two classification systems, they both have categories for unspecified anxiety disorders and these are commonly used in clinical work. The clinical diagnostic process has its problems, as symptoms are often variable and diverse and the cut-off points for pathological symptom scores may be difficult to define. Children and adolescents often present with mixed symptoms and diagnostic classifications can be difficult, which results in "not otherwise specified" diagnoses (Ford et al., 2003). Child and adolescent patients may present with symptoms of mixed anxiety and depression and sometimes the primary problem cannot be identified and named. The accuracy of the diagnoses reported by academic research could be compromised when these diagnoses are used. It is important to note that we still do not know about the relationship between depression and anxiety. For example, we do not know how much aetiology they share or how much are they acting as risk factors for each other (Krueger, 1999; Mathew et al., 2011; Wittchen et al., 2000).

2.2 The psychological development of children and adolescents

- Psychological development begins in the uterus and is impacted by various prenatal and perinatal factors and various other factors later in life.
- Anxiety has been associated with structural and functional alterations in the brain regions responsible for emotional processing.
- Being aware of the normal development of children and adolescents is the basis for evaluating psychiatric symptoms in children and adolescents.

An infant's psychological development begins in the uterus. Various factors, such as genetic factors, maternal well-being, stress, illnesses, medications and other environmental factors have an impact on the infant's psychological development, and these impacts are partly mediated by the alterations in brain development. Early adverse events are thought to be quite harmful for brain development and therefore have long-term effects. (Kumpulainen et al., 2016).

The development of the brain starts during the first gestational weeks and continues until young adulthood. The neural tube forms into multiple parts of the developing nervous system from four to 12 weeks of gestation and the neurons multiply and migrate during weeks 12 to 20. Rapid cell loss between 24 weeks of gestation and four postnatal weeks halve the number of neurons. Myelination begins in the third trimester and is mostly completed during childhood, but it can continue in certain areas even in adolescence and young adulthood. (Lenroot & Giedd, 2006)

Synaptogenesis of the neural cells starts prenatally during the third trimester and continues during the first years of life (Kumpulainen et al., 2016). After that, the number of synapses mostly decrease, but there are certain areas of the brain that only achieve the highest synapsis during early adulthood (Lenroot & Giedd, 2006). Grey matter volume peaks before adolescence and then pruning takes place (Johnson et al., 2009). The prefrontal cortex is the area that is responsible for higher-executive functioning and the maturation of prefrontal lobes continues until the third decade of life (Kolk & Rakic, 2022). Therefore, adolescents do not necessarily have the same abilities for high cognitive functions as adults. The limbic system comprises of the amygdala, hippocampus, thalamus and hypothalamus and is responsive of emotional responses, whereas the cognitive processing of emotions occurs in the prefrontal cortex (Davidson, 2002). The connectivity between amygdala and cortical regions have been reported to continue to develop in adolescence and it has been suggested that this explains emotional and behavioural challenges and even sensitivity to psychiatric disorders (Jalbrzikowski et al., 2017).

The fear response reaches excessive levels in anxiety disorders and therefore we can expect to see structural or functional changes in fear-related brain areas, such as the amygdala (Ledoux, 2004). Anxiety has been associated with hyperactivity in the brain regions responsible for emotional processing and reward circuity (Chavanne et al., 2021). Hyperactivity has been observed in the amygdala, insula and medial prefrontal cortex (Chavanne et al., 2021; Etkin & Wager, 2007). In addition, the hippocampus and medial prefrontal cortex play significant roles in fear extinction and these areas have been therefore targeted as treatment foci for anxiety disorders (Brooks & Stein, 2015).

In addition to functional alterations, structural changes have also been found in children and adolescents with anxiety disorders. Alterations have been observed in the prefrontal cortex, amygdala and hippocampus in some studies (Gold et al., 2017; Mueller et al., 2013; Strawn et al., 2016), but not all studies have found these alterations (Merz et al., 2018).

Psychological development refers to the development of cognitive skills, social skills, moral, sexuality and regulating a person's behaviour. This development is impacted by the aforementioned brain development and by genetics, physical development, hormones and environmental factors. Early life adversities are known to have a huge impact on a child's psychological well-being. (Kumpulainen et al., 2016).

Attachment with caregivers is of major importance in the first years of life. Secure attachment to parents helps a child to regulate emotions (Cooke et al., 2019). The child learns to regulate information and emotions by following the examples given by the caretakers and, as the child grows, the capacity for self-regulation increases. Empathy develops during the first years of life and the child begins to separate his emotions from true events at the age of three. Cognitive, motor and social skills develop vastly in pre-school children. Play and imagination play major roles in a child's mental development. At early school age, cognitive, social and behavioural skills continue to develop and peers become more important. (Kumpulainen et al., 2016)

With regard to anxiety disorders, it should be noted that separation from caregivers causes fear and anxiety for infants and toddlers as a normal developmental process. Continued separation anxiety into older age might fulfil the clinically relevant diagnostic criteria for separation anxiety. In pre-school children, different kinds of fears are part of their normative development. If these fears are prolonged, or excessive, they may become clinically significant disorders, specific phobias. (Beesdo et al., 2009)

Adolescence forms a unique developmental phase, in which psychological development is strongly attached to physical development (APA, 2002). The individual's personality develops and adolescence offers the chance to detach themselves from childhood and form their own identity and autonomy (WHO, 2014). The development of the brain during adolescence includes reorganization, which provides a second chance to repair some of the damage that has happened. This brain reorganization together with hormonal changes creates biopsychological tension, which is crucial for development. However, at the same time there is a risk that emotional and behavioural disturbances will emerge. These developmental tasks include an adolescent gaining control over their identity, sexuality and autonomy. There are large hormonal and physical changes during puberty and

some individuals might perceive these changes as scary and threatening. Girls usually develop earlier than boys. We know that those who develop before or after the average age for peer development have an increased risk for mental problems during adolescence. (Kumpulainen et al., 2016)

Peers are of major importance for adolescents and their sense of belonging is crucial. Comparing themselves with peers and the fear of being different are very common (APA, 2002). Adolescents often worry about their appearance and think about their identity and sexuality and the importance of peers is highlighted. It is part of normal development to have social insecurity and even anxiety at this age. Therefore, it is logical that social anxiety disorder typically emerges during adolescence (Beesdo et al., 2009). Adolescents are cognitively and emotionally immature, which can also be explained by the brain maturation discussed earlier. Psychological regression is part of the normative development. The behaviour can remind personality disorder behaviour with splitting, dramatizing, narcissism and impulsivity. Psychological regression is necessary for psychological development but it is also potentially harmful if the developmental process slows down, or goes in wrong direction. (Kumpulainen et al., 2016)

2.3 Epidemiology of anxiety disorders

- The importance of anxiety disorders among children and adolescents is highlighted by the high prevalence rates.
- It is notable that the subthreshold symptoms for anxiety are still much more common than diagnosed anxiety disorders and that only some of the individuals with clinically significant anxiety symptoms receive treatment.
- Different anxiety disorders tend to appear at different ages.

Epidemiology is an area of research that studies health-related phenomena, including how diseases are distributed within populations and what the determinants are for diseases (Susser, 2006; Van den Broeck et al., 2013). Diseases result from various determinants and an accepted explanation is the complex interactions of genetic, environmental, behavioural and social factors (Seletano & Szklo, 2014). This concept was first understood during the 20th century, although epidemiological discussions were already taking place in ancient Greece (Van den Broeck et al., 2013).

As epidemiology studies the extent to which the certain disease presents in a certain population, the aetiological factors leading to the disease, the prognosis of the disease, and evaluates the treatments used to treat the disease, it formulates the basis for public health care policies. Epidemiological studies provide guidelines on how to prevent certain diseases and the level of and kind of resources that are needed to treat the disease. (Van den Broeck et al., 2013; Seletano & Szklo, 2014)

The term prevalence means how many cases with the disease exist in a certain population during a certain time period (Susser et al., 2006). The term pooled prevalence refers to a meta-analytic calculation of the prevalence rates from different studies (Polanczyk et al., 2015). Pooled worldwide prevalence rate for childhood and adolescence mental disorders before the age of 19 years has been estimated to be 13.4%. Anxiety disorders were the most prevalent mental disorder, with a pooled prevalence of 6.5%. These rates were calculated by a meta-analysis that comprised community-based studies from 27 countries in all continents. The estimates were obtained by examining diagnosed disorders with functional impairment. (Polanczyk et al., 2015)

This finding highlights the role of anxiety disorders as a major mental health problem among children and adolescents. It is worth noting that only a third to a half of the adolescents who suffer from anxiety disorders receive some form of a treatment (Niermann et al., 2021). A European study of several countries found that 5.8% of the adolescents had clinically relevant self-rated anxiety symptoms, but the rate for anxiety symptoms that did not meet clinical criteria was as high as 32% (Balázs et al., 2013). These subthreshold symptoms might be significantly unpleasant for the individual, even if they do not fulfil the diagnostic criteria.

Age is an important factor when interpreting the prevalence of different anxiety disorders, as anxiety disorder subtypes emerge at different ages. The typical age for the onset of selective mutism, separation anxiety disorder and specific phobias are before a child starts school. Social phobia, generalized anxiety disorder and panic disorder usually emerge during adolescence (Beesdo et al., 2009).

2.3.1 Treated incidence of anxiety disorders – recent time trends

- Internalizing or emotional symptoms have increased among adolescent girls.
- Service use has increased.
- The incidence of diagnosed anxiety disorders has been increasing in both primary and specialized health care services.

According to a systematic review, the prevalence of internalizing symptoms has increased among adolescent girls in the 21st century, but not among toddlers or children (Bor et al., 2014). Increases were found in the prevalence of anxiety symptoms (John et al., 2015; Knaappila et al., 2021; Parodi et al., 2022; Thorisdottir et al., 2017). In Finland, increase in emotional symptoms have been found among adolescent girls (Mishina et al., 2018; Torikka et al., 2014). Clear increases were also observed for self-rated social anxiety and generalized anxiety symptoms among adolescents, of both genders (Knaappila et al., 2021). Studies have reported no significant increases in emotional symptoms in eight-year-olds, but fluctuations have been observed (Lempinen et al., 2019; Sourander et al., 2016). Service use has increased in community samples, especially for children with severe problems (Lempinen et al., 2019).

Whereas prevalence describes the number of all the cases in a certain population, the term incidence refers to the number of new cases in a certain population during a certain time period. The term cumulative incidence means the proportion of incident cases in a certain cohort over a certain period of time. (Susser et al., 2006).

Furthermore, the term treated incidence refers to the incidence measured in a service system, which distinguishes it from the incidence measured in community samples. The cumulative treated incidence for psychiatric and neurodevelopmental disorders increased in both sexes over a 10-year period in a Finish register sample. The treated cumulative incidence of ICD-10 F40–F41 diagnoses at 18 years of age for those born in 1997 was 4.6% for girls and 1.8% for boys. (Gyllenberg et al., 2018)

It is not just Finland that has seen increases in child and adolescent treatment rates for anxiety disorders. Other countries have reported increases, such as Denmark, Norway, the UK and the USA (Ask et al., 2020; Cybulski et al., 2021; Hansen et al., 2021; Olfson et al., 2014; Seidl et al., 2021). The rates have varied,

depending on the study design. Increased treated incidence rates have been observed in both primary care (Ask et al., 2020; Cybulski et al., 2021; John et al., 2015) and specialized services (Ask et al., 2020; Gyllenberg et al., 2018). Referral rates to specialized services have also increased (Hansen et al., 2021). Table 2 describes the time trend studies that have reported results on the treated incidence of anxiety disorders.

Table 2. Previous time trend studies on treated incidence of anxiety disorders.

STUDY ***COUNTRY***	**DESIGN** ***DATA SOURCES***	**SAMPLE SIZE** ***AGE RANGE***	**YEARS OF BIRTH** ***YEARS OF DIAGNOSES*** **STUDIED TIMEPOINTS AND TIME INTERVAL**	**DIAGNOSES**	**RESULTS**
ASK ET AL., 2020 ***NORWAY***	Nationwide register study *Primary and secondary healthcare, prescriptions*	13,276 diagnoses in primary care, 12,284 in secondary care *Age range 3 to 17y.*	Born 1991 to 2013 *Diagnoses given in 2008 to 2015 or 2010 to 2015* 2010–2015 yearly for five years	Primary care codes, prescriptions and ICD-10: F40, F41, F42, F43.1, F93.0, F93.1, F93.2.	Treated incidence increased from 2010 to 2015 from 2.24 to 4.35 per 1000 inhabitants in primary health care and from 2.06 to 3.74 in secondary health care.
CYBULSKI ET AL., 2021 ***UK***	Registers *Primary care*	9,133,246 *Age range 1 to 20y.*	1994 to 2017 *2013 to 2018* Comparison of 2013 vs 2018 in four age groups (6–9; 10–12; 13–16; 17–19), five-year interval for all.	Anxiety disorder, no ICD-codes provided	Treated incidence rates increased from 2013 to 2018 (IRR 3.5; 95% CI 3.18–3.89). **Girls:** 6–9y: IRR 3.2, 95% CI 2.6–3.9. 10–12y: IRR 4.6, 95% CI 4.0–5.3. 13–16y: IRR 4.6, 95% CI 4.1–5.1. 17–19y: IRR 2.6, 95% CI 2.3–3.0. **Boys:** 6–9y: IRR 3.2, 95% CI 2.7–3.8. 10–12y: IRR 3.5, 95% CI 2.9–4.2. 13–16y: IRR 3.4, 95% CI 3.0–3.9. 17–19y: IRR 2.8, 95% CI 2.3–3.3.

GYLLENBERG ET AL., 2018 ***FINLAND***	Nationwide Register study *Specialized health care*	Boys born in 1987 F40–41: 95 F93–94: 51. Boys born in 1997 F40–41: 273 F93–94: 261. Girls born in 1987 F40–41: 184 F93–94: 82 Girls born in 1997 F40–41: 695 F93–94: 477 *Age range 12 to 18y.*	1987 and 1997 born (2 cohorts) *Diagnosed as 12 to 18 yr. old.* Comparison of 1887 born vs 1997 born by the age of 18y.	F40, F41 (excluding F41.2), separately F93, F94	The cumulative incidence in specialized services increased between the two cohorts: **Boys:** F40–F41: cumulative incidence %: from 0.6 (0.5–0.8) to 1.8 (1.6–2.0) F93–F94: from 0.3 (0.2–0.4) to 1.7 (1.5–1.9). **Girls:** F40–F41: from 1.3 (1.1–1.5) to 4.6 (4.3–5.0) F93–F94: from 0.6 (0.4–0.7) to 3.2 (2.9–3.5)
HANSEN ET AL., 2021 ***DENMARK***	Register data of regional referral diagnoses to child and adolescent psychiatric services. *Primary health care diagnoses referred to specialized services*	For anxiety disorders only referral rates reported. The whole sample size in 2005: 480; in 2010: 1225; in 2018: 2233. *Age range 0 to 18y.*	1987–2018 *2005, 2010 and 2018* Comparison of referral diagnoses in 2005, 2010 and 2018	F40-F42, F93	Referral rates were 5.6% in 2005, 3.2% in 2010 and 10.8% in 2018. OR from 2005 to 2018 2.02 (95% CI 1.34–3.05). OR from 2010 to 2018 3.66 (95% CI 2.59–5.18).

JOHN ET AL., 2015 ***UK***	Register data covering primary health care *Primary health care*	Anxiety disorder dg: boys 1186, girls 2111. Panic disorder dg: boys 457 girls 1142 *Age range 6 to 18y.*	6–10, 11–14 and 15–18y or 6–14 and 15–18 age ranges were used *2003 to 2011* 2003–2011 yearly time points for 8 years	Chronic anxiety, generalized anxiety disorder, anxiety state, mixed anxiety and depression, panic attacks, panic disorder, emotional disorders with an onset usually in childhood	Increase in the treated incidence from 2003 to 2011 from 1.82 cases (per 1000 PYAR) to 2.37 (IRR=1.20, 95% CI 1.02–1.41). Treated incidence of panic attack/ panic disorder increased from 0.73 to 1.09 (IRR=1.38, 95% CI1.11–1.72).

CI=confidence interval; IRR=incidence rate ratio; PYAR=person years at risk; OR=odds ratio.

These time-trend studies examined the changes in treated incidence from 2000 to 2018. The treated incidence rates may have changed dramatically in the last few years due to the COVID-19 pandemic. Treated incidence rates for mental health visits mostly decreased at the beginning of the pandemic, although the incidence of self-harm acts increased (Wan Mohd Yunus et al., 2022). Anxiety and depressive symptoms increased among children and adolescents (Racine et al., 2021) and it is possible that the treated incidence rates during the middle of the pandemic increased after lock-down periods. This was seen in paediatric psychologist and psychiatrist consultations in the USA (Leith et al., 2022). The real impact of the pandemic on anxiety disorders will be discovered in the future.

2.4 Aetiology of anxiety disorders

- The aetiology of anxiety disorders is multifactorial and not entirely understood.
- Diathesis-stress theory explains the risk of developing an anxiety disorder: the genes and the environment interact and predispose the individual to a certain level of a risk.
- The role of prenatal and perinatal factors has not been studied thoroughly.

The aetiology of anxiety disorders is not entirely understood, but we do know it comprises multiple factors, including genetics and environmental factors (Ask et al., 2021; Beesdo et al., 2009). Diathesis-stress hypothesis has been an accepted theory for developing an anxiety disorder, meaning that the genes and the environment, both individually and together, predispose the individual to a certain level of liability developing a disorder (Ask et al., 2021). An umbrella review examined protective and risk factors for anxiety disorders. Only early physical and sexual trauma were found to be reliably associated with an increased risk of social anxiety disorder. When the authors also looked studies with smaller sample sizes, they found that possible risk factors for some anxiety disorders were dysthymia, depression, insecure attachment in childhood, neuroticism, behavioural inhibition, parental anxiety disorder and female sex. (Fullana et al., 2020)

Figure 1 lists the factors that have been associated with child and adolescent anxiety disorders and are therefore suggested to be part of the aetiology. These aetiological factors will be further explored later on in this thesis. Some factors that have been associated with anxiety disorders may be aetiological factors or

consequences of anxiety disorders, such as lifestyle factors or psychiatric comorbidities. The main interest of this thesis was the role of prenatal and perinatal factors in the development of child and adolescent anxiety disorders. Although other aetiological components will be briefly discussed, this thesis contains a more comprehensive literature review for prenatal and perinatal factors.

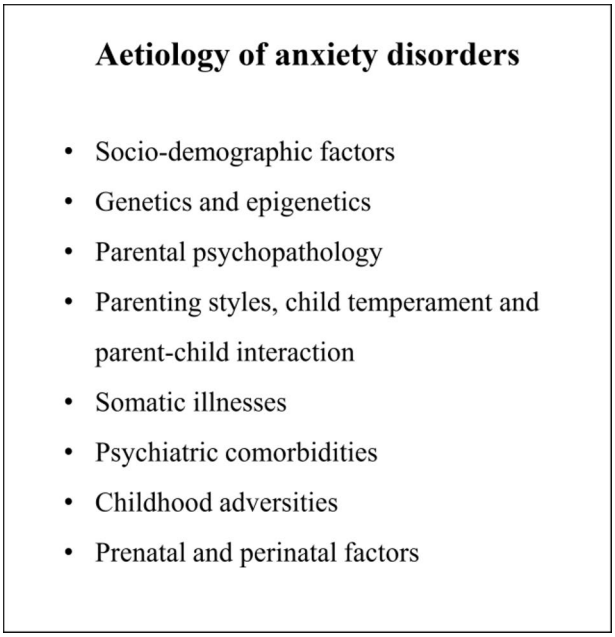

Figure 1. Aetiology of anxiety disorders.

2.4.1 Socio-demographic factors

- Socio-demographic factors often create a hereditary continuum of certain risks for generations, including the risk of mental disorders.
- Various sociodemographic factors have been associated with anxiety disorders, but the findings have also been controversial.
- Only few register-based studies have examined links between socio-demographic factors and anxiety disorders.

Socio-demographic factors have been associated with various behavioural and mental disorders that often create a hereditary continuum for generations (Conger, 2015). Low socio-economic status (SES), low education level, being a single parent and psychiatric disorders often accumulate in families and create a multi-fold risk for children's mental health problems. Evidence of sociodemographic factors that increase the risk of child's mental health problems have been reported. These are being a single parent (Davis et al., 2010; Weitoft et al., 2003), low level of parental education (Davis et al., 2010; Sonego et al., 2013), parental unemployment (Davis et al., 2010), low parental income (Hakulinen et al., 2020) and low SES (Reiss, 2013).

When it comes to anxiety disorders, links to socio-demographic factors have been quite controversial. Gender might be the only exception, as female predominance for anxiety disorders has been supported by many studies in both adolescents or adulthood (Beesdo et al., 2009; Bøe et al., 2021; Merikangas & Almasy, 2020; Remes et al., 2016). Females have 1.7 higher lifetime odds of developing an anxiety disorder than males (McLean et al., 2011). However, the incidence of anxiety disorders seems to be higher for boys during childhood (Dalsgaard et al., 2020; Esbjørn et al., 2010; Wesselhoeft et al., 2015).

Low income has been associated with anxiety disorders in some smaller cross-sectional or cohort studies (Goodman et al., 1998) (Costello et al., 1996; Roberts et al., 2007), whereas others have found no association (McLaughlin et al., 2012). It is interesting that generalized anxiety disorder has also been associated with high income (Mendes et al., 2013). Low SES was presented as a risk factor for different anxiety disorders in one cross-sectional study (Wichstrøm et al., 2012), yet other study did not find any association (Dougherty et al., 2013). An African study found significant associations between low parental education (Abbo et al., 2013), but an Australian study did not support this finding (Spence et al., 2018).

Register-based studies have large power due to their extensive sample sizes. Register-based studies on socio-demographic risk factors for child and adolescent anxiety disorders have been described in Table 3. Low parental income increased the odds for anxiety disorders in Norwegian children and adolescents (Kinge et al., 2021). Low SES increased the odds for anxiety disorders (Guhn et al., 2020) and elective mutism (Koskela et al., 2020). Parental unemployment was associated with higher odds for anxiety disorders (Hyland et al., 2016). Parental separation or single parenting were associated with higher odds for anxiety disorders (Guhn et al., 2020; Hyland et al., 2016), as well as for elective mutism (Koskela et al., 2020). Urbanicity was associated with increased odds for anxiety disorders in Denmark, both in children and adolescents (Helenius et al., 2014; Hyland et al., 2016) and in mixed age groups (Vassos et al., 2016).

Maternal age as a risk factor for child developmental problems has been observed to follow a J-shaped curve (Falster et al., 2018). Both young and advanced maternal age were associated with increased risks of anxiety disorders in one study (Larsen et al., 2021). Other studies found that advanced maternal age increased the risk (Guhn et al., 2020), and young maternal age was a protective factor (Kingston et al., 2015). However, some studies did not find any associations between maternal age and anxiety disorders (Helenius et al., 2014; Hyland et al., 2016; Steinhausen et al., 2016). No associations were observed for elective mutism in a Finnish study (Koskela et al., 2020). Studies reporting findings on maternal age have been described in Table 3 and Table 8.

Table 3. Previous register studies on socio-demographic risk factors and child and adolescent anxiety disorders.

STUDY ***COUNTRY***	**DATA SOURCE**	**COHORT**: BIRTH YEARS *AGE RANGE* SAMPLE SIZE OF ANXIETY DISORDER CASES	**DIAGNOSES**	**SOCIO-DEMOGRAPHIC RISK FACTORS OF INTEREST**	**RESULTS FOR ANXIETY DISORDERS**
GUHN ET AL., 2020 ***CANADA***	Medical service plan database.	Born 1993 to 1995 *5 to 15* N=7,867	ICD-10: F40–F43	Maternal age and birth place, parental marital status, SES	**Maternal age 36 to 40y: OR 1.14 (95% CI 1.05–1.24); Maternal age >40y: OR 1.41 (95% CI 1.16–1.72) (vs maternal age 25 to 30y.)**; **Mother's birthplace outside Canada: OR 0.74 (95% CI 0.70–0.78); Single parenting: OR range 1.26-1.82 depending on the category (vs married); Family's subsidized status OR 1.25 (95% CI 1.19, 1.32) (vs unsubsidized).**
HELENIUS ET AL., 2014 ***DENMARK***	National registers, psychiatric in- and outpatient data.	Case probands born 1952 to 2000, three generations. *< 18* N=1,373	ICD-8: 300.0 ICD-10: F41 and F93.0	Parental age, month of birth, region of residence	**Region of residency Copenhagen vs other regions: OR 1.24 (95% CI 1.08–1.42).** Parental age NS; month of birth NS.

HYLAND ET AL. 2016 ***DENMARK***	National registers, psychiatric in- and outpatient data.	Born in 1984 *10 to 21* N=1,772	ICD-8: 300, 305, 308.00 ICD-10: F40–F49	Parental age and unemployment, family dissolution, urbanicity	**Parental unemployment: OR 1.26 (95% CI 1.13–1.41); Family dissolution: OR 1.64 (95% CI 1.47–1.83); Urbanicity: OR 1.17 (95% CI 1.06–1.29).** Paternal age > 40 or Maternal age > 40 NS.
KINGE ET AL., 2021 ***NORWAY***	National registries, primary and specialized services.	Cases were 5 to 17 in 2008 to 2016 *5 to 17* N= 62,763	ICD-10: F40–44, F93–93.2 ICPC-2 codes from primary health care: P74, P79, P82	Parental income	**For girls OR 0.87 (95% CI 0.86–0.88) and for boys OR 0.86 (0.85–0.87) for each 10% higher level of parental income.**
KOSKELA ET AL., 2020 ***FINLAND***	National registers, psychiatric in- and outpatient data.	Born between January 1987 and March 2009 *3 to 15* N=860	ICD-9: 3132C ICD-10: F94.0	Parental age, Maternal SES, maternal marital status, parental immigration status, urbanicity	**OR for elective mutism: Paternal age 35–39: OR 1.4 (95% CI 1.1–1.8); Paternal age >40: OR 1.8 (95% CI 1.4–2.4) (vs 25 to 29y.)**. Compared to highest SES class, **low SES OR 2.0-2.8 depending on the category. Maternal single status: OR 2.0 (95% CI 1.4–3.0).** Maternal age, parental immigration status or urbanicity NS.
STEINHAUSEN ET AL., 2016 ***DENMARK***	National registers, psychiatric in- and outpatient data.	Born in 1969 to 1986 *< 40 y.* n=746	ICD-8: 300.2 ICD-10: F40	Parental age, birth month, region of residency	Odds ratios for phobic disorders: Paternal or maternal age >35 at birth NS; Birth month NS; Region of residency: other regions vs Copenhagen NS.

In results the bolded values are significant results. CI=confidence interval; NS=not significant; OR=odds ratio.

2.4.2 Other aetiological factors than prenatal and perinatal factors

- The aetiology of anxiety disorders comprises various factors.
- A number of other factors have been associated with anxiety disorders in addition to prenatal and perinatal factors. These include: genetics and epigenetics, parental psychopathology, parental behaviour, child temperament and familial interactions, socio-demographic factors, somatic diseases, psychiatric comorbidities, stress, and childhood adversities.

A meta-analysis of genetic studies for anxiety disorders found a strong familial aggregation for panic disorder, generalized anxiety disorder, and phobias and concluded that the heritability rate was 30–40% (Hettema et al., 2001). Although heritability rate is substantial, it is lower than, for example, bipolar disorder or schizophrenia (Bienvenu et al., 2011; Hilker et al., 2018). This highlights the impact that other factors, not just genetic factors, to contribute to the risk of developing anxiety disorders. A twin study found that genes predispose individuals to two different anxiety disorder groups in different ways. One group covered generalized anxiety disorder, panic disorder and agoraphobia and the other group was specific phobias (Hettema et al., 2005). The PDE4B gene has been identified as a potential risk locus for anxiety (Meier et al., 2019).

Epigenetic alterations mean chemical changes in DNA without alterations in the genetic sequence, and epigenetic alterations have been used to explain the changes in phenotypes (Suzuki & Bird, 2008). Their impact on the development of psychiatric disorders has been increasingly of interest. Early life factors, such as perinatal environmental factors, can alter the genetic expression through methylation without altering the genetic code. These can cause long-lasting effects and could increase the susceptibility for developing a mental disorder (Nemoda & Szyf, 2017; Stein, A. et al., 2014). Epigenetics and anxiety disorders have mostly been studied among animals, but human studies have found differences in DNA methylation between cases with anxiety disorders and controls (Schiele & Domschke, 2018).

Familial concordance has been repeatedly reported for anxiety disorders (Helenius et al., 2014; Li et al., 2008, 2011; Merikangas et al., 1999; Steinhausen et al., 2016). A child's risk of anxiety disorders has been reported be particularly high

when both parents suffer from anxiety (Dierker et al., 1999). One study found a stronger association between maternal and offspring anxiety disorders than between paternal and offspring disorders (Li et al., 2008). Furthermore, one study reported a higher risk of concordance for female offspring (Ranney et al., 2021).

In addition to parental anxiety disorders, other forms of parental psychopathology have also been associated with offspring anxiety disorders. Some studies have shown associations between parental depression and child anxiety disorders (Ayano et al., 2021). The risk was also increased when a parent had mixed anxiety and depression (Beidel & Turner, 1997) or parents had any psychiatric diagnoses (Steinhausen et al., 2009). Parental bipolar disorder has been associated with an increased risk of child anxiety disorders (Ayano et al., 2021), and so have parental substance abuse disorders (Clark et al., 2004; Hill et al., 2000; Lieb et al., 2000). Notably, children born to mothers who abused substances were less likely to have anxiety disorders than the offspring of mothers with anxiety or affective disorders (Dierker et al., 1999). Furthermore, children with anxiety disorders were more likely than controls to have fathers with substance abuse disorders, but not after controlling with paternal anxiety (Hughes et al., 2009). No association was found between parental schizophrenia and anxiety disorders in offspring in a meta-analysis by Ayano et al. (2021), although other forms of parental severe psychiatric disorders were found to increase the risk. Parental psychopathology has been shown to affect child development as early as in utero (Stein, A. et al., 2014). Parental prenatal, perinatal and postnatal mental well-being and associations with offspring anxiety disorders are discussed in 2.5.1.

Parental modelling may be one of the mechanisms explaining why anxiety disorders transfer from parents to children (Murray et al., 2009). The quality of parenting and different parenting styles may serve as relevant mediators between parental psychopathology and offspring anxiety disorders. For example, maternal intolerance for distress and emotional impulsivity could be one parental behaviour mediator (Casline et al., 2021). Maternal anxiety has been associated with mothers being overprotective (Jones et al., 2021), and overprotective parenting with anxiety disorders (Murray et al., 2009). Overprotective and rejective parenting and lack of emotional warmth have been associated with social phobia in adolescents (Knappe et al., 2009; Lieb et al., 2000). Temperamental inhibition, lack of maternal encouragement and maternal intrusiveness in early childhood have been associated with an increased risk of child anxiety symptoms (Lawrence et al., 2020). On the other hand, another study found that maternal warmth was associated with decreased child anxiety symptoms at school age (Anderson, S. L. et al., 2021), and a meta-analysis concluded that positive parenting was associated with fewer internalizing symptoms (Clayborne et al., 2021). However, another meta-analysis

concluded that parenting styles only had modest associations with child anxiety (McLeod et al., 2007).

Parenting styles have also been studied together with child temperament, which is a better approach, as it considers the duality of parent-child interactions (Hirshfeld-Becker et al., 2012; Murray et al., 2009). Certain temperamental features have been associated with the tendency to develop an anxiety disorder in childhood or adolescence. These, partly overlapping traits, are behavioural inhibition, neuroticism and trait-anxiety (Beesdo et al., 2009). Behavioural inhibition is a widely studied temperamental pattern, which can be described as shyness and caution towards unfamiliar things (Kagan, 1989; Murray et al., 2009). This temperamental character does not necessarily continue throughout a child's life (Degnan & Fox, 2007), but it has been associated with later anxiety disorders, especially social phobia, in multiple studies (Fullana et al., 2020). In addition, behavioural inhibition in children has been associated with parental anxiety disorders (Murray et al., 2009). Neuroticism is a personality trait that has been associated with anxiety disorders (Fullana et al., 2020). Among adolescents, neuroticism was associated with maintaining internalizing symptoms (Williams et al., 2021). Affect intolerance comprises distress tolerance and anxiety sensitivity and has been associated with self-reported or parent-reported anxiety in children and adolescents (Shaw et al., 2021).

On the other hand, resilience has been found to be protective against mental health problems, such as anxiety (Hu et al., 2015). Resilience plays a significant role in overcoming childhood adversities, which have been shown to increase the odds for anxiety disorders (Sahle et al., 2021). Childhood adversities include early physical and sexual trauma, which were shown to increase the risk of anxiety disorders in adults in an umbrella review (Fullana et al., 2020). Early adversities have been found to be even stronger predictor for anxiety disorders than for depression (Phillips et al., 2005).

In addition to severe traumatic experiences during childhood, other childhood stressors have also been associated with anxiety symptoms or disorders. These factors are somatic illnesses (Carroll et al., 2022; Cobham et al., 2020; LaGrant et al., 2021; Yardeni et al., 2020), sleeping problems (Chan et al., 2020), use of digital media (Roberston et al., 2022), peer stress (Chiu et al., 2021; Islam et al., 2020), loneliness (Xerxa et al., 2021), cultural factors (Eckersley, 2006), climate worries (Theron et al., 2022), pandemics (Bohlken et al., 2021; Kostev et al., 2021), terrorism and war (Slone & Mann, 2006).

2.4.3 Psychiatric comorbidities

- The term comorbidity means multiple disorders present at the same time or sequentially. The timing for comorbidities may be defined in various ways.
- The term itself is complex and various mechanism may lie beneath the co-occurrence or succession between the disorders.
- Comorbidities commonly occur with anxiety disorders, such as depressive disorders, neurodevelopmental disorders, conduct disorders and substance use disorders.

The term comorbidity means the existence of two or more disorders in the same individual (Angold et al., 1999). Comorbidities are highly prevalent among children and adolescents with anxiety disorders (Essau et al., 2000, 2018). The concept of comorbidity is complex. The timing of the definition varies as the disorders can occur at the same time or sequentially. Comorbidities commonly overlap. When they are sequential, one disorder precedes the other and the diagnoses may therefore be seen as primary or secondary diagnoses. (Angold et al., 1999; Susser, 2006)

The division into primary or secondary diagnoses is not always straightforward (Mathew et al., 2011; Wittchen, 1996; Wittchen et al., 2000). This phenomenon should be viewed with integrity, as the diagnostic criteria for psychiatric disorders have been devised by humans and it is not known if the criteria for separating distinct disorders are real (Angold et al., 1999). Two psychiatric diagnoses could actually have common vulnerability factors and could merely be a manifestation of one mental health issue (Krueger, 1999; Mathew et al., 2011; Wittchen et al., 2000).

Comorbidities are common with anxiety disorders and high prevalence rates have been shown for depressive disorders, neurodevelopmental disorders, conduct disorders and substance use disorders. Comorbid depression is prevalent in 30–60% of cases with anxiety disorders (Essau et al., 2000; Lamers et al., 2011; Saha et al., 2021). The risk of depression was two to four times higher in adolescents and young adults with anxiety disorders when they were compared to controls without mental disorders (Essau et al., 2018; Wittchen et al., 2000). Despite the uncertainty of the concept of comorbidity described above, an accepted explanation for the causality of these disorders is that anxiety precedes depression more often than vice-versa (Lamers et al., 2011; Wittchen et al., 2000). Adults with comorbid anxiety and depressive disorders have been found to have more childhood trauma

experiences and more neuroticism than those with just an anxiety disorder or just a depressive disorder. They were also more likely to have earlier onset of symptoms, more severe symptoms and longer duration of symptoms. (Lamers et al., 2011).

Another common comorbidity group comprises neurodevelopmental comorbidities, such as autism, ADHD and learning difficulties. Comorbid anxiety disorders could either be derived from the same neurological determinants or from shared aetiological factors or be secondary by nature. It has been estimated that 25–50% of children and adolescents with ADHD also have anxiety disorders. The possible explanation for this comorbidity is shared neurobiology or increased stress about their performance, either in social or academic situations (D'Agati et al., 2019). Children with autism spectrum disorders commonly have anxiety disorders and prevalence-rates of 40% have been reported (Simonoff et al., 2008). In particular, children with high intelligence quotients have been found to have more anxiety symptoms (Mingins et al., 2021).

Externalizing disorders can be divided into early onset and late onset disorders. Early onset externalizing disorders comprise oppositional-defiant disorder, conduct disorder and ADHD. Late onset externalizing disorders are anti-social behaviour and substance use disorder. Both early and late onset externalizing disorders have been associated with incident anxiety disorders and explanations for this could be chance, shared aetiology or causality (Knappe et al., 2022). Smoking has been associated with anxiety disorders (Morissette et al., 2007). Nicotine exposure in adolescence could increase the risk of anxiety disorders through neuronal and molecular pathways (Laviolette, 2021). On the other hand, nicotine can be a self-help method to try to relieve anxiety (Morissette et al., 2007). Cannabis is another drug commonly used by adolescents and young adults with anxiety disorders. There is no clear consensus on the relationship between cannabis and anxiety, but multiple studies have found an association between cannabis use and an increased risk of anxiety (Stiles-Shields et al., 2021). Other drug use has also been associated with elevated levels of anxiety (Rogers et al., 2021).

Eating disorders are also relatively common comorbidities with anxiety disorders. It has been estimated that 40%–70% of patients with eating disorders also have anxiety disorders (Swinbourne & Touyz, 2007). Furthermore, gaming disorders were shown to be associated with increased levels of anxiety symptoms in a Chinese community sample of adolescents (Wei et al., 2022).

2.5 Prenatal and perinatal risk factors for anxiety disorders

In addition to the various aetiological factors discussed so far, there are multiple prenatal and perinatal factors that may have an impact on the development of

anxiety disorders. The prenatal or antenatal period is the time before birth, whereas the perinatal period starts from 22 completed weeks of gestation and ends seven completed days after birth. The postnatal period is the first six weeks after birth (WHO, 1992).

In the 1980s a British epidemiologist called David Barker observed that intrauterine growth restriction increased the susceptibility for metabolic diseases in adulthood (Barker & Osmond, 1988; Barker et al., 1989). Barker's hypothesis was that maternal malnutrition and other factors leading to poor foetal growth programme the foetus to reserve their dietary intake and this leads to an increased risk of later metabolic illnesses (Hales & Barker, 1992). Later research found that being pregnant during a famine was associated with psychiatric disorders in offspring (Susser et al., 1992). Barker's hypothesis has led to further research into how prenatal and perinatal factors impact later child development, including mental disorders (Kim et al., 2015).

2.5.1 Maternal mental health and stress during pregnancy

- Prenatal depression and other mental health problems are highly prevalent among pregnant women.
- Maternal perinatal mental health problems have been associated with various somatic and psychiatric developmental outcomes in their offspring.
- There have been very few studies on anxiety disorders among offspring, but an association with maternal depression or stress might exist.

Parental mental health problems serve as a risk factor for anxiety disorders in offspring through genetics and behaviour (Murray et al., 2009). Maternal perinatal mental health problems have been associated with various developmental outcomes among offspring, such as increased risks of poor foetal growth and preterm birth (Upama & Al., 2021). Furthermore, maternal mental health problems during pregnancy have been associated with child and adolescent mental and behavioural disorders (Borchers et al., 2021; Rogers et al., 2020; Stein, A. et al., 2014; Tuovinen et al., 2021). Maternal mental health problems during pregnancy also have many adverse outcomes for the mother herself and these problems can further increase the risk for her offspring having adverse outcomes. Poor prenatal mental health has been associated with somatic problems during pregnancy and delivery and has also been reported to have an impact on maternal postpartum health

(McKee et al., 2020). Postpartum depression is more likely after antenatal anxiety (Goodman et al., 2014) and postnatal depression poses a considerable risk to a child's development (Slomian et al., 2019). It is also worth noting that paternal perinatal mental health problems have been associated with an increased risk of adverse outcomes in offspring (Stein, A. et al., 2014).

Prenatal depression is highly prevalent among expectant mothers (7–13%) (Gavin et al., 2005; Wallwiener et al., 2019). The prevalence rate estimate for anxiety disorders among pregnant women was 16.9% in a German cohort (Wallwiener et al., 2019), whereas a systematic review reported that the prevalence varied between 4% and 39% (Goodman et al., 2014). These high variations could be partly explained by the different definitions of anxiety disorders.

Maternal depression and stress may increase maternal cortisol levels (Seth et al., 2016). Increased cortisol exposure may alter foetal development processes, including neurodevelopment and development of the hypothalamus-pituitary-adrenal (HPA) axis (Seckl, 2004). Altered neurodevelopment or HPA-axis functions could lead to mental health outcomes (Cottrell & Seckl, 2009). Maternal stress increases the levels of the placental corticotropin releasing hormone, which has been associated with cognitive and emotional deficits in young children through cortical thinning (Sandman et al., 2018).

Overall, maternal perinatal mental health or stress and child and adolescent anxiety disorders have not been studied much. The existing results are also somewhat controversial. Antenatal depressive symptoms were associated with anxiety disorders in offspring in the Avon Longitudinal Study of Parents and Children but anxiety symptoms were not (Capron et al., 2015). An Australian case-control study found that prenatal stress was more prevalent among offspring with anxiety disorders than offspring with depressive disorder or controls with neither (Phillips et al., 2005). Other studies have not reported associations for depressive symptoms, poor mental health or distress and anxiety disorders in offspring (Allen et al., 1998; Kingston et al., 2015; Lavallee et al., 2011). A Finnish study found that maternal prenatal depressive, anxiety and stress symptoms were associated with increased risks for child emotional and behavioural problems, but anxiety disorders were not studied separately (Tuovinen et al., 2021). No significant associations were found between maternal prenatal depression and combined depressive and anxiety disorders in offspring at four years of age (Galbally et al., 2020). Maternal postnatal depression (Morales-Munoz et al., 2022) and distress (Kingston et al., 2015) have been associated with offspring anxiety disorders. Table 4 presents the relevant studies that have focused on maternal mental health during pregnancy and child and adolescent anxiety disorders.

Table 4. Previous studies on maternal prenatal mental health and child and adolescent anxiety disorders.

STUDY ***COUNTRY***	**STUDY DESIGN**	**COHORT:** **SAMPLE SIZE** ***SAMPLE SIZE OF ANXIETY DISORDER CASES*** **AGE RANGE**	**DIAGNOSES**	**STUDIED EXPOSURE OF INTEREST**	**RESULTS FOR ANXIETY DISORDERS**
ALLEN ET AL., 1998 ***USA***	Cohort	N=579 *(n=54)* ≤ 18 yr.	Anxiety disorders	Maternal emotional health measured by retrospective questionnaire from mothers.	Maternal mental health NS in the adjusted analysis.
CAPRON ET AL., 2015 (THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN ALSPAC) ***UK***	Cohort	N=4,303 *(n=283)* 18 yr.	Anxiety disorders	Parental antenatal depression measured with EPDS and anxiety measured with CCEI at 18 weeks gestation.	**Maternal depressive symptoms* (OR 1.75; 95% CI 1.19–2.58).** Maternal antenatal anxiety significant only in the unadjusted model (OR 1.43; 95% CI 1.06–1.94). No significant association for paternal symptoms.
HIRSHFELD-BECKER ET AL., 2004 ***USA***	Family cohort	N=306; 188 with parental PD and MD, 26 with parental PD, 47 with parental MD, 95 with no parental PD or MD. *(With two or more ADs n=54)* 5 to 25	Multiple anxiety disorders	Emotional problems requiring counselling. Measured with retrospective maternal interview.	**For multiple anxiety disorders: emotional problems requiring counselling* (OR 2.6; 95% CI 1.3–5.5)**

KINGSTON ET AL., 2015 ***CANADA***	Register-based cohort	N=18,836 *(n=591)* ≤ 5 yr.	ICD-10: F40–F43, F93 Clinical diagnoses, ICD-9 or 10, or prescribed anxiolytic medication	Maternal psychological distress (diagnoses or medication from the registers).	**Maternal psychological distress from birth to 12 months (OR 1.28; 95% CI 1.001–1.64).** Prenatal psychological distress significant only in unadjusted analyses.
LAVALLEE ET AL., 2011 ***SWITZERLAND***	Case-control	N= 150 children with separation anxiety disorder *(n=106)*, control children *(n=44)* 4 to 14 yr.	Separation anxiety disorder	Stress during pregnancy measured by retrospective questionnaire from mothers.	Stress during pregnancy NS.
PHILLIPS ET AL., 2005 ***AUSTRALIA***	Case-control	N=691 61 adolescents with depression, 61 with anxiety disorders, 569 controls. *(n=61)* 15 yr.	Anxiety disorders	Prenatal stress measured by questionnaires for mothers during pregnancy, the sample was consisted of mothers with depressive symptoms.	**Prenatal stress (OR=1.22, 95% CI=1.04–1.43).**

In results the bolded values are significant results. CCEI=the Crown Crisp Experiential Index; CI=confidence interval; EDPS=the Edinburgh Postnatal Depression Scale; NS=not significant; OR=odds ratio.

2.5.2 Maternal medication and health risk behaviours during pregnancy

- Maternal medications and substance use are potentially harmful for the foetus.
- Other lifestyle factors, such as diet, may also be harmful for the development of the foetus.
- Familial sociodemographic and psychiatric problems might confound the associations between medications or substances and offspring psychiatric outcomes.
- There have been very few studies on maternal medication and substance use during pregnancy and anxiety disorders in offspring.

Mothers may need medication during pregnancy. In addition, problematic drug and substance use may occur during pregnancy. Many of these drugs can be harmful for the foetus. Although maternal mental disorders might increase the risk of mental disorders in offspring, so could the medications used to treat these mental disorders.

Maternal medication and substance use have rarely been studied with regard to anxiety disorders in their offspring. Many studies have found associations between antidepressants and somatic, neurodevelopmental or psychiatric outcomes in offspring (El Marroun et al., 2014). However, the findings for selective serotonin reuptake inhibitors (SSRIs) and anxiety disorders in offspring have been minor. One study found that maternal SSRI use increased the risk of offspring depression, but the risk for anxiety disorders was respective to the offspring whose mothers had psychiatric history without medication (Malm et al., 2016). Other studies that examined maternal psychotropic medication and anxiety disorders in offspring could not be found. However, one study found that maternal psychotropic medication had no effect on internalizing behaviours (Misri et al., 2006).

There have been few studies on other medication, apart from psychotropic drugs. High-dose corticosteroid treatment during pregnancy was associated with anxiety related disorders in offspring in a large birth Danish cohort, even after controlling for siblings (Laugesen et al., 2022). Antenatal maternal corticosteroid therapy has been associated with an increased risk of generalized anxiety disorder and generalized social phobia in offspring with extremely low birth weight (Van Lieshout et al., 2015). Prenatal exposure to antibiotics was associated with anxiety disorders in Finnish sample of children, adolescents and young adults (Lavebratt et

al., 2019), and with combined mood and anxiety disorders in a Canadian register-based study of children (Delara et al., 2021).

Maternal smoking during pregnancy is relatively common, although it has decreased in Finland in recent years. In 2019, around 11% of women in early pregnancy smoked (Kiuru et al., 2020). Smoking during pregnancy is more common among teenagers and young women (Kiuru et al., 2020; Rumrich et al., 2019). It may cause foetal growth restriction and alterations in brain structure and functions (Ekblad et al., 2015). Strong associations have been observed between maternal smoking and externalizing problems in offspring, but the associations with internalizing symptoms have been more controversial and weaker (Tien et al., 2020). A meta-analysis found a slightly increased risk of mood disorders (Duko et al., 2020). Not many studies were found that focused on maternal smoking and anxiety disorders. An increased risk was found for generalized anxiety disorders (Corrêa et al., 2022), but with no other significant associations among children and adolescents (Hill et al., 2000; Hirshfeld-Becker et al., 2004; Meier et al., 2017; Sarala et al., 2022). Meier et al. (2017) observed an increased risk from maternal smoking, but sibling analyses indicated that the association was explained by shared familial factors. The significant association that Sarala et al. (2022) found between maternal smoking during pregnancy and anxiety disorders in adult offspring disappeared when the authors controlled for offspring substance use, socio-demographics and parental psychopathology.

Maternal alcohol use during pregnancy may cause foetal alcohol spectrum disorder, which is characterized by various physical and neurological defects (Vorgias & Bernstein, 2021). In rodents, even peri-conceptional alcohol exposure was associated with anxious behaviour and alterations in hippocampal gene expression (Lucia et al., 2019). In humans, pre-pregnancy alcohol exposure has been associated with behavioural issues in toddlers (Knudsen et al., 2014). A systematic review reported that two-thirds of the reviewed studies found an increased risk of offspring anxiety and depression after prenatal alcohol exposure. The other third did not report an association (Easey et al., 2019). Two studies have found a specific association between maternal alcohol use in pregnancy and increased risk of child and adolescent anxiety disorders (Fryer et al., 2007; Hill et al., 2000).

Different substances can understandably affect the development of the central nervous system (Ross et al., 2015) and increased externalising problems have been observed (Ross et al., 2015; Ruisch et al., 2018). In the United States, the increasing opioid problem has also been prevalent among pregnant mothers (Haight et al., 2018). Substance use often occurs together with mental health problems and domestic violence, and the more these problems co-occur, the more likely it is for the offspring to suffer from behavioural and emotional problems

(Whitaker et al., 2006). Only two studies were found that examined the associations between illegal drug use during pregnancy and offspring anxiety disorders. The sample sizes were small and unrepresentative. (Morrow et al., 2009; Owens & Hinshaw, 2013)

In addition to medication and substances, there are also other lifestyle factors that are potentially harmful for the development of the central nervous system and the increased risk of child mental disorders. A Danish birth cohort study found an association between high caffeine intake during pregnancy and any psychiatric problems and anxiety or depressive problems in offspring (Hvolgaard Mikkelsen et al., 2017). However, two mother-child cohorts, from Netherlands and the USA, did not find any associations between caffeine exposure and child emotional or behavioural problems (Klebanoff & Keim, 2015; Loomans et al., 2012).

The quality of a pregnant woman's diet can also have impact on foetal development. Different nutritional habits have been associated with offspring mental health. Prenatal maternal consumption of unhealthy food has been associated with externalizing and internalizing behaviour in offspring (Jacka et al., 2013). High maternal blood concentrations of omega-3-fatty acid during pregnancy have been associated with fewer emotional symptoms in five-year-old children (Loomans et al., 2014). Low serum B12-vitamin levels around 12 weeks of gestation have been associated with excessive infant crying (Goedhart et al., 2011). Low maternal vitamin-D levels during pregnancy have been associated with offspring ADHD (Sucksdorff et al., 2021). Studies examining maternal diet and anxiety disorders in offspring have not been conducted so far to the best of this author's knowledge.

2.5.3 Maternal somatic problems during pregnancy

- Different somatic problems are highly common among pregnant women and they may impact on foetal neurodevelopment in various ways.
- Infertility, polycystic ovary syndrome, obesity and high blood pressure have been associated with anxiety disorders in offspring in some studies.

Different somatic problems and conditions are common among pregnant women. They impact foetal development through various pathways, such as hormonal changes, inflammation and hypoxemia. Studies for anxiety disorders in offspring exist, but are relatively scarce.

Infertility problems are common, yet associations with anxiety disorders in offspring have rarely been studied. A Finnish register-based study found that maternal polycystic ovary syndrome and non-ovulatory infertility problems were both associated with an increased risk of anxiety disorders in offspring (Chen et al., 2020). An older cohort study found no significant associations with infertility or infertility treatments and offspring, mother or teacher reported emotional symptomology (Zhu et al., 2011). Polycystic ovary syndrome has been associated with offspring neuropsychiatric disorders (Cesta et al., 2020; Kosidou et al., 2016; Kosidou et al., 2017). The mechanism has been explained by prenatal androgen exposure, independent from familial confounding. The risk was higher for girls, even when they were compared to cousins with shared familial factors (Cesta et al., 2020).

Hirshfeld-Becker et al. (2004) studied a wide range of maternal pregnancy problems and anxiety disorders in offspring. They also combined some of the problems, such as 'maternal physical illness during pregnancy' or 'multiple pregnancy problems', which were both associated with an increased risk of anxiety disorders in offspring (Hirshfeld-Becker et al., 2004). Similarly, some studies found that combined pregnancy problems were associated with overanxious disorder (Cohen et al., 1989), but not with separation anxiety disorder (Lavallee et al., 2011).

Maternal obesity during pregnancy is increasingly common in Finland (Teramo et al., 2018). In 2019, 42% of pregnant women were overweight and 17% were obese (Kiuru et al., 2020). Maternal high body mass index (BMI) has been associated with multiple metabolic complications and inflammation during pregnancy (Huda et al., 2010). Associations between maternal obesity and several neurocognitive and psychiatric disorders in offspring have been reported (Kong et al., 2018; Kong, Chen, et al., 2020; Kong, Nilsson, et al., 2020). Maternal obesity has been associated with offspring ADHD, intellectual disability, cerebral palsy, autism spectrum disorders and psychotic disorders (Edlow, 2018; Kong et al., 2018; Kong, Chen, et al., 2020; Kong, Nilsson, et al., 2020). However, the causality in these findings is unclear, as it might be the mother's inflammatory status that is affecting the developing foetus or shared genes or other lifestyle factors (Edlow, 2018; Kong, Chen, et al., 2020; Li et al., 2021).

Maternal obesity has been also found to increase the risk of anxiety disorders in offspring (Chen et al., 2020; Gong et al., 2022; Kong, Nilsson, et al., 2020). Obesity increases the prevalence of other maternal somatic problems, such as maternal diabetes and hypertension (Kiuru et al., 2020), which could further increase the offspring's risk of adverse outcomes. Obese women have also an increased risk of antenatal and postnatal depression and antenatal anxiety (Molyneaux et al., 2014).

Hypertension is a common comorbidity with obesity, but hypertensive disorders during pregnancy may also occur without obesity. Hypertensive disorders during pregnancy include chronic hypertension, gestational hypertension, mild, moderate or severe pre-eclampsia and eclampsia. They also include HELLP syndrome, named after the findings: haemolysis, elevated liver enzyme levels, and low platelet levels. Prevalence estimates vary greatly across the world. In Finland, 6–7% pregnant women have gestational hypertension and 2–3% have pre-eclampsia (Laivuori et al., 2021). Hypertensive disorders are thought to impact the developing foetus in various ways. Hypertension in the mother leads to increases in cortisol levels, it disrupts the oxygen supply to the foetus and it increases oxidative stress (Causevic & Mohaupt, 2007; Moisiadis & Matthews, 2014; Sinha & Dabla, 2015; Wang et al., 2009). Hypertension in pregnancy has been observed to hinder the invasion of uterine spiral arteries into the placental trophoblast, which decreases placental perfusion and impairs oxygen supply (Lyall et al., 2013). Decreased blood flow may also result in oxidative stress, which increases the amount of free oxygen radicals (Betteridge, 2000). Brain tissue has been observed to be especially sensitive to oxygen radicals (Halliwell, 2006).

The effects of maternal hypertension on somatic problems in offspring have been well acknowledged by various studies. There is evidence for increased risk of offspring hypertension, metabolic and immunological problems (Ferreira et al., 2009; Pinheiro et al., 2016), but also for neurological and neuropsychiatric conditions, such as ADHD, autism spectrum disorders and behavioural and emotional problems (Burnett et al., 2011; Dachew et al., 2018, 2020; Getahun et al., 2013; Lahti-Pulkkinen et al., 2020). Associations for anxiety disorders in offspring have also been observed, although the findings have been inconsistent (Dachew et al., 2019; Hirshfeld-Becker et al., 2004; Kingston et al., 2015; Lahti-Pulkkinen et al., 2020). Two of these studies found an increased risk of anxiety disorders (Dachew et al., 2019; Hirshfeld-Becker et al., 2004), but two did not (Kingston et al., 2015; Lahti-Pulkkinen et al., 2020).

Common metabolic disorders during pregnancy include obesity and hypertension, as previously discussed, and diabetes mellitus. Type 1 diabetes has been more common in Finland than elsewhere in the world (DIAMOND, 2006), although the prevalence has decreased in recent years (Parviainen et al., 2020). The incidence rates for gestational diabetes and type 2 diabetes are increasing (Ferrara, 2007; Zhou et al., 2016) and both are very prevalent among pregnant women. Gestational diabetes was diagnosed in 19% of women who gave birth in Finland in 2019 (Kiuru et al., 2020). Type 2 diabetes mellitus and gestational diabetes are highly comorbid with obesity. Pregestational diabetes combined with obesity has been associated with several neuropsychiatric outcomes, especially ADHD and autism spectrum disorders (Kong et al., 2018; Kong, Chen, et al., 2020; Kong,

Nilsson, et al., 2020). Any type of diabetes was not associated with neurodevelopmental disorders without obesity, but diabetic status further increased the risk for some disorders (Kong et al., 2018; Kong, Nilsson, et al., 2020). The results have been similar for anxiety disorders: associations have been found between diabetes and anxiety disorders in offspring, but these associations were only significant when there was comorbid overweight or obesity (Kong, Nilsson, et al., 2020). Another register-based study did not find an association between diabetes and child anxiety disorders (Kingston et al., 2015). One study used diabetes as a confounder, but was not associated with child and adolescent anxiety disorders in the multivariate analysis (Dachew et al., 2019).

Inflammation plays a significant role in metabolic diseases (De Candia et al., 2019; Gregor & Hotamisligil, 2011). Type 2 diabetes is also recognized as an autoimmune disease (De Candia et al., 2019). Other common autoimmune problems during pregnancy are thyroid problems and the most common in hypothyroidism, which is prevalent in 0.5% of pregnancies (Stagnaro-Green et al., 2011), and subclinical hypothyroidism, which is prevalent in 2–3% of pregnancies (Alexander et al., 2017). Hypothyroidism during pregnancy may lead to miscarriage, preterm birth, or foetal growth restriction (Carney et al., 2014; Tong et al., 2016). Furthermore, thyroid hormones are essential for foetal brain development, and that development is likely to be impaired if hypothyroidism is left untreated (Patel et al., 2011). Thyroid problems during pregnancy have been associated with psychiatric outcomes in offspring, such as schizophrenia, ADHD, oppositional-defiant-disorder and conduct disorders (Ghassabian et al., 2012; Gyllenberg et al., 2016; Young et al., 2020). In addition, Young et al. (2020) found an association with social anxiety disorder, but not with other specific anxiety disorders.

The immunological responses in metabolic and autoimmune diseases could serve as pathways to psychopathology (Jeppesen & Benros, 2019; Raison et al., 2006). Maternal inflammation during pregnancy has been associated with child internalizing symptoms (Giollabhui et al., 2019). Immunology could also mediate the impact of maternal infections and developmental changes in children. Animal studies have observed that maternal infections were associated with the development of the central nervous system in offspring (Boksa, 2010). In humans, associations have been found between prenatal and perinatal infections and psychotic disorders (Brown & Patterson, 2011; Davies et al., 2020) and depressive symptoms in offspring (Simanek & Meier, 2015). Maternal infections and anxiety disorders in offspring have not been studied much. An association was found between maternal infections and anxiety disorders in offspring in a cohort study by Hirshfeld-Becker et al. (2004). Furthermore, mother-reported vaginal infections or

vaginal discharge were associated with increased risk of youth PTSD and social phobia (Betts et al., 2015).

Studies on other obstetrical issues have been scarce. Vaginal bleeding during pregnancy was associated with anxiety disorders in offspring in one study (Hirshfeld-Becker et al., 2004), but not in another one (Kingston et al., 2015). Previous miscarriages or previous experience of giving birth to a stillborn baby were associated with anxiety disorders in offspring in one study (Allen et al., 1998). The role that oxytocin play in mental well-being is increasingly being studied. One paper reported that elevated third trimester oxytocin-levels were associated with childhood emotional disorders, but this topic needs to be explored further (Galbally et al., 2020).

2.5.4 Gestational age and weight for gestational age at birth

- There has been research on gestational age, birth weight and weight for gestational age as risk factors for various psychiatric outcomes in offspring.
- Preterm birth has been associated with anxiety disorders in offspring in some studies, but the associations have only been significant for children and adolescents born late preterm and early term.
- Low birth weight and small for gestational age have not been associated with anxiety disorders in children or adolescents in previous studies, but associations have been found among older offspring or when broader outcomes were included.

Term birth means that a child is born at 37–42 weeks of gestation, as this is regarded as a normal duration for a pregnancy. Less than 37 weeks of gestation is regarded as a preterm birth. The WHO (WHO, 2018) divides preterm birth into five categories and these are described in Table 5.

Birth weight has been the more traditional way of measuring foetal growth, but it is noteworthy that it does not consider gestational age in its definition. Therefore, low birth weight may indicate either preterm birth of an appropriately grown infant or full-term birth of a poorly grown infant. The WHO definition for low birth weight is less than 2500g (WHO, 2022). Low birth weight can be further categorized as seen in Table 5.

Foetal growth restriction means limited foetal growth in utero for various reasons. Weight for gestational age (WGA), describes new-born weight adjusted

for the gestational weeks and is therefore a valid measurement for foetal growth in utero. WGA is defined in Finland using the standard deviation (SD) units: <-2SD is small for gestational age (SGA), -2SD to +2SD appropriate for gestational age (AGA) and >+2SD is large for gestational age (LGA).

Table 5. Categories for prematurity and birth weight by WHO (WHO, 2018; WHO, 2022).

DEFINITION OF THE TERM OF BIRTH	**GESTATIONAL WEEKS**
EXTREMELY PRETERM	< 28
VERY PRETERM	28 to 32
MODERATE TO LATE PRETERM	32 to 37
TERM	37 to 42
POSTTERM	>42
DEFITION OF LOW BIRTH WEIGHT	BIRTH WEIGHT IN GRAMS
EXTREMELY LOW BIRTH WEIGHT	< 1000
VERY LOW BIRTH WEIGHT	< 1500
LOW BIRTH WEIGHT	< 2500

2.5.4.1 Preterm birth

In Finland, 5–6% of children are born preterm (Kiuru & Gissler, 2019; Kiuru et al., 2020), but the prevalence is notably higher in developing countries and the mean worldwide estimate is 10.6% (Chawanpaiboon et al., 2019). Preterm birth has been associated with later somatic problems, such as metabolic disorders, as well as with neurodevelopmental and mental health problems (Saigal & Doyle, 2008). As early as in adolescence preterm-born individuals have a higher risk of chronic multimorbidity (Heikkilä et al., 2021). Brain development is rapid during the last weeks of pregnancy and this means that the preterm brain is extremely vulnerable to disturbances (Volpe, 2009). Preterm birth is commonly accompanied by hypoxia, which may delay neural maturation (Salmaso et al., 2014). Preterm-born individuals often encounter abnormal environments, both prenatally and postnatally, and multiple mechanisms leading to developmental changes can occur at different perinatal stages (Vogel et al., 2018).

Preterm birth has been shown to be a risk factor for later psychiatric disorders, such as schizophrenia (Abel et al., 2010), eating disorders (Larsen et al., 2021). ADHD (Nosarti et al., 2012; Sucksdorff et al., 2015), depression (Upadhyaya et al.,

2021) and reactive attachment disorder (Upadhyaya et al., 2020). Anxiety disorder studies have been relatively small cohort studies (less than 100 cases) (Burnett et al., 2014; Jaekel et al., 2018; Johnson et al., 2010; Morris et al., 2021; Rogers et al., 2013; Treyvaud et al., 2013). Only one of those small studies found an increased risk of anxiety disorders among children born late preterm (Rogers et al., 2013). Large register-based studies provide more reliable knowledge on these associations, as sample sizes are big and perinatal events are available from registers, which excludes memory bias. The register studies that have examined preterm birth and anxiety disorders are described in Table 6.

Seven register studies were found that examined preterm birth and anxiety disorders (Abel et al., 2010; Guhn et al., 2020; Kingston et al., 2015; Lahti et al., 2015; Larsen et al., 2021; Monfils Gustafsson et al., 2009; Xia et al., 2021), but only two of them focused on children and adolescents (Guhn et al., 2020; Kingston et al., 2015). The other study comprised 7,800 children and adolescents with anxiety disorders, and reported that being born late preterm or early term were risk factors for anxiety disorders (Guhn et al., 2020). The other study of 590 children as young as five years of age found that preterm birth decreased the risk (Kingston et al., 2015). The other five register studies focused on mixed age groups and broader diagnostic outcomes and produced contradictory results (Abel et al., 2010; Lahti et al., 2015; Larsen et al., 2021; Monfils Gustafsson et al., 2009; Xia et al., 2021).

2.5.4.2 Weight for gestational age

In Finland, the rate for newborn infants with low birth weight has been consistent, at approximately 4.2% (Kiuru et al., 2020). Low birth weight has been associated with neuropsychiatric outcomes, mood and anxiety disorders in mixed age groups according to a recent meta-analysis (Anderson, P. J. et al., 2021). One of the previously mentioned register studies also studied birth weight independent of gestational age, and found a linear association with anxiety-related disorders among an adult population (Abel et al., 2010). However, the findings for child and adolescent anxiety disorders have been modest. Smaller cohort studies did not find associations between low or very low birth weight and child and adolescent anxiety disorders (Breslau & Chilcoat, 2000; Elgen et al., 2013; Indredavik et al., 2004; Nomura et al., 2007). One small cohort found an association between extremely low birth weight and an increased risk of generalized anxiety disorder (Botting et al., 1997).

Weight for gestational age is a more suitable definition when studying poor foetal growth. Being born SGA indicates foetal growth restriction, which can result from placental, foetal, maternal or genetic factors (Sharma et al., 2016). It is commonly due to insufficient functioning of the placenta, which leads to poor

transition of nutrients and hypoxemia. This could lead to neurodevelopmental interference (Nardozza et al., 2017). Being born SGA has various somatic consequences (Nardozza et al., 2017) and it has been associated with altered brain development (Dudink et al., 2022). In addition, several studies have found associations with later psychiatric disorders (Abel et al., 2010; Larsen et al., 2021; Monfils Gustafsson et al., 2009).

The findings for child and adolescent anxiety disorders have been negligible in both smaller cohorts (Indredavik et al., 2004) and larger register-studies (Guhn et al., 2020; Kingston et al., 2015). However, associations have been made between being born SGA and later anxiety related disorders in studies with mixed age groups and broader classifications of outcome diagnosis (Abel et al., 2010; Larsen et al., 2021; Monfils Gustafsson et al., 2009). The register studies on SGA and anxiety disorders are shown in Table 6.

Table 6. The register studies examining preterm, birth, weight for gestational age and birth weight.

STUDY *COUNTRY*	SAMPLE SIZE *ANXIETY DISORDER SAMPLE SIZE* AGE RANGE	EXPOSURES	OUTCOME	CONFOUNDERS	RESULTS FOR ANXIETY DISORDERS
ABEL ET AL., 2010 ***SWEDEN AND DENMARK***	1.49 million *19,346* adults	BW, GA, WGA	ICD-10 diagnoses of our interest F40–F48.	Maternal psychiatric diagnoses, parental social class, employment status, occupational class	**Significant linear finding with birth weight and anxiety related disorders, the lower the weight, the higher the odds. BW 500-1499g: OR 1.59 (95% CI 1.30–1.94); SGA: OR, 1.32 (95%CI, 1.20–1.46); GA less than 37 weeks: OR 1.40 (95% CI 1.27–1.54).**
GUHN ET AL., 2020 ***CANADA***	89,404 *7,867* 5 to 15 yr.	Multiple exposures studied, of our interest GA, WGA	ICD-10 F40–F43.	All the exposures were studied in the same multivariate model: sex, birth type, birth weight, gestational age, Apgar score, maternal age, immigrant status, marital status, maternal socioeconomic status.	**Late preterm birth OR 1.12 (95% CI 1.00–1.25); Early term birth OR 1.06 (95% CI 1.00–1.13).** Early preterm and preterm birth NS; SGA and LGA NS.
KINGSTON ET AL., 2015 ***CANADA***	18,836 *591* ≤5	Multiple exposures studied, of our interest: GA and WGA.	ICD-10 F40–F43, F93 or prescription of medication.	All the exposures were studied in the same multivariate model: maternal age, education, income, relationship status, parity, type of delivery, antepartum hemorrhage, social isolation, relationship distress, psychological distress, diabetes, hypertension, substance use, infant sex, Apgar score, gestational age, small for gestational age, breastfeeding initiation.	**Preterm birth OR 0.67 (95% CI 0.45–0.999).** SGA NS.

LAHTI ET AL., 2015 ***FINLAND***	12,597 *318 (159 men, 159 women)* adults	GA, WGA	ICD-10 diagnoses of our interest F40–F48.	Sex, year of birth, socioeconomic position in childhood, and mothers' marital status at childbirth.	**All subjects: GA more than 42 weeks: HR 1.41 (95% CI 1.02–1.96). Men: more than 42 weeks: HR 1.60 (95% CI 1.02–2.52).** Women NS. Preterm birth NS; SGA and LGA NS.
LARSEN ET AL., 2021 ***DENMARK***	1,167, 043 *15,205* 6 to 27	Multiple exposures studied, of our interest: GA, WGA	ICD-10 diagnoses of our interest: F40, F41.	Sex, age, calendar-time, and maternal history of the same psychiatric disorder	**Preterm birth of <33 weeks HR 1.32 (95% CI 1.15–1.51); Post term birth ≥42 weeks HR 0.93 (95% CI 0.88–0.99); SGA HR 1.25 (95% CI 1.16–1.35).**
MONFILS GUSTAFSSON ET AL. 2009 ***SWEDEN***	304,275 *1,251 (419 boys, 832 girls)* 12 to 23	GA, WGA	Hospitalization with a diagnosis of anxiety or adjustment disorders, ICD-9 300A, 300C, 300D, 300W, 300X, 308, 309.	Medical diagnoses related to pregnancy or delivery (hypertensive disease, diabetes, anaemia, bleeding, instrumental deliveries, birth trauma, asphyxia, Apgar scores and neonatal jaundice) Maternal age, parity, parental education, maternal marital status, parental country of origin.	**Boys at term SGA vs. AGA: OR 1.70 (95% CI 1.18–2.45) Girls at term SGA vs AGA: OR 1.49 (95% CI 1.14–1.94)** Preterm birth vs term NS.
XIA ET AL., 2021 ***DENMARK***	2.3 million *Unknown (prevalence in total 46.9/1000)* Adults, a separate analysis for those < 22y.	GA	ICD-10 diagnoses of our interest F40–F48.	Sex, calendar year of birth, maternal age at delivery, maternal country of origin, maternal education level, and parental history of mental illness.	**Preterm birth was in linear association with anxiety related disorders. Very preterm associated with an increased incidence ratio for anxiety related disorders among <22y. olds: IRR 1.24 (95% CI 1.12–1.38)**

In results the bolded values are significant results. AGA=appropriate for gestational age; BW=birth weight; CI=confidence interval; GA=gestational age; HR=hazard ratio; IRR=incidence rate ratio; LGA=large for gestational age; NS=not significant; OR=odds ratio; SGA=small for gestational age; WGA=weight for gestational age.

2.5.5 Delivery and birth related factors

- Caesarean section has been associated with psychological development in offspring.
- Previous studies have also found associations between caesarean section and anxiety disorders in offspring.
- Birth is often accompanied by different perinatal adversities, which could have an impact on the neurodevelopment of the child.
- Only a few studies have focused on links between Apgar scores or neonatal monitoring and anxiety disorders and other perinatal adversities have been studied even less.

2.5.5.1 Birth type

There are multiple factors associated with delivery and birth, that might contribute the development of a child. The type of birth is the first to begin with. There were 45 870 births in Finland in 2019 and the birth rate has been declining since 2011. Caesarean sections accounted for 17.5% of deliveries in 2019, which was the highest rate ever recorded in Finland, although the rate has been somewhat stable at 16–17% during the past 20 years. Only 5.1% of the caesarean sections were emergency sections, which means that planned caesarean sections are common. Other assisted deliveries have increased as well, such as vacuum assisted deliveries and induced deliveries. The use of epidural anaesthesia has also increased. (Kiuru et al., 2020)

Birth by caesarean section may be accompanied by perinatal adversities, increased stress, infections, exposure to antibiotics and immunological differences due to altered microbiome exposure (Lobel & DeLuca, 2007; Mylonas & Friese, 2015; Wampach et al., 2018; Yassour et al., 2016). These are all possible mechanisms that cause alterations in a child's neurodevelopment and behaviour. Birth by caesarean section has been associated with a higher risk of a variety of neuropsychiatric or psychiatric disorders (Chudal et al., 2014; Larsen et al., 2021; Polo-Kantola et al., 2014; Sucksdorff et al., 2018; Zhang et al., 2019), although some studies have stated that the association for neuropsychiatric disorders could be explained by familial confounding (Curran et al., 2015, 2016; Zhang et al., 2021).

Five earlier register-based studies were identified that examined caesarean section and later child and adolescent anxiety disorders (Chen et al., 2020; Guhn et al., 2020; Kingston et al., 2015; Larsen et al., 2021; Zhang et al., 2021). Four of these five studies observed an increased risk of anxiety disorders (Chen et al., 2020; Guhn et al., 2020; Larsen et al., 2021; Zhang et al., 2021), although adjusting for specific indications for caesarean section made the associations disappear for both planned and unplanned caesarean sections in one study (Zhang et al., 2021). Furthermore, one study did not find any association (Kingston et al., 2015). Other delivery styles, such as forceps or breech deliveries, were not associated with anxiety disorders in offspring, according to one study (Guhn et al., 2020). The literature on register-based studies that have examined the associations between birth type and child and adolescent anxiety disorders are described in Table 7.

Table 7. Register studies on birth type and offspring anxiety disorders.

STUDY COUNTRY	SAMPLE SIZE ANXIETY DISORDER SAMPLE SIZE AGE RANGE	EXPOSURES	OUTCOME	CONFOUNDERS	RESULTS FOR ANXIETY DISORDERS
CHEN ET AL., 2020 ***FINLAND***	1,097,753 *24,746* 4 to 22	Polycystic ovary syndrome. Additional analyses included caesarean section.	ICD-10 F40–43 and F93	Maternal age, parity, immigrant status, marital status, smoking, maternal purchase of psychotropic drugs during pregnancy and maternal systemic inflammatory disease.	**No polycystic ovary syndrome and caesarean section HR 1.13 (95% CI 1.10–1.15).**
GUHN ET AL., 2020 ***CANADA***	89,404 *7,867* 5 to 15	Multiple exposures studied. The ones of our interest: caesarean section, forceps and breech deliveries.	ICD-10: F40–F43	All the exposures were studied in the same multivariate model: sex, birth type, birth weight, gestational age, Apgar score, maternal age, immigrant status, marital status, maternal socioeconomic status.	**Caesarean section OR 1.12 (95% CI 1.06–1.19).** Forceps and breech deliveries NS.
KINGSTON ET AL., 2015 ***CANADA***	18,836 *591* ≤5	Multiple exposures studied. The ones of our interest: caesarean section.	ICD-10 F40–F43, F93, prescription of medication.	All the exposures were studied in the same multivariate model: maternal age, education, income, relationship status, parity, type of delivery, antepartum hemorrhage, social isolation, relationship distress, psychological distress, diabetes, hypertension, substance use, infant sex, Apgar score, gestational age, small for gestational age, breastfeeding initiation.	Caesarean section NS.

LARSEN ET AL., 2021 ***DENMARK***	1,167, 043 *15,205* 6 to 27	Multiple exposures studied. The ones of our interest: caesarean section.	ICD-10 F40, F41	Sex, age, calendar-time, and maternal history of the same psychiatric disorder.	**Caesarean section HR 1.06 (95% CI 1.01–1.11).**
ZHANG ET AL., 2021 ***SWEDEN***	1,179, 341 *41,929* 6 to 23	Caesarean section	ICD-10 F40, F41, F43.	Model 2: sex, year of birth, gestational age, parental age, parity, maternal education, smoking, and maternal and paternal history of psychiatric disorders. Model 3: Further adjusted for maternal hypertension, diabetes, infections during pregnancy, foetal malpresentation, large for gestational age, polyhydramnios, oligohydramnios and preeclampsia. For planned caesarean section: further adjusted for pelvic disproportion. For unplanned caesarean section: further adjusted for pelvic disproportion, placental disorders, dystocia, failed induction, and foetal distress.	**Planned caesarean section Model 2 HR 1.10 (95% CI 1.05–1.16);** Model 3 HR 1.07 (95% CI 1.00–1.14). **Unplanned caesarean section Model 2 HR 1.08 (95% CI 1.03–1.13);** Model 3 HR 1.02 (95% CI 0.96–1.09).

In results the bolded values are significant results. CI=confidence interval; HR=hazard ratio; NS=not significant; OR=odds ratio.

There are numerous reasons for increases in assisted deliveries, including advanced maternal age. In 2019 15.2% of mothers giving birth were more than 35 years old (Kiuru et al., 2020). Maternal age was presented as a possible risk factor in 2.4.1. and the results of previous studies on maternal age can be seen in Table 3 and Table 8.

2.5.5.2 Birth outcomes

Perinatal adversities can occur before birth, at birth or postnatally after birth. This chapter focuses on infant related birth outcomes, which occur at the very first moments and days after birth.

Apgar score was developed in 1952 by an American physician named Virginia Apgar and it is a general well-being marker of newborn infants at one, five and 10 minutes of age (AAP, 2015). A low Apgar score indicates disturbances in colour, pulse, reflexes, muscle tone or respiratory function in a newborn infant. A low Apgar score at one-minute is a general descriptive value of a newborn infant's status and the five-minute Apgar score also measures the possible resuscitation outcome. (Watterberg et al., 2015)

Apgar score was not originally designed to be used for predicting neurological outcomes, but as it describes the status of newborn infant right after birth (Watterberg et al., 2015), its relationship with later psychiatric problems has been examined. Low Apgar score has previously been associated with neuropsychiatric disorders such as autism spectrum disorders (Polo-Kantola et al., 2014) and ADHD (Sucksdorff et al., 2018). Furthermore, a five-minute Apgar score of less than seven has been associated with an increased odds for anxiety disorders in offspring (Kingston et al., 2015), whereas a one-minute Apgar score has not (Guhn et al., 2020).

Low umbilical artery pH is a more accurate indicator of birth asphyxia (Vandenbussche et al., 1999) and umbilical artery pH is now routinely measured from newborn infants in Finland. It has been suggested that ischemia or hypoxia in utero are the mechanisms for altered neurodevelopment (Getahun et al., 2013). No studies could be found that examined newborn well-being with umbilical artery or venous pH and associations with later child or adolescent anxiety disorders.

Newborn infants are treated in a neonatal intensive care unit (NICU) if they are premature, or have infections or breathing problems. Therefore, NICU treatment can also be studied as a general well-being marker of infants. Being admitted to a NICU has been associated with adverse child developmental outcomes but maternal socio-demographic and mental health factors have also contributed to these associations (Grunberg et al., 2019). The association between NICU admissions and internalizing behaviour in toddlers was mediated by infant

dysregulation and depressive symptoms in mothers (Montirosso et al., 2018). Only small cohort studies have examined the effect of NICU treatment on anxiety disorders and they found associations between NICU treatment and childhood specific phobias (Chiorean et al., 2020) and separation anxiety (Chiorean et al., 2020; Karabel et al., 2012).

In addition to previously described birth outcome factors, a number of other factors have been studied with regard to child and adolescent anxiety disorders. Breathing problems or being born addicted to drugs have been associated with comorbid anxiety disorders in population with ADHD (Owens & Hinshaw, 2013). Perinatal human immunodeficiency virus (HIV) infections were not associated with anxiety disorders when subjects were compared to perinatally HIV-exposed uninfected adolescents (Elkington et al., 2016; Mellins et al., 2009, 2012). Interestingly, one study observed that perinatally HIV-infected individuals were less anxious than those infected later in life. This could be because those that were infected later presumably experienced more prejudice, stigma and multiple issues in their lives (Sherr et al., 2018). Perinatal adversities were associated with externalizing and internalizing disorders in children with low hair cortisol levels, which was interpreted possible alterations in their HPA systems (Fuchs et al., 2020).

Most of the perinatal factors that have been studied have been modest and so have the numbers of children or adolescents with anxiety disorders. Only three register-based studies could be found and those are described in Table 8.

Table 8. Register studies on birth outcomes and later anxiety disorders among children and adolescents.

STUDY *COUNTRY*	SAMPLE SIZE ANXIETY DISORDER SAMPLE SIZE AGE RANGE	EXPOSURES	OUTCOME	CONFOUNDERS	RESULTS FOR ANXIETY DISORDERS
GUHN ET AL., 2020 ***CANADA***	89,404 *7,867* 5 to 15	Multiple exposures studied. The ones of our interest: 1-min Apgar score and maternal age.	ICD-10 F40–F43	All the exposures were studied in the same multivariate model: sex, birth type, birth weight, gestational age, Apgar score, maternal age, immigrant status, marital status, maternal socioeconomic status.	**Advanced maternal age OR 1.14 to 1.41 depending on the category.** 1-min Apgar score NS.
KINGSTON ET AL., 2015 ***CANADA***	18,836 *591* ≤5	Multiple exposures studied. The ones of our interest: 5-min Apgar score, maternal age and initiation of breast feeding at the hospital.	ICD-10 F40–F43, F93, or prescription of medication.	All the exposures were studied in the same multivariate model: maternal age, education, income, relationship status, parity, type of delivery, antepartum hemorrhage, social isolation, relationship distress, psychological distress, diabetes, hypertension, substance use, infant sex, Apgar score, gestational age, small for gestational age, breastfeeding initiation.	**5-min Apgar score ≤ 7 OR 1.76 (95% CI 1.20–2.58); Maternal age < 20 at birth OR 0.66 (95% CI 0.43–0.97).** Initiation of breast feeding at the hospital NS.
LARSEN ET AL., 2021 ***DENMARK***	1,167,043 *15,205* 6 to 27	Multiple exposures studied. The ones of our interest: 5-min Apgar score, and maternal age.	ICD-10 F40, F41	Sex, age, calendar-time, and maternal history of the same psychiatric disorder.	**Young maternal age < 20y OR 1.26–1.71 depending on the category; Advanced maternal age OR 1.11 to 1.18 depending on the category; Young paternal age OR 1.30 to 1.66 depending on the category.** 5-min Apgar score NS.

In results the bolded values are significant results. CI=confidence interval; NS=not significant; OR=odds ratio.

2.6 Prenatal and perinatal risk factors for specific anxiety disorders

- There is still inadequate knowledge on how the aetiology of specific anxiety disorders differ from each other.
- Prenatal and perinatal risk factors have not been studied much for separate specific anxiety disorders and no register studies were found.

The knowledge on how the aetiology of specific anxiety disorders differ from each other is still inadequate. Anxiety disorders can be examined as an entity, comprising all the different specific and unspecific anxiety disorder diagnoses, or as separate, more specific anxiety disorders. Prenatal and perinatal risk factors are one source that can be used to examine possible differences in the aetiology of different anxiety disorders.

Prenatal and perinatal risk factors have not been studied much for specific anxiety disorders and no register-based studies exist to the best knowledge. The cohort and case-control studies have often been very small, with less than 20 subjects with certain specific anxiety disorder (Botting et al., 1997; Martini et al., 2010; Morrow et al., 2009). Some have even not reported the sample size for specific anxiety disorder group (Faltyn et al., 2021; Fryer et al., 2007; Hirshfeld-Becker et al., 2008; Young et al., 2020). In addition, many have examined a combination of pregnancy problems instead of any specific problems (Faltyn et al., 2021; Lavallee et al., 2011). The only study with a reasonable cohort size that reported associations between specific risk factors and specific anxiety disorders in childhood or adolescence, observed that NICU treatment increased the risk of childhood specific phobias and separation anxiety (Chiorean et al., 2020).

2.7 Summary and gaps in the literature

- The role of perinatal factors for anxiety disorders has remained poorly understood.
- Previous studies have mainly focused on broader outcomes and childhood onset disorder diagnostic codes have been often lacking.
- No register-based studies were found that examined prenatal or perinatal factors and specific anxiety disorders.

Anxiety disorders are common among children and adolescents. Time-trend studies of treated incidence have varied greatly and demonstrated certain limitations. These were diagnostic variance, including other disorders as well as anxiety disorders, only studying a narrow age group, or only studying the temporal change between two time points. All these methodological differences make comparing studies complicated and limit the generalization of the results. For example, changes could reflect fluctuations rather than solid trends when only two time points are compared.

The aetiology of anxiety disorders is complex, including genetic and environmental factors. Whereas child temperament, parental psychopathology, parenting styles and childhood adversities have been acknowledged as risk factors, the role of perinatal factors has been less understood. Previous findings have been greatly controversial and the studies described earlier have varied greatly regarding the study designs and the diagnostic categorization of anxiety disorders. Large sample sizes have been scarce. No previous literature review has been conducted on prenatal and perinatal risk factors for anxiety disorders.

Register studies on prenatal or perinatal risk factors child and adolescent anxiety disorders have been rare and childhood onset diagnostic codes have been mainly lacking. The sample sizes of children and adolescents with anxiety disorders have been moderate, even in register studies as all the bigger register studies have included adults in their samples. The knowledge on associations between gestational age or weight for gestational age and anxiety disorders remains unclear and they had not been studied in continuous models before. Although comorbidities are highly common among children with anxiety disorders, no studies have examined their impact on the associations between preterm birth, poor foetal growth and anxiety disorders. Caesarean section has been covered by few studies before, only one has studied planned and unplanned caesarean section separately (Zhang et al., 2021). No register studies were found that examined prenatal or perinatal factors and specific anxiety disorders.

3 Aims

The main aim of this thesis was to broaden the knowledge of different prenatal and perinatal risk factors for anxiety disorders among children and adolescents. The more detailed aims are listed below:

1) To review the existing literature of the prenatal and perinatal risk factors for anxiety disorders among children and adolescents (study I).
2) To provide an overview of the sample of Finnish Prenatal Study of Anxiety disorders (FIPS-Anx) by examining the treated incidence, time trends of treated incidence, common comorbidities, and the associations between socio-demographic factors and anxiety disorders in our sample (study II). The hypothesis was based on literature that showed that the treated incidence had increased and low SES increased the odds for anxiety disorders.
3) To examine the associations between preterm birth or poor foetal growth and anxiety disorders (study III). The aim was to study the specific anxiety disorders separately and to include the common comorbidities in the analyses. The hypothesis for this study was that preterm birth would increase the risk for anxiety disorders.
4) To examine the associations between other common perinatal factors and anxiety disorders, including birth type, umbilical pH, Apgar scores and neonatal hospitalization (study IV). The aim was also to study specific anxiety disorders separately.

4 Materials and Methods

4.1 Systematic review (study I)

The first study was a systematic review on prenatal and perinatal risk factors for child and adolescent anxiety disorders. It was conducted according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati et al., 2009). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO). The literature search was conducted by the two researchers, who shared first authorship, using the PubMed (Medline) and PsycInfo in October 2019. The search terms were optimised for each database following a consultation with a librarian. In addition, searches were carried out on Scopus and MedNar to cover the possible grey literature based on reviewer's request.

The inclusion criteria were as follows: peer-review journal paper published in English from the inception to 25 October 2019 and human studies that examined anxiety disorders among children and adolescents, up to 19 years of age. Experimental, genetic and qualitative studies and systematic reviews were excluded. Studies were also excluded if separate results could not be found for subjects under 19 years of age. We did not concentrate on OCD or PTSD and excluded studies if these disorders were their main focus.

Both authors conducted the search on their own, then cross-checked their findings. Title and abstract screening were performed by the two authors independently and duplicates were removed. Then full-text review was carried out by both authors independently. The aim of the full-text review was to assess, whether the paper fulfilled both the inclusion criteria and the quality assessment, which was carried out using tools from the Joanna Briggs Institute (JBI, 2019). A third opinion was obtained from the senior researchers if needed. Cohen's kappa was calculated for the interrater agreement rate. The data were extracted into a shared table, which included: author, year of publication, country, study design, sample size, age of the study participants, outcome variables, outcome measures and results. The data extraction was verified by the co-author.

4.2 Register-based studies (studies II-IV)

4.2.1 Study design

Studies II–IV were register-based nested case-controls studies that studied the same sample. The materials and methods are described here as an entity. A nested case-control design means that the cases have been identified and matched with controls within a birth cohort. The cohort was a nationwide birth cohort of individuals born alive from singleton pregnancies in Finland between 1 January 1992 and 31 December 2006. The cases were individuals diagnosed with an anxiety disorder by specialized health care services between 1998 and 2012. The cases and controls and all the exposures, confounders and outcome variables were obtained from three national registers: the Care Register for Health Care (THL, 2021), the Finnish Medical Birth Register (THL, 2017) and the Finnish Population Register Centre (DVV, 2022). The study design is described in Figure 2.

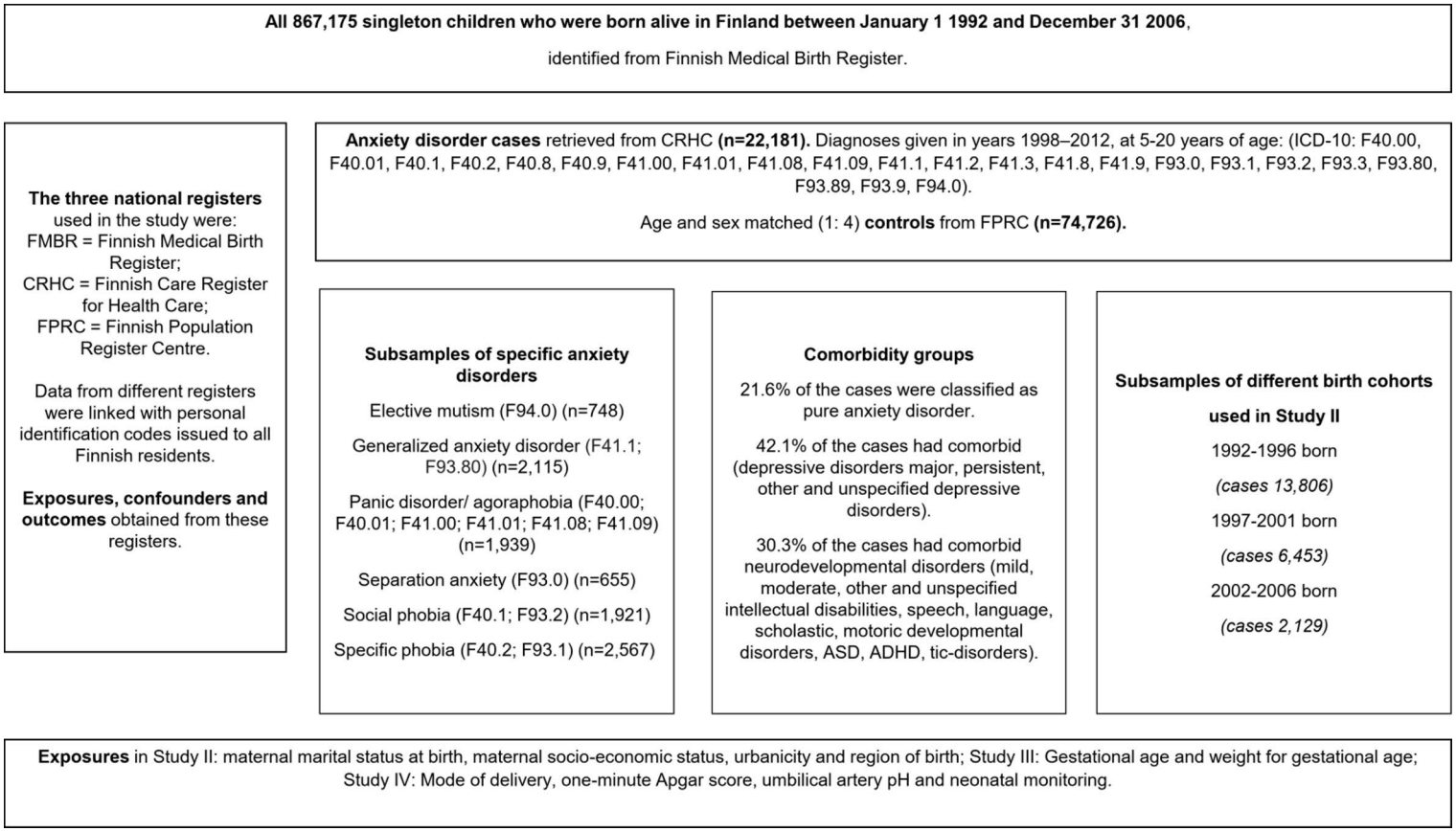

Figure 2. Study design. ADHD = Attention deficit hyperactivity disorder; ASD = Autism spectrum disorder; CRHC = the Finnish Care Register for Health Care; FMBR = the Finnish Medical Birth Register; FPRC = the Finnish Population Register Centre.

4.2.2 The national registers

Finland has high-quality national registers, which contain a wide range of data on Finnish residents. These registers are quite unique worldwide as not many countries have comparable nationwide register data. The data in the national registers can be linked with the personal identification code, that is issued for each Finnish resident (Figure 3).

Figure 3. The national registers. Modified from study III.

The Care Register for Health Care (THL, 2021) was formerly known as the Finnish Hospital Discharge Register, and has been computerized since 1969. It includes all the diagnoses given by specialized health care. From 1998 onwards it has included both inpatient and outpatient records. Before that only inpatient data were recorded. The diagnoses have been validated as ranging from fair to very good (Sund, 2012). ICD-10 has been used in Finland since 1996. Before that the Care Register contained ICD-9 and ICD-8 codes. The Care Register was used to obtain the case diagnoses for studies II–IV. In addition, the diagnoses of possible comorbidities, parental psychopathology and maternal prenatal and perinatal diagnoses were obtained from the Care Register.

The Finnish Medical Birth Register (THL, 2017) has existed since 1987. It contains data on maternal, foetal and new born treatment during prenatal, perinatal and postnatal periods. It includes all infants born from ≥22 weeks of gestation or weighting ≥500g (THL, 2021). However, over the years perinatal factors have been routinely measured and recorded to an increasing extent. This means that data from

the 1990s is not as well recorded as later data. More variables are now included in the registers and the data is also more comprehensive, which decreases the amount of missing data. In studies II–IV the variables identified from the Finnish Medical Birth Register included gestational age, weight for gestational age, number of previous births, maternal smoking during pregnancy, maternal diagnoses during pregnancy (verified by data from the Finnish Care Register for Health Care), maternal age, maternal SES and marital status, as well as birth type, Apgar-scores, umbilical artery pH and neonatal monitoring.

The Finnish Population Register Centre (DVV, 2022) contains information on Finnish-born individuals and Finnish residents. Data on paternal age, region of birth, urbanicity and maternal immigrant status were obtained from the Population Register for studies II–IV.

The register data were accessed and analysed by the statisticians and data managers based on the analysis plan and requests by the authors. The use of these national registers and the linkage of the information about the individuals was approved by the Data Protection Ombudsman. The Ethics Committee of the Hospital District of Southwest Finland provided ethical approval for the study, although no ethical approval is now required for register-based studies.

4.2.3 The sample

The sample was a nested case-control sample within a nationwide birth cohort of individuals born alive from singleton pregnancies. Originally the sample had been formed by gathering all singleton births between 1987–2012 with diagnoses of anxiety disorders, OCD or stress-related disorders and those cases had each been matched with four controls from the same risk-set. Studies II–IV used 1992–2006 birth cohort of cases with anxiety disorders. The whole birth cohort comprised 867,175 subjects and 22,388 cases were diagnosed with an anxiety disorder by specialized services between 1998–2012. Cases who had received a diagnosis before the year they turned six, with no subsequent diagnosis after that age, were excluded (n=88). The anxiety disorder diagnoses that were included are described in Table 9. OCD and stress-related disorders were not included in the anxiety disorder diagnoses due to the ideology of different aetiological processes, which is also supported by DSM-5 (APA, 2013).

The plan was for the sample to follow a nested case-control design and to pair each case with four age (±30 days) and sex matched controls. Controls were identified from the Population Register Centre. They fulfilled the age and sex matching criteria and had not received an anxiety disorder diagnosis during the 1992–2012 study period, or during an additional follow-up period until the end of 2016. In addition, the controls were free of OCD and stress-related diagnoses

(ICD-10 codes F42–F43) due to the sampling method described above. Cases and controls with severe or profound mental retardation were excluded (ICD-10 codes F72 and F73). Some controls from the original matching were excluded if they received an anxiety disorder diagnosis during the additional follow-up period of 2012–2016 or if relevant data were missing.

The number of cases and controls varied between studies II–IV depending on the comprehensiveness and accuracy of the data for these individuals. The number of cases varied from 22,181 (studies III and IV) to 22,388 (study II) and for the controls they ranged from 74,726 (studies III-IV) to 76,139 (study II).

Table 9. Anxiety disorders diagnoses by ICD-10.

ICD-10 DIAGNOSTIC CODE	NAME OF THE ANXIETY DISORDER	EXAMINED AS A SPECIFIC ANXIETY DISORDER
F40.0 (F40.00, F40.01)	Agoraphobia	Combined with panic disorder: F40.00, F40.01, F41.00, F41.01, F41.08, F41.09
F40.1	Social phobia	F40.1 and F93.2
F40.2	Specific phobias	F40.2 and F93.1
F40.8	Other phobic anxiety disorder	
F40.9	Phobic anxiety disorder, unspecified	
F41.0	Panic disorder	Combined with agoraphobia: F40.00, F40.01, F41.00, F41.01, F41.08, F41.09
F41.1	Generalized anxiety disorder	F41.1 and F93.80
F41.2	Mixed anxiety and depressive disorder	
F41.3	Other mixed anxiety disorders	
F41.8	Other specific anxiety disorders	
F41.9	Anxiety disorder, unspecified	
F93.0	Separation anxiety disorder of childhood	F93.0
F93.1	Phobic anxiety disorder of childhood	F40.2 and F93.1
F93.2	Social anxiety disorder of childhood	F40.1 and F93.2
F93.80	Generalized anxiety disorder of childhood	F41.1 and F93.80
F93.89	Other childhood emotional disorders	
F93.9	Childhood emotional disorder, unspecified	
F94.0	Elective mutism	F94.0

The samples in each study were further divided and these subdivisions are described in Figure 2. Study II examined cases from three consecutive birth cohorts (born in 1992–1996, 1997–2001, 2002–2006) and subgroups of specific anxiety disorders and psychiatric comorbidities from the oldest birth cohort born in 1992–1996. These comorbidities and their diagnostic codes are described in Table 10. Study III examined the subgroups of specific anxiety disorders: generalized anxiety disorder, panic disorder/agoraphobia, separation anxiety disorder, social phobia and specific phobias. It also examined the comorbidity groups: pure anxiety disorders, anxiety disorders with comorbid depression and anxiety disorders with comorbid neurodevelopmental disorders. The comorbidity groups were chosen based on the literature, which showed that preterm birth and poor foetal growth were associated with neurodevelopmental and depressive outcomes. These were also shown to be common comorbidities in our sample. These comorbidity groups and their diagnostic information can be seen in Table 11. Study IV separately examined specific anxiety disorders: elective mutism, generalized anxiety disorder, panic disorder/agoraphobia, separation anxiety disorder, social phobia and specific phobias.

Table 10. The psychiatric comorbidities that were examined in study II.

PSYCHIATRIC DIAGNOSIS	ICD-10 CODE
SCHIZOPHRENIA SPECTRUM DISORDERS	F20-F29
BIPOLAR DISORDERS	F30, F31
UNIPOLAR DEPRESSIVE DISORDERS	F32-F39
OCD	F42
STRESS-RELATED AND DISSOCIATIVE DISORDERS	F43, F44
SOMATOFORM DISORDERS	F45
EATING DISORDERS	F50
PERSONALITY AND HABIT-IMPULSE DISORDERS	F60-F63
SUBSTANCE ABUSE DISORDERS	F10-F19
AUTISM SPECTRUM DISORDERS	F84
ADHD	F90
INTELLECTUAL DISABILITY	F70, F71, F78, F79 (F72, F73 excl.)
OTHER CHILDHOOD EMOTIONAL DISORDERS	F94.1, F94.2
CONDUCT AND OPPOSITIONAL DISORDERS	F91-F92
TIC DISORDERS	F95
LEARNING AND COORDINATION DISORDERS	F80-F83

Table 11. Comorbidity groups that were examined in study III.

COMORBIDITY GROUP	INCLUSION AND EXCLUSION CRITERIA	ICD-10 CODES
PURE ANXIETY DISORDERS	Any anxiety disorder AND no other psychiatric disorders (except for other anxiety disorders)	F40, F41, F93, F94.0 AND no F10-F99, except for the codes above
COMORBID DEPRESSIVE DISORDERS GROUP	Any anxiety disorder AND any depressive disorder (major, persistent, other and unspecified depressive disorder)	F40, F41, F93, F94.0 AND F32-F39
COMORBID NEURODEVELOPMENTAL DISORDERS GROUP	Any anxiety disorder AND any neurodevelopmental disorder (mild, moderate, other and unspecified intellectual disability, speech, language, scholastic, motoric developmental disorder, ASD, ADHD, tic-disorder)	F40, F41, F93, F94.0 AND F70, F71, F78-F84, F90, F95

4.2.4 The exposure variables

Studies II–IV examined the associations between different prenatal and perinatal factors and child and adolescent anxiety disorders. Study II focused on socio-demographic risk factors, study III on preterm birth and poor foetal growth, and study IV on delivery mode and birth outcomes. The exposures and their categorizations are listed in Table 12.

There were four exposure variables in study II, which were maternal SES, maternal marital status, urbanicity and region of birth. All were measured at birth. Maternal SES and marital status were obtained from the Finnish Medical Birth Register, and urbanicity and region of birth were collected from the Finnish Population Register Centre. Maternal SES was divided into four categories: upper white collar (experts and managers), lower white collar (clerical workers), blue collar (manual workers), others (entrepreneurs, students, people who were unemployed and stay-at-home parents). We found that 6.5% of the cases and 5.1% of the controls were missing the data on maternal SES and a multiple imputation

method was used to address the missing data in the analyses. Maternal marital status at birth was dichotomized as single or married/ in a relationship. The missing data percentages were 11.1% in the cases and 7.4% in the controls, and multiple imputation was used. The region of birth was categorized as Southern, Northern, Western and Eastern Finland. Urbanicity was categorized as urban, semi-urban or rural, following the definitions used by Statistics Finland (Statistics Finland, 1989).

In study III there were two exposure variables: gestational age (GA) and weight for gestational age (WGA). They were obtained from the Birth Register. GA was categorized following the WHO categories: extremely to very preterm (less than 32 gestational weeks), moderate to late preterm (32-36 gestational weeks), term (37-41 gestational weeks as the reference category) and post term (42 gestational weeks or more) (WHO, 2018). In addition, we studied GA in weekly categories (week 40 was the reference category) and as a continuous variable. The use of continuous models has been suggested to be preferable when the variable is continuous by nature (Bennette & Vickers, 2012). We combined 23 and 24 weeks of gestation due to small number of infants born at those weeks of gestation. GA was confirmed with a first trimester ultrasound. WGA has been calculated using the national gender-specific birth weight distribution standards at a given gestational age (Sankilampi et al., 2013). It was divided into five categories: less than -2 SD, from -2SD to -1SD, from -1 SD to +1SD (reference category), from +1SD to +2SD and more than +2 SD. In addition, WGA was examined as a continuous variable. A total of 1,617 subjects were excluded because the information on GA or birth weight was not available (n=1,614), or the WGA was incorrectly recorded (>±10SD) (n=3).

In study IV, there were four exposure variables: birth type, the one-minute Apgar score, umbilical artery pH and neonatal monitoring. All these variables were obtained from the Birth Register. Birth type was divided into four categories, two vaginal birth categories and two caesarean section categories. These categories were spontaneous unassisted vaginal cephalic deliveries, other vaginal deliveries (induced, vacuum or forceps and breech), planned caesarean section and unplanned caesarean section (urgent, emergency or other). The one-minute Apgar score was dichotomized as ≥7 or <7. The umbilical artery pH was both dichotomized as ≥7.15 or <7.15, and treated as a continuous variable. Umbilical artery pH was only available for 43.1% of the sample in the Birth Register. Neonatal monitoring was carried out in a NICU or maternal postpartum ward and dichotomized as ‘yes’ or ‘no’.

Table 12. Exposure variables in studies II–IV.

EXPOSURE VARIABLE	DATA SOURCE	CATEGORIZATION
STUDY II		
MATERNAL SES	The Finnish Medical Birth Register	Upper white collar Lower white collar Blue collar Others
MATERNAL MARITAL STATUS AT BIRTH	The Finnish Medical Birth Register	Married or in a relationship Single
THE REGION OF BIRTH	The Finnish Population Register Centre	Southern Finland Northern Finland Western Finland Eastern Finland
URBANICITY	The Finnish Population Register Centre	Urban Semi-urban Rural
STUDY III		
GESTATIONAL AGE	The Finnish Medical Birth Register	Extremely to very preterm Moderate to late preterm Term Post term Weekly categorization Continuous
WEIGHT FOR GESTATIONAL AGE	The Finnish Medical Birth Register	Less than -2 SD From -2SD to -1SD From -1 SD to +1SD From +1SD to +2SD More than +2 SD Continuous
STUDY IV		
BIRTH TYPE	The Finnish Medical Birth Register	Vaginal spontaneous, unassisted Other vaginal Planned caesarean section Unplanned caesarean section
THE ONE-MINUTE APGAR SCORE	The Finnish Medical Birth Register	≥7 <7
UMBILICAL ARTERY PH	The Finnish Medical Birth Register	≥7.15 <7.15 Continuous
NEONATAL MONITORING	The Finnish Medical Birth Register	Yes No

4.2.5 The confounders

The covariates that were examined as possible confounders were all obtained from the Care Register, the Birth Register or the Population Register. They were originally chosen for each study based on existing literature and then their associations with exposures and outcomes were tested in order to include them in the study. Covariate testing was carried out on a number of variables, but not every variable was included in every study. These variables were maternal and paternal age at birth, maternal SES at birth, maternal marital status at birth, maternal immigration status, urbanicity, region of birth, number of previous births, the one-minute Apgar score, gestational age, weight for gestational age, maternal smoking during pregnancy, maternal substance abuse diagnoses, maternal other psychiatric diagnoses, and paternal psychiatric diagnoses. All the confounders are described in Table 13, as well as the data sources, categorizations and references for their associations with anxiety disorders.

Table 13. Confounders used in the studies II–IV, source of data, categorization and references for their associations with anxiety disorders.

COVARIATE	DATA SOURCE	USED AS A CONFOUNDER IN STUDY II, III, OR IV	USED AS AN EXPOSURE IN STUDY II, II OR IV	CATEGORIZATION	REFERENCES FOR THE ASSOCIATIONS WITH ANXIETY DISORDERS
MATERNAL AGE	Birth Register	III, IV		≤19 years 20-29 30-39 ≥40	Guhn et al., 2020; Kingston et al., 2015
PATERNAL AGE[A]	Population Register	III, IV		≤19 years 20-29 30-39 ≥40	Koskela et al., 2020 for selective mutism
URBANICITY	Population Register	III	II	Urban Semi-urban Rural	Helenius et al., 2014
MATERNAL SES	Birth Register	III, IV	II	Upper white collar Lower white collar Blue collar Others Missing	Guhn et al., 2020; Hyland et al., 2016
MATERNAL IMMIGRANT STATUS	Population Register	III		Born in Finland Not born in Finland	Guhn et al., 2020
MATERNAL MARITAL STATUS AT BIRTH	Birth Register	III	II	Married or in a relationship Single	Guhn et al., 2020, Hyland et al., 2016, Koskela et al., 2020 for selective mutism
MATERNAL SMOKING DURING PREGNANCY	Birth Register	III, IV		Yes No	Moylan et al., 2015 for internalising behaviours

MATERNAL SUBSTANCE ABUSE DURING PREGNANCY	Care Register and Birth Register	III, IV		Yes No	Clark et al., 2004; Fryer et al., 2007; Hill et al., 2000
MATERNAL PSYCHIATRIC DISORDERS	Care Register and Birth Register	III, IV		Yes No	Helenius et al., 2014; Lawrence et al., 2020 Koskela et al., 2020 for selective mutism
PATERNAL PSYCHIATRIC DISORDERS[A]	Care Register and Birth Register	III		Yes No	Helenius et al., 2014; Lawrence et al., 2020 Koskela et al., 2020 for selective mutism
NUMBER OF PREVIOUS BIRTHS	Birth Register	III, IV		0 ≥1	Carballo et al., 2013 for mental disorders
THE ONE-MINUTE APGAR SCORE	Birth Register	III	IV	<7 ≥7	Kingston et al., 2015 for five-minute Apgar score
GESTATIONAL AGE	Birth Register	IV	III	Extremely to very preterm Moderate to late preterm Term Post term	Guhn et al., 2020
WEIGHT FOR GESTATIONAL AGE	Birth Register	IV	III	Less than -2 SD From -2SD to -1SD From -1 SD to +1SD From +1SD to +2SD More than +2 SD	Abel et al., 2010; Monfils Gustafsson et al., 2015

[A]covariate was examined as potential confounder although no literature was found because it has been shown to associate with other mental health disorders.

Note, the variables were used as confounders only, if it was associated with both the exposure and the outcome in the covariate testing.

The paternal factors were missing (n=1,144), if the paternity of the subject was unknown.

Those that were missing data on gestational age or weight for gestational age were excluded from the sample in studies III and IV.

4.2.6 Statistical methods

The frequencies of cases, controls, exposures and possible confounders were calculated for each study (II–IV). Outcome frequencies were calculated for cases with regard to any anxiety disorder (studies II–IV), specific anxiety disorders (studies II–IV), separate birth cohorts (study II) and comorbidity groups (studies II–III).

The treated incidence and cumulative treated incidence were calculated in study II. The population at risk for the treated incidence comprised all living children in Finland at the end of year 2012. The yearly treated incidence was calculated as the number of individuals with certain ages in the birth cohort as the denominator and the number of incident cases for that age as the numerator. The yearly treated incidence of anxiety disorders was presented per 100 people at risk. The treated incidence was calculated for the whole study sample as well as for the three birth cohorts (Figure 2). The yearly cumulative treated incidence was calculated for the whole sample and for the three birth cohorts at 10, 15 and 20 years of age by using the Kaplan-Meier estimate. The cumulative treated incidence was one minus the estimated survival function. The cumulative treated incidence is presented with odds ratios (OR) and 95% confidence intervals (CI). Gender specific calculations were carried out. The log-rank test was used to find out if the gender differences in the incidence rates were statistically significant.

The possible confounders were tested before the multivariate model was constructed. The association between possible confounders and exposures within the controls were tested using Pearson's chi-square test. The associations between the possible confounders and anxiety disorders were tested with conditional logistic regression in the case-control model. If statistical significance ($p<0.05$) was obtained by both of these steps, the covariate was accepted as a confounder for the adjusted analyses. Conditional logistic regression was used in studies II–IV to examine the associations between the exposures and outcomes. Unadjusted and adjusted result odds ratios (OR) and 95% confidence intervals (CI) were calculated.

The missing data were addressed differently between the studies. In study II, multiple imputation was used to handle the missing data. In study III and IV, separate categories of missing data were used for maternal SES but complete data were used for the other confounders as the missing data was less than 5% of the sample. We examined whether there was multicollinearity between maternal SES, marital status and smoking in the anxiety data by using Spearman's correlation. We also examined whether there was clustering of the missing values of these three variables. A two-sided $p<0.05$ was considered statistically significant. The statistical analyses were carried out using Statistical Analysis Software (SAS) version 9.4.

5 Results

5.1 Systematic review

The literature search on PubMed and PsycInfo yielded 7,332 papers after the duplicates were removed. The preliminary screening identified 88 papers that were eligible for full-text screening. Another six papers were identified by searching the references of the included papers. Full-text screening yielded 34 studies, and after the quality appraisal there were 31 eligible studies that were reviewed. A flow diagram of the study selection process is shown in Figure 4. The inter-rater agreement rate for the selected studies was 97%, and Cohen's kappa was 0.79.

The 31 studies that were reviewed were published between 1998 and 2019 and originated from various countries. The USA was the most common country of origin. There were two case-control studies and 29 cohort studies, including three register-based studies. The sample sizes varied from 69 to 89,404 and the sample sizes for subjects with diagnosed anxiety disorders varied from four to 7,867. The diagnostic tools used to assess anxiety disorders varied greatly between the studies and the majority of the studies had used DSM-III/IV classification (n=27). The other four used the ICD-9/10 classifications. The prenatal and perinatal exposures had been obtained from official records in 18 studies, while the other 13 studies used questionnaires that were completed by mothers or other caregivers. Three of those studies collected the data during pregnancy and 10 studies collected the data retrospectively.

The studies reported findings on prenatal factors or factors related to birth outcomes. Overall, only a few exposures had been studied by more than one or two studies. Exposures that were examined by more than two studies were maternal blood pressure and smoking, preterm birth, weight for gestational age and birth weight. The findings mostly disagreed when there were multiple studies that had examined the same exposure.

The results are described among other literature in Chapter 2: Literature Review. Maternal somatic illnesses seemed to increase the risk of anxiety disorders except for diabetes. Around half of the studies that examined maternal mental health during pregnancy found that maternal perinatal mental health problems were associated with an increased prevalence of offspring anxiety disorders. Maternal

smoking during pregnancy was not associated with an increased risk in most of the studies. The results for gestational age, weight for gestational age, delivery modes and other birth outcomes can be seen in Table 14. This table describes the risk factor findings from the systematic literature review that were also examined in studies III–IV.

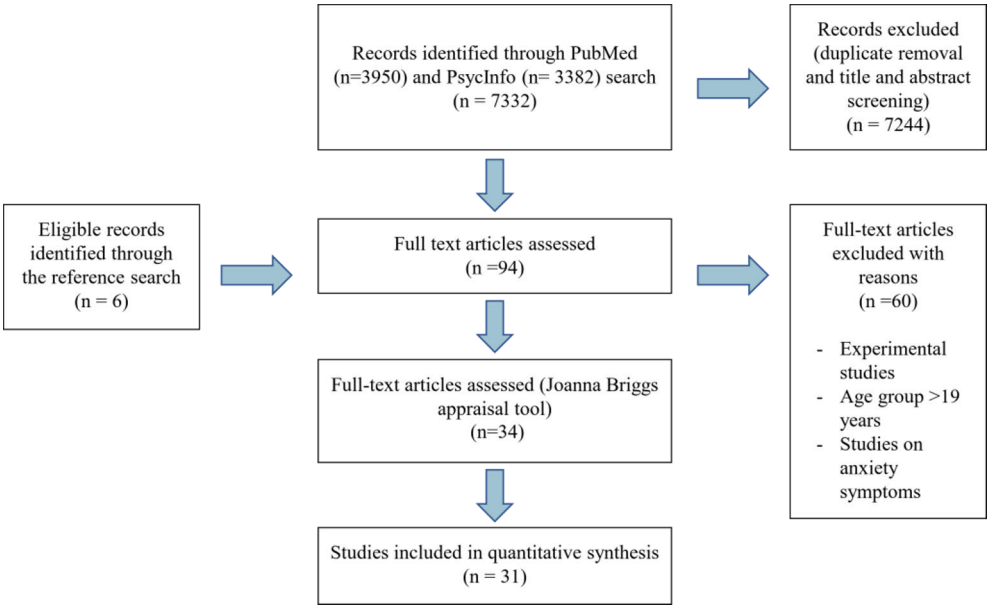

Figure 4. The PRISMA flow diagram of study selection in study I. Modified from the study I.

Table 14. The associations between prenatal and perinatal risk factors and anxiety disorders, a combination of the findings from the literature review (study I) and studies II–IV

RISK FACTOR	ADJUSTED OR AND (95% CI) FOR THE ASSOCIATION WITH ANXIETY DISORDERS	FINDINGS FROM THE SYSTEMATIC LITERATURE REVIEW	REFERENCES FOR FINDINGS OF THE SYSTEMATIC LITERATURE REVIEW
PRETERM BIRTH[B]		No association for extremely preterm/ extremely low birth weight.	Burnett et al., 2014
		No association for very preterm/ very low birth weight.	Jaekel et al., 2018
		No association for extremely preterm birth.	Johnson et al., 2010
		No association for very preterm birth.	Treyvaud et al., 2013
		No association for early preterm birth.	Guhn et al., 2020
		No association for post term birth.	Guhn et al., 2020
		Decreased risk for preterm birth.	Kingston et al., 2015
		Increased risk for late preterm birth.	Guhn et al., 2020
		Increased risk for late preterm birth.	Rogers et al., 2013
		Increased risk for early term birth.	Guhn et al., 2020
<32 GESTATIONAL WEEKS	**1.39 (1.11 to 1.75)**		
32-36	**1.13 (1.03 to 1.23)**		
37-41	Reference		
≥42	1.03 (0.95 to 1.12)		

WEIGHT FOR GESTATIONAL AGE[C]		No association. No association. No association.	Guhn et al., 2020 Indredavik et al., 2004 Kingston et al., 2015
<-2SD	**1.29 (1.17 to 1.42)**		
-2SD TO -1SD	**1.08 (1.03 to 1.14)**		
-1SD TO +1SD	Reference		
+1SD TO +2SD	0.98 (0.92 to 1.03)		
>+2SD	0.99 (0.90 to 1.09)		
BIRTH TYPE[D]		No association for forceps delivery. No association for breech delivery. No association for caesarean delivery. **Increased risk for caesarean delivery.**	Guhn et al., 2020 Guhn et al., 2020 Kingston et al., 2015 Guhn et al., 2020
VAGINAL SPONTANEOUS, UNASSISTED	Reference		
OTHER VAGINAL	1.04 (0.97 to 1.12)		
PLANNED CAESAREAN SECTION	1.06 (1.00 to 1.13)		
UNPLANNED CAESAREAN SECTION	**1.11 (1.04 to 1.18)**		
THE ONE-MINUTE APGAR SCORE[E]			
≥7	Reference		
<7	1.04 (0.97 to 1.13)	No association. **Increased risk.**	Guhn et al., 2020 Kingston et al., 2015
UMBILICAL ARTERY PH		NA	
≥7.15	Reference		
<7.15	**NA**		
NEONATAL MONITORING[E]		NA	
NO	Reference		
YES	1.02 (0.95 to 1.09)		

The bolded results represent statistically significant findings.

[A]adjusted with maternal SES and marital status, urbanicity and region of birth
[B] adjusted for maternal age, paternal age, maternal substance use diagnoses, maternal other psychiatric diagnoses, no. of previous births, maternal marital status, maternal SES, maternal smoking, Apgar-score, region of birth, maternal immigrant status.
[C] Adjusted for maternal age, paternal age, maternal substance use diagnoses, maternal other psychiatric diagnoses, paternal psychiatric diagnoses, no. of previous births, maternal marital status, maternal SES, maternal smoking, Apgar-score, region of birth, maternal immigrant status.
[D] adjusted for Apgar score, neonatal monitoring, maternal age, paternal age, number of previous deliveries, maternal psychiatric history, maternal smoking, maternal socioeconomic status, gestational age, weight for gestational age, maternal hypertensive disorders, maternal diabetes, maternal fear of giving birth.
[E] adjusted for Apgar score, neonatal monitoring, maternal age, paternal age, number of previous deliveries, maternal psychiatric history, maternal smoking, maternal socioeconomic status, gestational age, weight for gestational age.

5.2 Descriptive results of studies II-IV

There were 22,181 (studies III and IV) to 22,388 (study II) cases and 74,726 (studies III–IV) to 76,139 (study II) controls. The descriptive results reported here are from the sample used in studies III–IV, which contained 22,181 cases. Females represented 55.4% of the cases. The mean age at the time of an anxiety disorder diagnosis was 12.7 ±3.7 years (range 5–20 years). There were 88 cases that received anxiety disorder diagnosis only before six years of age and not after that. These cases were not included in the study, as detailed in the exclusion criteria. Unspecific anxiety disorders accounted for 75% of the case diagnoses. The sample sizes for specific anxiety disorders were: elective mutism (n=810), generalized anxiety disorder (n=2,115), panic disorder and/or agoraphobia (n=1,939), separation anxiety disorder (n=655), social phobia (n=1,921), and specific phobias (n=2,567). The mean (and SD) age in years for each specific anxiety disorder was 8.1 (3.1) for elective mutism; 12.2 (3.7) for generalized anxiety disorder; 15.3 (2.6) for panic disorder/agoraphobia; 9.8 (2.7) for separation anxiety disorder; 14.5 (3.1) for social phobia; 9.9 (3.0) for specific phobias. The age range was 5–20 years for all.

5.3 Time trends in treated incidence and cumulative treated incidence of anxiety disorders

The annual treated incidence was calculated for each age for the total sample and for both genders. Boys had more incident treated anxiety disorders at 6–12 years of age than girls but girls had more at the ages of 13–20 ($p<0.001$ for both). A steep increase in the treated incidence was seen in girls from 12–17 of age, but the

increase was somewhat stable for boys during at those ages. Figure 5 shows the treated incidence curves for the whole sample and for both genders.

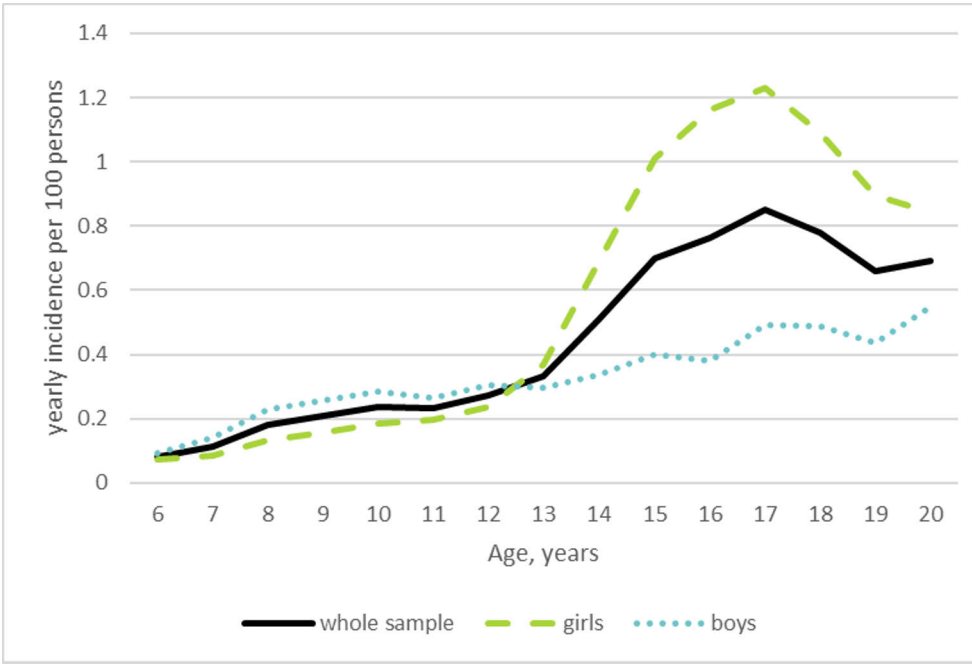

Figure 5. Treated incidence of anxiety disorders in the whole sample and for both genders.

The cumulative treated incidence curves are shown for the entire sample as well as for both genders in Figure 6. The cumulative treated incidence was also calculated between the three birth cohorts, which are described in detail in Table 15. The cumulative treated incidence rates were as follows. For the oldest birth cohort, born in 1992–1996, it was 5.7% (95% CI 5.60–5.82) by the age of 20 and 0.4% (95% CI 0.36–0.41) by the age of 10. For the birth cohort born in 1997–2001, it was 0.9% (95% CI 0.91–0.99) by the age of 10. For the youngest cohort, born in 2002–2006, it was 1.5% (95% CI 1.46–1.62) by the age of 10. There was a clear increase in the cumulative treated incidence rates between the cohorts, as shown in Figure 7. Similar trends were observed in both genders.

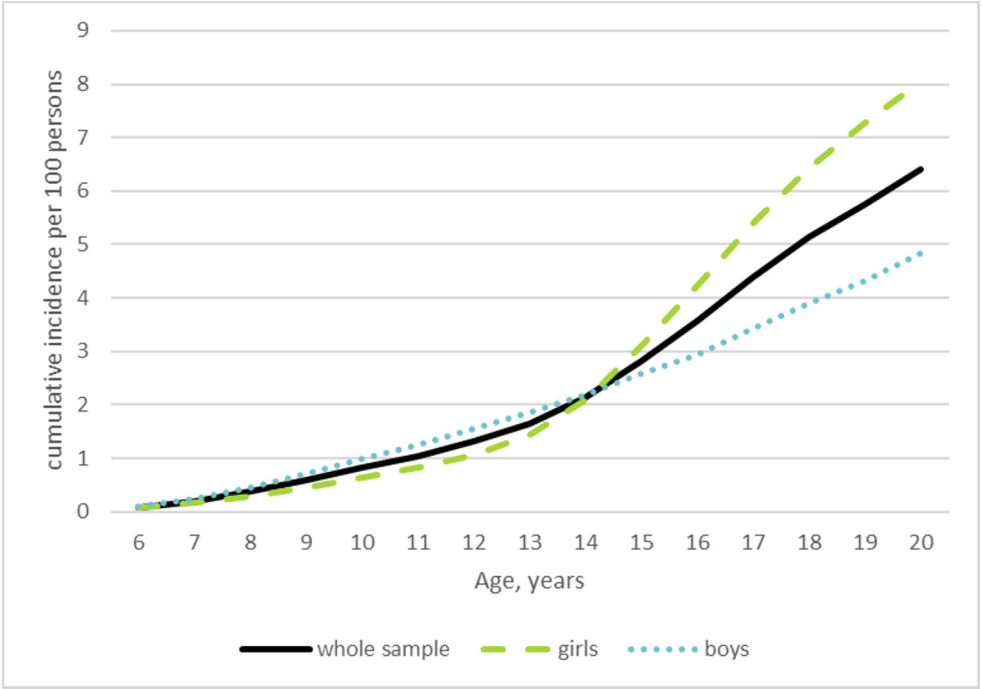

Figure 6. The cumulative treated incidence for the whole sample and for both genders.

Table 15. The birth cohort subsamples in Study II. Modified from study II.

THE BIRTH COHORT BIRTH YEARS ***AGE RANGE***	**SAMPLE SIZE** **TOTAL, N** ***FEMALES, N (%)*** **MALES, N (%)**	**MEAN AGE AT FIRST DIAGNOSIS (SD)** **TOTAL** ***FEMALES*** **MALES**
ENTIRE SAMPLE BORN 1992–2006 ***6–20 YEARS***	22,388 *12,628 (56.4)* 9,760 (43.6)	11.3 (2.9) *11.6 (3.1)* 10.9 (2.7)
BIRTH COHORT BORN 1992–1996 ***6–20 YEARS***	13,806 *8,793 (63.7)* 5,013 (36.3)	15.1 (2.9) *15.5 (2.5)* 14.4 (3.3)
BIRTH COHORT BORN 1997–2001 ***6–15 YEARS***	6,453 *3,043 (47.2)* 3,410 (52.8)	11.0 (2.4) *11.6 (2.5)* 10.5 (2.2)
BIRTH COHORT 2002–2006 ***6–10 YEARS***	2,129 *792 (37.2)* 1,337 (62.8)	7.8 (1.3) *7.7 (1.3)* 7.8 (1.2)

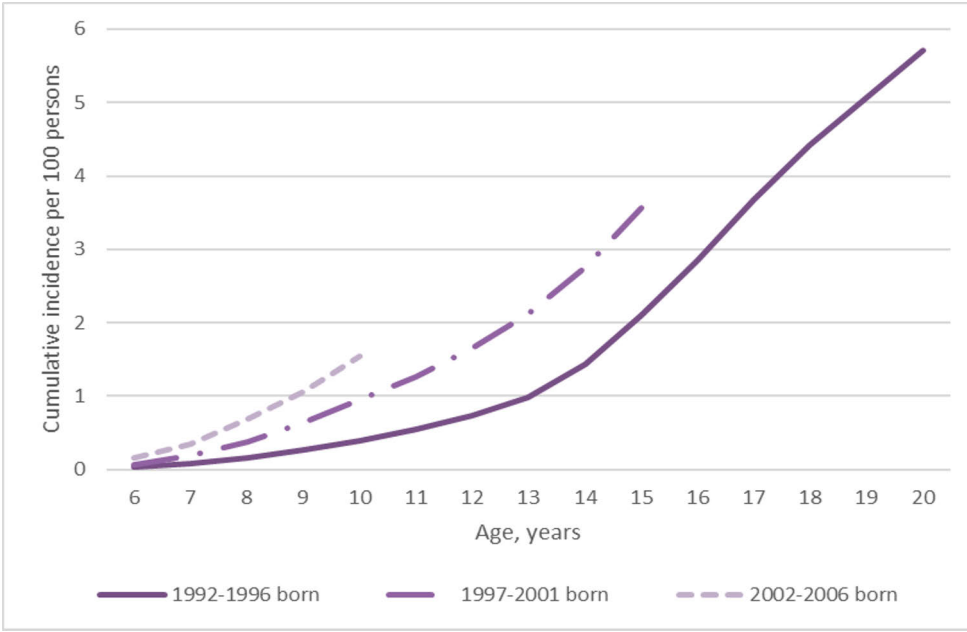

Figure 7. Cumulative treated incidence rates for three subsample birth cohorts. Modified from study II.

5.4 Socio-demographic risk factors and anxiety disorders

The associations between socio-demographic factors and anxiety disorders are described in Figure 8. Lower SES class (OR 1.53, 95% CI 1.45–1.61) and maternal single status (OR 2.02, 95% CI 1.87–2.17) increased the odds for anxiety disorders. In addition, those born in urban areas and in Southern Finland seemed to have increased odds of being diagnosed with an anxiety disorder.

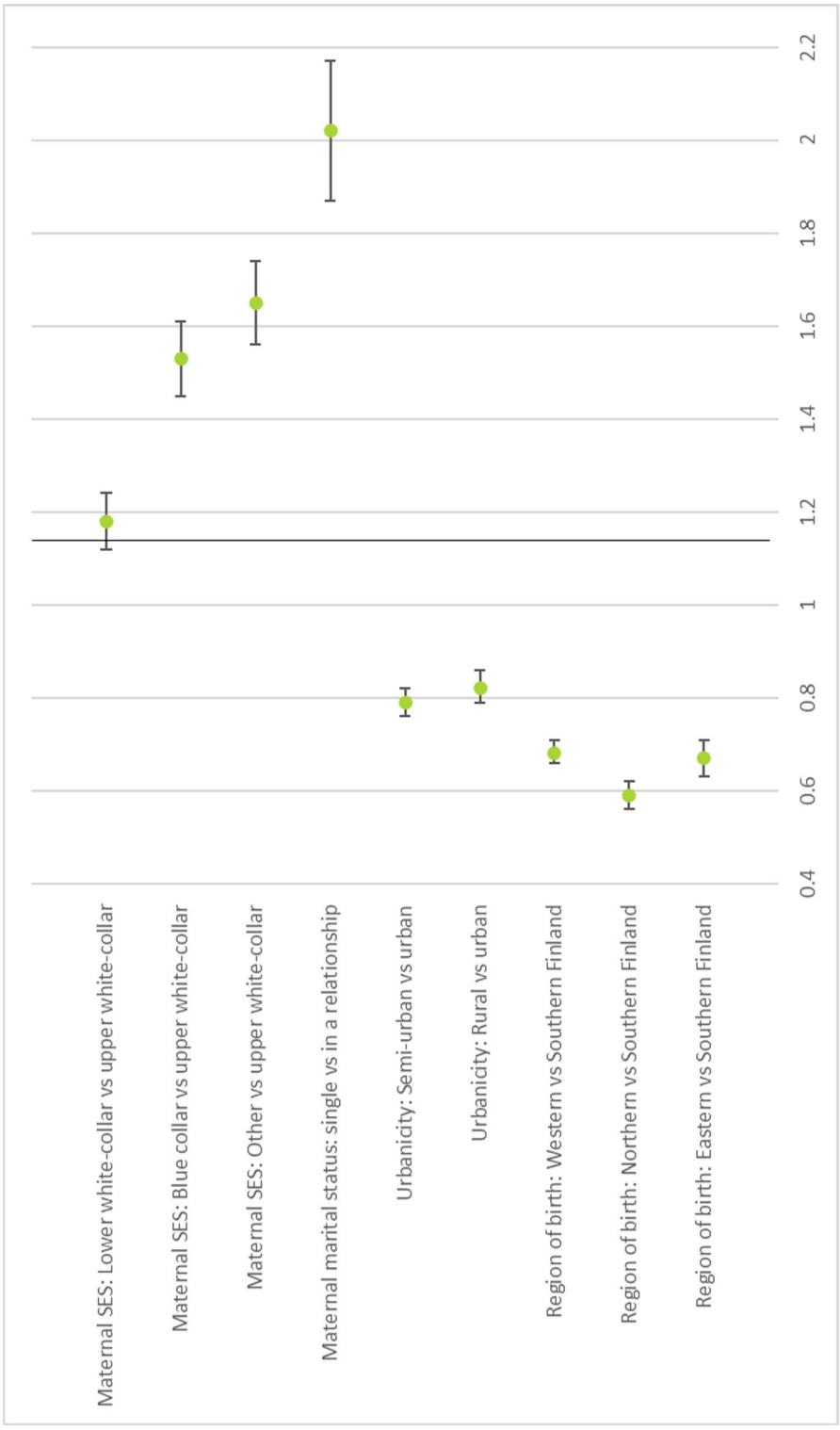

Figure 8. The associations between socio-demographic factors and anxiety disorders.

5.5 Comorbidities

Comorbidities were examined in study II in the oldest cohort, born from 1992–1996. This showed there were 13,806 cases with a diagnosed anxiety disorder and 4,301 (31.15%) cases were diagnosed with comorbid unipolar depressive disorder, which was the most common comorbidity. Neurodevelopmental disorders were also highly represented, as 11.6% had comorbid learning and coordination disorders, 6.3% had ADHD, and 4.5% had comorbid autism spectrum disorders. The prevalence rates of comorbidities in the oldest subsample are presented in Figure 9. Significant differences ($p<0.001$) were observed between genders with regard to many of the comorbidities: ADHD (females 2.4%, males 13.1%), ASD (females 2.3%, males 8.1%), eating disorders (females 8.9%, males 1.6%), learning and coordination disorders (females 7.5%, males 18.9%), and tic disorders (females 0.4%, males 2.3%).

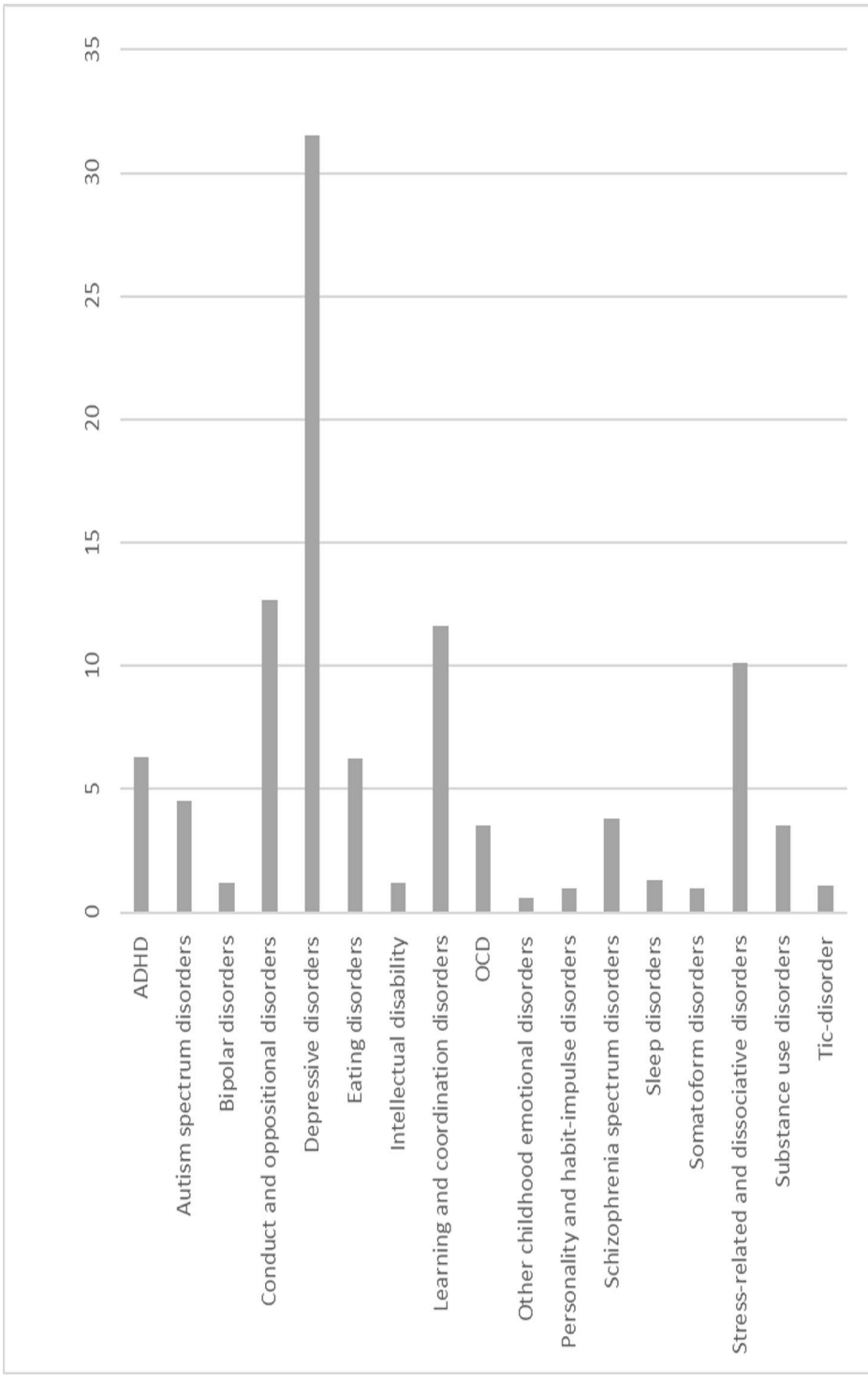

Figure 9. Prevalence of comorbidities in the subsample of 1992–1996 born cases. Modified from study II.

5.6 Preterm birth and anxiety disorders

Preterm birth was studied using GA in four categories, weekly, and as a continuous variable. The frequencies of GA, WGA, and the gender distribution and confounders included in the analyses can be seen in Table 16. All the studied confounders, except for paternal psychiatric disorders, were significantly associated with GA and anxiety disorders ($p<0.05$).

Table 16. The frequencies of the exposure variables and the confounders used in study III. Modified from study III.

COVARIATE	CASES N (%) TOTAL N = 22,181	CONTROLS N (%) TOTAL N = 74,726	MISSING
EXPOSURE VARIABLE			0
GESTATIONAL AGE			
<32	160 (0.7)	358 (0.5)	
32–36	965 (4.4)	2,756 (3.7)	
37–41	19,978 (90.1)	68,194 (91.3)	
≥42	1,078 (4.9)	3,418 (4.6)	
WEIGHT FOR GESTATIONAL AGE			0
<-2SD	873 (3.9)	2,087 (2.8)	
-2SD TO -1SD	3,700 (16.7)	10,697 (14.3)	
-1SD TO +1SD	14,235 (64.2)	49,523 (66.3)	
+1SD TO +2SD	2,635 (11.9)	9,695 (13.0)	
>+2SD	738 (3.3)	2,724 (3.7)	
CONFOUNDERS			
MATERNAL AGE AT BIRTH			0
≤ 19	1,032 (4.7)	1,879 (2.5)	
20–29	11,587 (52.2)	38,743 (51.9)	
30–39	8,775 (39.6)	32,056 (42.9)	
≥ 40	787 (3.6)	2,048 (2.7)	
PATERNAL AGE AT BIRTH			1,144
≤ 19	321 (1.5)	482 (0.7)	
20–29	8,704 (40.2)	28,675 (38.7)	
30–39	10,170 (46.9)	37,940 (51.2)	
≥ 40	2,478 (11.4)	6,993 (9.4)	
NUMBER OF MOTHERS' PREVIOUS BIRTHS			66
0	9,548 (43.1)	29,692 (39.8)	
≥ 1	12,614 (56.9)	44,987 (60.2)	
MISSING	19	47	

THE ONE-MINUTE APGAR SCORE			0
<7	928 (4.2)	2,873 (3.8)	
≥7	21,253 (95.8)	71,853 (96.2)	
MATERNAL SMOKING DURING PREGNANCY[A]			2,110
YES	5,481 (25.3)	11,064 (15.1)	
NO	16,208 (74.7)	62,044 (84.9)	
MATERNAL SUBSTANCE ABUSE DISORDERS			0
YES	1,878 (8.5)	1,890 (2.5)	
NO	20,303 (91.5)	72,836 (97.5)	
MATERNAL PSYCHIATRIC DISORDERS			0
YES	7,615 (34.3)	10,627 (14.2)	
NO	14,566 (65.7)	64,099 (85.8)	
PATERNAL PSYCHIATRIC DISORDERS			1,144
YES	6,108 (28.2)	10,613 (14.3)	
NO	15,565 (71.8)	63,477 (85.7)	
MISSING	508	636	
MATERNAL MARITAL STATUS AT TIME OF BIRTH[A]			7,431
MARRIED/IN A RELATIONSHIP	18,638 (93.8)	67,620 (97.1)	
SINGLE	1,224 (6.2)	1,994 (2.86)	
MATERNAL SES AT TIME OF BIRTH[A]			NA
UPPER WHITE-COLLAR WORKER	2,700 (12.2)	11,516 (15.4)	
LOWER WHITE-COLLAR WORKER	8,957 (40.4)	33,667 (45.1)	
BLUE-COLLAR WORKER	4,712 (21.2)	13,817 (18.5)	
OTHERS	4,523 (20.4)	12,374 (16.6)	
MISSING	1,289 (5.8)	3,352 (4.49)	
REGION OF BIRTH			31
RURAL	3,857 (17.4)	16,176 (21.7)	
SEMI-URBAN	3,240 (14.6)	13,016 (17.4)	
URBAN	15,078 (68.0)	45,509 (60.9)	
MATERNAL IMMIGRANT STATUS			0
IMMIGRANT	520 (2.3)	1,980 (2.7)	
NOT IMMIGRANT	21,661 (97.7)	72,746 (97.4)	

The ORs and 95% CIs for the associations between categorized GA and anxiety disorders are presented in Figure 10. In the unadjusted model, extremely to very preterm and moderate to late preterm births were associated with increased rates of anxiety disorders (OR 1.52, 95% CI 1.26–1.84 and OR 1.20, 95% CI 1.11–1.29, respectively). In the adjusted model, the association remained statistically significant for extremely to very preterm births (aOR 1.39, 95% CI 1.11–1.75) and for moderate to late preterm births (aOR 1.13, 95% CI 1.03–1.23). Post term birth was associated with an increased risk of anxiety disorders in the unadjusted model (OR 1.08, 95% CI 1.00–1.16), but not in the adjusted model (aOR 1.03, 95% CI 0.95–1.12). The weekly categorized gestational age and the ORs for anxiety disorders are presented in Figure 11. The continuous model showed an inverse linear association between GA and anxiety disorders ($p<0.001$), and can be seen in Figure 12.

Only 21.6% of the cases were classified as a pure anxiety disorder, meaning that they did not have comorbid psychiatric diagnoses during the study period. There were 4,789 cases in the pure anxiety disorder group and 16,098 controls. In the comorbidity group of depressive disorders, there were 9,337 cases and 31,238 controls. In the comorbidity group of neurodevelopmental disorders, the numbers were 6,714 and 22,930, respectively. The associations between preterm birth and anxiety disorders in these groups are presented in Figure 10. Interestingly, the associations between GA and anxiety disorders became insignificant in the pure anxiety disorder group. However, extremely to very preterm birth remained significant in both comorbidity groups and moderate to late preterm birth also remained significant in the group with comorbid neurodevelopmental disorders.

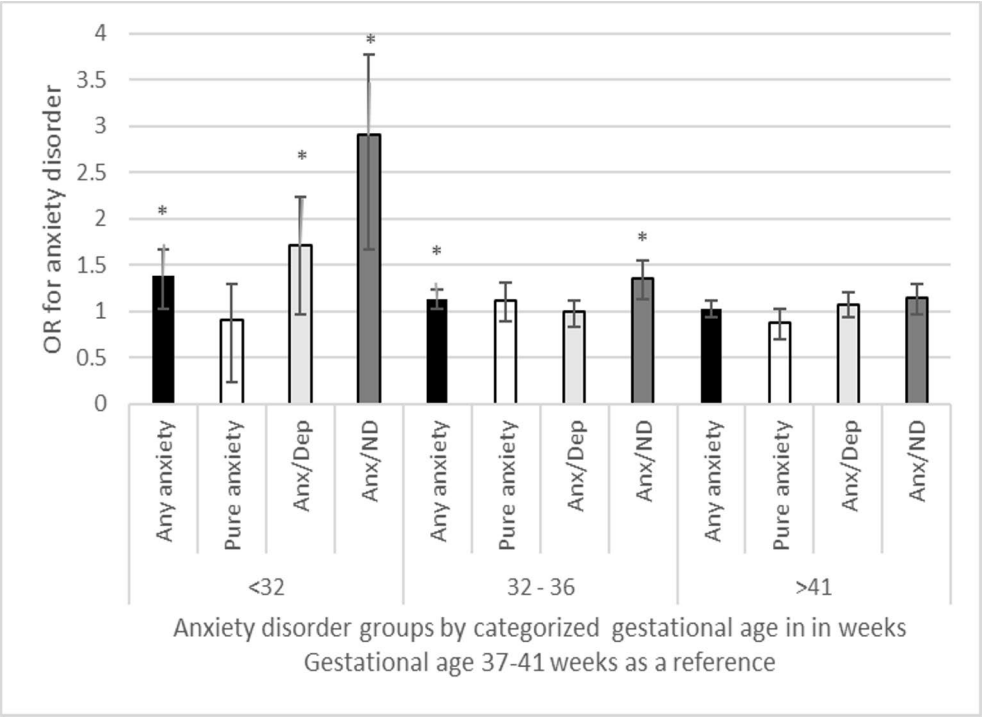

Figure 10. Gestational age and anxiety disorders in the comorbidity groups. * for significant results (p<0.05). Anx=Anxiety disorder; Dep=Depressive disorder; ND=Neurodevelopmental disorder; OR=Odds ratio.

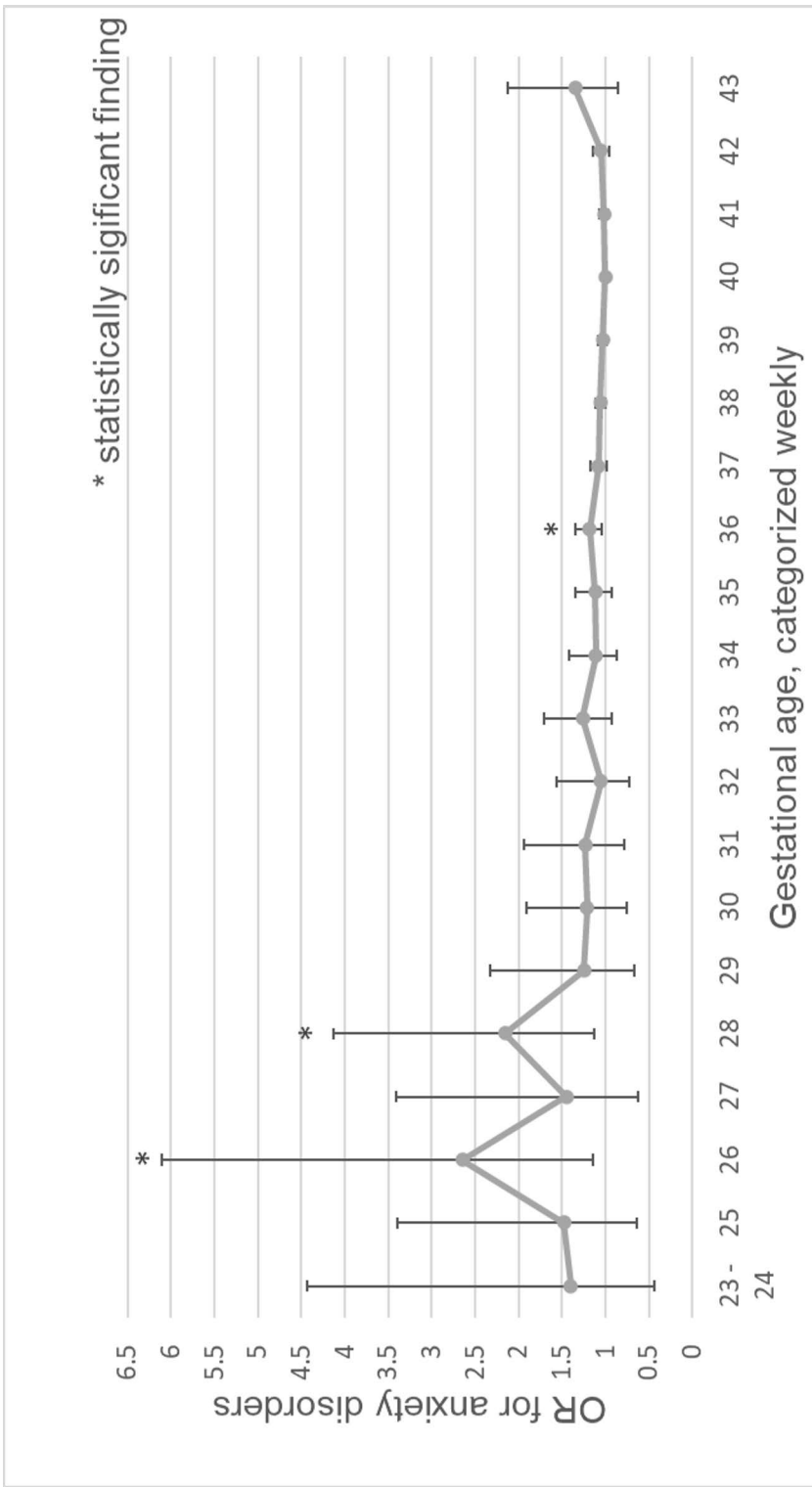

Figure 11. The associations between weekly categorized gestational age and anxiety disorders. OR=Odds ratio. Modified from study III.

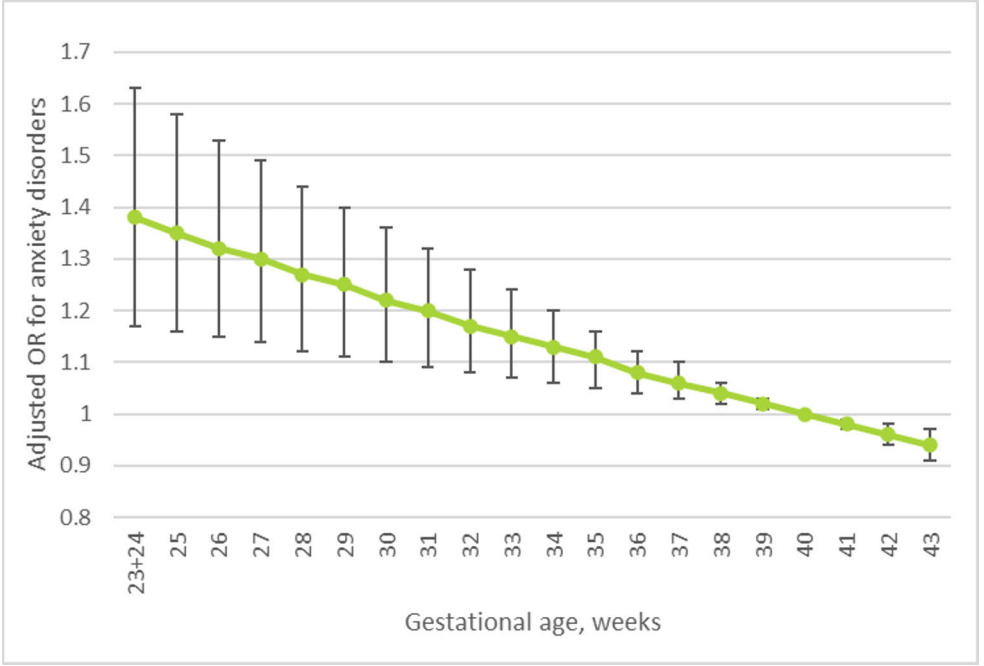

Figure 12. Linear association between gestational age and anxiety disorders. Modified from study III.

5.6.1 Specific anxiety disorders

There were statistically significant associations in the unadjusted analyses between categorized preterm birth and increased risks for generalized anxiety disorder and specific phobias. These remained partly significant in the fully adjusted analyses, including after adjustments for depressive and neurodevelopmental disorders. Moderate to late preterm birth was associated with increased odds for generalized anxiety disorder (aOR 1.72, 95% CI 1.22–2.43) and post-term birth with decreased odds for separation anxiety disorder (aOR 0.46, 95% CI 0.21–0.98). In the continuous analyses there was an inverse linear association between GA and specific phobias (p=0.002) after the adjustment for the previously mentioned confounders, including the comorbidities.

5.7 Poor foetal growth and anxiety disorders

Weight for gestational age was studied as both a categorized and continuous variable. Confounders included in the analyses can be seen in Table 16. All the studied confounders were significantly associated with WGA and anxiety disorders ($p<0.05$). In the categorized model, being born SGA was associated with an increased risk of anxiety disorders in the unadjusted model: WGA <-2SD (OR

1.45, 95% CI 1.33–1.57) and WGA -2SD to -1SD (OR 1.20, 95% CI 1.15–1.26). In the adjusted model, the results remained significant: WGA <-2SD (aOR 1.29, 95% CI 1.17–1.42) and WGA -2SD to -1SD (aOR 1.08, 95% CI 1.03–1.14). The associations between WGA and anxiety disorders are shown in Figure 13. The continuous analysis revealed an inverse linear association between WGA and anxiety disorders ($p<0.001$). This is shown in Figure 14.

When the sample was stratified into the comorbidity groups, the associations between WGA and pure anxiety disorders became statistically insignificant. A WGA of less than -2SD was associated with an increased risk of anxiety disorders in the group of comorbid depressive disorders in both the unadjusted (OR 1.35, 95% CI 1.19–1.54) and adjusted (aOR 1.19, 95% CI 1.02–1.39) analyses. Similarly, WGA -2SD to -1SD was associated with an increased risk of anxiety disorders with comorbid depression in both the unadjusted (OR 1.21, 95% CI 1.13–1.29) and adjusted (aOR 1.09, 95% CI 1.01–1.18) analyses. In the group of comorbid neurodevelopmental disorders, the respective ORs were as follows. For a WGA of less than -2SD OR was 2.03 (95% CI 1.78–2.32), and aOR was 1.81 (95% CI 1.53–2.14). For a WGA of -2SD to -1SD OR was 1.29 (95% CI 1.20–1.39) and aOR was 1.14 (95% CI 1.04–1.24). These are shown in Figure 13.

5.7.1 Specific anxiety disorders

In the unadjusted models there were significant associations between SGA and increased risks for generalized anxiety disorder, separation anxiety disorders, social phobia and specific phobias. However, only those for specific phobias remained significant in the further adjusted analyses (aOR 1.58, 95% CI 1.18–2.13). There were no significant associations between WGA and specific anxiety disorders in the fully adjusted continuous analyses.

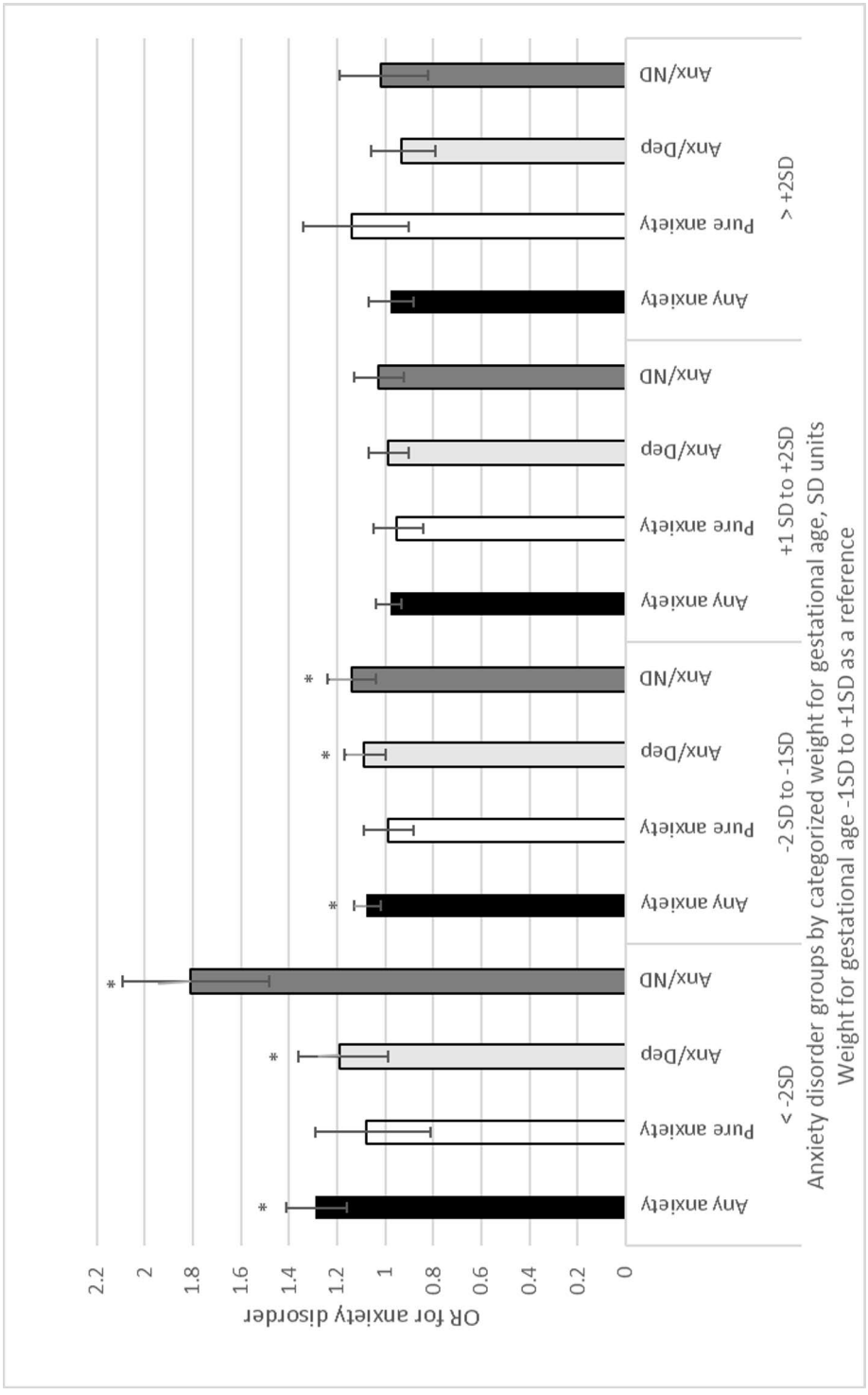

Figure 13. Weight for gestational age and anxiety disorders in the comorbidity groups. *for significant results ($p<0.05$). Anx=Anxiety disorder; Dep=Depressive disorder; ND=Neurodevelopmental disorder; OR=Odds ratio; SD=Standard deviation.

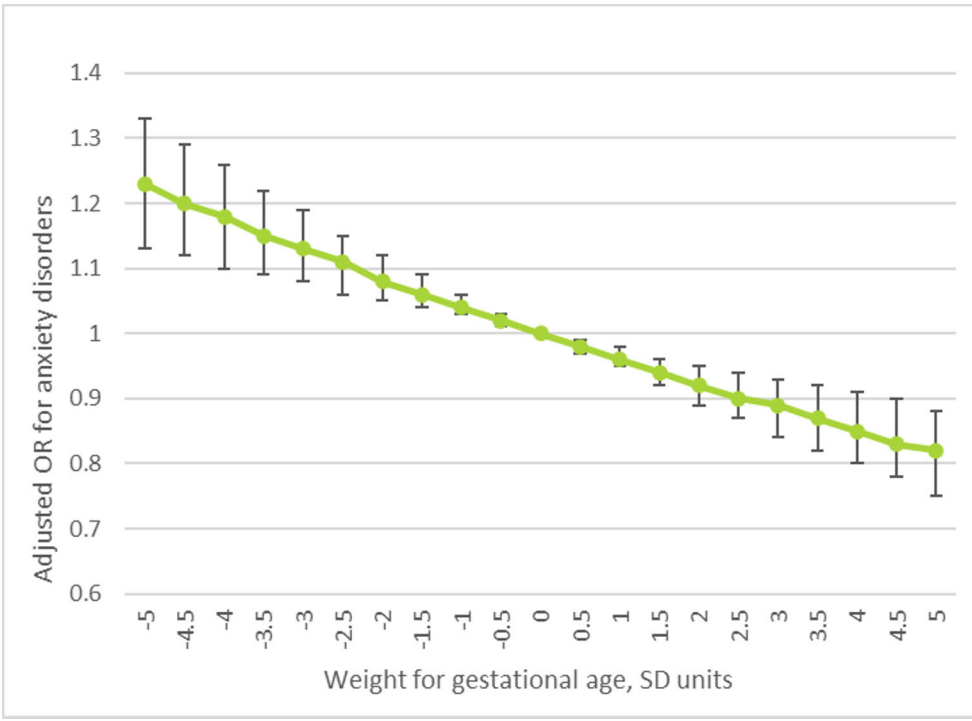

Figure 14. Linear association between weight for gestational age and anxiety disorders. Modified from study III.

5.8 Birth type and anxiety disorders

Birth type and birth outcomes were examined in study IV. The confounders for birth type are listed in Table 17. Birth by planned and unplanned caesarean sections were associated with increased ORs for anxiety disorders, with aORs of 1.08 (95% CI 1.02–1.15) and 1.12 (95% CI 1.05–1.19) respectively. After the additional confounding for maternal diagnoses commonly related to caesarean section was accounted for, birth by an unplanned caesarean section was associated with increased odds for anxiety disorders (aOR 1.11, 95% CI 1.04–1.18). The association between birth by planned caesarean section and anxiety disorders was not significant, but did show a tendency. No associations were observed for other birth categories. These results are described in Table 18.

Table 17. The confounders used in study IV. Modified from study IV.

COVARIATE	CASES N (%) TOTAL N = 22,181	CONTROLS N (%) TOTAL N = 74,726	MISSING
MATERNAL AGE			0
≤19	1,032 (4.7)	1,879 (2.5)	
20–29	11,587 (52.2)	38,743 (51.9)	
30–39	8,775 (39.6)	32,056 (42.9)	
≥40	787 (3.6)	2,048 (2.7)	
PATERNAL AGE			1,144
≤19	321 (1.5)	482 (0.7)	
20–29	8,704 (40.2)	28,675 (38.7)	
30–39	10,170 (46.9)	37,940 (51.2)	
≥40	2,478 (11.4)	6,993 (9.4)	
NUMBER OF PREVIOUS BIRTHS			66
0	9,548 (43.1)	29,692 (39.8)	
≤1	12,614 (56.9)	44,987 (60.2)	
MATERNAL PSYCHIATRIC HISTORY (SUBSTANCE USE DISORDERS EXCLUDED)			0
YES	7,625 (34.4)	10,684 (14.3)	
NO	14,556 (65.6)	64,042 (85.7)	
MATERNAL SUBSTANCE USE			0
YES	1,878 (8.5)	1,890 (2.5)	
NO	20,303 (91.5)	72,836 (97.5)	
MATERNAL SMOKING (NO COLLINEARITY WAS OBSERVED BETWEEN MATERNAL SES AND SMOKING)			2,110
YES	5,481 (25.3)	11,064 (15.1)	
NO	16,208 (74.7)	62,044 (84.9)	
MATERNAL SES (NO COLLINEARITY WAS OBSERVED BETWEEN MATERNAL SES AND SMOKING)			NA
UPPER WHITE-COLLAR WORKERS	2,700 (12.2)	11,516 (15.4)	
LOWER WHITE-COLLAR WORKERS	8,957 (40.4)	33,667 (45.1)	
BLUE-COLLAR WORKERS	4,712 (21.2)	13,817 (18.5)	
OTHERS	4,523 (20.4)	12,374 (16.6)	
MISSING	1,289 (5.8)	3,352 (4.5)	

GESTATIONAL AGE			0
≤31 WEEKS	160 (0.7)	358 (0.48)	
32–36	965 (4.4)	2,756 (3.7)	
37–41	19,978 (90.1)	68,194 (91.3)	
≥ 42	1,078 (4.9)	3,418 (4.6)	
WEIGHT FOR GESTATIONAL AGE			0
< -2SD	873 (3.9)	2,087 (2.8)	
-2SD TO +2SD	20,570 (92.7)	69,915 (93.6)	
>2SD	738 (3.3)	2,724 (3.7)	
THE ONE-MINUTE APGAR SCORE			58
≥7	21,253 (96.0)	71,853 (96.3)	
<7	891 (4.0)	2,751 (3.7)	
NEONATAL MONITORING			0
NO	20,258 (91.3)	69,111 (92.5)	
YES	1,923 (8.7)	5,615 (7.5)	
MATERNAL HYPERTENSION PRE-ECLAMPSIA OR ECLAMPSIA			58
YES	948 (4.3)	2,845 (3.8)	
NO	21,233 (95.7)	71,881 (96.2)	
MATERNAL DIABETES			58
YES	1,230 (5.6)	3,237 (4.3)	
NO	20,951 (94.5)	71,489 (95.7)	
FEAR OF GIVING BIRTH			58
YES	218 (1.0)	412 (0.6)	
NO	21,963 (99.0)	74,314 (99.5)	

Specific anxiety disorders were examined separately. Birth by planned caesarean section was associated with increased ORs for generalized anxiety disorder, social phobia and specific phobias in the unadjusted model. Birth by unplanned caesarean section was associated with increased ORs for generalized anxiety disorder, separation anxiety disorder, social phobia and specific phobias in the unadjusted model. In the adjusted analyses, birth by planned caesarean section was only associated with increased odds for specific phobias (aOR 1.24, 95% CI 1.04–1.48). This association remained significant after the additional adjustment for maternal diagnoses (aOR 1.21, 95% CI 1.01–1.44). These associations for specific phobias are shown in Table 18.

Table 18. Associations between birth type and any anxiety disorder and specific phobias.

BIRTH TYPE	CASES FOR ANY ANXIETY DISORDER N (%) (N=22,181)	CONTROLS FOR ANY ANXIETY DISORDER N (%) (N=74,726)	UNADJUSTED ANALYSES, OR (95% CI)	ADJUSTED ANALYSES[A], OR (95% CI)	ADDITIONAL ADJUSTMENT FOR BIRTH TYPE[B], OR (95% CI)
SPONTANEOUS VAGINAL CEPHALIC	17,132 (77.3)	59,147 (79.2)	Reference	Reference	Reference
VAGINAL OTHER	1,279 (5.8)	4,283 (5.7)	1.04 (0.98 to 1.11)	1.04 (0.97 to 1.12)	1.04 (0.97 to 1.12)
PLANNED CAESAREAN SECTION	1,794 (8.1)	5,541 (7.4)	**1.11 (1.05 to 1.18)**	**1.08 (1.02 to 1.15)**	1.06 (1.00 to 1.13)
UNPLANNED CAESAREAN SECTION	1,969 (8.9)	5,697 (7.6)	**1.19 (1.13 to 1.26)**	**1.12 (1.05 to 1.19)**	**1.11 (1.04 to 1.18)**
BIRTH TYPE	**CASES FOR SPECIFIC PHOBIAS N (%) (N = 2,567)**	**CONTROLS FOR SPECIFIC PHOBIAS N (%) (N=8,665)**	**UNADJUSTED ANALYSES, OR (95% CI)**	**UNADJUSTED ANALYSES[A], OR (95% CI)**	**ADDITIONAL ADJUSTMENT FOR BIRTH TYPE[B] OR (95% CI)**
SPONTANEOUS VAGINAL CEPHALIC	1,911 (74.4)	6,789 (78.4)	Reference	Reference	Reference
VAGINAL OTHER	171 (6.7)	541 (6.3)	1.12 (0.93 to 1.34)	1.08 (0.89 to 1.32)	1.07 (0.88 to 1.31)
PLANNED CAESAREAN SECTION	234 (9.1)	622 (7.2)	**1.36 (1.16 to 1.59)**	**1.24 (1.04 to 1.48)**	**1.21 (1.01 to 1.44)**
UNPLANNED CAESAREAN SECTION	251 (9.8)	707 (8.2)	**1.28 (1.09 to 1.49)**	1.17 (0.98 to 1.39)	1.15 (0.97 to 1.37)

The bolded results are statistically significant findings. CI=confidence interval; OR=odds ratio.

[A]Adjusted for Apgar score, neonatal monitoring, maternal age, paternal age, number of previous deliveries, maternal psychiatric history, maternal smoking, maternal socioeconomic status, gestational age, weight for gestational age.
[B] Further adjusted for maternal hypertensive disorders, maternal diabetes, maternal fear of giving birth.

5.9 Birth outcomes and anxiety disorders

The one-minute Apgar score, umbilical artery pH and neonatal monitoring were examined as birth outcome exposures for anxiety disorders in study IV. The same confounders listed in Table 17 were used, with the addition of birth type in the multivariate model. It was notable that the more valid five-minute Apgar-score was only recorder for 2.9% of the cases and therefore could not be used. Umbilical artery pH was unavailable for 56.9% of the cases.

All exposures, apart from umbilical artery pH, were associated with increased ORs for anxiety disorders in the unadjusted models. However, in the adjusted model, there were no significant associations between birth outcomes and anxiety disorders. The unadjusted and adjusted ORs are described in Table 19.

Specific anxiety disorders were studied separately. Low Apgar scores were associated with increased odds for specific phobias and neonatal monitoring was associated with increased odds for elective mutism, separation anxiety disorder and specific phobias in the unadjusted analyses. No associations emerged for umbilical artery pH. The only association found in the adjusted analyses was neonatal monitoring, which increased the OR for specific phobias (aOR 1.28, 95% CI 1.07–1.52). The unadjusted and adjusted ORs for specific phobias are described in Table 19.

Table 19. The unadjusted and adjusted odds ratios and 95% confidence intervals for birth outcomes and any anxiety disorder and specific phobias.

EXPOSURE	CASES FOR ANY ANXIETY DISORDER N (%) (N=22,181)	CONTROLS FOR ANY ANXIETY DISORDER N (%) (N=74,726)	UNADJUSTED ANALYSES, OR (95% CI)	ADJUSTED ANALYSES[A], OR (95% CI)
THE ONE-MINUTE APGAR SCORE				
≥7	21,253 (96.0)	71,853 (96.3)	Reference	Reference
<7	891 (4.0)	2,751 (3.7)	**1.10 (1.02 to 1.19)**	1.04 (0.97 to 1.13)
MISSING	37	122		
UMBILICAL ARTERY PH				
≥7.15	9,342 (91.3)	28,041 (91.6)	Reference	Reference
<7.15	890 (8.7)	2,563 (8.4)	1.08 (0.98 to 1.19)	NA
MISSING	11,949	44,122		
NEONATAL MONITORING				
NO	20,258 (91.3)	69,111 (92.5)	Reference	Reference
YES	1,923 (8.7)	5,615 (7.5)	**1.18 (1.12 to 1.24)**	1.02 (0.95 to 1.09)
MISSING	0	0		

EXPOSURE	CASES FOR SPECIFIC PHOBIAS (N = 2,567)	CONTROLS FOR SPECIFIC PHOBIAS (N=8,665)	UNADJUSTED ANALYSES, OR (95% CI)	ADJUSTED ANALYSES[A], OR (95% CI)
THE ONE-MINUTE APGAR SCORE				
≥7	2,440 (95.2)	8,323 (96.3)	Reference	Reference
<7	122 (4.8)	323 (3.7)	**1.29 (1.04 to 1.60)**	1.01 (0.79 to 1.28)
MISSING	5	19		
UMBILICAL ARTERY PH				
≥7.15	1,209 (90.0)	3,591 (90.3)	Reference	Reference
<7.15	134 (10.0)	384 (9.7)	1.08 (0.85 to 1.38)	NA
MISSING	1,224	4,690		
NEONATAL MONITORING				
NO	2,264 (88.2)	7,962 (91.9)	Reference	Reference
YES	303 (11.8)	703 (8.1)	**1.52 (1.32 to 1.76)**	**1.28 (1.07 to 1.52)**
MISSING	0	0		

The bolded results are statistically significant findings. CI=confidence interval; OR=odds ratio.

[A]Adjusted for birth type, Apgar score, neonatal monitoring, maternal age, paternal age, number of previous deliveries, maternal psychiatric history, maternal smoking, maternal socioeconomic status, gestational age, weight for gestational age.

6 Discussion

6.1 Main findings

This thesis examined the associations between prenatal and perinatal risk factors and child and adolescent anxiety disorders. In addition, study II examined time trends in the incidence of child and adolescent anxiety disorders.

First of all, the systematic literature review revealed that studies on prenatal and perinatal factors for child and adolescent anxiety disorders were scarce. Many of the potential risk factors were only examined by one or two studies and the results often disagreed. Although maternal somatic problems and preterm birth were observed to be possible risk factors, other factors seemed to play little role in the development of offspring anxiety disorders.

Second, it was found that the treated incidence of child and young adolescent anxiety disorders increased from 1998 to 2012. It remains to be seen, whether the increase also existed among older adolescents as the observed increase between the birth cohorts could also indicate that children were being diagnosed at earlier ages.

Third, this thesis showed that maternal low SES and mother being single at the time of birth, as well as living in Southern Finland and in urban area, increased the odds for children and adolescents to be diagnosed with an anxiety disorder by specialized services.

Fourth, preterm birth and being born SGA linearly increased the odds for being diagnosed with an anxiety disorder. However, the conditions with common comorbidities, namely depressive and neurodevelopmental disorders, seemed to explain these associations.

Fifth, birth by caesarean section, especially an unplanned caesarean section, increased the odds for child and adolescent anxiety disorders. In contrast, the one-minute Apgar score and umbilical artery pH did not show significant associations with child and adolescent anxiety disorders.

Sixth, the studied prenatal and perinatal factors did not show much of an association for specific anxiety disorders, except for specific phobias. Preterm birth, being born SGA, birth by planned caesarean section and neonatal monitoring showed significant associations for increased odds for specific phobias in children and adolescents.

6.2 Methodological discussion

6.2.1 Study I

Study I followed the accepted guidelines for conducting a systematic review. The PRISMA protocol (Liberati et al., 2009) was followed and the study plan was registered on PROSPERO. The quality assessments of the studies were carried out with a validated tool from the Joanna Briggs Institute (Moola et al., 2015). Despite these measures, there were some methodological limitations. First of all, a systematic review does not produce statistical data in a similar way as a meta-analysis does (Crowther & Lim, 2010). The search terms may not have been optimal, although they were carefully considered and a librarian was consulted. The search produced a great number of papers and only a small number were relevant. The reviewed studies were considerably heterogenic and this made summarising the results difficult. The reviewed studies had often retrospectively gathered information on the perinatal events from parents, which could have led to recall bias. The systematic literature search was carried out using two databases, which could be regarded as a minimal number of sources for a systematic review. However, the two databases that we used were Pubmed and PsycInfo, which are very relevant databases for the subject being explored and it is unlikely that we missed any relevant studies. An additional search was conducted on grey literature using Scopus and MedNar following a journal peer-review request. Papers that were not published in English were excluded and this could be a further limitation.

6.2.2 Study design in studies II-IV

The register-based studies used the nested case-control method, which meant that a defined birth cohort formed the source population. Each subject with an incident case diagnosis was matched with four controls by their sex and date of birth (±30 days). They were all alive and living in Finland at the time of the incident diagnosis. Controls can be defined as those, who have not developed the certain disease of the cases by the time the case was diagnosed (Susser et al., 2006). In these studies II-IV, the controls were free of the case diagnosis until 2016.

The original data request covered a broad set of diagnoses, including anxiety disorders, OCD, stress-related disorders and childhood onset emotional disorders. Modifications were made to create the anxiety disorder sample for this study. Only those with ICD-10 diagnoses F40–F41, F93, F94.0 were classified as cases. It should be noted that only diagnoses from specialized services were included with regard to the cases and controls.

The nested case-control design has its strengths and limitations. The strengths are that it is cost-efficient and data collection is less effortful when compared to a cohort design, which might eventually comprise considerably fewer cases. There is only a minor loss of statistical efficiency in the nested case-control design, compared to a cohort design. The attrition rate can be challenging in traditional cohort studies and those who develop a disorder, may not participate in the study. Compared to traditional case-control designs, nested case-control design offers the opportunity for longitudinal research. This is because the exposure variables can be examined retrospectively, prior to the case diagnosis, and also confounder data is more reliably recorded. Therefore, recall bias is not an issue. The number of controls for each case can be also higher in a nested case-control design and the controls are from the same population as the cases due to the cohort setting. The cases are also more likely to represent the general population, as there is no selection bias. In addition, the incidence can be studied directly in a nested case-control design, which is not possible in traditional case-control design. (Ernster, 1994)

We were able to examine a nationwide birth cohort in our study and a huge number of cases were identified. Each control was identified by the time of their incident case diagnosis from the same risk-set. Controls were alive and living in Finland at the time of the identification, were matched by sex and age (±30 days) and did not have the case diagnosis. A nested case-control design is ideal for prenatal and perinatal epidemiology studies. Indeed, we were able to examine various prenatal or perinatal factors and include various confounders in the analyses.

The limitations of nested case-control design are that causal conclusions cannot be reached. Additional variables might exist that account for the associations found by the study. Although some of the studied exposures were exploratory, we aimed to base the studies on literature and research findings. To do this, we focused on previous studies about anxiety disorders or, if it did not exist, previous studies of other mental health disorders. In addition, potential confounders were carefully planned, studied and included in the analyses. However, the registers did not record all perinatal variables and there may be additional confounders that would explain some of the associations found in our studies.

6.2.3 The registers

The registers used in the studies were the Care Register for Health Care, the Finnish Medical Birth Register and the Finnish Population Register Centre. These are all perceived as valid data sources. Registers like these are quite unique globally as they contain nationwide data on multiple variables and the data on

individuals, as well as between individuals such as family members, can be linked through personal identification codes. Similar register-data is only available in other Nordic countries. These national registers enable researchers to examine large sample sizes and achieve large statistical power. A great variety of confounders can be used and the registers enable make it possible to gather data for longitudinal studies, because the data has been gathered prospectively, but can be examined retrospectively. Register samples are nationwide and representative of the whole Finnish population. This is because Finnish health care system receives financial support from municipalities and social insurance, which means that all Finnish residents can have access to the services provided. In addition, Finnish children and adolescents are well covered by the public health care system, which includes regular routine check-ups by pre-school and school aged children's healthcare services.

However, certain limitations should be taken into consideration regarding the use of these registers. The anxiety disorder diagnoses from the Care Register were only from specialized health care services. Although moderate and severe child mental health problems are most likely to be treated by specialized health care services, milder forms of anxiety could be treated by primary health care services. Symptoms of anxiety may even go unnoticed and remain untreated, as it has been shown that a great number of people with significant anxiety do not receive any form of treatment (Niermann et al., 2021). Furthermore, diagnostic information from private clinics was not recorded during the study period and some children and adolescents have treated their anxiety in private health care. These children could have ended up being used as controls. However, the effect of these misclassified children is likely to have been very minimal, due to the large sample size. Furthermore, the impact would have attenuated the associations rather than created false positive findings.

The anxiety disorder diagnoses in the Care Register have not been validated. Satisfactory validity has been observed for mental disorders in general (Sund, 2012), and a subsample of elective mutism diagnoses was found to be valid (Koskela et al., 2020). Another limitation regarding the diagnoses was the broad use of unspecific anxiety disorder diagnoses. It is worth noting that diagnosing child and adolescent anxiety can be difficult, due to the normal developmental phases, and possibly vague symptoms. Their anxiety symptoms can sometimes be mixed with symptoms of depression or other mental health problems. The severity of each anxiety disorder case was not defined in the Care Register, and it was not examined, whether the anxiety disorder diagnosis was primary or secondary for psychiatric comorbidities. These diagnostic limitations also affected the comorbidity diagnoses and parental diagnoses that were included in the studies.

Recording defects were also observed for perinatal factors, especially as some had only been recorded after the beginning of the study period. For example, maternal BMI had only been recorded since 2011 and therefore we could not use this. Similarly, the five-minute Apgar score and umbilical artery pH values were not recorded that often in 1990s. The missing data for other exposures were quite minimal but maternal SES and smoking were missing from more than 1000 cases. Paternal factors were also missing from 1144 individuals in our sample. Maternal SES class was categorization included the category of 'missing'. The adjusted analyses were carried out using the cases and controls that had all the required data.

Paternal age and psychiatric diagnoses were available, but we only used maternal variables for SES class. This decision was supported by previous findings that maternal education was more strongly associated with perinatal outcomes than paternal education (Mortensen et al., 2008).

6.2.4 The sample

The sample for studies II–IV was formed from an original sample of cases, born from 1987–2012, who had anxiety disorders, stress-related disorders or OCD. In studies II–IV, the sample consisted of just those cases diagnosed with anxiety disorders (ICD-10 codes F41–F41, F93, F94.0) and birth years were limited to 1992–2006. Furthermore, the years of getting the case diagnosis were limited to 1998–2012. These parameters enabled us to explicitly study anxiety disorders. We also aimed to include outpatient diagnoses for the whole sample, as this is where most anxiety disorders tend to be diagnosed. Outpatient diagnoses were only available from the Care Register from 1998 onwards. We wanted to create a uniform sample and therefore we restricted the cases to 6-20 years of age during the years of inclusion. This meant that we excluded early childhood period and the focus was in school-aged population. Only 88 children were only diagnosed before the year they turned six and not after. This small number indicates that excluding young children had little impact on the results. It should be noted that the sample only included subjects with an anxiety disorder who had sought treatment and received an anxiety disorder diagnosis from specialized health care services.

The controls were obtained from the Population Register Centre and chosen from the same risk set for each incident case diagnosis and followed until the end of 2016. They were free of any anxiety disorder diagnosis during that follow-up period. In addition, they were free of OCD and stress-related disorder diagnoses due to the original sampling method. However, we cannot be sure about whether they received an anxiety disorder diagnosis later in life, after 2016. Controls could also have had an undiagnosed anxiety disorder already during the study period. Again, this misclassification of controls would have alleviated the associations

between risk factors and anxiety disorders, rather than created false positive associations. In study III and IV, 207 cases and 1,410 controls were excluded from the sample because of missing data on gestational age or weight for gestational age. Again, the percentage of the sample with missing data was small and therefore the impact on the results was likely to be minimal.

Furthermore, the generalizability of the study findings was compromised by the fact that our sample only consisted of singleton pregnancies.

6.2.5 Statistical methods

The confounders were chosen based on existing literature and also tested for their relevance before they were included in the conditional logistic regression model. This removed unnecessary confounders and strengthened the significance of the results. Some residual confounding factors always exist and poor recording hindered the use of some perinatal factors.

We used the yearly treated incidence for 100 people at risk. This is an acceptable way of presenting such data, but confusion may arise when the results of different incidence studies are interpreted, as the definitions for denominators and numerators vary greatly. In addition, the term rate is somewhat problematic in incidence studies as it may be used to describe the proportion of incident cases and for the incidence ratio used for comparing multiple time points. (Spronk et al., 2019)

Handling of missing data is a common problem in epidemiological research. There are three ways to deal with the missing data: 1) only using complete case data, 2) using a missing category or 3) using imputation, which means replacing the missing data with a best estimate value (Groenwold et al., 2012). Imputation can be further divided into single and multiple imputation. Multiple imputation creates a value based on pooling different imputation values. The randomness of the missing data defines which method should be used. Complete case analysis can be used when the missingness is happening completely at random. It is preferable to use imputation when missingness is not happening at random. (Van der Heijden et al., 2006)

It has been suggested that the consequences are likely to be minor when less than 5–10% of the data is missing, the (Dong & Peng, 2013). In study II multiple imputation was used to handle the missing data, which was rather considerable for maternal SES, as it was 5.8% for the cases and 4.5% for the controls. In studies III and IV, complete case analysis and missing categories were both used for exposures and confounders. The imputation, and multiple imputation method could have been optimal for handling the missing data for maternal SES, smoking and marital status. However, all these variables were missing from less than 10% of the

sample and therefore the different methods used to handle the data are likely to have little effect.

The clustering of the missingness and the possible multicollinearity of maternal SES, smoking and marital status was examined. There was little clustering was and no multicollinearity was observed between these variables.

6.3 Discussion of the results

6.3.1 Systematic review

The systematic review found 31 articles that had studied prenatal and perinatal risk factors for child and adolescent anxiety disorders based on our inclusion and exclusion criteria. The main findings of the review were that literature does exist for prenatal and perinatal risk factors for anxiety, but only a few studies had examined the same exposures and the definition of outcomes varied. The studies also reported contradictory findings. These limitations demonstrate that the knowledge on prenatal and perinatal risk factors for anxiety disorders is still very limited. Preterm birth, especially late preterm birth, was associated with an increased risk of anxiety disorders. Maternal somatic illnesses could predispose offspring to anxiety disorders, although no findings were observed for maternal diabetes. Maternal perinatal mental health was not extensively studied and the findings for offspring anxiety disorders were weak. Furthermore, birth weight, size for gestational age and maternal smoking were not associated with child and adolescent anxiety disorders.

The associations between preterm birth and anxiety disorders, and the possible mechanisms behind those associations will be discussed in 6.3.4. Maternal somatic illness could have an impact on foetal development in various ways, such as neurodevelopmental changes or parental factors. One way is HPA-axis alterations caused by the foetus being exposed to excessive cortisol exposure (O'Donnell et al., 2012). Excess cortisol is possible in maternal hypertensive disorders (Causevic & Mohaupt, 2007) and maternal stress (O'Connor et al., 2003). Understandably, different somatic problems in the mother often increase her stress levels.

In addition, development may be altered when the oxygen supply to the foetus is disrupted or there is increased oxidative stress. These are best studied by examining maternal hypertensive disorders (Betteridge, 2000; Causevic & Mohaupt, 2007; Lyall et al., 2013; Moisiadis & Matthews, 2014; Sinha & Dabla, 2015; Wang et al., 2009). It has been observed that brain tissue is particularly sensitive to oxygen radicals (Halliwell, 2006), which could explain brain alterations and susceptibility for mental health problems among offspring. Inflammation contributes to many maternal somatic problems, infections and

metabolic diseases. Maternal prenatal inflammation has been associated with increased child internalizing symptoms (Giollabhui et al., 2019).

6.3.2 Time trends in treated incidence of anxiety disorders

The main findings in study II were that treated incidence rates were higher for boys when they were under 12 years old but after that girls' rates bypassed boys' rates. Increases in cumulative treated incidence were observed over time.

Firstly, the observed treated incidence rates follow the existing literature. Boys tend to have more anxiety disorders in childhood but girls' rates exceed boys' rates in adolescence (Dalsgaard et al., 2020; Wesselhoeft et al., 2015). Various reasons have been suggested for this phenomenon have been various. Genetics and biological factors have been proposed as vulnerability factors. Puberty starts earlier among girls and female sex hormones could impact on the sensitivity for experiencing stress and anxiety (Merikangas & Almasy, 2020; Wesselhoeft et al., 2015; Wiklund et al., 2012). Gender differences have been observed with regard to responding to stress and reacting to symptoms (Hetland et al., 2002; Rudolph, 2002). Furthermore, females are known to seek help more easily (Ladwig et al., 2000; Seidler et al., 2016). Cultural norms may have an impact on the way we observe anxiety in girls and boys and, on the other hand, assessment methods could favour recognising female anxiety (Merikangas & Almasy, 2020).

Secondly, the study observed that the treated incidence of anxiety disorders decreased in females after the age of 17. This could highlight the previously discussed impacts of puberty and hormones on anxiety susceptibility or it could reflect the Finnish service system. Children's and adolescent's mental health problems, including anxiety, are often treated by specialized services, whereas adult anxiety disorders are commonly treated in primary health care.

Thirdly, the cumulative treated incidence rates increased over time and this observation was also supported by previous literature (Cybulski et al., 2021; Gyllenberg et al., 2018). The increase seemed to be similar for both genders. The limited follow-up period meant that we could not monitor each birth cohort until adulthood. The youngest cohort was only followed up until the age of 10 and therefore we cannot show that the increase would continue to show a similar trend in older individuals. The increase seen at younger ages could also have reflected them being diagnosed at an earlier age. In the UK, the increases in treated incidence were higher in adolescents than in children (Cybulski et al., 2021). If this was also the case in Finland, the hypothesis of treated incidence rates actually increasing would be true rather than diagnoses at earlier ages. There are factors that could support the theory of actual increases in internalizing disorders. For example, notable decreases in sleep-time could have increased vulnerability to stress among

children and adolescents (Chan et al., 2020; Matricciani et al., 2012). In addition, cultural changes are creating more stressful atmospheres, including highlighted materialism and individualism (Eckersley, 2006). High screen-time has been associated with poorer mental health (Yang et al., 2013), excessive internet or mobile phone use have been associated with increased risk for self-harm (Wang et al., 2020), and social media use has been specifically associated with internalizing disorders (Tsitsika et al., 2014).

In Finland, community samples have shown that self-rated social anxiety and generalized anxiety symptoms have increased among adolescents of both genders (Knaappila et al., 2021). Emotional symptoms in general have increased among adolescent girls (Mishina et al., 2018). No significant changes in emotional symptoms were reported by a study of eight-year-olds (Sourander et al., 2016), but service use increased in the same study (Lempinen et al., 2019). Taken together, these findings suggest that there may be real increase in anxiety symptoms in general, but the increase in treated incidence is likely to come from increased help-seeking. Finnish child and adolescent mental health services have developed since the 1990s, which could partly explain the increased service use. At the same time, it can be assumed that the stigma of using such services has decreased and awareness has increased. It remains to be seen, what impact COVID-19 and the war in Europe have on the treated incidence rates for child and adolescent anxiety disorders.

6.3.3 Socio-demographic risk factors

The study found that low maternal SES and maternal single status at birth, living in Southern Finland and living in an urban area were associated with increased odds for anxiety disorders. The associations were similar for both genders. Some of these findings were supported by the literature. Firstly, low SES class increased the risk of anxiety disorders (Guhn et al., 2020; McLaughlin et al., 2012). Children from low SES classes may often experience chronic stressful life events and the long-term impact is thought to increase the risk of mental health problems, including anxiety (McEwen, 2013). Low SES has not just been associated with child mental health problems. It has also hindered cognitive development in children (Lee & Jackson, 2017). Socio-demographic disadvantages often create an inter-generational continuum (Conger, 2015).

Secondly, single motherhood at the time of the birth was associated with an increased odd for anxiety disorders, as found in a one register-study (Guhn et al., 2020). The reasons for that finding could be that single mothers are more likely to have low incomes and low educational levels (Crosier et al., 2007; Kendig et al., 2008; Targosz et al., 2003). Low SES was included in our analysis and this did not

entirely explain the impact of single status. Another reason could be the lack of social support that single mothers might experience (Crosier et al., 2007; Targosz et al., 2003). Undesirable parenting behaviours have also been observed to be more prevalent among single mothers than cohabiting mothers (Daryanani et al., 2016). Single mothers have been observed to have more mental health problems than mothers in a relationship (Agnafors et al., 2019; Targosz et al., 2003). It should be noted that we did not adjust for parental psychopathology in this study, as this study was more a general descriptive study of our sample. Adjusting for parental psychopathology might have impacted on the results.

Thirdly, living in an urban area was associated with increased odds for anxiety disorders. This finding has previously been described in Danish studies (Helenius et al., 2014; Hyland et al., 2016). Urbanicity has been associated with an overall psychopathology risk among adults (Penkalla & Kohler, 2014; Vassos et al., 2016). The finding that living in Southern Finland was associated with increased odds for anxiety disorders could be discussed together with urbanicity. The majority of Finnish inhabitants live in Southern Finland and urban areas (Statistics Finland, 2022). It has been previously observed that children and adolescents from Northern Finland use less psychiatric outpatient services and people from urban areas use more (Paananen et al., 2013). Obviously urban areas may also have better access to services and this could increase the treated incidence of anxiety disorders in urban areas. The impact that urbanicity has on mental health problems has been previously explained by two theories, the drift and breeder hypotheses. The drift hypothesis suggests that people might migrate selectively and this explains why people with mental health problems are concentrated in urban areas. The breeder hypothesis suggests that urbanicity itself works as a risk factor. (Verheij, 1996)

The breeder hypothesis could be supported by the fact that people living in urban areas have more stressful lives, due to higher population density, more hectic lifestyles, pollution and crime problems (Dekker et al., 2008; Peen et al., 2010). However, it is quite possible that diagnoses were more common in urban settings, because of better access to services and possibly more willing attitudes towards help-seeking (Jones et al., 2011; Paananen et al., 2013).

6.3.4 Preterm birth and poor foetal growth

Preterm birth was studied using four WHO gestational age categories, both as weekly categories and as a continuous model. Preterm birth was associated with an increased odd of child and adolescent anxiety disorders, both in the categorized and the continuous models. The weekly categorization model produced few significant results, possibly due to the lack of power. The association between preterm birth

and anxiety disorders was linear in the continuous model and the associations remained significant when adjusting for a comprehensive set of confounders.

No previous studies had examined gestational age weekly or as a continuous variable. Our systematic literature review concluded that the findings of previous studies had been contradictory (study I). Unlike our register-based study, the review found that only late preterm birth potentially increased the risk of later child and adolescent anxiety disorders. The inconsistencies between these studies could be explained by the differences in the study designs and their limitations. There were various differences in the study designs. First of all, as already mentioned, the age ranges covered by the samples and the outcome diagnoses varied substantially. In addition, the way that preterm birth was categorized varied. Paternal confounders were only considered in two studies (Larsen et al., 2021; Xia et al., 2021). Furthermore, none of the previous register-based studies examined the impact of comorbidities and, based on our results, that could explain the differences in the findings.

Our study found that the associations between preterm birth and anxiety disorders became non-significant after stratification for comorbidity groups. Comorbid depressive and neurodevelopmental disorders were highly prevalent in our sample in study II. Those comorbidities had previously been associated with preterm birth (Abel et al., 2010; Larsen et al., 2021; Monfils Gustafsson et al., 2009; Sucksdorff et al., 2015; Upadhyaya et al., 2021; Xia et al., 2021), and their high prevalence with anxiety disorders has been shown (Esbjørn et al., 2010; Essau et al., 2000; Kendall et al., 2010). Unknown comorbidities could have contributed to the inconsistent findings in previous register-based studies.

Several different mechanisms could explain why preterm birth could increase the risk of mental health disorders. Not only do children born preterm experience the world premature, they have often been reported to experience adversities at many stages prenatally, perinatally and postnatally. Preterm birth terminates foetal development in utero abruptly and the foetus and the immature brain are not yet ready for the world. The event is stressful for the foetus and the mother (Singer et al., 1999; Vogel et al., 2018). Preterm birth may be initiated by various prenatal problems, either maternal or foetal, including different infections and inflammatory states (Vogel et al., 2018).

These different types of adversities could lead to altered brain development or HPA-axis alterations, even independently (Vogel et al., 2018). In addition to those adversities, preterm birth itself may lead to changes in neurodevelopment (Nosarti et al., 2014). The preterm brain can be extremely vulnerable to disturbances in the infant's environment (Volpe, 2009). Alterations in the HPA-axis have also been recorded among preterm born individuals (Kajantie et al., 2007). It is noteworthy that that both prenatal and postnatal stress could lead to HPA-axis alterations.

Postnatal adversities and stress are common among those born preterm. For example, preterm born individuals might undergo invasive and painful procedures (Volpe, 2009) and these have been linked to alterations in the central nervous system (Duerden et al., 2018). Neonatal inflammation has also been associated with brain impaired cognitive development in toddlers and the mechanism is explained by brain alterations (O'Shea et al., 2013).

Perinatal parental stress is likely to be increased when there are prenatal and postnatal adversities, including possible NICU treatment. This parental stress could have an impact on their parenting behaviour and their attachment with their child (Korja et al., 2012) and this stress could also explain the increased risk of offspring anxiety disorders (Murray et al., 2009).

Study III did not just study preterm birth. It also looked at poor foetal growth, which was associated with increased odds for child and adolescent anxiety disorders in both the categorized and continuous models. The association was linear after fitting in the continuous model and the associations remained significant after the data were adjusted for possible confounders.

No significant associations have previously been observed between SGA and anxiety disorders among children and adolescents (Guhn et al., 2020; Indredavik et al., 2004; Kingston et al., 2015). However, three register-based studies reported associations between being born SGA and anxiety-related disorders among mixed age groups (Abel et al., 2013; Larsen et al., 2021; Monfils Gustafsson et al., 2009). Our review did not identify associations between low birth weight and anxiety disorders in children and adolescents. A meta-analysis of six studies found that being born very preterm, or with a very low birth weight, was a risk factor for adolescent anxiety symptoms (Sømhovd et al., 2012).

Foetal growth restriction indicates that the foetal environment is not optimal. Brain development was reportedly altered among individuals with poor foetal growth, which can be explained by placental insufficiency and, therefore, a lack of oxygen and excessive oxygen radicals (Dudink et al., 2022). In addition, other important nutrients, particularly glucose, may be poorly transferred poorly due to placental malfunctioning. In addition, alteration in the HPA-axis have also been associated with poor foetal growth. (Swain et al., 2008)

When comorbidities were included in the analyses, the significant associations between poor foetal growth and pure anxiety disorders were lost, but associations remained significant for the comorbidity groups of depressive and neurodevelopmental disorders. It is worth to note that we studied WGA without further stratifications, meaning we did not separate those born preterm or term or neither did we separate those who had specific reasons, like genetic variance, for being born SGA.

The impact that comorbidities had on preterm birth and poor foetal growth could be discussed from various angles. The term comorbidity is not very clear. The term may be used just to indicate a precise co-occurrence of two disorders, or comorbidities may be seen as primary or secondary. In addition, the psychiatric classification system has been devised by humans, it is constantly evolving and not all the disease entities are necessarily biologically accurate (Angold et al., 1999).

A few different theories could explain why preterm birth or poor foetal growth were not associated with anxiety disorders and why the associations were only significant in the comorbidity groups. The aetiologies for anxiety, depressive and neurodevelopmental disorders might differ from each other and if that was the case it would indicate that there are no real associations between preterm birth, poor foetal growth and anxiety disorders. This hypothesis would highlight the aetiological differences between these disorders.

Another explanation is that one disorder could be secondary to the other, which was not examined in our study. In that case, the primary disorder could serve as a risk factor for the following disorder. If the comorbidities were primary, they could increase the risk of an anxiety disorder and again this would highlight that preterm birth or poor foetal growth does not have an impact on the development of anxiety disorders per se. However, this explanation becomes more complicated given that neurodevelopmental disorders are already common in early childhood, whereas depressive disorders are more commonly thought to be secondary to anxiety disorders (Wittchen et al., 2000).

The comorbidity groups could also have represented the more severe cases of anxiety disorders. Following the same ideology, pure anxiety disorders could also be a different disease entity to anxiety disorders with comorbidities. In addition, there could be some additional prenatal factors or genetic influences that increase the impact that preterm birth and poor foetal growth have on the development of psychopathology.

6.3.5 Birth type

This study found that birth by caesarean section increased the odds for anxiety disorders in the unadjusted and in the first adjusted model. The association between birth by planned caesarean and anxiety disorders became insignificant after an additional adjustment, which included maternal somatic diagnoses, but still showed a tendency. The association between birth by unplanned caesarean and anxiety disorders remained significant even in the additional analysis.

The finding that caesarean section increased the odds for anxiety disorders in the unadjusted and first adjusted model agreed with three previous register studies (Chen et al., 2020; Guhn et al., 2020; Larsen et al., 2021). However, two previous

studies did not report such association (Kingston et al., 2015; Zhang et al., 2021). The definition of anxiety disorders varied a lot in these studies, and not all studies performed comprehensive adjustments. The most comprehensive of these studies, from Sweden, studied planned and unplanned caesarean separately, but Zhang et al. (2021) did not find significant associations in the fully adjusted models. The reasons for these discrepancies could be due to the differing outcomes and age groups between the studies. Whereas Zhang et al. (2021) included stress-related disorders, they did not include childhood onset disorders. Study IV concentrated more precisely on child and adolescent anxiety disorders. Furthermore, Zhang et al. (2021) included numerous perinatal confounders for caesarean sections. Their final adjustments made the associations between birth by caesarean section and anxiety disorders insignificant. In study IV, only confounders that were known to be associated with caesarean sections and anxiety disorders were included. One limitation in study IV was that all possible perinatal factors may not have been included as confounders due to limited data in the Birth Register. However, significant indicators for foetal distress, namely Apgar scores, umbilical artery pH and neonatal monitoring were included as confounders.

Birth by caesarean section has been associated with neuropsychiatric and psychiatric outcomes (Brander et al., 2016; Chudal et al., 2014; Polo-Kantola et al., 2014; Sucksdorff et al., 2018). There are few hypothetical theories that explain these associations and these could be applicable for anxiety disorders as well. Those mechanisms include immunological alterations, prenatal and perinatal complications and parental factors.

The exposure to the microbiome during birth by caesarean section differs from the vaginal microbiome. That may lead to altered immunology in the child (Wampach et al., 2018). Not only is the microbiome altered by a caesarean section, but it is noteworthy that the administration of maternal antibiotics is common in caesarean sections and this could also lead to alterations in immunology (Yassour et al., 2016). These microbiome changes and immunological alterations have been associated with increased risk of somatic illnesses (Cho & Norman, 2013). They could also hypothetically lead to altered neurodevelopment in line with the theory of the gut-brain axis (Pronovost & Hsiao, 2019). In a study of rodents, the gut microbiome was related to altered neurodevelopment and emotional behaviour (Mayer et al., 2015).

Prenatal and perinatal adversities are common with caesarean sections (Mylonas & Friese, 2015). These could independently lead to altered neurodevelopment as discussed earlier in this thesis. Maternal somatic problems, infections or foetal distress could lead to the need of caesarean section and the infant's wellbeing may also deteriorate postnatally.

Maternal mental health, stress and behaviour are also important factors that need to be discussed. One study found that mothers who requested caesarean section had more mental health problems than other mothers giving birth (Sydsjö et al., 2015). In addition, mothers who undergo caesarean section may experience emotional distress and perceived loss of control (Lobel & DeLuca, 2007). These could have an impact on maternal behaviour and the attachment between the mother and her child. The maternal brain response has been observed to differ after caesarean section and oxytocin has been proposed as a possible mechanism for that (Swain et al., 2008).

The finding of that birth by caesarean section increased the risk of child and adolescent anxiety disorders is important due to the continued increase in caesarean sections (Betran et al., 2016). Although confounders were carefully selected in our study, some residual confounding factors may have existed, as the registers did not contain comprehensive data for all perinatal events. The ICD-10 diagnostic code for fear of giving birth was only added in 1997 (Saisto & Halmesmäki, 2003; WHO, 1992) and was not available for the oldest subjects. Furthermore, the generalizability of these findings is compromised by the globally varying rates of caesarean sections.

6.3.6 Birth outcomes

Study IV examined birth outcomes in addition to birth type. The one-minute Apgar-score, umbilical artery pH and neonatal monitoring were examined as birth outcome factors that could have associations with child and adolescent anxiety disorders. When any anxiety disorder was studied as the outcome, the Apgar score and neonatal monitoring increased the odds for anxiety disorders in the unadjusted analysis. No significant findings emerged in the adjusted analysis. However, neonatal monitoring was associated with specific phobias in the adjusted analysis and this is discussed in the following chapter on specific anxiety disorders.

One previous study found an association between having a low Apgar score and child and adolescent anxiety disorders, but it should be noted that the five-minute Apgar score was studied instead of the one-minute score (Kingston et al., 2015). Another study reported no associations between the one-minute Apgar score and anxiety disorders (Guhn et al., 2020). Furthermore, another study that included young adults did not find any association between the five-minute Apgar score and anxiety disorders. As mentioned earlier, the Apgar score is a very general measurement of a newborn infant's well-being and is not valid for indicating asphyxia or predicting neurological outcomes (Watterberg et al., 2015). The five-minute Apgar score could better describe an infant's status, as it reflects their

possible resuscitation status (Watterberg et al., 2015). Unfortunately, the five-minute Apgar score values were poorly recorded in the Birth Register.

No associations were observed between categorized or continuous umbilical artery pH and anxiety disorders. We were unable to find previous studies that had examined umbilical artery or venous pH and anxiety disorders. No studies were found that reported results for neonatal monitoring and all anxiety disorders. Two cohort studies examined neonatal monitoring and anxiety disorders, but they only reported findings for specific anxiety disorders and will therefore be discussed with regard to specific anxiety disorders.

The specific limitations for this study included the limited availability of the exposures. Although the one-minute Apgar score was well recorded, the five-minute score was available for not more than 2.9% of the sample. Umbilical artery pH was only available for less than half the sample. In addition, umbilical artery pH values may have contained incorrect recordings, as these were measured for clinical use.

6.3.7 Specific anxiety disorders

The associations between prenatal and perinatal risk factors and specific anxiety disorders were studied separately in studies III and IV. In the adjusted models, preterm birth was associated with increased odds for generalized anxiety disorder and post-term birth with a decreased rate of separation anxiety disorder. In the continuous analyses, inverse linear associations were observed between preterm birth and specific phobias. SGA was associated with an increased odd for specific phobias in the adjusted analyses, but no associations were significant when fitted in the linear model. It was noteworthy that the associations between preterm birth, poor foetal growth and specific phobias remained significant, even after controlling for the comorbidities of depressive and neurodevelopmental disorders. Birth by planned caesarean section was associated with increased odds for specific phobias, but not with other specific anxiety disorders. The only observed association for the birth outcomes was neonatal monitoring increasing the odds for specific phobias. In conclusion, specific phobias had the most associations with perinatal factors.

Previous register-studies on perinatal risk factors have not examined specific anxiety disorders separately. A meta-analysis on smaller studies showed significant associations between preterm born children and increased risks for unspecified anxiety disorders, generalized anxiety disorders and specific phobias (Fitzallen et al., 2021). The same mechanisms could apply to the associations between preterm birth, poor foetal growth and specific phobias, as discussed in the chapter for all anxiety disorders.

No previous studies could be found that examined birth type and specific anxiety disorders. Again, the mechanism could be very similar to the one that explained the associations between caesarean delivery and specific phobias than for any anxiety disorders. In addition, it is important to consider maternal phobias, as mothers with psychiatric disorders are more likely to undergo caesarean sections (Sydsjö et al., 2015). Fear, anxiety or phobias are commonly behind a mother's request for a caesarean (Jenabi et al., 2020). It is known that phobic disorders run in families (Hettema et al., 2001; Steinhausen et al., 2016). Although adjustments were made for maternal psychiatric disorders, and for fear of giving birth, it is possible that residual maternal anxiety was not recorded in registers.

With regard to neonatal monitoring, two relatively small cohort studies found somewhat similar findings. NICU treatment was associated with specific phobias and separation anxiety in children (Chiorean et al., 2020). This association could be explained by residual perinatal confounders or mediated through stress pathways. NICU treatment increases a newborn infant's stress (D'Agata et al., 2016). The infants may undergo multiple, painful and frightening procedures. These treatments may also continue during their life if they have more severe conditions. These experiences can be traumatic. Experiencing trauma is thought to be a possible aetiological factor for specific phobias (LeBeau et al., 2010). Painful procedures in NICUs have been associated with alterations in brain development (Brummelte et al., 2012). Stress-response alterations have also been observed after painful NICU treatments (Provenzi et al., 2016).

An infant's stress could also be increased by parental separation and by parental stress. Parental stress could impact independently on child's risk for anxiety, as it may impact on parental behaviour and parent-child interactions (Grunberg et al., 2019). Parents could also be oversensitized for their child's susceptibility to medical coniditions, due to the rough first moments of their child's life (Tallandini et al., 2014). NICU treatment in the 1990s was different from today, as parental participation is now desirable (Ahlqvist-Björkroth et al., 2017) and parental visits have increased (Latva et al., 2007). These changes may impact a child's well-being through both decreased infant and parental stress (Ahlqvist-Björkroth et al., 2017). One study found that children with less frequent parental visits in NICU were prone for behavioural problems later in life (Latva et al., 2004)

Aetiological differences for each specific anxiety disorder have previously been observed with regard to genetics (Hettema et al., 2005) and environmental factors (Fullana et al., 2020; Shanahan et al., 2008). The findings of this thesis indicate that aetiological differences may also be found in perinatal factors. These associations need to be further examined. The limitations of the findings for specific anxiety disorders were that the sample sizes were still modest because the vast majority of the diagnoses were classified under unspecific anxiety disorders.

The sample size for specific phobias was the largest and this could explain, why the findings concentrated on specific phobias. In addition, those mothers with undiagnosed anxiety and less severe phobias could have been missed. Their unrecorded anxiety could, nevertheless, have contributed to the associations.

It is important to recognise that this thesis contains novel findings, as the role of prenatal factors for specific anxiety disorders have not been studied much and no previous register-based studies were found. These findings may provide the basis for future research including even larger samples and more detailed research on specific anxiety disorder separately.

7 Conclusions

This thesis aimed to examine the associations between a wide range of prenatal and perinatal factors and anxiety disorders and the treated incidence of anxiety disorders. First, the background was comprehensively studied by conducting the systematic review. Then a nested case-control design examined several factors in a nationwide birth cohort of Finnish children and adolescents. Although several significant findings were observed between prenatal and perinatal factors and anxiety disorders, many of the associations could also be explained by comorbid conditions and residual confounding. Even if prenatal and perinatal factors have been shown to associate strongly with other mental health outcomes, findings of this thesis support the complex multifactorial aetiology model for anxiety disorders instead of providing major results for just prenatal or perinatal factors.

The treated incidence rates for anxiety disorders have increased over the years, at least in children. This increase could be due to increased anxiety symptomatology among children and adolescents, increased treatment seeking, reduced availability of primary interventions or diagnosing children at younger ages. In the future, Finland's health service system could decrease the burden of specialized services and the suffering of children and adolescents by offering adequate and effective early interventions. It is important to examine early risk factors in order to identify those in risk of anxiety disorders.

Low maternal SES and maternal single status at the time of the birth increased the odds for child and adolescent anxiety disorders. The odds were also higher for people living in Southern Finland and urban areas. These findings could be considered when planning possible selective prevention strategies.

The inverse linear association observed between preterm birth, poor foetal growth and anxiety disorders is of interest although the findings were alleviated by comorbid conditions, which are common among children and adolescents with anxiety disorders. Although the full impact of the comorbidities for the associations between preterm birth or poor foetal growth remain unknown, these findings highlight the importance of acknowledging the possible risks for those born preterm or SGA. They also highlight the importance of considering comorbidities when examining and treating anxiety disorders.

The rates for caesarean section are globally increasing and it is very important to identify possible later developmental issues. Birth by unplanned caesarean section was associated with increased odds for child and adolescent anxiety disorders. Although this association could be explained by residual perinatal and maternal confounders, this finding is significant. The other birth outcome factors that were studied were not associated with child and adolescent anxiety disorders. In addition, specific anxiety disorders were separately studied and specific phobias had the most associations with the examined perinatal variables. In contrast there were few findings for other specific anxiety disorders.

The findings of this study are not just adding to the knowledge about anxiety disorders. They are also raising new research questions.

7.1 Implications for future research

This study provides information on prenatal and perinatal factors and anxiety disorders in children and adolescents and raises questions for future research. There are multiple prenatal and perinatal factors which could potentially play a role in the development of anxiety disorders. This was evident also in our systematic review. However, not all prenatal and perinatal factors were studied in our case-control sample and factors such as maternal somatic or mental well-being during pregnancy could be studied in the future. Birth by caesarean section could be further studied by examining the possible remaining perinatal adversities. Studies could aim to collect even more comprehensive data on prenatal and perinatal factors, especially on mother's stress and mental well-being. Sibling studies would be optimal in distinguishing the impact of prenatal or perinatal factors and familial factors. To date, there are only few studies on maternal medications and a lack of biomarker studies for anxiety disorders.

The quantity and quality of the recorded data has improved over time and so have maternal and neonatal care and child and adolescent psychiatric services. Studies examining children and adolescents born in the 21st century could benefit from better availability of multiple variables. This would enable those studies to reflect the current prevalence of issues and treatment of perinatal period and anxiety disorders more accurately.

This thesis focused also on questions about anxiety disorder diagnoses. The diagnostic accuracy, disease entities and the interface with comorbidities are still not clear. Aetiological differences and commonalities between anxiety disorders and depressive disorders and between specific anxiety disorders need to be studied further in the future. Even larger sample sizes, genetic studies and sibling studies could provide more answers to these questions.

Diagnostic procedures for anxiety disorders may vary between clinics and clinicians and this sample showed that the use of unspecific diagnoses has been common. This is understandable from a clinical perspective as the symptoms reported by children and adolescents, or their parents, may be imprecise, fluctuate and be mixed with normal developmental processes. However, the ideal situation would be to aim for more accurate diagnoses and to only use unspecific diagnoses when necessary.

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