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A Population-based Register Study

Minna Sucksdorff

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To my family

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder, which is characterized by impairing symptoms of hyperactivity, inattention and impulsivity. ADHD is known to be highly heritable, but pre- and perinatal risk factors are also thought to play a role in the etiology of the disorder. The aim of this thesis was to investigate the association between ADHD and prenatal and perinatal risk factors such as preterm birth, fetal growth, obstetric risk factors, fetal exposure to nicotine and maternal vitamin D levels.

The data consisted of 10 409 cases, born between 1991 and 2005, who had received a diagnosis of ADHD by the end of 2011. Four controls were identified for each case and matched by sex and the place and date of birth (n=40 141). The data was obtained by combing information from three nationwide registers: the Care Register for Health Care (previously called the Finnish Hospital Discharge Register), the Finnish Medical Birth Register and the Finnish Population Register Centre. In addition, for a subsample of cases born between 1998 and 1999 (n=1079 case-control pairs) maternal sera samples were obtained from the Finnish Maternity Cohort biobank.

We found that preterm birth was a risk factor for ADHD and that each declining week increased the risk. Furthermore, poor fetal growth increased the risk of ADHD. In addition, birth by planned C-section and perinatal adversities leading to lower Apgar scores were associated with an increased risk of ADHD.

Fetal exposure to nicotine measured by cotinine was associated with an increased risk for later ADHD and the risk showed a dose-response relationship. Moreover, low maternal vitamin D levels during pregnancy were associated with an increased risk for ADHD in the offspring.

This thesis study identified several prenatal and perinatal factors that were associated with an increased risk of ADHD. The study setting cannot prove definite causal inferences and entirely rule out environmental and genetic effects. Nevertheless, all of the identified risk factors represent unfavorable fetal circumstances and highlight the importance of maternal wellbeing for offspring neurodevelopment.

KEYWORDS: ADHD, Attention-deficit/hyperactivity disorder, prematurity, prenatal, perinatal, mode of delivery, smoking during pregnancy, cotinine, vitamin D, nationwide registers

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
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TIIVISTELMÄ

Aktiivisuuden ja tarkkaavaisuuden häiriö eli ADHD on yleinen lapsuusiässä alkava neuropsykiatrinen häiriö, jolle on ominaista arkielämää haittaava yliaktiivisuus, tarkkaamattomuus ja impulsiivisuus. ADHD:n synnyssä perinnöllisen alttiuden lisäksi pre- ja perinataalisilla tekijöillä on oma merkityksensä. Tämän väitöskirjatutkimuksen päämääränä oli selvittää ADHD:n yhteyttä syntymäviikkoihin ja sikiöaikaiseen kasvuun, syntymävaiheen ja muihin raskausajan mahdollisiin riskitekijöihin, sikiökautiseen nikotiinialtistukseen sekä äidin raskaudenaikaiseen D-vitamiinitasoon.

Tutkimuksen aineisto koostui 10 409 lapsesta, jotka olivat syntyneet vuosina 1991–2005, ja saaneet erikoissairaanhoidossa ADHD:n diagnoosin. Heistä kullekin kaltaistettiin neljä verrokkia iän, sukupuolen ja syntymäpaikan mukaan (n=40 141). Aineisto koostettiin yhdistämällä tietoja Hoitoilmoitusrekisteristä, Syntymärekisteristä ja Väestörekisterikeskuksesta. Väitöskirjatutkimuksen osatöissä, joissa tutkittiin äidin raskaudenaikaisia verinäytteitä, aineistona toimi vuosina 1998-1999 syntyneet ADHD-diagnoosin saaneet lapset (n=1079) ja kullekin yksi verrokki.

Ennenaikainen syntymä osoittautui merkittäväksi ADHD:n riskitekijäksi. ADHD:n riski oli sitä suurempi, mitä varhaisemmilla syntymäviikoilla lapsi oli syntynyt. Sikiön epäsuotuisa kasvu lisäsi ADHD-riskiä. Matalammat vastasyntyneen Apgar-pisteet olivat myös yhteydessä kohonneeseen ADHD:n riskiin. Syntymä suunnitellulla keisarileikkaukella lisäsi hieman ADHD-riskiä.

Sikiön altistuminen nikotiinille oli yhteydessä kohonneeseen ADHD-riskiin. Altistusta mitattiin äidin seerumin kotiniinipitoisuuksilla. Lisäksi äidin matala raskaudenaikainen D-vitamiinitaso lisäsi jälkeläisen ADHD-riskiä.

Löysimme monia tekijöitä, jotka lisäsivät ADHD:n riskiä. Tutkimusasetelma ei kuitenkaan voi täysin todistaa syys-seuraussuhteita ja kokonaan poissulkea geneettisten ja ympäristön tekijöiden vaikutusta. Löydetyille tekijöille oli yhteistä epäsuotuisat olosuhteet raskausaikana. Tämä korostaa raskaudenaikaisen hyvinvoinnin merkitystä jälkeläisen myöhempään mielenterveyteen.

AVAINSANAT: ADHD, Aktiivisuuden ja tarkkaavaisuuden häiriö, keskosuus, prenataalinen, perinataalinen, synnytystapa, raskaudenaikainen tupakointi, kotiniini, D-vitamiini, kansalliset rekisterit

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Abbreviations

AAP	American Academy of Pediatrics
ADHD	Attention-deficit/hyperactivity disorder
AGA	Appropriate for gestational age
APA	American Psychiatric Association
CI	Confidence interval
CRHC	Care Register for Health Care
DSM	Diagnostic and Statistical Manual for Mental Disorders
FPRC	Finnish Population Register Centre
FHDR	Finnish Hospital Discharge Register
FIPS	Finnish Prenatal Study
FMBR	Finnish Medical Birth Register
FMC	Finnish Maternity Cohort
ICD	International Classification of Disease
LGA	Large for gestational age
WGA	Weight for gestational age
NICU	Neonatal intensive care unit
OR	Odds ratio
SD	Standard deviation
SE	Standard error
SGA	Small for gestational age
THL	The Finnish Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)
WHO	World Health Organization
25(OH)D	25-hydroxivitamin D

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 Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, Sourander A. Preterm Birth and Poor Fetal Growth as Risk factors of Attention-Deficit/Hyperactivity Disorder. *Pediatrics*, 2015; Sep: 136(3):e599–608.

II Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Gissler M, Sourander A. Lower Apgar Scores and Caesarean Sections Are related to Attention-Deficit/ Hyperactivity Disorder. *Acta Paediatrica*, 2018; 107 (10), 1750–1758.

III Sourander A, Sucksdorff M, Chudal R, Surcel HM, Hinkka-Yli-Salomäki S, Gyllenberg D, Cheslack-Postava K, Brown AS. Prenatal Cotinine Levels and ADHD among Offspring. *Pediatrics*, 2019; 143(3):e20183144.

IV Sucksdorff M, Brown AS Chudal R, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Gyllenberg D, Sourander A. Maternal Vitamin D Levels and the risk of Offspring Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2021¸ Jan; 60(1):142–151.

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) -often called simply by its abbreviation ADHD- is a common neurodevelopmental disorder. It is characterized by impairing symptoms of inattention, hyperactivity and impulsivity. The symptoms of ADHD begin in childhood, have a chronic course, and tend to adversely affect the academic achievements and social interactions of the individual (Subcommittee on Attention-Deficit/Hyperactivity Disorder et al., 2011). The diagnosis requires that the symptoms are age-inappropriate and long-standing, and that they present across more than one setting i.e. at home and at school.

ADHD is in fact a diagnostic category in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (APA, 1994). The broadly equivalent diagnosis used mostly in Europe -and thus also in Finland- is called Hyperkinetic disorder. Hyperkinetic disorder is defined in the WHO's International Classification of Diseases, ICD (World Health Organization, 1992). This thesis will refer to ADHD both when discussing the ICD-10 based diagnosis Hyperkinetic disorder as well as the DSM-based diagnosis of ADHD. The diagnostic classification will be presented in the next chapter of this thesis.

ADHD can be described as a heterogeneous neurodevelopmental disorder as the phenotype varies from a mostly hyperkinetic to a predominantly inattentive type (Mahone & Denckla, 2017). Approximately two-thirds of children and adolescents with ADHD also have at least one comorbid developmental or psychiatric condition (Larson, Russ, Kahn, & Halfon, 2011).

It is estimated that ADHD affects around 5 % of the child population worldwide, which therefore makes it a significant public health issue (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, the diagnostic classifications and cultural factors affect how much the ADHD is screened, diagnosed and treated within each society (Smith, 2017). There are some differences between various countries and cultures in the recognition and acceptance of ADHD. Therefore, the surroundings where the child is growing up also play a role; what is considered impairing might vary depending on the surrounding expectations and requirements (Taylor, 2011).

While getting acquainted with the history of ADHD, one cannot avoid noticing a certain debate in the literature about how much of ADHD can be explained by inherited or biological factors and how much by environmental elements. It is acknowledged that ADHD does have a strong heritable component, but environmental factors and gene-environment interactions appear to play an important role in the development of the disorder as well.

Pregnancy is an essential period of unique sensitivity for the later health of an individual. The environment in the womb influences the genetically pre-programmed development of the fetus. The current understanding is, that the course of an indvidual's development may be modified by prenatal factors like the mother's nutrition, infections, psychiatric status, medications, substance use and perinatal events (Freedman, Hunter, & Hoffman, 2018). Information is constantly accumulating on the importance of antenatal maternal well-being and fetal growth as the earliest modifiers for later adverse mental health outcomes (O'Donnell & Meaney, 2017).

Concerning ADHD, no single risk factor, however, is necessary nor sufficient to explain the disorder (Thapar & Cooper, 2016). Many genetic and environmental factors may contribute to the risk of ADHD. The pattern of inheritance seems to be multifactorial. Gene-environment interactions are possibly the mechanisms by which certain environmental risk factors increase the risk of ADHD in some individuals (Faraone et al., 2015; Thapar & Cooper, 2016). It seems that what is inherited is a set of traits rather than the actual disorder. The inherited traits may be a predisposition to react to certain environmental factors such as psychosocial risk factors (Taylor, 2011).

In the Nordic countires, the population-based studies utilizing nationwide registers provide an excellent setting for studying psychiatric epidemiology and various risk factors. The comprehensive, prospectively accumulated data concerning perinatal, health-related and demographic factors can be utilized to conduct epidemiological research with large data sets. This also enables taking into account several potential confounding factors (Smith, 2017). In Finland, the archived maternal sera samples add to this comprehensive nationwide register data.

Untreated ADHD is a significant risk factor for lower academic achievement, criminality, accidents, substance misuse and even mortality (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015). ADHD sets a costly price on an individual, family, schools and health care. Therefore it is important to improve understanding of the disorder's etiology, to enable earlier identification, treatment, and even prevention and to diminish the burden of the disorder for individuals and society (Mahone & Denckla, 2017).

2 Review of the Literature

2.1 The diagnostic classification of ADHD

Psychiatric disorders worldwide are mostly classified using two different diagnostic systems; 1) the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), and 2) the WHO's International Classification of Diseases (ICD). Currently the DSM-5 and the ICD-10 are in use. ADHD is a category in the DSM and the broadly equivalent diagnosis in the ICD is called Hyperkinetic disorder.

The contemporary definition of ADHD is relatively new dating back to only a few decades ago (APA, 1994). However, children presenting with symptoms of inattention, hyperactivity, and impulsivity have been described in the literature by several authors already more than 200 years ago (Lange, Reichl, Lange, Tucha, & Tucha, 2010). The recognition and treatment of ADHD date to the second half of the 20th century (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014).

The American Psychiatric Association's second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) first described a "Hyperkinetic reaction of Childhood" in 1968. In 1980, DSM-III defined "Attention Deficit Disorder", ADD and created the first reliable diagnostic criteria for the disorder (Faraone et al., 2015). Subtypes were first introduced with the DSM-III, and included ADD with or without hyperactivity. Thereby attention and more so inattention, instead of hyperactivity, became the central characterizing feature of the disorder (Mahone & Denckla, 2017). Furthermore, etiological formulations were replaced with a description of the observable behavior (Taylor, 2011).

A subsequent revision, DSM-III-R, renamed the condition to its present form "Attention-Deficit/Hyperactivity Disorder" and DSM-IV further defined inattentive, hyperactive / impulsive and combined subtypes (APA, 1994). The currently used DSM-V extended the age of onset to 12 years, whereas in DSM-IV (and ICD-10) it was 7 years (American Psychiatric Association, 2013).

In Finland, the diagnostic classification is based on the International Classification of Diseases (ICD). The ICD-10 has been used since 1996 (World Health Organization, 1993). From 1987 to 1995 the diagnoses were coded according to ICD-9, and from 1969 to 1986 according to ICD-8. The ICD-8 included the

"Hyperkinetic disorder" and successive revisions (ICD-9 and ICD-10) have maintained it as the name of the category into which hyperactive, impulsive, and inattentive children should be included (Taylor, 2011).

The currently used ICD-10 defines hyperkinetic disorder (diagnostic code F90 in ICD-10) as a psychiatric disorder emerging in early childhood. It is characterized by enduring and severe, developmentally inappropriate inattention, hyperactivity and impulsivity. The symptoms must be present across different settings (i.e. home *and* school) and they must significantly impair academic, social and work performance (World Health Organization, 1993). The duration of the disabling and age-inappropriate symptoms must have lasted for at least six months and must have commenced before the age of seven years. In addition, a mood disorder, mania, anxiety disorder, pervasive developmental disorder or psychosis may not be present.

The ICD-10 criteria do not distinguish the subtypes (Thapar & Cooper, 2016). However, in clinical practice the three different phenotypes can be identified as the predominantly inattentive type, the predominantly hyperactive-impulsive type and the combined type. The current clinical guidelines in Finland (Käypä Hoito suositus) recommend the use of the F90.0 diagnostic code also for the inattentive type, with a verbal addition to indicate the subtype (Puustjärvi et al., 2017). The ICD-10 and DSM-IV criteria for hyperkinetic disorder / ADHD overlap, but the DSM-IV criteria are generally broader and the ICD-criteria stricter; the ICD captures more severely affected individuals (Lahey et al., 2006; Thapar & Cooper, 2016; Tripp, Luk, Schaughency, & Singh, 1999)

The diagnostic classification of ADHD in the ICD-10 is presented in Appendix 1.

2.2 Epidemiology of ADHD

2.2.1 Prevalence

ADHD is a common disorder among children worldwide. The prevalence estimates of the disorder vary somewhat depending on the study and the diagnostic criteria. A few systematic reviews have examined the community prevalence of ADHD.

The first broad systematic review and meta-analysis conducted in 2007 that covered over 100 studies, reported a worldwide prevalence estimate of 5.3% for ADHD (Polanczyk et al., 2007). This study included both DSM and ICD based diagnoses and studies from all continents. A more recent meta-analysis by the same authors reported a prevalence rate of 3.4% for ADHD based on 33 community studies that simultaneously investigated the prevalence rates of multiple mental

disorders based on DSM and ICD criteria (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015).

A meta-analysis published in 2012, which covered 97 studies using DSM-IV criteria for ADHD, reported a prevalence estimate of 5.9–7.1% (Willcutt, 2012). In the subanalyses of this study, the prevalence was found to be similar whether ADHD was defined by parent ratings, teacher ratings or by professionals. Another meta-analysis published in 2015, which examined studies using DSM based diagnoses (different DSM editions), reported a prevalence rate of 7.2% for ADHD (Thomas, Sanders, Doust, Beller, & Glasziou, 2015).

Based on these studies, there does not seem to be any obvious variation between the community prevalence of ADHD between different geographical locations i.e. continents. Variation in the reported prevalence rates appears to be explained by methodological differences between different studies. From a global perspective, there is, however, an underrepresentation of studies from low- and middle-income countries (Sayal, Prasad, Daley, Ford, & Coghill, 2018).

In a Finnish study examining register-based diagnoses from specialized health care among children born in 1996, the cumulative incidence of ADHD by age 14 was 2.0% (Gyllenberg et al., 2014). The lower prevalence rate is explained by the sample consisting only of patients treated in specialized services. In a study based on parent and teacher questionnaires, 7.1% of Finnish children aged 8 to 9 years were reported having an ADHD diagnosis (Almqvist et al., 1999).

According to a systematic review published in 2014 and covering 135 studies from the past three decades, there is no evidence to suggest an increase in the number of children in the population who meet the criteria for ADHD when standardized diagnostic criteria are used (Polanczyk et al., 2014). This is supported by two Nordic studies. A Finnish study that found no increase in ADHD *symptoms* in reports by parents or teachers during a time period from 1989 to 2013 (Sourander, Lempinen, & Brunstein Klomek, 2016). A Swedish study examining ADHD symptoms in the general population between 2004–2014 reached the same conclusion: no evidence of an increase in ADHD-like traits (Rydell, Lundström, Gillberg, Lichtenstein, & Larsson, 2018).

By contrast, the number of people with *clinically diagnosed* ADHD has, however, been increasing. A population-based cohort combining data from Nordic countries reported that the cumulative incidence of registered diagnoses have increased over the past 20 years (Atladottir et al., 2015). Moreover, the number of children and adolescents receiving stimulant medication for ADHD has substantially increased in high-income countries over the past two or three decades (Dalsgaard, Nielsen, & Simonsen, 2013; McCarthy et al., 2012). In Finland, the trend in the number of children and adolescents using stimulant medication has continued to steadily increase between 2008 and 2018 (Vuori, Koski-Pirilä, Martikainen, &

Saastamoinen, 2020). As an example among boys aged 6 to 12 years, 1.26% were using stimulant medication in 2008, whereas in 2018 the percentage was 4.42%. The increase is primarily thought to reflect better identification and improved access to treatment. However, some concern has also been raised that, in some instances, this could also be suggestive of overdiagnosis (Sayal et al., 2018). In addition, the demands of society have perhaps changed to a direction where symptoms are less well tolerated and not compatible with the demands of schools or working life.

2.2.2 Comorbidity

Approximately two thirds of children and adolescents with ADHD have at least one comorbid condition in addition to ADHD based on a cross-sectional analysis on children and adolescents aged 6 to 17 years (Larson et al, 2011). The comorbidities typically include learning disabilities, autism spectrum disorder, depression and anxiety (Larson et al., 2011). ADHD also shows high comorbidity with behavioral problems such as oppositional defiant disorder and conduct disorder, which may lead to a worse prognosis in children with ADHD (Thapar & Cooper, 2016).

2.2.3 Gender differences

ADHD is more common among boys than among girls, but the extent of male predominance varies depending on the study. It is affected by whether the study is based on clinical, treated samples or whether the study reports a community based prevalence. In clinical samples the male / female ratio is reported to be approximately 7–8:1 whereas in community samples it is approximately 2–3:1 (Biederman et al., 2002; Sayal et al., 2018; Thapar & Cooper, 2016). It appears that the phenotype in girls is somewhat different: typically manifesting with less comorbid disruptive behavior, and thus creating a referral bias and a barrier to care.

2.2.4 Other demographic characteristics

Based on current literature, receiving a diagnosis of ADHD or medication for it, is more common among children who are at a younger relative age compared to their classmates (Holland & Sayal, 2019; Sayal, Chudal, Hinkka-Yli-Salomäki, Joelsson, & Sourander, 2017). A previous study on this data showed that the children who had a younger relative age in the school class were more likely to receive a diagnosis of ADHD. Children born between September and December had an incidence ratio of 1.64 (95% CI 1.48–1.81) compared to children born between January and April (Sayal et al., 2017). The difference was seen between children born in January and December so the winter season as such could not be accounted for for this finding.

This finding suggests that adults could be misattributing signs of relative immaturity as symptoms of ADHD.

The literature concerning birth order and ADHD has shown somewhat inconsistent results. Some studies have found a higher risk for ADHD among first-born children compared to younger siblings and also compared to single children (Marín et al., 2014; Reimelt et al., 2021). Younger parental age has also been shown to be a risk factor for offspring ADHD (Chudal et al., 2015; McGrath et al., 2014).

2.3 Etiology of ADHD

2.3.1 Genetics

ADHD is thought to be multifactorial by etiology. It is suggested to be a highly heritable disorder. According to twin studies, the heritability estimates of ADHD are approximately 70–80% (Faraone et al., 2015). The first-degree relatives of individuals with ADHD have a 5- to 10-fold increased risk in developing ADHD themselves (Faraone et al., 2015).

However, no single gene nor mutation can explain the genetic component of ADHD. ADHD is associated with multiple genes of small effect, and gene–environment interactions (Mahone & Denckla, 2017). Genome-wide association studies have found several statistically significant genetic loci at the genome-wide level (Faraone & Larsson, 2019). Several different kinds of genetic variants have been associated with ADHD risk. These include common DNA sequence variants called single nucleotide polymorphisms (SNPs) which occur in over 5% of the population. However, it appears that these variants have only a small effect and associations are reported only when thousands of SNPs occur together (Thapar & Cooper, 2016).

In addition, some individuals present with rare chromosomal mutations such as deletions and duplications called copy number variants (CNVs) that have also been associated with a risk of ADHD. They are rare and occur in less than <1% of the population, but have a larger effect size in affected individuals (Thapar & Cooper, 2016).

There is also considerable overlap between the genes associated with ADHD and those associated with schizophrenia, autism and mood disorders (Faraone et al., 2015; Thapar & Cooper, 2016). The candidate genes that have previously been associated with ADHD mostly involve genes responsible for dopamine, serotonin and noradrenaline regulation.

2.3.2 The background for studying prenatal exposures in neuropsychiatric disorders

The background for studying the effect of the prenatal environment on later health outcomes is primarily based on the British epidemiologist David J. Barker's observations on the association between low infant birth weight and a later risk for hypertension, coronary heart disease and metabolic problems (Barker & Osmond, 1988; Barker, Winter, Osmond, Margetts, & Simmonds, 1989). The Barker's hypothesis was that maternal malnutrition and other factors leading to poor fetal growth seem to program the fetus to adverse tissue differentiation in a manner that predisposes to later illness (Kim, Bale, & Epperson, 2015; O'Donnell & Meaney, 2017).

The same mechanisms have been proposed to be able to prenatally program offspring development towards neuropsychiatric problems. Among the first scientific evidence on prenatal insults and later psychiatric problems is the association between prenatal nutritional deficiency and offspring schizophrenia. The Dutch Hunger winter in 1944-1945 allowed for retrospective evaluation of the effect of prenatal famine on offspring risk of schizophrenia. Due to a German blockade towards the end of World War II, the food supplies in the cities of Western Netherlands rapidly ran out resulting in extreme famine and malnutrition. The famine ended abruptly on liberation in the spring of 1945. This unique, historical cohort exposed to prenatal nutritional deficiency during conception, was compared to an unexposed cohort conceived either just before or immediately after the Hunger Winter. The outcome was that the most exposed cohort, conceived at the height of the famine, showed a two-fold risk for schizophrenia later in their life (Susser et al., 1996).

Similarly, infections experienced by the pregnant mother, particularly influenza, have been among the earliest exposures of research interest for later psychiatric or neurodevelopmental disorders, especially schizophrenia (Mednick, Machon, Huttunen, & Bonett, 1988). Studies have suggested that viral infections at critical phases of the pregnancy may lead to adverse outcomes either in genetically predisposed individuals or in individuals who later experience severe life stress (Mednick et al., 1988).

These earliest observations have further expanded the field of studying prenatal exposures to other neuropsychiatric disorders such as autism and ADHD. Concerning ADHD, literature from the the past two decades has linked various environmental factors and exposures with increased risk for ADHD. Different prenatal and perinatal factors, environmental toxins, dietary factors and psychosocial factors have been associated with an increased risk of ADHD in epidemiological studies (Sciberras, Mulraney, Silva, & Coghill, 2017; Thapar, Cooper, Eyre, &

Langley, 2013) Overall, estimates have concluded that between 10 to 40 % of the variance associated with ADHD is accounted for these kind of environmental risk factors (Banerjee, Middleton, & Faraone, 2007; Sciberras et al., 2017). The mechanisms by which environmental factors mediate susceptibility, are however not yet well understood (Mill & Petronis, 2008).

2.3.3 Epigenetics and gene-environment interplay

Epigenetics examines factors that alter genomic function, but can change due to the effect of the environment. These factors are inherited and do not change the actual DNA sequence, but can cause changes to genomic functions. These include DNA methylation, histone modification, and effects on RNA. They affect the regulation of gene expression and gene silencing, and can thus affect the developing phenotype. Unlike the DNA sequence, which is very stable, epigenetic processes are tissue-specific and very dynamic (Mill & Petronis, 2008).

It appears that early life experiences like stress, inflammation or infection, and non-optimal parental care, are able to program the brain towards vulnerability or on the ther hand resilience to a disease. Environmental insults- not just chemical, but also psychosocial- can mediate gene expression through epigenetic modulation during certain sensitive developmental periods (Bale et al., 2010; Szyf, Weaver, & Meaney, 2007). Epigenetic processes can fine-tune brain development to determine how an individual develops and how he or she responds to exposures and experiences later in life (Bale, 2015). Parental care, the early social environment, as well as chemical toxins appear to -either directly or via interactions with direct genetic factors- affect the risk of childhood ADHD (Mill & Petronis, 2008).

2.3.4 Psychosocial risk factors

Early psychosocial adversity is considered to be a likely etiological risk factor for many mental health problems, including ADHD (Østergaard et al., 2016, Thapar, Cooper, Eyre, & Langley, 2013). Psychosocial risk factors such as low income, family adversity, and harsh or hostile parenting have been associated with child ADHD (Thapar, Cooper, Eyre, & Langley, 2013). A systematic review published in 2016 reported a consistent association from across five continents between socio-economic disadvantage and child ADHD (Russell, Ford, Williams, & Russell, 2016). Children from families with a lower SES had about a 2-fold risk for ADHD compared to their peers in high-SES families. The studies measured various combinations of parental income, education, occupation and single parenthood as indicators of SES.

A large population-based study from Denmark studied whether the Rutter's indicators of adversity in infancy were early predictors for the development of ADHD (Østergaard et al., 2016). The Rutter's indicators of adversity include low social class, severe marital discord, large family size, paternal criminality, maternal mental disorder, and placement in out-of-home care. The study showed that these indicators for adversity assessed in infancy strongly predicted child ADHD. There was a dose-response relationship between the indicator scores and the risk for developing ADHD (Østergaard et al., 2016).

It also appears that the accumulation of many risk factors on the same individual displays a cumulative effect. A Finnish study that identified e.g. parental depressive symptoms, a negative family atmosphere and child's shorter sleep duration as risk factors for ADHD symptoms, also reported that children with several risk factors together had the highest risk for ADHD symptoms (Huhdanpää et al., 2020).

The difficulty lies in investigating the direction of the relationship between psychosocial adversity and child ADHD. For example, family conflicts may be seen more often seen in in families with a child with ADHD. (Thapar, Cooper, Eyre, & Langley, 2013). The child's ADHD may negatively affect the mother–child relationship and result in the use of negative parenting styles. It appears that negative mother–child relationships arise as a consequence of the ADHD symptoms rather than vice versa, and even improve with treatment or parent training (Thapar, Cooper, Eyre, & Langley, 2013, Huhdanpää et al., 2020). However, exposure to severe, early deprivation seems to be different and causal, which has been shown for example in studies on Romanian orphans (Thapar & Cooper, 2016).

It is possible that even if psychosocial adversity might not play a causal role in the etiology of ADHD, these factors may contribute to the outcome of the child and result in secondary adverse consequences (Thapar, Cooper, Eyre, & Langley, 2013). In addition, many of the adverse psychosocial factors may be a consequence or a manifestation of the parent's own ADHD.

2.3.5 General environmental and prenatal risk factors

Many environmental and especially prenatal risk factors have been associated with an increased risk of ADHD in epidemiological studies. Previous research has reported associations with maternal substance use and stress during pregnancy, prematurity, low birth weight and a number of other pregnancy, labor, delivery or infancy complications (Banerjee et al., 2007; Sciberras et al., 2017). There are three rather recent review articles covering the role of prenatal and environmental risk factors and ADHD (Banerjee et al., 2007; Froehlich et al., 2011; Sciberras et al., 2017).

Maternal alcohol use during pregnancy has been associated with an increased risk of ADHD symptoms in offspring in some studies, whereas others have not found any association (Banerjee et al., 2007; Rodriguez et al., 2009; Langley, Heron, Smith, & Thapar, 2012; Sundquist, Sundquist, & Ji, 2014). Possibly biased self-reporting of alcochol use and a strong correlation with social adversity complicate the research on this topic. Furthermore, due to difficulties in obtaining reliable research methods, there is a lack of studies investigating a possible association between maternal illicit drug use and ADHD symptoms (Sciberras et al., 2017).

There is conflicting evidence about a possible risk increase associated with maternal anti-depressant use during pregnancy and ADHD (Clements et al., 2015; Laugesen, Olsen, Telén Andersen, Frøslev, & Sørensen, 2013). As with many other identified risk factors, sibling models have attenuated some observed positive associations. Maternal major depressive disorder and maternal stress in pregnancy have been associated with offspring ADHD in some studies, but these studies have also had some limitations concerning genetic confounding and family psychosocial factors (Clements et al., 2015; Sciberras et al., 2017).

Some studies have reported a link between paracetamol use during pregnancy and an increased risk of ADHD, but a recent meta-analysis suggested, that based on their bias analyses, the previously reported associations may also be affected by unmeasured confounding such as parental health conditions (Masarwa, Platt, & Filion, 2020).

The research evidence concerning environmental toxins has identified a link between lead exposure and ADHD (Banerjee et al., 2007; Froehlich et al., 2011). However the effect size of this risk factor has been considered to be modest. There is also some evidence of links between exposure to mercury and hyperactivity and a lack of manganese and hyperactivity (Banerjee et al., 2007). Another group of developmental toxin widely studied in relation to neurodevelopment is the class of polychlorinated biphenyls i.e. PCBs. They are highly stable organic chlorine compounds earlier widely used as heat-resistant insulators, sealing compounds etc., that are now recognized as environmental toxins. There are some studies showing a positive association between prenatal PCB exposure and child inattention (Banerjee et al., 2007; Schantz, Widholm, & Rice, 2003).

In this thesis the role of 1) prematurity and fetal growth, 2) obstetric and neonatal risk factors, 3) maternal smoking and 4) maternal vitamin D deficiency will be discussed more thoroughly in the following chapters, as they are the focus of this doctoral research.

2.4 Prematurity and ADHD

2.4.1 Definitions of prematurity

According to WHO the definition of birth requires that the pregnancy has lasted 22 weeks or that the fetus weighs at least 500 grams (World Health Organization, 1996). The WHO defines preterm birth as a birth before 37 completed weeks of gestation. In Finland, the incidence of preterm deliveries is approximately 5–6%, but the incidence varies substantially between different countries (Gissler & Kiuru, 2019). The incidence of prematurity is about 18% in some African countries and 12–13% in the U.S. (Blencowe et al., 2012).

Preterm births can be further divided into: extremely preterm (<28 weeks), very preterm (28–<32 weeks), and moderate or late preterm (32–<37 completed weeks of gestation). About 5% of preterm births occur at less than 28 weeks, about 15% at 28–31 weeks, about 20% at 32–33 weeks, and 60–70% at 34–36 weeks. In Finland, infants born before week 32 or weighing less than 1500 grams account for 0.9% of all births (Gissler & Kiuru, 2019).

Preterm birth may result after 1) spontaneous labor with intact membranes (40–45%), 2) preterm premature rupture of membranes (PPROM) (25–30%), or 3) labor induction or caesarean delivery for maternal or fetal indications (30–35%) (Blencowe et al., 2012; Goldenberg, Culhane, Iams, & Romero, 2008). Spontaneous preterm birth is a multifactorial process. In about half of the cases, the precise cause of the spontaneous preterm labor remains unidentified (Menon, 2008). The risk factors for preterm labor include a multiple pregnancy, an individual or family history of preterm deliveries, young or advanced maternal age, short interpregnancy intervals, low maternal body-mass index, hypertensive disease of pregnancy, and infections (Goldenberg et al., 2008). Depending on the predisposing factors and its triggers, preterm birth cannot be considered only as a premature termination of gestation, but rather as an abnormal, stressful and inflammatory event for both the mother and fetus (Gotsch et al., 2009).

2.4.2 Prematurity as a risk factor of ADHD

The population-based studies investigating the association between prematurity and diagnosed ADHD are presented in Table 1.

With the remarkable advances in perinatal and neonatal care over the past few decades, the survival and the developmental prognosis of preterm infants has substantially improved. The vast majority of preterm infants today survive without

major neurodevelopmental disabilities. However, there is a rising concern about later challenges with inattention and hyperactivity and learning difficulties by school age.

The association between prematurity and attention problems is an extensively studied topic especially in numerous cohort studies examining questionnaire-based ADHD symptoms. In a number of studies, premature birth and low birth weight have been shown to increase the risk of ADHD.

Four Nordic population-based studies have shown an increased risk of diagnosed ADHD related to preterm birth (D'Onofrio et al., 2013; Halmoy, Klungsoyr, Skjaerven, & Haavik, 2012; Lindstrom, Lindblad, & Hjern, 2011; Linnet et al., 2006). Late-preterm children in these studies have also had a moderate, but steady risk of ADHD. In addition, a slightly increased risk related to early-term birth has been reported in studies from Denmark, Sweden, and Australia (Lindstrom et al., 2011; Linnet et al., 2006; Silva, Colvin, Hagemann, & Bower, 2014). A case-control study from Catalonia, Spain found similar results; the prevalence of ADHD increased as gestational age decreased and the effect was still seen among late preterm children (Perapoch et al., 2019). In addition, a recent register study from Norway reported higher rates of prescription of psychostimulant drugs among individuals with all degrees of preterm birth compared with those born at term (Bachmann, Risnes, Bjørngaard, Schei, & Pape, 2021).

A few other studies, however, have shown contradictory results. A large birth cohort study from the United States found no increased incidence of ADHD in late-preterm children (Harris et al., 2013). In a large Australian study, a lower gestational age did not remain as a risk factor for ADHD after adjustment for all confounders (Silva et al., 2014). In addition to specific methodological aspects, the similarity of the health care systems in the Nordic countries may explain consistent findings from the Nordic studies compared to studies from the United States and Australia. In addition, in the study by Silva et. al, the authors stated that their final models adjusted for such a large number of factors, that it is possible it resulted in reduced precision, and may have blurred real associations (Silva et al., 2014).

Table 1. Population-based studies on gestational age and ADHD.

Author, Publication year, Country	Study Design	ADHD diagnosis	Sample size Time of birth	Patients' age range and time of evaluation	Classification of gestational weeks	Confounders	Results	Measures of association
Linnet *et al.* 2006, Denmark	Population-based register study Case-Control	ICD-10	n=834 cases, n=20 100 controls (matched for sex, birth date) -Born between 1980 and 1994	Hyperkinetic disorder before 1999 (from Danish Psychiatric Central Register)	26–33 34–36 37–39 40–42 (ref) 43–44	Socioeconomic factors (income, education, cohabiting), parental age, parity, familial psychopathology (also siblings), smoking available from 1991	Children born preterm and close to term had an increased risk hyperkinetic disorder	RR_{adj} <34: 3.3. (95% CI 2.0–5.4) 34–36: 1.6 (95% CI 0.99–2.5) 37–39: 1.2 (95% CI 1.0–1.5)
Lindström *et al* 2011, Sweden	Population-based register study	The purchase of stimulant medication (data from The Swedish Prescribed Drug Register)	1,180,616 children followed n=7506 ADHD cases -Born between 1987 and 2000	Stimulant use in 2006, age range 6-19 years	23–28, 29–32, 33–36, 37–38, 39–41 (ref.) >42	Year of birth, gender, county, birth order, maternal age, education, smoking, single parenthood, public welfare, parental psychiatric disorder, Apgar scores and SGA status	Preterm birth and early term birth increases stepwise the risk of ADHD	OR_{adj} 23–28: 2.1 (95% CI 1.4–2.7), 29–32: 1.6 (95% CI 1.4–1.7), 33–34: 1.4 (95% CI 1.2–1.7), 35–36: 1.3 (95% CI 1.1–1.4), 37–38: 1.1 (95% CI 1.1–1.2)

Author, Publication year, Country	Study Design	ADHD diagnosis	Sample size Time of birth	Patients' age range and time of evaluation	Classification of gestational weeks	Confounders	Results	Measures of association
Gustafsson *et al.* 2011, Sweden	Population-based (city of Malmö)	DSM-IV	n=237 cases, n=31 775 controls Born between 1986 and 1996 (the remaining children born in 1986–2006 in Malmö)	5–17 years at time of diagnosis	<32 32–36 37–41 >42	Maternal smoking, age, Apgar scores, gender, year of birth	ADHD was significantly associated with preterm birth before week 32	OR_{adj} <32: 3.05 (95% CI 1.39-6.71)
Halmoy *et al*. 2012, Norway	Population-based case-control study, record linkage	ICD-10	n=2323 cases Born between 1967–1987 Controls were the remaining population	Diagnosis between 1997–2005	<28 28–32 33–36 37–41 (ref) >42	Maternal age, parity, maternal education, marital status, infant gender	Preterm birth and especially extreme preterm birth increased the risk of ADHD	RR_{adj} <28: 5.0 (95% CI 2.1–11.8) 28–32: 1.2 (95% CI 0.7–2.0) 33–36: 1.3 (95% CI 1-0–1.5)
Harris *et al*. 2013, U.S.A. (Rochester, Minnesota)	Population-based birth cohort	school or medical records met either: 1)DSM-IV criteria 2) positive ADHD questionnaire results 3) clinical diagnosis	5699 children included, n=1509 had ADHD or learning difficulties - Born between 1976 and 1982	Cumulative incidence by the age of 19 years	<34 34–36 37–42 >42	Adjusting for maternal education and several perinatal complications	No statistically significant differences in the cumulative incidence for developing ADHD in late preterm versus term-born children	cumulative incidence: 34 to >37 weeks 7.7 % vs. >37 weeks 7.2 % *P*=0.84

Author, Publication year, Country	Study Design	ADHD diagnosis	Sample size Time of birth	Patients' age range and time of evaluation	Classification of gestational weeks	Confounders	Results	Measures of association
D'Onofrio *et al*. 2013, Sweden	Population-based register study	ICD-9 or ICD-10	The whole Swedish population born during the time period 1980–2001 for ADHD	Diagnosis by 2009 Up to age 19 years	23–27 28–30 31–33 34–36 37–42	Parental age Education Criminality Several models including fixed-effects model (controlling for shared variables among siblings)	Earlier gestational age was associated with increased risk of ADHD. The finding was independent of measured covariates and familial factors shared by siblings.	$HR_{basline}$ 23–27: 2.3 (95% CI 2.0–2.8)
Silva *et al*. 2014, Australia	Population-based, record-linkage, case-control	Stimulant use (requires ICD-10 or DSM IV diagnosis)	n=12 991 ADHD cases, n=30 071 controls Born between 1981 and 2003	Stimulant use between 2003–2007, age range 4–22 years	<29 29–32 33–36 37–38 39–41 (ref.) >41	-Initial model adjusting for year of birth and socio-economic index -adjusted model including all risk factors from the previous model (including several obstetric events)	-Preterm birth was not associated with ADHD -Early term delivery was a risk factor	Boys, OR_{adj} <29: 1.70 (95% CI 0.88–3.29), 29–32: 1.28 (95% CI 0.90–1.82), 33–36: 1.12. (95% CI 0.99–1.27,) 37–38: 1.07 (95% CI 1.00–1.14)
Perapoch *et al*. 2019, Spain	Observational, register-based matched cohort study	ICD diagnosis or prescription of ADHD medication	Total 7488 children included n=396 ADHD cases -born between 1995–2007 -3744 preterm and 3744 term born	analyzed until 2013	≤28 29–32 34–35 35–56 ≥ 37 (ref.)	controls matched by sex, age and primary care center, no further adjustments for confounders	Being born preterm was associated with an increased risk of ADHD also in late preterm children	HR: 35–36: 1.70 (95% CI 1.19–2.44) 33–34: 3.38, (95% CI 2.08–5.50) 29–32: 2.37 (95% CI 1.54–3.63) ≤28: 5.57 (95% CI 2.49–12.46)

Author, Publication year, Country	Study Design	ADHD diagnosis	Sample size Time of birth	Patients' age range and time of evaluation	Classification of gestational weeks	Confounders	Results	Measures of association
Bachmann et al. 2021, Norway	Nationwide register-based study	Prescribed psychostimulants	Followed 505 030 individuals born 1989–1998	Prescription from age 10 to 23 years	23–27 28–31 32–36 37–44 (ref.)	Child sex, birth year, birth weight, multiple birth status, maternal parity, relationship status, age, country of birth, and education, -also sibling models	Higher rates of prescription of psychostimulants in all degrees of preterm birth compared to term born individuals -remained significant in sibling comparisons	23–27: OR_{adj} : 2.7 (95% CI 2.1–3.4) 28–31: OR_{adj} :1.7 (95% CI 1.5–2.0) 32–36: OR_{adj} : 1.2 (95% CI 1.1–1.2)

ref= reference, OR= odds ratio, 95 % CI = 95 % Confidence Interval, RR= relative risk, HR=hazard ratio

2.5 Fetal Growth and ADHD

2.5.1 Measuring fetal growth

Fetal growth is a critical indicator of fetal well-being and development. Intrauterine growth is an important determinant for both perinatal morbidity as well as a marker for later postnatal life-course health risks (Kiserud et al., 2018). It is estimated that approximately 50% of an individual's birth size is mediated by genetic factors and the average birth size somewhat differs when different ethnic populations are compared. However, environmental factors such as the number of fetuses, parity, maternal size, medication, smoking, nutrition, and placental functioning also play a significant role in the achievement of a given birth size (Sankilampi, Hannila, Saari, Gissler, & Dunkel, 2013).

The traditional way to evaluate fetal growth is by measuring the birth weight of the newborn. Normal birth weight is typically defined as a birth weight between 2500 grams and 4000 or 4500 grams (Hughes, Black, & Katz, 2017). In Finland, approximately 4.2% of newborns have a birthweight under 2500 grams and approximately 2.4% over 4500 grams (Gissler & Kiuru, 2019).

The birth weight does not take into account the effect of gestational age. Weight for gestational age (WGA) is thus considered as a better indicator of appropriate or inappropriate fetal growth. The term small for gestational age (SGA) refers to a neonate whose birth weight is 2 standard deviations (SD) below the mean (≤−2 SD) for the newborn's gestational age based on data derived from a suitable reference population (Lee, Chernausek, Hokken-Koelega, Czernichow, & International Small for Gestational Age Advisory Board, 2003). In some instances, SGA is may also be defined as birth weight or length below the 10^{th} percentile for gestational age (Lee et al., 2003; Sharma, Shastri, Farahbakhsh, & Sharma, 2016). In this work, the definition -2 SD is used. The term appropriate for gestational age (AGA) describes a newborn whose birth weight is within -2 and +2 standard deviations for the gestational age. The term large for gestational age (LGA) refers to a neonate, whose birth weight exceeds +2 standard deviations above the mean for that infant's gestational age. In order for these measures to be reliable, the gestational age needs to be accurate- either based on the last menstrual period or verified by a first trimester ultrasound examination.

The term intrauterine growth restriction (IUGR) is defined as fetal growth rate that is less than normal for the growth potential of that specific infant taking into account the race and gender of the fetus. The causes of IUGR may be placental, fetal, maternal or genetic (Sharma et al., 2016).

Suboptimal fetal growth has been associated with a risk of various noncommunicable diseases; especially the well-established relation between birth weight and the risk of later metabolic health has lead to the concept of the "developmental origins of health and disease" (DoHaD) (O'Donnell & Meaney, 2017). Furthermore, in the past few decades, evidence has accumulated linking fetal growth with behavioral and mental health outcomes later in life (Schlotz & Phillips, 2009).

2.5.2 Fetal growth as a risk factor of ADHD

The population-based studies and large cohort studies investigating the association are presented in Table 2.

Poor fetal growth has been associated with an increased risk of ADHD (Class, Rickert, Larsson, Lichtenstein, & D'Onofrio, 2014; Franz et al., 2018; Pettersson, Larsson, D'Onofrio, Almqvist, & Lichtenstein, 2019). The majority of these studies have examined the relation of birth weight and later ADHD. There are fewer studies investigating the association between the weight for gestational age and the risk of ADHD. In addition, many studies that examine birth weight do not report the proportion of low birth weight children that were also premature, and so have not separated the effect of gestational age from the effect of birth weight (Linnet et al., 2006; Sciberras et al., 2017).

The population-based studies that have examined the weight for gestational age and later diagnosed ADHD are scarce. A Norwegian population-based study found an increasing risk for ADHD with a decreasing weight for gestational age (Halmoy et al., 2012). A Danish study that used a low birth weight *at term* (<2500 g) as an indicator of poor fetal growth, showed an increased risk of ADHD compared to those with a normal birth weight at term (Linnet et al., 2006). In contrast, a study from Australia did not find an increased risk of ADHD among SGA children in the adjusted model (Silva et al., 2014). However, the authors pointed out that their final models adjusted for such a large number of factors, that this may have also reduced precision and blurred real associations.

A large Australian cohort study found no statistically significant associations between SGA status and overall questionnaire-based attention problems. They only found an association between SGA and self-reported attention problems among term-born girls (O'Keeffe, O'Callaghan, Williams, Najman, & Bor, 2003). However, a cohort study combing data from two cohorts – the UK and Brazil – examined questionnaire based attention problems in 7-year-old children and SGA and found that attention problems based on parental SDQ-questionnaires were associated with SGA status in both cohorts (Murray et al., 2016).

Table 2. The literature on weight for gestational age and ADHD.

Author, publication year, country	Study Design	ADHD diagnosis	Sample size, Time of birth	Patient Age and dg time	Classification of weight for gestational age	Confounders	Results	Measures of association
Linnet et al 2006, Denmark	Population-based register study Case-Control	ICD-10	n=834 cases n=20 100 controls (matched for sex, birth date) Born between 1980 and 1994	Hyperkinetic disorder before 1999 (from Danish Psychiatric Central Register)	IUGR defined as birth weight <2500 grams at or above term	Socioeconomic factors, parental age, parity, familial psychopathology, Smoking available from 1991	Children born **at term** with birth weight between 1500 g and 2499 g had a more than 90% increased risk of ADHD compared to those with birth weight above 2999 grams	-1500-2499 g: RR_{adju}= 1.9 (95% CI 1.2–2.9) -2500–2999 g: RR_{adj}= 1.5 (95% CI 1.2–1.8)
Halmoy et al, 2012, Norway	Population-based cohort study, record linkage	ICD-10	n=2323 cases Controls were the remaining population Born between 1967–1987	Diagnosis between 1997 and 2005	SGA (<10th percentile of birth weight for gestation)	Maternal age, parity, maternal education, marital status, infant gender	Being SGA, both at term or preterm, increased the risk of ADHD	-overall RR_{adj}=1.3 (95% CI 1.1–1.4) -for term babies RR_{adj}=1.2 (95% CI 1.1–1.4) - for preterm babies RR_{adj}=1.6 (95% CI 1.0–2.5)

Author, publication year, country	Study Design	ADHD diagnosis	Sample size, Time of birth	Patient Age and dg time	Classification of weight for gestational age	Confounders	Results	Measures of association
Silva et. al, 2014, Australia	Population based, record-linkage, case-control	Stimulant use (requires ICD-10 or DSM IV diagnosis)	n=12 991 ADHD cases n=30 071 controls Born between 1981 and 2003	Stimulant use between 2003–2007, age range 4–22 years	SGA, AGA, LGA	-Initial model adjusting for year of birth and socio-economic index -adjusted model including all risk factors from the previous model (including several obstetric events	SGA status carried an elevated risk in the partially adjusted model, but became insignificant the final model. LGA status showed no risk.	
O'Keeffe et al. 2003, Australia	Cohort study	no diagnoses, CBCL by parents and Youth self-report	n=5059 mothers and n=5051 adolescents filled questionnaires Born between 1981–1984	questionnaires at age 14 years	SGA (≤3th percentile of birth weight for gestation according to Australian curves)	information on social risk factors (maternal age, education, income, marital status) -not reported for attention problems	-No statistically significant association between SGA status and overall attention problems -only association between SGA status and self-reported attention problems among term-born girls	

Author, publication year, country	Study Design	ADHD diagnosis	Sample size, Time of birth	Patient Age and dg time	Classification of weight for gestational age	Confounders	Results	Measures of association
Murray et al. 2016, UK	Cohort study including two cohorts (UK and Brazil)	no diagnoses, SDQ and DAWBA	-source cohort 10 358 -DAWBA-based ADHD disorders n=234 cases -SDQ-based attention problems n=1199	assessment at approximately 7 years of age	SGA (<10th percentile of birth weight for gestation)	maternal, family and demographic variables (maternal education, income, maternal age at delivery) gestational (smoking, alcohol use, and depression during pregnancy) and perinatal variables (mode of delivery and Apgar score at 5 min).	-SDQ-based attention problems were associated with SGA status in both cohorts -For DAWBA-based clinical-level ADHD-diagnoses association was only seen in the Brazilian cohort	-SDQ: OR=1.59, (95% CI 1.20–2.19) in UK and OR=1.35, (95% CI 1.04–1.75) in Brazil -DAWBA: OR=1.69 (95% CI 1.02–2.82) in Brazilian cohort, no association in UK cohort

OR= odds ratio, 95 % CI = 95 % Confidence Interval, RR= relative risk, CBCL= The Child Behavior Checklist, DAWBA= The Development and well-being assessment, SDQ= Strengths and Difficulties questionnaire

2.6 Obstetric and perinatal risk factors and ADHD

2.6.1 The mode of delivery and ADHD

The population-based register studies on the mode of delivery and ADHD are summarized in Table 3.

In Finland, the rate of caesarean sections (C-sections) has remained at a stable level of about 16–17% since the beginning of this millennium. In 2018, 16.7% of all births occurred by C-section. Planned C-sections accounted for 6.7%, urgent C-sections for 9.2% and emergency C-sections for 0.9% of all births. Vacuum extraction was used in 9.6% of all births in 2018, and has slightly increased over the past years. The vacuum extraction rate was 6.0 % in 2000 and 8.7% in 2010. Vaginal breech births have been at a stable level of 0.6% over the past two decades. Induced labors have increased from 14.4.% in 2000 to 30.5% of births in 2018 (Gissler & Kiuru, 2019).

The changes in obstetric care possibly reflect changes in the parturients' profile such as the increasing age. The mean age of women giving birth in Finland has continued to rise over the past decades. In 2018 the mean age of all parturients was 31 years and 23.7% of all parturients were over 35 year old women (Gissler & Kiuru, 2019).

The common reasons for an elective C-section include previous C-sections, cephalopelvic disproportion, breech presentation and psychosocial indications such as the fear of childbirth (Stjernholm, Petersson, & Eneroth, 2010). A mother's request for a C-section without medical indications is less frequent in Finland compared to some countries with a high C-section rate. Although the life-saving role of C-sections in specific complications is indisputable, there is evidence of a higher risk for certain adverse child outcomes compared with vaginal birth (Sandall et al., 2018).

Over the recent years, a growing interest towards the long-term consequences of birth by C-section has emerged. Birth by C-section is known to affect the early life of a child, as it alters the microbial colonization of the newborn infant and may affect other factors such as the early adaptation of the newborn and initiation of lactation in the mother.

Research evidence has shown an association between birth by elective C-sections and later asthma, atopic disease and even autism (Cuppari et al., 2015; Curran et al., 2015; Rusconi et al., 2017). However, studies examining the association between ADHD and C-sections have shown controversial results mostly due to variation in adjusting for confounding factors (Curran, Cryan et al., 2016; Gustafsson & Kallen, 2011; Halmoy et al., 2012; Silva et al., 2014; Zhang et al., 2021).

Recently, one meta-analysis on the mode of delivery and ADHD has been published (Xu et al., 2020). The meta-analysis included nine hospital-based or population registry studies from eight countries. According to the pooled data available, it was found that C-sections were associated with a small risk increase of ADHD (OR 1.14 95% CI 1.11–1.17). The association was seen both after elective (OR 1.15, 95% CI 1.11–1.19) and emergency C-sections (OR 1.13, 95% CI 1.1–1.17). However, in the three studies that included matching for siblings, the associations did not remain statistically significant in the sibling analyses (Axelsson et al., 2019; Curran, Khashan et al., 2016; Zhang et al., 2021).

Table 3. The literature on the mode of delivery and ADHD.

Author, publication year, country	Data source, study design and study years	ADHD outcome definition	Sample size	Confounders	Measures of association	Results and additional information
Gustafsson et al, 2011, Sweden	Population-based register / cohort, 1986–1996	DSM-IIIR and DSM-IV	total N=32 012, including 237 ADHD cases	not available	-elective C-sections OR_{unadj}: 1.60 (95% CI 0.85–3.03) emergency C-sections OR_{unadj}: 0.74 (95% CI 0.42–1.36)	No significant associations
Halmoy et al., 2012, Norway	Population-based register / cohort, 1967–1987	ICD-10	total N= 1 170 073, including 2323 ADHD patients	Maternal age, parity, maternal education, marital status, infant gender, year of birth	OR_{adj}: 1.3 (95% CI 1.1.–1.5)	-C-sections were associated with an increased ADHD risk, -all C-sections reported together
Silva et al., 2014, Australia	Population-based register / case-control, 1980–2003	DSM-IV or ICD-10	n=12 991 ADHD cases, n=30 071 controls	Marital status, parity, smoking, numerous obstetric complications (e.g. threatened abortion or preterm labor, maternal urinary tract infection, pre-eclampsia, induction or augmentation of labor, fetal distress, cord prolapse etc.) gestational age, birthweight, maternal age, Apgars, year of birth and socioeconomic status	-elective C-section in partially adjusted model OR for boys: 1.15 (95% CI 1.06–1.25) OR for girls: 1.17 (95% CI 1.01–1.36) -emergency C-section in partially adjusted model OR for boys: 1.10 (95% CI 1.01–1.19) OR for girls: 1.03 (95% CI 0.88–1.22) -In final model all C-sections reported together and were insignificant	When adjusting for all confounders, C-sections were not associated with ADHD

Author, publication year, country	Data source, study design and study years	ADHD outcome definition	Sample size	Confounders	Measures of association	Results and additional information
Curran et al. 2016, United Kingdom	Population-based register / cohort, 2000–2002	questionnaire	total N=13 141, including n=173 reported cases of ADHD	SGA, gestational age, maternal high blood pressure/pre-eclampsia, smoking, firstborn child, child gender, bleeding or threatened miscarriage, poverty, ethnicity, maternal age, education, depression and BMI.	-elective C-sections $OR_{adjusted}$:0.54 (95% CI 0.18–1.65) -emergency C-sections $OR_{adjusted}$:1.28 (95% CI 0.61–2.66)	No association between the mode of delivery and ADHD was found
Curran et al., 2016, Sweden	Population-based register / cohort, 1990–2008	ICD-10 or ADHD medication prescription	total N=1 722 548, including n=47 778 ADHD cases	Year of birth, infant gender, maternal age, smoking, gestational age, Apgars, maternal and paternal country of birth, SGA, LGA, firstborn, family income, maternal and paternal depression	-elective C-sections $HR_{adjusted}$: 1.15 (95% CI 1.11–1.20) -emergency C-sections $HR_{adjusted}$: 1.15 6 (95% CI 1.12–1.20) -in the sibling analyses: elective C-sections $HR_{adjusted}$: 1.05 (95% CI 0.93–1.18) -emergency C-sections $HR_{adjusted}$: 1.13 6 (95% CI 1.01–1.26)	C-sections were associated with an increased risk of ADHD, but in the sibling-matched analyses only emergency C-sections remained significant

Author, publication year, country	Data source, study design and study years	ADHD outcome definition	Sample size	Confounders	Measures of association	Results and additional information
Axelsson et al., 2018, Denmark	Population-based register / cohort, 1997–2010	ICD-8 or ICD-10 or redeemed ADHD prescriptions	total N=671 592, including n=17 971 ADHD cases	Childhood antibiotics, mode of delivery, maternal and parental age, education, maternal marital status, smoking, infant sex and Apgars, instrument use at delivery, use of ventilator, asphyxia, parental epilepsy, pre-eclampsia or hypertension, gestational diabetes, parity, induction of labor, maternal antibiotics and infections during pregnancy and parental ADHD history	Descriptive models: -elective C-sections $HR_{adjusted}$:1.11 (95% CI 1.05–1.17) -emergency C-sections $HR_{adjusted}$:1.10 (95% CI 1.04–1.16) Sibling–matched analyses: -elective C-sections $HR_{adjusted}$:1.03 (95% CI 0.91–1.16) -emergency C-sections $HR_{adjusted:}$1.09 (95% CI 0.97–1.24)	In the descriptive analyses ADHD risk was increased for children born by elective and emergency C-section. In the fully-adjusted sibling models C-sections were not associated with ADHD risk
Zhang et al., 2021, Sweden	Population-based register study, born between 1990–2003	ICD-9 and ICD-10 diagnoses or dispensing of ADHD medication	n=52 257 ADHD cases	Wide spectrum of maternal characteristics and pregnancy complications including e.g. age, parity, education level, smoking during pregnancy, psychiatric history, paternal age and psychiatric history, birth complications and neonatal characteristics	Planned C-section and ADHD: HR 1.17 (95% CI 1.12–1.23) Intrapartum C-sections: HR 1.10 (95% CI 1.05–1.15) -became nonsignificant in the model adjusting for maternal siblings and cousins	Planned C-sections and intrapartum C-sections associated with an increased risk of ADHD, but did not remain significant in the sibling and cousin analyses

OR= odds ratio, 95% CI = 95% Confidence Interval, HR= hazard ratio

2.6.2 Apgar scores and ADHD

The Apgar scores were developed in 1952 by an American physician, Virgina Apgar, to rapidly evaluate the condition of the newborn. The Apgar score comprises of five components: (1) color; (2) heart rate; (3) reflexes; (4) muscle tone; and (5) respiration. Each of these features is given a score of 0, 1, or 2. Thereby the maximum possible Apgar score of an infant is 10. The scores are evaluated at 1 minute and 5 minutes after birth. The Apgar score is a accepted as a convenient method for reporting the status of the newborn and for evaluating a response to possible resuscitation. An initial need of resuscitation should be evaluated even before the 1 minute Apgars scores are given (AAP, 2015).

Low Apgar scores alone are not a specific indicator of birth asphyxia. Asphyxia is defined as a condition of inadequate gas exchange that leads to hypoxemia, hypercapnia, and metabolic acidosis (Low, 1997). It is typically a deprivation of oxygen to a newborn that lasts long enough to cause harm to the fetus' organs, the inability to initiate breathing after birth, and possibly damage to the brain. Low Apgar scores may also be a result of maternal sedation or anesthesia, congenital malformations and trauma, and they are affected by interobserver variability. A healthy preterm infant with no asphyxia may obtain a low Apgar score only due to immaturity and slower adaptation to extrauterine life (AAP, 2015).

The Apgar scores were not developed to predict an individual's later developmental outcomes, but they have been extensively studied in relation to later adverse neurologic outcomes such as cerebral palsy and neonatal encephalopathy (Leinonen et al., 2018)..

Prenatal hypoxia has been suggested to play a role in the etiology of ADHD as well. There are a number of studies examining the association of Agar scores and ADHD. In Nordic population-based studies the lowest Apgar scores have been associated with the highest risk for ADHD (Gustafsson & Kallen, 2011; Halmoy et al., 2012; Li, Olsen, Vestergaard, & Obel, 2011). A large Danish study reported that in children with Apgar scores of 1 to 4, the risk for ADHD was 75% higher compared to children with Apgar scores of 9 or 10 (HR 1.75, 95% CI 1.15–2.11). Children with Apgar scores of 5 to 6 had a 63% higher risk for ADHD (HR 1.63, 95% CI 1.25–2.11) (Li et al., 2011). Similar findings were reported from a Norwegian population-based study: children with Apgar scores under 4 had a risk ratio of 2.8 (95% CI 1.2–6.8) and children with Apgar scores under 7 had a RR of 1.6 (95% CI 1.0–2.5) in the adjusted analyses (Halmoy et al., 2012). A Swedish study reported a risk increase of the same magnitude, although not statistically significant: Apgar scores under 7 showed an OR of 2.17 in the multivariate model (95% CI 0.93–5.06) (Gustafsson & Kallen, 2011).

In addition, a large cohort study from the United States reported similar findings: adjusted OR was 1.31 (95% CI 1.08–1.57) for Apgar scores under 7 in children aged

5 to 11 years (Getahun et al., 2013). In contrast, a large Australian study failed to find any such associations (Silva et al., 2014). All of the above-mentioned studies examined the association of ADHD and Apgar scores at five minutes of age.

2.6.3 Umbilical pH measurements, hypoxia and ADHD

In addition to the Apgar scores, the measurement of umbilical artery blood pH has been widely adopted in the developed countries for assessing the condition of newborn infants (Casey, McIntire, & Leveno, 2001). There are normally three umbilical vessels; two arteries and one vein. The umbilical arteries carry de-oxygenated blood from the fetus to the placenta, and the umbilical vein carries oxygenated blood from the placenta to the fetus.

The normal pH value of the umbilical artery is approximately 7.25 (SD 0.07) in term born infants (Skiöld, Petersson, Ahlberg, Stephansson, & Johansson, 2017). A low umbilical artery pH indicates that the fetus is in a state of biochemical decompensation at the moment of birth (Vandenbussche, Oepkes, & Keirse, 1999). In other words, the metabolic state of the fetus has shifted towards acidosis due to hypoxia at that moment. This in turn increases the risk of infant morbidity (Nagel et al., 1995).

Hypoxia in utero or at birth has also been suggested to play a possible etiological role in the development of ADHD. Longer lasting ischemia-hypoxia is a well known pathway to poor fetal growth and shorter lasting hypoxia plays a key role in many obstetric complications (Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016). Ischemia-hypoxia can be considered as a common element of multiple prenatal risk factors, including low birth weight, prematurity, various obstetric complications, and maternal smoking during pregnancy (Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016). Literature suggests that ischemic-hypoxic conditions during pregnancy resulting from acute and chronic perinatal events may have adverse consequences on fetal brain development that are not yet apparent at birth (Getahun et al., 2013). The possible mechanisms resulting in neurodevelopmental vulnerability for ADHD are hypothesized to act through altered ischemia-hypoxia response pathway gene expression and epigenetic alterations (Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016).

There are only a few studies examining the association of umbilical artery pH and later ADHD problems and they have yielded contradictory results. A study utilizing Finnish register data found a 23% increased risk of ADHD among children born with an umbilical cord artery pH of less than 7.10 (Mikkelsen et al., 2017). In contrast, a Dutch study found no relationship between umbilical artery pH and ADHD symptoms by the age of four (Wildschut et al., 2005). Moreover, a German study found no difference in the umbilical artery pH values of children who developed ADHD and the remaining study cohort (Schwenke et al., 2018).

2.6.4 Other obstetric risk factors of ADHD

The relation between various other obstetric complications and their relation to later neurodevelopment have been topics of research interest as well. Maternal hypertension or preeclampsia, the induction or augmentation of labor and breech presentation are among the prenatal risk factors that have been implied to play a possible role in the neurodevelopmental outcomes of the offspring.

Hypertensive disorders during pregnancy can be either chronic hypertension, a pregnancy-induced hypertension or preeclampsia (American College of Obstetricians and Gynecologists, 2013). In preeclampsia the hypertension is accompanied by proteinuria and there may also be manifestations from other organs. The proteinuria reflects the endothelial leak that is the key characteristic of the preeclampsia syndrome. When complicated with convulsions or coma, the condition is called eclampsia (Malik & Kumar, 2017). Preeclampsia may affect the growth of the fetus and it is a common indication for premature termination of the pregnancy.

Preeclampsia has been linked to adverse neurodevelopment and there is also evidence of an association to ADHD. In 2018, a meta-analysis was published on the topic of hypertensive disorders and neurodevelopmental disorders in the offspring. The meta-analysis investigated ten studies with adjusted estimates of an association of hypertensive disorders and ADHD. A significant association was seen and the pooled adjusted OR was 1.29 (95% CI 1.22–1.36). The association was significant for both preeclampsia and ADHD as well as for other hypertensive disorders of pregnancy and ADHD (Maher et al., 2018). A previous meta-analysis published in 2016 and going through mostly the same studies, reached similar conclusions. They reported a pooled OR 1.31. (95 % CI 1.23–1.40) (Zhu et al., 2016). Furthermore, a large, recent population-based study utilizing Swedish register-data found that preeclampsia increased the risk of ADHD by approximately 15 % after controlling for potential confounding factors. The finding was seen in pre-eclampsia with SGA as well as in preeclampsia without SGA. The association remained significant in sibling-matched analyses and was independent of gestational age (Maher et al., 2020). Similar findings were reported by a recent Norwegian study; maternal preeclampsia showed an adjusted OR of 1.18 (95 % CI 1.05–1.33) for ADHD in children born at term. Additional analyses showed that preeclampsia increased the risk independently of gestational age (Sun, Moster, Harmon, & Wilcox, 2020).

The incidence of induced labors has increased over the past decades both globally and in Finland (Gissler & Kiuru, 2019; Mozurkewich et al., 2011). The induction of labor may be indicated by medical or obstetrical complications or may be requested for non-medical reasons. The methods include oxytocin, intravaginal prostaglandins, amniotomy and oral or vaginal misoprostol (Mozurkewich et al., 2011). Oxytocin is also used for augmentation of labor when the progression of labor is considered insufficient. Oxytocin is nonpeptide hormone essential in delivery and

lactation, but also a potent modulator of maternal behavior, social interactions and psychosocial function (Lee, Macbeth, Pagani, & Young, 2009).

Some studies have reported an association between the induction of labor and ADHD (Kurth & Haussmann, 2011; Silva et al., 2014). However, a large Swedish family-based study found that this association was attenuated after adjusting for factors that cousins and siblings share (Wiggs et al., 2017). The augmentation of labor has also shown contradictory results (Henriksen, Wu, Secher, Obel, & Juhl, 2015; Kurth & Haussmann, 2011; Silva et al., 2014).

The majority of fetuses obtain the normal, cephalic presentation close to term. Nevertheless, approximately 3–4% of fetuses will be in breech presentation at the time of term delivery (Tunde-Byass & Hannah, 2003). Breech presentation may be caused by an underlying fetal or maternal abnormality or may also be an otherwise benign variant (Hofmeyr, Hannah, & Lawrie, 2015). Possible reasons for breech presentation include reduced fetal motility, uterine malformations and multiple pregnancies. The breech presentation is a common indication for an elective C-section. In Finland, the proportion of vaginal breech deliveries was about 0.6% of all births (Gissler & Kiuru, 2019).

Breech presentation has also been suggested to be associated with later neurodevelopmental difficulties. A meta-analysis published in 2016 went through the results of four studies and reported a significant association between breech presentation and later ADHD. The pooled OR was 1.14 (95% CI 1.06–1.23). The authors speculated that breech presentation may be a risk factor for a more difficult delivery and thus result in fetal distress (Zhu et al., 2016).

2.6.5 Neonatal illnesses, neonatal treatment and ADHD

Neonatal illnesses, especially those resulting from fetal distress and hypoxia, have been associated with later inattention and hyperactivity problems. A large cohort study from California found that ischemic-hypoxic conditions at birth increased the risk for ADHD in children aged 5 to 11 years (OR 1.16, 95% CI 1.11–1.21). They reported that birth asphyxia, neonatal respiratory distress syndrome and preeclampsia were associated with ADHD also after accounting for the effect of gestational age (Getahun et al., 2013). A population-based study from Denmark showed that neonatal seizures, intraventricular hemorrhages, hypoglycemia, pulmonary hypertension and sepsis were risk factors of ADHD. Neonatal morbidity was however less common among children later developing ADHD that among those later presenting with autism (Atladottir, Schendel, Parner, & Henriksen, 2015).

2.7 Maternal smoking and offspring ADHD

Despite the known harmful effects of tobacco exposure on fetal development, considerable number of women continue to smoke during pregnancy. In Finland, approximately 14% of women aged 20 to 54 years smoke regularly (*Tupakkatilasto 2018*). The proportion of pregnant women who report smoking throughout their pregnancy is approximately 7% (Gissler & Kiuru, 2019). The proportion of women who report smoking throughout the pregnancy in Finland has decreased from 1991 to 2009, but the number of women who smoke during early pregnancy has remained at a stable level during this time (Ekblad, Gissler, Korkeila, & Lehtonen, 2014).

Tobacco smoke contains over 4000 chemical constituents. Out of them, nicotine and carbon monoxide are of major concern because of their known toxic effects on the fetus and newborn. Nicotine and carbon monoxide cross the placenta, and with chronic exposure, their levels in the fetal compartment exceed those in the maternal compartment (Rogers, 2008). The fetal effects of the other potentially toxic constituents of tobacco are still largely unknown, as most research has concentrated on the fetal effects of nicotine exposure. Smoking exposure is known to affect placental growth and differentiation, and contribute to fetal hypoxia through uterine ischemia (Rogers, 2008). Maternal smoking during pregnancy has been associated with several adverse child and pregnancy outcomes such as preterm delivery, poor fetal growth, sudden infant death syndrome and increased infections in childhood (Huang et al., 2018).

2.7.1 Self-reported maternal smoking and ADHD

The population-based studies on maternal smoking and offspring ADHD are presented in Table 4.

There is a vast body of literature across different populations supporting an association between maternal smoking during pregnancy and an increased risk of offspring ADHD (Huang et al., 2018; Langley, Rice, van den Bree, M. B., & Thapar, 2005; Obel et al., 2009; Tiesler & Heinrich, 2014). Population-based register studies from the Nordic countries and Australia have reported consistent associations between prenatal smoking exposure and child ADHD. In these studies maternal smoking during pregnancy has been shown to increase the risk of offspring ADHD by nearly up-to two-fold compared to controls with no tobacco exposure during pregnancy (Gustavson et al., 2017; Joelsson, Chudal, Talati et al., 2016; Lindblad & Hjern, 2010; Obel et al., 2016; Silva et al., 2014; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014; Zhu, J. L. et al., 2014).

Table 4. Population-based studies on maternal smoking and offsrpring ADHD.

Author, Publication year, Country	Study design	Diagnostic criteria, Data source	Sample size	Exposure	Covariates	Results
Lindblad and Hjern, 2010, Sweden	Register-based, national cohort	ADHD medication	n=6510 ADHD cases / 982 856 source children	maternal self-reported smoking during pregnancy: none, 1–9 or ≥10 cigarettes per day	child age, year of birth, sex, county of residence, maternal age, birth order, maternal education, single parent, social assistance, maternal/paternal psychiatric/addictive disorders, small for gestational age, and low Apgar score	-Children of mothers who to smoke ≥10 cigarettes per day: OR_{adj}: 1.89 (95% CI 1.75–2.04) compared to nonsmokers -In the within-mother-between-pregnancy model the OR_{adj} was 1.26 (95% CI 0.95–1.58)
Silva et al., 2014, Australia	Population-based register / case-control	DSM-IV or ICD-10	n=12 991 ADHD cases, n=30 071 controls	maternal self-reported smoking	marital status, parity, smoking, numerous obstetric complications (e.g. threatened abortion or preterm labor, maternal urinary tract infection, pre-eclampsia, induction or augmentation of labor, fetal distress, cord prolapse etc.) gestational age, birthweight, maternal age, Apgars, year of birth and socioeconomic status	-For boys OR_{adj} 1.86 (95% CI 1.53–2.27) -For girls OR_{adj} 1.67 (95% CI 1.07–2.61)
Skoglund et al., 2014, Sweden	Register-based national cohort	ICD10, DMV-IV or medication	n=19 891 ADHD cases of out 813 030 source children	maternal self-reported smoking during pregnancy: none, 1–9 or ≥10 cigarettes per day	-gender, birth year, mother's parity, maternal age, cohabitation status, maternal highest education, and mother's country of birth -model adjusting for cousins and siblings	Children of mothers who to smoke ≥10 cigarettes per day $HR_{ajd:}$2.04 (95% CI 1.95–2.13) compared to remaining population -insignificant in sibling models

Author, Publication year, Country	Study design	Diagnostic criteria, Data source	Sample size	Exposure	Covariates	Results
Zhu et al., 2014 , Denmark	population-based cohort study	ICD-10	cohort of 84 803 children out of which n=2009 ADHD cases	parental self-reported smoking	maternal age, parity, alcohol intake during pregnancy, parental socioeconomic status, parental psychopathology, and child's gender, father's smoking status	-HR_{adj} of smoking mothers with a smoking partner: 1.82 (95% CI 1.60–2.10) compared to offspring of non-smokers -HR_{adj} for smoking mothers with a non-smoking partner 1.63 (95% CI 1.36–1.94)
Obel et al., 2016, Denmark	Register-based national cohort	ICD-10 or medication	source population 968 665 out of which n=17 381 ADHD cases	maternal self-reported smoking during pregnancy: none, 1–9 or ≥10 cigarettes per day	sex, birth year, parity, mother's age	HR_{adj} for smokers compared non-smokers 2.19 (95% CI 2.09–2.29) -in different sibling analyses much of the association disappeared
Gustavson et al., 2017, Norway	Register-based national cohort	ICD-10	104 846 children out of which n=2035 ADHD cases	maternal self-reported smoking, paternal smoking, grandmother's smoking when pregnant with the mother	-maternal and paternal age, education, ADHD symptoms, BMI, maternal alcohol consumption during pregnancy, parity, child's birth year, and geographical region	-HR_{adj}: 1.48 (95% CI 1.30–1.68) compared to general population -not a greater effect than when taking into account sibling, father and grandmother information
Ekblad et al., 2017 Finland	Population-based cohort, register-linkage	ICD-10	n=150 168 sibling-pairs	maternal self-reported smoking	child's sex and birth year, first sibling's psychiatric morbidity (only for the second sibling), maternal age, parity, marital status, and psychiatric morbidity	For women who had quitted smoking OR_{adj} 0.74 (95% CI 0.66–0.82) for externalizing diagnoses compared to their previous pregnancy when they had smoked

ref= reference, OR= odds ratio, 95% CI = 95% Confidence Interval, HR= hazard ratio

However, there has been some debate as to whether the observed risk is caused by the actual tobacco exposure during pregnancy or whether the tobacco use in pregnancy is an indicator of other risk factors such as unmeasured familial or genetic confounding. Examples include low socioeconomic status, young age of childbearing, poor family functioning and parental psychiatric problems. There is also evidence that individuals with ADHD are more likely to become daily smokers (Rhodes et al., 2016).

In recent years, designs utilizing sibling and family designs have been published. There is also one study utilizing data from pregnancies conceived with assisted reproductive technologies where the pregnant woman is genetically unrelated to the developing fetus (Thapar et al., 2009). These studies have suggested that the association could mostly be explained by familial confounding (D'Onofrio et al., 2008; Gustavson et al., 2017; Langley, Heron, Smith, & Thapar, 2012; Lindblad & Hjern, 2010; Obel et al., 2016; Skoglund et al., 2014). Based on these studies the associations between tobacco exposure and ADHD have attenuated in sibling comparisons and when analyzing the effect of paternal smoking. However, not all sibling studies have reached this conclusion. A Finnish study with over 150 000 sibling pairs found that if the mother stopped smoking between the pregnancies, the second sibling did not have an increased risk of externalizing diagnoses, including ADHD. Furthermore, if the mother started smoking between the pregnancies, a significantly higher risk was observed in the second sibling (Ekblad, Lehtonen, Korkeila, & Gissler, 2017). Moreover, the information on maternal smoking has been based solely on maternal self-report in all of the above studies.

2.7.2 Cotinine

Self-reported smoking may not always be reliable. A number of studies have shown that self-reports typically underestimate the true smoking prevalence. This is particularly common among populations in which smoking is socially undesirable such as among pregnant women (Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). In previous studies maternal self-reported smoking has been shown to underestimate true smoking by 8% to 28% (Dietz et al., 2011; Shipton et al., 2009; Tong et al., 2015).

Cotinine is a metabolite of nicotine and considered as the most reliable way to objectively quantify exposure to nicotine. Nicotine has a short half-life and it is metabolized into cotinine in the liver. The half-life of nicotine is approximately only 2–3 hours, whereas for cotinine it is approximately 20 hours (Ahijevych, Tyndale, Dhatt, Weed, & Browning, 2002; Kim, S., 2016). The blood cotinine measurements can therefore detect an individual's smoking a few days prior to sampling. Cotinine measurements can be used to identify smokers, individuals using nicotine

replacement therapy and nonsmokers exposed to environmental tobacco smoke. Cotinine can be detected from blood, urine or saliva and the cut-off values vary between the different samples (Connor Gorber et al., 2009).

2.7.3 Maternal cotinine levels and offspring ADHD

There are no previous studies on maternal, prenatal cotinine levels and diagnosed offspring ADHD. There are three studies evaluating the association between maternal cotinine levels and childhood behavioral outcomes reporting inconsistent results. Dürr et al. found no association between maternal cotinine measured in mid-gestation and later adverse child behavior among 1016 study participants. The behavior was assessed at five to nine years by parents filling the Strengths and Difficulties questionnaire (Dürr et al., 2015). The study eventually composed of few participants (n=57) with identified adverse behavior. Eskenazi et al. found no association between maternal cotinine during pregnancy and maternal report of child activity among five-year-old children in a cohort of 1605 participants (Eskenazi & Bergmann, 1995). The assessment of child activity was based on a simple set of questions to the mother instead of a standardized questionnaire. A large proportion of children were considered “active” by their mothers, only a fraction of whom are likely to fit the clinical definition of hyperactivity. In contrast, Minatoya et al. reported an increased risk of hyperactivity/inattention measured though Strenghts and Difficulties questionnaire filled by parents of 3216 5-year old participants whose mothers’ prenatal cotinine were measured in the third trimester (Minatoya et al., 2019).

2.8 Maternal vitamin D levels and offspring ADHD

2.8.1 Vitamin D

Vitamin D is a prohormone and group of secosteroids responsible for multiple biological effects in the human body. Vitamin D is currently recognized not only for its importance in bone health and development, but also for other health benefits, including effects on autoimmune diseases, cancer, and cardiovascular disease (Holick, 2009). Vitamin D deficiency during pregnancy has been linked to adverse maternal and fetal outcomes such as preeclampsia, gestational diabetes, low birth weight and preterm birth (Aghajafari et al., 2013).

Vitamin D is available from the sunlight, diet (such as fatty fish and egg yolks) and from dietary supplements. The sunlight converts 7-dehydrocholesterol to previtamin D_3. Vitamin D_3 is metabolized in the liver to 25-hydroxyvitamin (25(OH)D). The 25-hydroxivitamin D is further metabolized into 1,25-

dihydroxyvitamin D in the kidneys, which is the active form in the body (Holick, 2007).

The 25-hydroxyvitamin (25(OH)D) is the main circulating form of vitamin D and it is used to determine a patient's vitamin D status (Holick, 2007). The vitamin D levels may be reported in ng/ml or nmol/L depending on the studies. To convert ng/ml to nmol/L, the concentration is multiplied by 2.496 (Munger et al., 2016).

There is not a clear consensus as to what are the criteria of sufficient concentrations of 25(OH)D for the general public and for pregnant women especially. The Institute of Medicine, in their report from 2011 evaluated that 25(OH)D concentrations of at least 30 nmol/L would prevent deficiency with respect to bone health (Ross et al., 2011). Different guidelines define an optimal 25(OH)D concentration for pregnant and lactating women to be either over 75 nmol/L or perhaps already levels over 50 nmol/L would be sufficient in most women (Dodds et al., 2016). In Finland a recommendation for a vitamin D supplementation pregnant women (10 micrograms per day) began in 2004.

Definitions for vitamin D deficiency in clinical practice vary as well. Some regard levels below 30 nmol/l as deficiency and levels between 30 and 50 nmol/l as insufficiency. Others define deficiency as 25(OH)D under 50 nmo/l and levels between 50 and 75 nmol/l as insufficiency (Holick, 2007; Ross et al., 2011).

The discovery that most tissues and cells have a vitamin D receptor, has opened new insights into the function of vitamin D (Holick, 2007). For example, brain, prostate, breast and colon tissues as well as immune cells have vitamin D receptors and respond to the active form of vitamin D (Holick, 2007). In recent years, evidence has started to accumulate on the importance of vitamin D to the central nervous system and in relation to mental health (Groves, McGrath, & Burne, 2014; Kesby, Eyles, Burne, & McGrath, 2011). Some studies have shown an association between vitamin D deficiency during pregnancy and autism and schizophrenia (Eyles et al., 2018; Vinkhuyzen et al., 2017).

2.8.2 Maternal vitamin D deficiency as a risk factor of offspring ADHD

The studies examining prenatal vitamin D levels and the risk of offspring ADHD or ADHD-like symptoms are presented in Table 5.

Previous literature concerning vitamin D levels during pregnancy or at birth, have yielded contradictory results possibly due to the relatively small number of participants limiting the statistical power, variation in addressing important confounding factors, variation in the time point of the vitamin D measurements and child assessment methdos. Previous literature has mostly investigated the association

to ADHD-like symptoms. There are only two studies on diagnosed ADHD cases (Gustafsson et al., 2015; Strom et al., 2014).

Studies by Morales et al. and Daraki et al. found associations between lower maternal 25(OH)D levels measured in early pregnancy and ADHD-like symptoms (Daraki et al., 2018; Morales et al., 2015). Mossin and colleagues found a correlation between higher umbilical cord 25(OH)D concentrations and lower parent-rated ADHD problems in toddlers (Mossin et al., 2017).

However, two studies based on 25(OH)D in late pregnancy (Strom et al., 2014) or umbilical cord (Gustafsson et al., 2015) did not find any association with offspring ADHD diagnoses. One study examining 25(OH)D levels in mid pregnancy and cord blood found no associations with offspring hyperactivity at age 4 or externalizing behavior at age 7 in a psychologist's assessment (Keim, Bodnar, & Klebanoff, 2014).

2.9 Gaps in the existing literature

The literature on the prenatal and perinatal risk factors of ADHD consists of a vast body of investigations with heterogeneous methods, variation in controlling for confounding factors and partly inconclusive findings. Many studies lack important confounding factors, compose of a limited sample size reducing statistical power or have studied ADHD symptoms instead of diagnosed ADHD. The Finnish nationwide registers –along with other Nordic registers- allow for a population-based approach to the selected study questions and enable using prospectively collected data on the exposures and registered diagnoses in large samples.

Despite the extensive literature on the association between prematurity and ADHD, the risk of ADHD had not previously been studied by each week of fetal maturity. In addition, many previous population-based studies have had the limitation of not adjusting for parental psychiatric history or maternal substance use. There has also been a lack of studies examining fetal growth by weight for gestational age and ADHD while taking into account important confounding factors related to fetal growth. The earlier literature on many other prenatal or obstetric risk factors have yielded conflicting results and have lacked important confounding factors related to maternal mental health, smoking and social background.

There has been a lack of studies objectively measuring maternal smoking during pregnancy instead of relying on self-reported smoking. There have been no previous studies on maternal cotinine levels and diagnosed ADHD in the offspring. Furthermore, there have been no previous studies on maternal vitamin D levels in early pregnancy and diagnosed ADHD in the offspring.

Table 5. The litetarure on prenatal vitamin D levels and ADHD.

Author, publication year, country	Study design	ADHD outcome definition and age	Sample size	Time point of vitamin D measurement	Confounders	Results
Strom et al., 2014, Denmark	cohort study	Psychostimulant medication or hospital admission up to 22 years of age	n=24 ADHD cases / 850 participants	3rd trimester	Parity, maternal age, BMI, smoking, education, offspring sex, and season of birth	Maternal 25(OH)D ≤50 nmol/l was not associated with offspring ADHD
Keim et al. 2014, United States	cohort study	Behaviour analyzed by pscyhologist (hyperactivity at age 4 or externalizing behavior at age 7)	3896 participants	before gestational week 26 and at birth (umbilical cord)	Maternal education, age, parity, race, BMI, marital status, smoking, gestational age, month of blood draw and study site	No associations between maternal or cord 25(OH)D and offspring hyperactivity at age 4 or externalizing behavior at age 7
Gustafsson et al., 2015, Sweden	case-control study	DSM-IV diagnosis from 5 to 17 years of age	n=202 ADHD cases and 202 controls	at birth (umbilical cord)	Maternal age, smoking, season of birth, maternal BMI, parity and maternal height	No significant association between ADHD and vitamin D levels (OR 0.99, 95% CI 0.97–1.02)
Morales et al., 2015, Spain	cohort study	Psychologist report of total ADHD-like symptoms at 4–5 years of age	1650 participants	1st trimester	Area of study, child's sex, child's age at evaluation, and maternal education	Higher maternal 25(OH)D levels were associated with lower risk of ADHD-symptoms -Per 10 ng/ml increase symptoms decreased by 11% (IRR 0.89, 95% CI 0.80–0.98)
Mossin et al., 2017, Denmark	cohort study	Parental reported ADHD score at 2.7 years of age	1233 participants	at birth (umbilical cord)	Maternal age, BMI, smoking status, alcohol consumption, educational level, parity, parental psychiatric disease, sex of child, child age and season of birth	An inverse association between cord 25(OH)D and offspring ADHD-symptoms was seen -adjusted odds of being in the ≥90th percentile decreased by 11% per 10 nmol/l increase in 25(OH)D)
Daraki et al. 2018, Greece	cohort study	Maternal report of ADHD like symptoms at age 4 years	487 participants	1st trimester	Child age at assessment, maternal age, education, parity, smoking, BMI, and child sex	Children of women in the high 25(OH) D tertile had 40% decreased number of total ADHD-like symptoms (IRR 0.60, 95% CI 0.37–0.95)

OR: odds ratio; CI: confidence interval; IRR: Incidence relative risk, 25(OH)D: 25-hydroxyvitamin

3 Aims

The objective of this thesis was to examine the association of prenatal and perinatal risk factors with the risk of later ADHD on a population-based level. The specific aims were:

1. The aim was to study the association between gestational age and ADHD and the association of weight for gestational age and ADHD. The hypothesis was that prematurity and poor fetal growth increase the risk of ADHD.
2. The aim was to explore the associations between perinatal risk factors such as maternal high blood pressure, induction of labor, the mode of delivery, birth presentation, Apgar scores, NICU admission and umbilical artery pH, and the risk of ADHD. The hypothesis was that perinatal adversities increase the risk of later ADHD.
3. The aim was to investigate the association between fetal nicotine exposure and the risk of offspring ADHD. The hypothesis was that fetal exposure to nicotine is associated with an increased risk of offspring ADHD with a possible dose effect.
4. The aim was to examine the association between maternal 25-hydroxyvitamin D levels in early pregnancy and the risk of diagnosed offspring ADHD. The hypothesis was that maternal vitamin D deficiency is associated with a higher risk of offspring ADHD.

4 Materials and Methods

4.1 Study Design

This study is based on the Finnish Prenatal Study, which is a population-based register study examining early developmental events and later psychiatric disorders. The study investigating ADHD (FIPS-ADHD) is a nested case-control study derived from all live births in Finland between January 1, 1991 and December 31st, 2005 (N=900 603). Out of these, only singletons were included as the study's source population (N=870 695). For the first two studies the study population included the full data comprising of all ADHD cases born between 1991 and 2005 (n=10 409). For the last two studies a subsample of ADHD cases born between 1998 and 1999, was utilized (n=1320). A flowchart of the study design can be seen in Figure 1.

4.2 The Health care system in Finland

The health care system in Finland is based on universal health coverage. The public health care system includes primary health care and specialized health care. The primary health care includes health care centers, maternity and child welfare clinics and school health services. The checkups at the maternity, child welfare and school health care are free of charge, and virtually all children in Finland use these services. The specialized health care services are provided in both inpatient and outpatient settings. Children suspected of having ADHD are usually referred from school health care or child welfare clinics to specialized outpatient clinics where they are assessed by a child psychiatrist or neurologist. The current guidelines also enable trained general practitioners in the primary health care to diagnose ADHD based on local agreements.

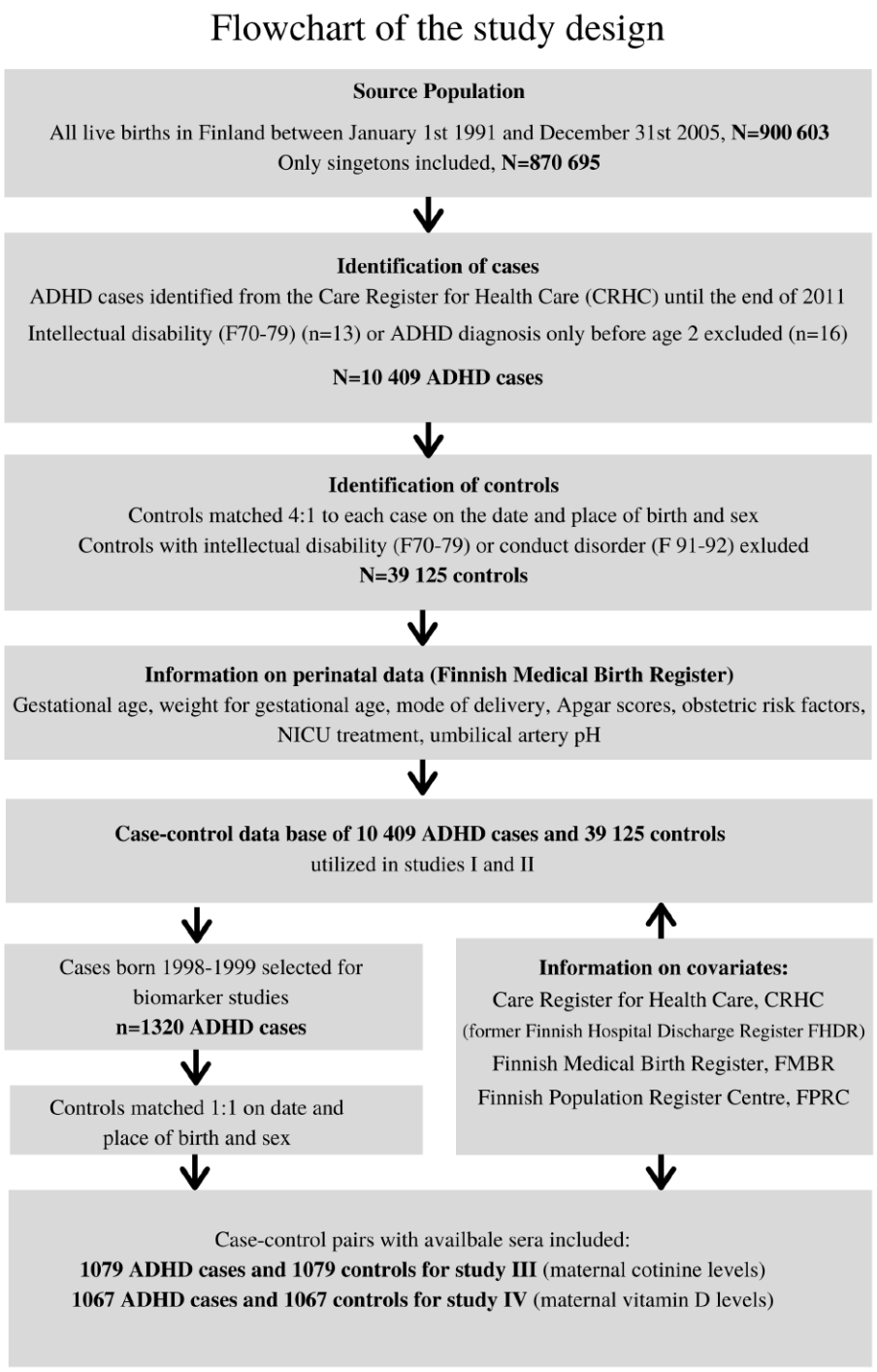

Figure 1. Flowchart of the study design.

4.3 Registers used in the study

This study utilizes information from three nationwide registries: The Care Register for Health Care (CRHC), The Finnish Medical Birth Register (FMBR) and the Finnish Population Register Centre (FPRC). All residents in Finland receive a unique personal identification code at birth or migration. This number enables linkage of information from various sources.

4.3.1 The Care Register for Health Care (CRHC)

The Care Register for Health Care is a continuation of the Finnish Hospital Discharge Register (FHDR) and is maintained by the National Institute of Health and Welfare (THL). The Finnish Hospital Discharge Register is one of the oldest individual hospital discharge registers. The purpose of the register is to collect data on the activities of health centres, hospitals and other institutions in order to enable planning, research and maintain statistics. The Care Register for Health Care includes all inpatient diagnoses since January 1, 1967 and outpatient diagnoses from specialized health care since January 1, 1998. Since 2011 also diagnoses from primary health care have been included. From 1987 to 1995 the diagnoses in the Care Register for Health Care were coded according to ICD-9 classification (World Health Organization, 1977) and from 1996 onwards according to ICD-10 classification (World Health Organization, 1992). The register information include the patient's personal identification code, area of residence, hospital ID, admission and discharge days and the patient's main diagnosis and three subsidiary diagnoses at discharge.

The validity of the ADHD diagnosis in the Care Register for Health Care has been evaluated in a previous study showing that 88% of subjects examined met the DSM-IV diagnostic criteria for ADHD (61 out of 69 examined children) (Joelsson, Chudal, Gyllenberg et al., 2016). In addition, the accuracy of the diagnoses has been found to be good for the diagnosis of mental disorders in general (Aro, Koskinen, & Keskimäki, 1990). A systematic review from 2012 also reported that the validity and accuracy of the diagnoses in the register varies from satisfactory to very good (Sund, 2012).

In this thesis the Care Register for Health Care was used to identify the cases, to check for the controls' diagnoses and to the collect the psychiatric diagnoses of the parents. In some of the manuscripts, the Care Register for Health Care is referred to by its former name FHDR.

4.3.2 The Finnish Medical Birth Register (FMBR)

The Finnish Medical Birth Register (FMBR) was established in 1987 and is also maintained by the National Institute of Health and Welfare (THL). The Finnish Medical Birth Register contains comprehensive data on all newborns in Finland during the neonatal period up to seven days of age. Data include maternal personal identification code, name, occupation, municipality, citizenship, marital status, reproductive history, health-related behaviors e.g. self-reported smoking, obstetric and perinatal events, the child's personal identification code, gender, gestational age, growth indicators, Apgar scores at 1 and 5 minutes, umbilical artery pH and items of neonatal care up to seven days of age.

In this thesis the Finnish Medical Birth Register was utilized to identify the study exposures in studies I and II and to collect information about potential covariates in all studies.

4.3.3 The Finnish Population Register Centre (FPRC)

The Finnish Population Register Centre (FPRC) is a digital national archive containing basic information about the citizens of Finland. The data include name, personal identification code, address, citizenship and native language, family relations and date of birth and death (if applicable). In this thesis the Finnish Population Register Centre was used to identify the controls and obtain information about the parents of the cases and the controls and information on the place of birth.

4.3.4 Linkage of the register information

The above-mentioned unique personal identification code enables linkage of information from several sources. The personal identification code was used to combine information from the registers. This was done by the data manager of the research center. After this the data was anonymized. The researchers themselves did not have access to the personal information.

4.4 Identification of the cases and controls

4.4.1 Identification of the cases

This study followed all singleton children born in Finland between January 1st 1991 and December 31st 2005 for ADHD diagnoses until December 31st 2011 (diagnostic codes F90 in ICD-10 or 314 in ICD-9) in the Care Register for Health Care. We

excluded children who had received an ADHD diagnosis before the age of two years, but not after that (n=16) and children diagnosed with severe or profound mental retardation (F72–73 in ICD-10 or 318 in ICD-9) (n=13).

A total of 10,409 children with ADHD were included in the study. For study I, cases for whom information on gestational age or birth weight was not available were excluded (n=87), resulting in 10 322 ADHD cases for study I. The most recently registered diagnoses, which were all ICD-10 codes, were used for identification.

4.4.2 Identification of the controls

Each case was matched with four controls based on their date of birth (±30 days), sex and place of birth. The controls were identified by linking the Care Register for Health Care and the Population Register Centre. The controls were to be alive and residing in Finland at the time of the case's diagnosis. The controls were not to have a diagnosis of ADHD, severe or profound mental retardation (F72–73 in ICD-10 or 318 in ICD-9) nor conduct disorder, which could possibly be misdiagnosed ADHD (ICD-10: F91–F92). This resulted in 39,125 controls (out of the initially identified 40,141 possible controls).

4.4.3 Cases and controls in the sera studies

For the studies utilizing maternal serum samples (studies III and IV) a subsample of ADHD cases born between January 1st 1998 and December 31st 1999 were selected. The controls were matched 1:1 to the case subjects on sex, date of birth and place of birth. Among the 1320 cases identified, sufficient sera was available for 1079 case-control pairs for study III and 1067 case-controls pairs for study IV. There was no difference in the distribution of the covariates between the included cases and those with insufficient serum. The only exception was for paternal age in study III, where the mean paternal age among cases not included was 1.2 (SD 6.9) years older than that of the included cases (p=0.02).

4.5 Study variables in studies I and II

4.5.1 Gestational Age and Birth Weight for Gestational Age

Data on gestational age and birth weight were obtained from the FMBR. Gestational age was calculated mainly based on information of the last menstrual period, but it has been verified, and corrected if needed, with a first trimester ultrasound since the

late 1980s (Pihkala, Hakala, Voutilainen, & Raivio, 1989). The gestational age was analyzed by each completed gestational week, using week 40 as the reference. Due to a limited number of infants born in week 23, we combined them with the infants born in week 24. In addition, gestational age was analyzed as a continuous variable.

The weight for gestational age was calculated according to national sex-specific birth weight distribution standards at a given gestational age. The references are derived from all newborns in Finland born between 1996 and 2008 (Sankilampi, Hannila, Saari, Gissler, & Dunkel, 2013). We divided the weight for gestational age into nine categories by a change of 0.5 standard deviations (SD). The categories were thereby below -2 SD, from -2.00 to -1.51 SD, from -1.50 to -1.01 SD, from -1.00 to -0.51 SD, from -0.50 to +0.50 SD (reference), from 0.51 to 1.00 SD, from 1.01 to 1.50 SD, from 1.51 to 2.00 SD and above 2 SD. We also analyzed weight for gestational age as a continuous variable.

Additional analyses were made by gender to examine both gestational age and weight for gestational age in categories. Due to a limited amount of extremely preterm females among the cases, in these additional analyses the gestational age was categorized as ≤28, from 29 to 31, from 32 to 33, from 34 to 36, from 37 to 38, from 39 to 40 (reference) and ≥42 weeks.

4.5.2 Perinatal Factors

Data on the obstetric and perinatal factors were obtained from the FMBR. Maternal factors included high blood pressure and uterine bleeding, which were classified as yes/no. Blood pressure exceeding 140/90 was classified as high. Maternal high blood pressure included both chronic hypertension and pregnancy induced hypertension including preeclampsia. Uterine bleeding was included if it required hospitalization.

Delivery related factors included the induction of labor (yes/no), the mode of delivery, and birth presentation. The mode of delivery was classified into five categories: vaginal cephalic, vaginal breech, vacuum or forceps assisted delivery, elective cesarean and other cesarean delivery (urgent or emergency). Vacuum was used in 5-7% of deliveries during the study period whereas forceps were only used in 0.1% of the deliveries. The cesarean section rate was 16% (Gissler & Kiuru, 2019). For additional analyses in subgroups by gestational age, vaginal breech and vacuum or forceps assisted deliveries were merged into one class due to the small numbers. Birth presentation was classified into three categories: cephalic, breech (including lower limb), or other (i.e. transverse, oblique, or upper limb).

Apgar scores at 1 minute were classified as 0–4, 5–6, 7–8, or 9–10. For additional analyses in subgroups by gestational age, Apgar scores 0-6 were merged into one class due to small numbers. Data on Apgar scores at 5 minutes were not

comprehensively available for the study period. Neonatal treatment was defined as admission to intensive care or monitoring (NICU).

4.5.3 Umbilical artery pH

Information on the umbilical artery pH was obtained from the FMBR. Measuring the umbilical artery pH gradually became routine in Finland with an increasing number of hospitals adopting the use of measuring umbilical pH. The umbilical artery pH measurement was available for 4,569 cases (43.9%) and 16,339 controls (41.8%). The measurements represented the whole study period and were missing for a similar proportion of cases and controls. The umbilical artery pH was analyzed as a continuous variable. Outliers were excluded (n=2, controls with pH 7.97 and 7.99). The umbilical artery pH measurements ranged between 6.62 and 7.63 (mean 7.26, SD 0.086).

4.6 The sera studies (studies III and IV)

4.6.1 The Finnish Maternity Cohort (FMC)

The Finnish Maternity Cohort (FMC) consists of 2 million serum samples collected during the first and early second trimester of pregnancy (5th to 95th percentile: months 2–4 of pregnancy) from over 950,000 women since the beginning of 1983. Following informed consent, blood samples have been collected at Finnish maternity clinics for the purpose of screening for congenital infections (HIV, hepatitis B and syphilis). One maternal serum sample is collected from each pregnancy. After the screening of congenital infections, approximately 1–3 milliliters of serum from each pregnancy are stored at -25°C in a protected biorepository at Biobank Borealis in Oulu, Finland, and are available for scientific research (Gissler & Surcel, 2012).

The median gestational age of serum collection for subjects in this study was 10 weeks (interquartile range: 8–12 weeks). Linkage between FMC data and the register information was possible using the personal identification code.

4.6.2 Maternal Cotinine

Maternal cotinine levels were measured from the FMC samples of the cases born between 1998 and 1999 and matched controls (1:1) with available sera (see 4.4.3). The cotinine measurements were conducted blind to case/control status and involved 1079 case-control pairs and one sample for each participant.

Serum cotinine levels were measured using a commercially available quantitative immunoassay kit (OraSure Technologies, Bethlehem, PA, USA) which has a reported sensitivity of 96–97%, and a specificity of 99–100%. The intra-assay variation of the method is 3.5–6.2% and the inter-assay variation is 6.0–9.6%. The results were obtained as continuing variable by ng/ml.

Cotinine was examined as a continuous measure. Due to the skewed distribution of cotinine, the variable was log-transformed before statistical analyses for the purpose of reaching a normal distribution.

We further examined maternal cotinine also categorized into deciles and as a three-class categorical variable: reference (<20ng/ml); moderate exposure (20–50 ng/ml); and heavy exposure (>50 ng/ml). The deciles for the case and control groups in the analyses were derived from the cut-off points of maternal cotinine levels that defined the deciles in the control group. The cut-off points for the three-class categorical variable were based on the recommendation of the cotinine immunoassay producer and have been used in previous studies based on the FMC serum bank (Niemelä et al., 2016). The cut-off value of the reference category (<20ng/ml) was set to distinguish non-smokers from smokers and thus contained also non-smokers passively exposed to tobacco smoke.

4.6.3 Maternal 25(OH)D

Maternal 25(OH)D measurements were carried out blind to case/control status and involved 1067 case-control pairs, one sample for each participant (see 4.4.3). The 25(OH)D levels were measured from archived maternal serum using a chemiluminescence microparticle immunoassay (CMIA) by an Architect i2000SR automatic analyzer (Abbott Diagnostics) according to the manufacturer's instructions. The CMIA was selected as the method of choice after evaluation of the assay by comparing the Architect i2000 method with high-performance liquid chromatography (HPLC). Comparing the 25(OH)D results showed a high correlation of 0.922 and reproducibility of the CMIA was high (R=0.98). In addition, analysis of a set of commercially available quality control samples (six different samples) showed that the resulting levels of 25(OH)D were within the SD range of the reference results.

Coefficients of variation, derived from repeated quality control samples included in the assay with the study samples, were calculated. In control samples with "high" 25(OH)D levels (>100 nmol/L), the coefficient of variation (CV) were 3.2%, in samples with "medium" 25(OH)D levels (~80 nmol/L), the CV was 3.1%, and with "low" 25(OH)D levels (<40 nmol/L), the CV was 3.6%. In blinded quality control pairs in which 25(OH)D levels were not known, the coefficients of variation were 1.1%.

4.7 Confounding factors

Potential confounding factors associating with the studied exposures (pre- and perinatal risk factors) and the outcome (ADHD) were identified from the literature. The data concerning these variables, were then obtained from the Finnish Medical Birth Register and the Care Register for Health Care. The confounding factors that were included in the adjusted analyses varied between each separate study and are summarized in Table 6. The variables considered for analyses included: parental age, maternal smoking during pregnancy (self-reported), the number of previous births, parental psychiatric history, maternal alcohol or substance abuse, parental diagnosis of ADHD, maternal socioeconomic status (SES), maternal marital status, parental immigration background, gestational age, weight for gestational age, urbanity of birth place, gestational week of blood draw, season of blood collection and biomarker-based smoking status.

Maternal smoking during pregnancy was classified as a binary variable (yes/no). The number of previous births was categorized as 0 or ≥1. Maternal marital status was classified as a binary variable (married / in a relationship or single). Maternal SES categories were based on existing national classifications that are used in the Finnish Medical Birth Register. Maternal SES was divided into four categories based on occupation and educational background: 1) managers and professionals 2) clerical support workers 3) manual workers and 4) others (e.g. students and housewives) or missing (if the data was not available).

A parent was defined as having a psychiatric history if he or she had any psychiatric diagnoses registered in the CRHC during his or her lifetime: F10–F99 based on the ICD-10: mental and behavioral disorders (Corresponding diagnoses based on the ICD-9 (291–316) and the ICD-8 (291–309) were also included). For mothers the disorders due to alcohol or substance abuse were tested as a separate variable (diagnoses of ICD-10 F10-19, ICD-9: 291, 292, 303, 304, 305, and ICD-8: 291, 303, 304). Both parental psychiatric history and maternal substance abuse were classified as a binary variable (yes/no). The urbanity of the birth place was categorized into rural, semi-urban and urban according to a categorization by Statistics Finland. The immigrant status of the parent was categorized as binary variable (yes/no).

For study II a combined six-category variable was created to include gestational age and weight for gestational age as one variable in the model: 1) preterm and SGA, 2) preterm and AGA, 3) preterm and LGA, 4) term and SGA, 5) term and AGA and 6) term and LGA. For study IV the season of blood collection was defined as Winter (December-February), Spring (March-May), Summer (June-July) and Autumn (September-November). In addition for study IV a variable of biomarker-based smoking status was included (cotinine < or > 20 ng/ml).

The guidelines of the current epidemiologic literature recommend that covariates should be considered as potential confounders and included in the adjusted models if they meet both of the following criteria: (1) association with exposure; (2) association with the outcome (Rothman, Greenland, & Lash, 2008; Susser, Ezra, Schwartz, Morabia, & Bromet, 2006). We thereby tested the association of each covariate and the exposure under study as well as the outcome (see 4.8.) However, for further reassurance we also ran analyses with adjustments for potential confounders or mediators identified from the literature. These are mentioned in Table 6.

Table 6. The covariates that were considered for analyses (tested) and included (based on association with exposure and outcome) in the studies I–IV.

Covariate	Source	study I		study II		study III		study VI	
		tested	inclu-ded	tested	inclu-ded	tested	inclu-ded	tested	inclu-ded
Maternal Age	FMBR	+	+	+	+	+	+	+	+
Paternal Age	FPRC	+	+	-	-	+	-	-	-
Maternal psychiatric history	CRHC	+	+	+	+	+	+	+	-
Paternal psychiatric history	CRHC	+	+	-	-	+	+	-	-
Maternal substance abuse	CRHC	+	+	+	+	+	+	+	-
Maternal ADHD	CRHC	-	-	-	-	+	-	+	-
Paternal ADHD	CRHC	-	-	-	-	+	-	+	-
previous births	FMBR	+	+	+	+	+	-	+	-
Maternal marital status	FMBR	+	+	-	-	-	-	-	-
Maternal SES	FMBR	+	+	+	+	+	+	+	+
Maternal smoking	FMBR	+	+	+	+	-	-	+	-
Mother immigrant	FPRC	+	-	-	-	-	-	+	-
Father immigrant	FPRC	+	+	-	-	-	-	-	-
Urbanity of birth place	FPRC / Statistics Finland	+	+	-	-	-	-	-	-
Gestational age	FMBR	-	-	+	+	+	-	+	-
Weight for gestational age	FMBR	-	-	+	+	+	+	+	-
Gestational week of blood draw	FMC	-	-	-	-	+	-	+	-
Season of blood collection	FMC	-	-	-	-	-	-	+	-
Maternal cotinine	FMC	-	-	-	-	-	-	+	-

FMBR= Finnish Medical Birth Register, FPRC= Finnish Population Register Centre, CRCH= Care Register for Health Care, FMC= Finnish Maternity Cohort

4.8 Statistical Methods

Conditional logistic regression models were used to examine the associations between the exposures and ADHD in all studies. In the first stage, unadjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated. After that, adjustment was made for the covariates (explained below). A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SAS statistical software (SAS version 9.4; SAS Institute, Inc, Cary, NC).

The need to include possible potential confounders in the adjusted models was evaluated with statistical testing, and confounders were included in the regression models if they were associated with both the exposures *and* the outcome. First, the association of potential confounders and the exposure were tested among the controls. In studies I and II this was made by using the Pearson χ^2 test (or the Fisher's exact test where applicable). For studies III and IV, categorically defined potential confounders were tested with Student's t and F-tests, and for continuous potential confounders linear regression was used. Second, in all studies conditional logistic regression was then used to test for the association between potential confounders and the outcome, ADHD. In all studies, confounders were included in the regression models if they were associated with both the exposures and the outcome at $p<0.10$ to ensure to include also the covariates with borderline significance into the adjusted models.

For study I, the gestational age was analyzed by unit week as a categorical variable and as a continuous variable. The weight for gestational age was analyzed in nine categories (see 4.5.1) and as a continuous variable. For the analysis of gestational age and weight for gestational age as continuous variables, linear and quadratic models were fitted. The quadratic model was selected based on the Akaike's information criterion (AIC).

For study II, in addition to an adjusted model, a final model was created. Based on the results of the adjusted model, the examined risk factors with statistically significant associations at the level of $p <0.10$ were entered into the final model. However, NICU admission was not included, as it represented a consequence of all perinatal adversities. For Apgar scores and the mode of delivery, additional analyses were run on subgroups stratified by gestational age, with the categories <32, 32–36 and ≥37 weeks.

For study III, cotinine was initially examined as a continuous measure. Due to the skewed distribution, cotinine was log-transformed before analysis in order to achieve a normal distribution. In addition, we examined maternal cotinine as categorized into deciles. The deciles for the case and control groups in the analyses were derived from the cut-off points of maternal cotinine levels in the control group. The lowest decile was defined as the reference group. Furthermore, we analyzed

cotinine as a three-class categorical variable: reference (<20 ng/ml); moderate exposure (20–50 ng/ml); and heavy exposure (>50 ng/ml). The cut-off points for the three-class categorical variable were based on the manufacturer's recommendation and have been used in previous studies based on the FMC serum bank (Niemelä et al., 2016).

For study IV we first examined the association of ADHD and maternal 25(OH)D defined as a continuous variable. Due to the skewed distribution, 25(OH)D was log-transformed before analysis in order to achieve a normal distribution. Second, we examined maternal 25(OH)D categorized into quintiles. The cut-points for the quintiles of maternal 25(OH)D levels were based on the distribution in the control group. The highest quintile was defined as the reference group. In addition, we examined maternal 25(OH)D as a three-class categorical variable based on clinical categories: deficient (25(OH)D<30 nmol/L), insufficient (25(OH)D 30–49.9 nmol/L) and sufficient maternal vitamin D levels (25(OH)D>50 nmol/L), where the highest category was defined as the reference group.

4.9 Study Ethics

Approval for the utilization of the health register data and the linkage of the data for research was obtained from the Data Protection Ombudsman. Ethical approval for the study was provided by the Ethics Committee of the Hospital District of Southwest Finland and the New York State Psychiatric Institute IRB (due to collaboration with Columbia University and funding by the National Institutes of Health, NIH). In accord with the legislation in Finland, it was not necessary to obtain written consent from the study subjects in order to utilize their register data. For the sera studies, the pregnant mothers had given informed consent for their sera samples to be utilized for scientific research after the screening of infections.

5 Results

5.1 Descriptive results

Altogether 10 409 ADHD cases and 39 124 controls were included in the study. The mean age at the time of the ADHD diagnosis in the sample was 7.6 years (SD 2.9 years, range: 3–19 years). In total, 84% of the children with ADHD were males and 16% females. In the sera studies, the sample consisted of 1079 case-control pairs in study III and 1067 case-control pairs in study IV. In the sera studies the mean age at ADHD diagnosis was 7.3 years (SD: 1.9; range: 2–13.7 years) and the gender distribution was 85.5% male and 14.5% female among cases and controls. All of the ADHD diagnoses in the study were based on ICD-10 diagnoses.

5.2 Prematurity and ADHD

The study found that prematurity was a risk factor for ADHD also after adjustments for confounding factors. Based on the covariate testing, the adjusted model included parental age and psychiatric history, maternal substance use, smoking during pregnancy, number of previous births, SES, paternal immigrant status and municipality of birthplace. The study demonstrated that each declining week of gestation increases the risk of ADHD. Table 7 shows the frequencies of cases and controls by gestational age. Table 8 shows the ORs and the adjusted ORs for ADHD according to gestational age by each week of maturity.

The risk showed a dose effect with each declining week of gestation increasing the risk of ADHD when compared to week 40. An increased risk was also seen in late preterm and early term infants. The only exception was week 34 lacking statistical significance. Foe example, at week 25, the adjusted OR was 5.77 (95% CI 1.68–19.83), week 30, 3.55 (95% CI 2.02–6.23) and week 35, 1.41 (95% CI 1.12–1.78). The risk remained moderately elevated until early term birth (week 37 OR 1.31, 95% CI 1.16–1.47; week 38 OR 1.12, 95% CI 1.03–1.22). Figure 2 shows the adjusted risk for ADHD for the weekly increase in gestational categories and for as a continuous variable. Additional analyses for boys and girls in gestational age categories are presented Tables 9 and 10. The results showed no gender differences.

Table 7. Frequencies of ADHD cases and controls by gestational weeks at birth.

Gestational Age (weeks)	Cases, N (%)	Controls, N (%)
	N=10321	N =38355
23–24	14 (0.1)	4 (0.01)
25	11 (0.1)	6 (0.01)
26	17 (0.2)	6 (0.02)
27	19 (0.2)	18 (0.1)
28	23 (0.2)	20 (0.1)
29	30 (0.3)	25 (0.1)
30	36 (0.4)	43 (0.1)
31	45 (0.4)	47 (0.1)
32	41 (0.4)	84 (0.2)
33	72 (0.7)	111(0.3)
34	62 (0.6)	202 (0.5)
35	145 (1.4)	372 (1.0)
36	297 (2.9)	788 (2.1)
37	593 (5.8)	1765 (4.6)
38	1431 (13.9)	5050 (13.2)
39	2515 (24.4)	9725 (25.4)
40	2706 (26.2)	11112 (29.0)
41	1799 (17.4)	7248 (18.9)
42	451 (4.4)	1676 (4.4)
43	14 (0.1)	53 (0.1)

Table 8. ORs with 95% CI for associations between gestational age in weeks and ADHD.

Gestational Age (weeks)	Unadjusted OR	95% CI	p-value	Adjusted OR[a]	95% CI	p-value
23–24	14.59	4.79-44.47	<0.001	11.96	3.60-39.72	<0.001
25	7.05	2.60-19.13	<0.001	5.77	1.68-19.83	0.005
26	11.19	4.39-28.48	<0.001	5.85	1.87-18.25	0.002
27	4.35	2.27-8.31	<0.001	3.69	1.65-8.23	0.001
28	4.73	2.59-8.62	<0.001	3.34	1.67-6.69	<0.001
29	4.77	2.80-8.14	<0.001	3.34	1.80-6.18	<0.001
30	3.46	2.22-5.41	<0.001	3.55	2.02-6.23	<0.001
31	3.95	2.61-5.98	<0.001	2.87	1.77-4.64	<0.001
32	1.98	1.36-2.88	<0.001	1.96	1.25-3.07	0.004
33	2.61	1.93-3.53	<0.001	2.61	1.80-3.78	<0.001
34	1.26	0.95-1.69	0.11	1.01	0.70-1.46	0.94
35	1.61	1.32-1.97	<0.001	1.41	1.12-1.78	0.004
36	1.54	1.34-1.78	<0.001	1.48	1.25-1.74	<0.001
37	1.38	1.24-1.52	<0.001	1.31	1.16-1.47	<0.001
38	1.16	1.08-1.25	<0.001	1.12	1.03-1.22	0.008
39	1.06	0.998-1.13	0.058	1.08	1.003-1.15	0.042
40	reference			reference		
41	1.01	0.95-1.08	0.70	1.02	0.95-1.10	0.60
42	1.10	0.98-1.23	0.11	1.08	0.95-1.24	0.23
43	1.08	0.60-1.95	0.80	0.99	0.48-2.02	0.97

[a]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, number of previous births, urbanity of child's birth place and paternal immigrant status

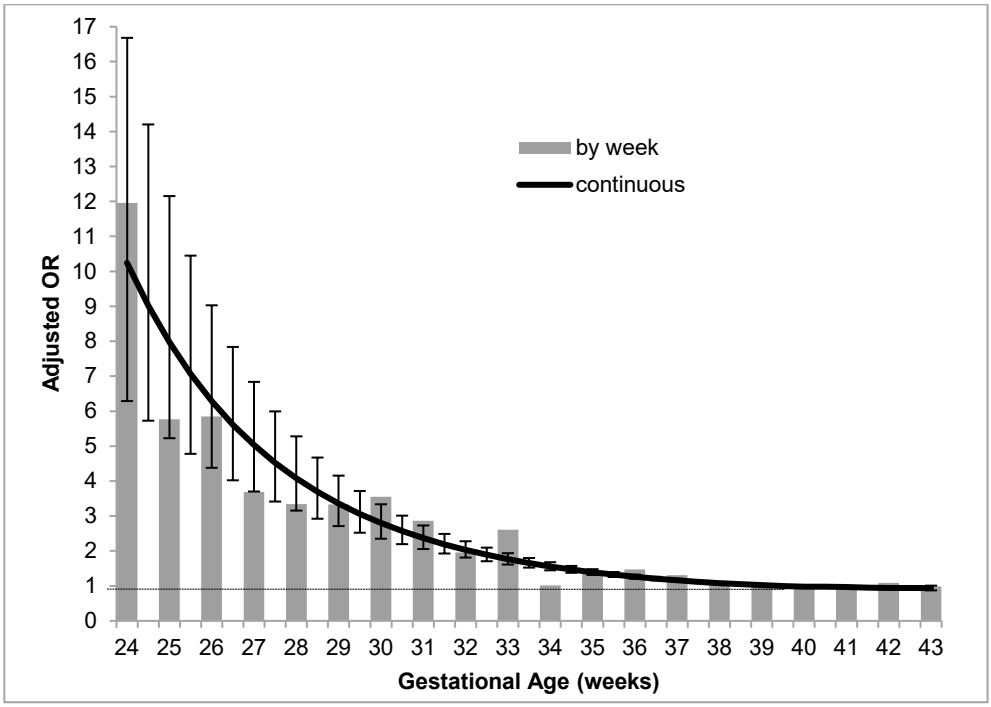

Figure 2. The association of ADHD and gestational age by each gestational week and by fitting a continuous model (with 95% CIs). From study I, reprinted with the permission of *Pediatrics*.

Table 9. Distribution of ADHD cases and controls according to gestational age categories in boys, and ORs with 95%.

Gestational Age (weeks)	Cases, N (%)	Controls, N (%)	Unadjusted OR (95 % CI)	p-value	Adjusted OR[a] (95 % CI)	p-value
	total N =8672	total N =32134				
≤28	67 (0.8)	50 (0.2)	5.30 (3.67–7.66)	<0.001	4.00 (2.56–6.26)	<0.001
29–31	98 (1.1)	97 (0.3)	4.01 (3.02–5.36)	<0.001	3.15 (2.25–4.41)	<0.001
32–33	86 (1.0)	174 (0.5)	1.91 (1.47–2.48)	<0.001	1.86 (1.35–2.56)	<0.001
34–36	425 (4.9)	1179 (3.7)	1.43 (1.27–1.60)	<0.001	1.31 (1.14–1.50)	<0.001
37–38	1707 (19.7)	5807 (18.1)	1.16 (1.09–1.24)	<0.001	1.10 (1.03–1.18)	0.007
39–41	5911 (68.2)	23377 (72.8)	reference		reference	
≥42	378 (4.4)	1450 (4.5)	1.03 (0.91–1.16)	0.65	1.004 (0.88–1.15)	0.98
in total	8672 (100%)	32134 (100%)				

[a]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, number of previous births, urbanity of child's birth place and paternal immigrant status

Table 10. Distribution of ADHD cases and controls according to gestational age categories in girls, and ORs with 95%.

Gestational age (weeks)	Cases, N (%)	Controls, N (%)	Unadjusted OR (95 % CI)	P-value	Adjusted OR[a] (95 % CI)	P-value
	Total N =1649	Total N =6221				
≤28	17 (1.0)	4 (0.1)	16.75 (5.62–49.95)	<0.001	9.89 (3.09–31.58)	<0.001
29–31	13 (0.8)	18 (0.3)	2.99 (1.46–6.14)	0.003	2.67 (1.09–6.53)	0.03
32–33	27 (1.6)	21 (0.3)	5.58 (3.14–9.91)	<0.001	5.74 (2.89–11.42)	<0.001
34–36	79 (4.8)	183 (2.9)	1.85 (1.40–2.43)	<0.001	1.64 (1.17–2.31)	0.004
37–38	317 (19.2)	1008 (16.2)	1.33 (1.16–1.54)	<0.001	1.31 (1.11–1.55)	0.002
39–41	1109 (67.3)	4708 (75.7)	reference		reference	
≥42	87 (5.3)	279 (4.5)	1.30 (1.01–1.68)	0.04	1.34 (0.99–1.81)	0.06
in total	1649 (100 %)	6221 (100 %)				

[a]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, number of previous births, urbanity of child's birth place and paternal immigrant status

5.3 Fetal Growth and ADHD

In the analyses investigating fetal growth, the study demonstrated that as weight for gestational age decreased below -1 SD, the risk of ADHD increased. The odds ratio for ADHD and weight for gestational age showed a U-shaped curve. Table 11 shows the frequencies of cases and controls according to fetal growth categories. Table 12 shows the risk for ADHD according to weight for gestational age.

Infants born SGA (<-2 SD) had an adjusted OR of 1.80 (95% CI 1.58–2.05) for ADHD. A statistically significantly increased risk was also seen in the groups with a weight for gestational age from -2 to -1.5 SD and from -1.5 to -1 SD resulting in adjusted ORs of 1.36 (95% CI 1.21–1.52) and 1.14 (95% CI 1.04–1.24), respectively. Infants born LGA (>2 SD) had an OR of 1.21 (95% CI 1.05–1.40) in the adjusted model. Figure 3 presents the results of the adjusted analysis examining the association of continuous weight for gestational age and ADHD. The OR shows a U-shaped curve with the highest risk for ADHD in the infants with poorest fetal growth, and the risk for ADHD rising again for LGA infants. The adjusted model included parental age and psychiatric history, maternal substance use, smoking during pregnancy, number of previous births, SES, paternal immigrant status and municipality of birthplace. Additional analyses for boys and girls and weight for

gestational age are presented in Tables 13 and 14. The results showed no gender differences, apart from the finding concerning an increased risk among LGA infants, which was seen only among boys.

Table 11 Frequencies of ADHD cases and controls for weight for gestational age.

Weight for gestational age SD[a]	Cases, N (%)	Controls, N (%)
	total N=10321	total N =38355
<-2.00	583 (5.7)	1069 (2.8)
-2.00 to -1.51	673 (6.5)	1707 (4.5)
-1.50 to -1.01	1187 (11.5)	3777 (9.9)
-1.00 to -0.51	1652 (16.0)	5956 (15.5)
-0.50 to +0.50	3551 (34.4)	14350 (37.4)
0.51 to 1.00	1219 (11.8)	5362 (14.0)
1.01 to 1.50	729 (7.1)	3195 (8.3)
1.51 to 2.00	385 (3.7)	1625 (4.2)
>2.00	342 (3.3)	1311 (3.4)
in total	10321 (100 %)	38355 (100 %)

[a]SD=standard deviation, according to national references derived from all newborns in Finland born in 1996–2008

Table 12. ORs with 95% CI for association between ADHD and weight for gestational age.

Weight for gestational age SD[a]	Unadjusted OR	95% CI	P-value	Adjusted OR[b]	95% CI	P-value
<-2.00	2.20	1.97–2.45	<0.001	1.80	1.58–2.05	<0.001
-2.00 to -1.51	1.59	1.44–1.75	<0.001	1.36	1.21–1.52	<0.001
-1.50 to -1.01	1.27	1.18–1.37	<0.001	1.13	1.04–1.24	0.005
-1.00 to -0.51	1.12	1.05–1.20	<0.001	1.02	0.95–1.11	0.54
-0.50 to +0.50	reference			reference		
0.51 to 1.00	0.92	0.85–0.99	0.018	0.99	0.91–1.08	0.85
1.01 to 1.50	0.92	0.84–1.01	0.075	0.97	0.88–1.08	0.62
1.51 to 2.00	0.96	0.85–1.08	0.47	1.09	0.95–1.24	0.22
>2.00	1.05	0.93–1.19	0.43	1.21	1.05–1.40	0.009

[a]SD=standard deviation, according to national references derived from all newborns in Finland born in 1996–2008

[b]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, no of previous births, urbanity of child's birth place and paternal immigrant status

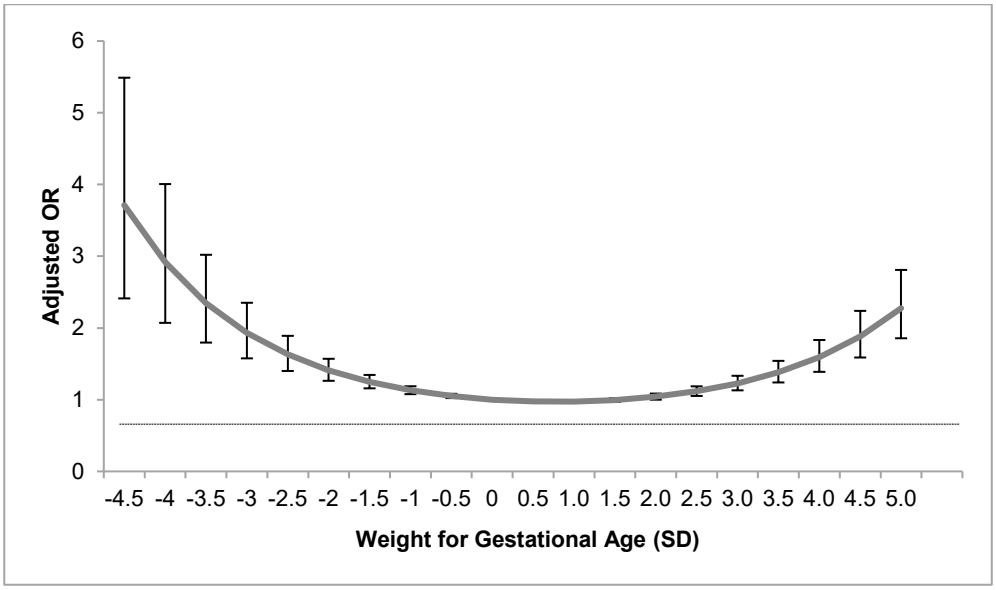

Figure 3. Association of ADHD and weight for gestational age by fitting a continuous model with 95 % CIs. From study I, reprinted with the permission of *Pediatrics*.

Table 13. Frequencies of ADHD cases and controls and ORs with 95% CI for associations between weight for gestational age and ADHD in boys.

Weight for gestational age SD[a]	Cases, N (%)	Controls, N (%)	Unadjusted OR (95 % CI)	P-value	Adjusted OR[b] (95 % CI)	P-value
	total N =8672	total N =32134				
<-2.00	465 (5.4)	904 (2.8)	2.05 (1.82–2.31)	<0.001	1.68 (1.45–1.94)	<0.001
-2.00 to -1.51	538 (6.2)	1418 (4.4)	1.51 (1.36–1.68)	<0.001	1.29 (1.13–1.46)	<0.001
-1.50 to -1.01	987 (11.4)	3129 (9.7)	1.26 (1.17–1.37)	<0.001	1.11 (1.01–1.23)	0.033
-1.00 to -0.51	1385 (16.0)	5022 (15.6)	1.10 (1.03–1.19)	0.008	1.02 (0.94–1.11)	0.68
-0.50 to +0.50	2996 (34.6)	12000 (37.3)	reference			
0.51 to 1.00	1056 (12.2)	4497 (14.0)	0.94 (0.87–1.02)	0.12	1.01 (0.93–1.11)	0.76
1.01 to 1.50	623 (7.2)	2692 (8.4)	0.93 (0.84–1.02)	0.13	0.97 (0.87–1.09)	0.64
1.51 to 2.00	321 (3.7)	1365 (4.3)	0.94 (0.83–1.07)	0.38	1.11 (0.96–1.28)	0.16
>2.00	301 (3.5)	1107 (3.4)	1.09 (0.95–1.25)	0.21	1.26 (1.08–1.47)	0.004
in total	8672 (100 %)	32134 (100 %)				

[a]SD=standard deviation, according to national sex-specific birth size references derived from all newborns in Finland born in 1996-2008

[b]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, no of previous births, urbanity of child's birth place and paternal immigrant status

Table 14. Frequencies of ADHD cases and controls and ORs with 95% CI for associations between weight for gestational age and ADHD in girls.

Weight for gestational age (SD)[a]	Cases, N (%)	Controls, N (%)	Unadjusted OR (95 % CI)	P-value	Adjusted OR[b] (95 % CI)	P-value
	N =1649	*N* =6221				
<-2.00	118 (7.2)	165 (2.7)	3.05 (2.36–3.94)	<0.001	2.46 (1.77–3.40)	<0.001
-2.00 to -1.51	135 (8.2)	289 (4.7)	1.99 (1.58–2.49)	<0.001	1.78 (1.36–2.32)	<0.001
-1.50 to -1.01	200 (12.1)	648 (10.4)	1.31 (1.09–1.57)	0.004	1.22 (0.99–1.52)	0.07
-1.00 to -0.51	267 (16.2)	934 (15.0)	1.21 (1.03–1.43)	0.021	1.05 (0.87–1.29)	0.61
-0.50 to +0.50	555 (33.7)	2350 (37.8)	reference			
0.51 to 1.00	163 (9.9)	868 (14.0)	0.79 (0.65–0.95)	0.014	0.85 (0.68–1.06)	0.15
1.01 to 1.50	106 (6.4)	503 (8.1)	0.89 (0.71–1.12)	0.34	0.98 (0.75–1.27)	0.85
1.51 to 2.00	64 (3.9)	260 (4.2)	1.04 (0.78–1.38)	0.81	0.97 (0.68–1.38)	0.87
>2.00	41 (2.5)	204 (3.3)	0.84 (0.59–1.19)	0.33	0.96 (0.65–1.41)	0.82
in total	1649 (100 %)	6221 (100 %)				

[a]SD=standard deviation, according to national sex-specific birth size references derived from all newborns in Finland born in 1996–2008
[b]Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, no of previous births, urbanity of child's birth place and paternal immigrant status

5.4 Obstetric and perinatal risk factors and ADHD

This study focused on obstetric and perinatal risk factors that were available from the FMBR. The frequencies of the cases and controls by risk factors are presented in Table 15. The risk factors that associated with ADHD in the adjusted analyses were: mother's high blood pressure, breech presentation, induced labor, elective C-section, urgent or emergency C-section, low Apgar scores and NICU admission. The adjusted model included maternal age, psychiatric history, substance abuse, smoking during pregnancy, SES, the number of previous births and the combined variable for gestational age and weight for gestational age (see 4.7.). In the final model breech presentation, induced labor, elective C-section and low Apgar scores remained as significant risk factors of ADHD. NICU admission was not included in the final model, as it represents a consequence of all perinatal adversities. The results are presented in Tables 16 and 17.

Low Apgar scores were associated with an increased risk for ADHD. In the final model, for Apgar scores 0–4, the OR was 1.41 (95% CI 1.18–1.68), for Apgar scores 5–6 the OR was 1.17 (95% CI 1.02–1.35) and for Apgar scores 7–8 the OR was 1.12

(95% CI 1.06–1.19) compared with Apgar scores of 9-10. This increasing trend of ORs for decreasing Apgar scores was also seen consistently in all groups stratified by gestational age (Table 18).

This study demonstrated an association between birth by elective C-section and ADHD: the OR was 1.15 (95% CI 1.05–1.26) in the final model. Birth by urgent or emergency C-section had an adjusted OR of 1.10 (95% CI 1.01–1.19), but was statistically insignificant in the final model. Breech presentation showed an OR of 1.22 (95% CI 1.05–1.42) in the final model. Vaginal breech delivery was, however, not significant. The mode of delivery by elective C-section consistently yielded the highest OR for ADHD within all groups stratified by gestational age (Table 19).

Table 15. Frequencies of ADHD cases and controls by obstetric and perinatal risk factors.

Exposures	**Cases, N (%)** total N=10409	**Controls, N (%) total N=39124**
High blood pressure		
No	9884 (95.1)	37342 (96.0)
Yes	505 (4.9)	1561 (4.0)
Uterine bleeding		
No	10194 (98.1)	38282 (98.4)
Yes	195 (1.9)	621 (1.6)
Birth presentation		
Cephalic	9814 (94.5)	36944 (95.0)
Breech	325 (3.1)	930 (2.4)
Other	250 (2.4)	1029 (2.7)
Mode of delivery		
Vaginal cephalic	7776 (74.7)	30142 (77.0)
Vaginal breech	35 (0.3)	100 (0.3)
Elective C-section	840 (8.1)	2883 (7.4)
Emergency / urgent C-section	1052 (10.1)	3259 (8.3)
Vacuum extraction / Forceps	652 (6.3)	2393 (6.1)
Unknown	54 (0.5)	347 (0.9)
Induction of labor		
No	8736 (84.1)	33109 (85.1)
Yes	1653 (15.9)	5794 (14.9)
Apgar scores (1 min)		
0–4	228 (2.2)	488 (1.3)
5–6	333 (3.2)	961 (2.5)
7–8	2131 (20.6)	7193 (18.6)
9–10	7662 (74.0)	30119 (77.7)
Neonatal treatment		
Normal	9066 (87.3)	35845 (92.1)
NICU / Monitoring	1323 (12.7)	3058 (7.9)
Umbilical artery pH	**N=4569**	**N =16337**
Mean (SD)	7.258 (0.087)	7.263 (0.086)
Range	6.62–7.63	6.62–7.60

Table 16. ORs with 95% CI for associations between obstetric risk factors and ADHD.

Exposures	Unadjusted OR	95 % CI	P-value	Adjusted OR[a]	95 % CI	P-value	Final Model OR[b]	95 % CI	P-value
High blood pressure									
No	Ref.			Ref.			Ref.		
Yes	1.22	1.10–1.35	<.001	1.11	0.99–1.24	.070	1.08	0.96–1.21	.20
Uterine bleeding									
No	Ref.			Ref.					
Yes	1.19	1.004–1.40	.045	1.068	0.89–1.28	.48			
Birth presentation									
Cephalic	Ref.			Ref.			Ref.		
Breech	1.32	1.16–1.50	<.001	1.30	1.13–1.49	<.001	**1.22**	**1.05–1.42**	**.008**
Other	0.91	0.79–1.05	.20	0.89	0.77–1.04	.14	0.85	0.73–0.99	.038
Mode of delivery									
Vaginal cephalic	Ref.			Ref.			Ref.		
Vaginal breech	1.33	0.90–1.96	.15	1.21	0.80–1.84	.37	1.01	0.66–1.55	.97
Elective C-section	1.13	1.04–1.22	.003	1.16	1.06–1.26	.001	**1.15**	**1.05–1.26**	**.003**
Emergency / urgent C-section	1.26	1.17–1.35	<.001	1.10	1.01–1.19	.032	1.07	0.98–1.16	.14
Vacuum extraction / Forceps	1.06	0.97–1.16	.23	1.07	0.97–1.18	.18	1.05	0.95–1.15	.39
Unknown	0.59	0.44–0.79	<.001	1.41	0.65–3.08	.39	1.40	0.64–3.07	.40
Induction of labor									
No	Ref.			Ref.			Ref.		
Yes	1.08	1.02–1.15	.011	1.09	1.02–1.16	.009	**1.09**	**1.02–1.17**	**.008**

Abbreviation Ref. = Reference. Bold indicates significant results in the final model.

[a]Adjusted for gestational age and weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and parity

[b]Final model included mother's blood pressure, birth presentation, mode of delivery, induction of labor and Apgar scores and adjusted for covariates gestational age and weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and parity

Table 17. ORs with 95% CI for associations between perinatal risk factors and ADHD.

Exposure	Unadjusted OR	95% CI	p-value	Adjusted OR[a]	95% CI	P-value	Final model OR[b]	95% CI	P-value
Apgar scores									
0–4	1.85	1.58–2.17	<.001	1.43	1.20–1.70	<.001	**1.41**	**1.18–1.68**	**<.001**
5–6	1.36	1.20–1.55	<.001	1.19	1.03–1.36	.017	**1.17**	**1.02–1.35**	**.026**
7–8	1.18	1.11–1.25	<.001	1.12	1.05–1.19	<.001	**1.12**	**1.06–1.19**	**<.001**
9–10	ref.			Ref.			Ref.		
Neonatal treatment									
Normal	Ref.			Ref.					
NICU / Monitoring	1.73	1.61–1.85	<.001	1.41	1.30–1.53	<.001			
Umbilical artery pH									
one for unit change	0.71	0.46–1.08	.11	0.71	0.45–1.13	.15			
pH=7.26 (SD 0.087)	reference								
for -1 SD change pH=7.17	1.03	0.99–1.07							
for +1 SD change pH=7.35	0.97	0.94–1.01							

Ref. = Reference. Bold indicates significant results in the final model.

[a]Adjusted for gestational age and weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and parity

[b]Final model included mother's blood pressure, birth presentation, mode of delivery, induction of labor and Apgar scores and adjusted for covariates gestational age and weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and parity. NICU not included as it represents a consequence of all perinatal adversities.

Table 18. Frequencies of ADHD cases and controls and ORs with 95% CI for associations between Apgar scores and ADHD stratified by gestational age.

	Cases, N (%)	Controls, N (%)	Unadjusted OR	95% CI	P-value	Adjusted OR[a]	95% CI	P-value	Final Model OR[b]	95% CI	P-value
Apgar scores	*N*=10318	*N*=38648									
<32 weeks											
0–6	101 (1.0)	68 (0.2)	5.88	4.31–8.02	<.001	4.52	3.22–6.36	<.001	4.33	3.07–6.11	<.001
7–8	64 (0.6)	59 (0.2)	4.43	3.10–6.33	<.001	3.69	2.49–5.47	<.001	3.49	2.35–5.19	<.001
9–10	32 (0.3)	44 (0.1)	2.95	1.86–4.68	<.001	2.68	1.61–4.44	<.001	2.63	1.58–4.36	<.001
32–36 weeks											
0–6	71 (0.7)	139 (0.4)	2.06	1.55–2.75	<.001	1.64	1.20–2.24	.002	1.60	1.17–2.19	.003
7–8	163 (1.6)	407 (1.1)	1.62	1.35–1.95	<.001	1.42	1.16–1.73	<.001	1.40	1.15–1.71	.001
9–10	383 (3.7)	1019 (2.6)	1.50	1.33–1.69	<.001	1.38	1.22–1.58	<.001	1.36	1.20–1.55	<.001
≥37 weeks											
0–6	377 (3.7)	1218 (3.2)	1.23	1.10–1.39	<.001	1.16	1.02–1.32	.02	1.15	1.01–1.31	.03
7–8	1879 (18.2)	6670 (17.3)	1.14	1.07–1.21	<.001	1.11	1.05–1.19	<.001	1.12	1.05–1.19	<.001
9–10	7248 (70.3)	29024 (75.1)	Ref.			Ref.			Ref.		

Ref. = Reference

[a]Adjusted for weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and the number of previous births

[b]Final model included mother's blood pressure, birth presentation, induction of labor, mode of delivery and Apgar scores and adjusted for covariates weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and the number of previous births

Among the pregnancy-related risk factors mother's high blood pressure had an OR of 1.22 (95% CI 1.10–1.35) in the univariate analysis, but the association became only borderline statistically significant in the adjusted analyses (adjusted OR 1.11, 95% CI 0.99–1.24) and was insignificant in the final model. Induced labor showed an OR of 1.09 (95% CI 1.02–1.17) in the final model. NICU admission had an OR of 1.41 (95% CI 1.30–1.53) in the adjusted model.

Umbilical artery pH was not associated with ADHD. The unadjusted OR for a calculated one unit change in pH was 0.71 (95% CI 0.46–1.08) in the analyses of pH as a continuous measure. The association was also insignificant in the adjusted model (OR 0.71, 95% CI 0.45–1.13). Calculated specific values showed that e.g. a change of -1 SD (from pH 7.26 to pH 7.17) showed an OR of 1.03 (95% CI 0.99–1.07).

Table 19. Frequencies of ADHD cases and controls and ORs with 95% CI for associations between the mode of delivery and ADHD stratified by gestational age.

	Cases, N (%)	Controls N (%)	Unadjusted OR	95% CI	P-value	Adjusted OR[a]	95% CI	P-value	Final model OR[b]	95% ci	P-value
	N=10319	*N*=38665									
Mode of delivery											
<32 weeks											
Elective C-section	25 (0.2)	19 (0.1)	5.33	2.90–9.80	<.001	4.35	2.24–8.45	<.001	3.94	2.00–7.77	<.001
Urgent / emergency C-section	98 (1.0)	85 (0.2)	4.55	3.40–6.10	<.001	3.69	2.66–5.11	<.001	3.37	2.41–4.72	<.001
Vaginal assisted or breech	5 (0.1)	6 (0.0)	3.39	1.03–11.11	.04	3.91	1.08–14.11	.04	3.09	0.86–11.16	.08
Vaginal cephalic	70 (0.7)	64 (0.2)	4.34	3.08–6.12	<.001	3.53	2.43–5.15	<.001	3.20	2.19–4.68	<.001
32–36 weeks											
Elective C-section	71 (0.7)	136 (0.4)	2.03	1.52–2.71	<.001	1.84	1.34–2.52	<.001	1.79	1.31–2.45	<.001
Urgent / emergency C-section	188 (1.8)	377 (1.0)	1.99	1.66–2.37	<.001	1.61	1.33–1.96	<.0001	1.52	1.25–1.85	<.001
Vaginal assisted or breech	20 (0.2)	70 (0.2)	1.19	0.72–1.96	.49	1.31	0.78–2.20	.32	1.25	0.74–2.11	.40
Vaginal cephalic	338 (3.3)	983 (2.5)	1.35	1.19–1.54	<.001	1.27	1.11–1.46	<.001	1.25	1.09–1.43	.001
≥37 weeks											
Elective C-section	734 (7.1)	2708 (7.0)	1.07	0.98–1.17	.11	1.14	1.04–1.24	.007	1.14	1.03–1.25	.009
Urgent / emergency C-section	784 (7.6)	2842 (7.4)	1.10	1.01–1.19	.03	1.04	0.95–1.14	.35	1.03	0.94–1.13	.56
Vaginal assisted or breech	658 (6.4)	2411 (6.2)	1.08	0.99–1.18	.10	1.08	0.98–1.19	.15	1.05	0.95–1.21	.35
Vaginal cephalic	7328 (71.0)	28964 (74.9)	Ref.			Ref.			Ref.		

Ref. = Reference

[a]Adjusted for weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and the number of previous births

[b]Final model included mother's blood pressure, birth presentation, induction of labor, mode of delivery and Apgar scores and adjusted for covariates weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, SES and the number of previous birth

5.5 Maternal cotinine levels and offspring ADHD

The mean cotinine level among cases was 27.4 ng/ml (SD 54.8, range 0.0–427.7 ng/ml) and 11.3 ng/ml (SD 34.5, range 0.0–320.0 ng/ml) among controls. Table 20 shows the distribution of serum cotinine levels and the corresponding self-reported smoking status. Among mothers of ADHD cases, in the category with moderate nicotine exposure (cotinine levels 20–50 ng/ml), 22.5 % of the women (18 out of 80) reported themselves as nonsmokers. In the category of heavy exposure (cotinine levels >50 ng/ml), 8.4 % of the women (18 out of 214) reported themselves as nonsmokers. The prevalence of self-reported smoking status increased with increasing serum cotinine levels. (P<.001).

Table 20. Maternal self-reported smoking and cotinine levels in ADHD cases.

	Self-reported smoking		
	No, n (%) N=738	Yes, n (%) N=314	in total, n (%) N=1052
Serum Cotinine ng/ml			
Reference (<20)	702 (92.6)	56 (7.4)	758 (100 %)
Moderate (20–49.9)	18 (22.5)	62 (77.5)	80 (100 %)
Heavy (≥ 50)	18 (8.4)	196 (91.6)	214 (100 %)

The adjusted analyses were performed using three models. In model 1 we included weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse, paternal age and paternal psychopathology as confounders. Model 2 contained the same confounders as in model 1 except for paternal psychopathology to specifically assess the effect of maternal factors. Model 3 was an additional model where gestational age was adjusted for instead of weight for gestational age to specifically address the effect of prematurity. In addition it included maternal SES, maternal age, maternal psychopathology, paternal age and paternal psychopathology as confounders. All models included adjustment for paternal age in order to address any potential selection bias, as there was a difference in paternal age among the included ADHD cases and those with missing serum samples.

There was a significant association between increasing log-transformed maternal cotinine levels and offspring ADHD both in the unadjusted analyses (OR 1.14; 95% CI 1.11–1.17) as well as in the adjusted analyses by conditional logistic regression models. In model 1 the OR was 1.09 (95% CI 1.06–1.12), in model 2 the OR was 1.10 (95% CI 1.06–1.13) and in model 3 the OR was 1.09 (95 % CI 1.06–1.13). The findings are shown in Table 21.

Table 21. Association between maternal serum cotinine (log-transformed variable) and offspring ADHD.

Maternal cotinine levels (ng/ml)	Case Median	Control Median	Association with maternal serum cotinine		
	27.4	11.3	OR	95% CI	*P* value
Log-transformed analysis					
Unadjusted			**1.14**	**1.11–1.17**	**<.001**
Model 1*			**1.09**	**1.06–1.13**	**<.001**
Model 2**			**1.10**	**1.06–1.13**	**<.001**
Model 3**'			**1.09**	**1.06–1.13**	**<.001**

*Model 1: Adjusted for birth weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse, paternal age and paternal psychopathology
** Model 2: Adjusted for birth weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse and paternal age.
***Model 3: Adjusted for gestational age, maternal SES, maternal age, maternal psychopathology, paternal age and paternal psychopathology

In the categorical analyses cotinine levels were categorized into three groups: heavy (cotinine level >50ng/ml), moderate (20-50ng/ml) and low or no nicotine exposure (<20nmg/ml) (Table 22). As shown in Table 23 heavy exposure was associated with offspring ADHD in the unadjusted analyses (OR 2.95; 95% CI 2.25–3.88) as well as in the adjusted analyses both in model 1 (OR 2.21; 95% CI 1.63–2.99) and in model 2 (OR 2.27; 95% CI 1.68–3.07). Moderate cotinine levels were associated with offspring ADHD in the unadjusted analyses (OR 1.92; 95% CI 1.33–2.77) but did not remain significant in the adjusted models (In model 1: OR 1.27, 95% CI 0.84–1.92; in model 2: OR 1.31, 95% CI 0.87–1.96).

Table 22. Maternal serum cotinine (three-class categorical variable) and offspring ADHD, frequencies.

Median maternal cotinine levels (ng/ml)	Cases 27.4		Controls 11.3	
	N	**%**	**N**	**%**
Reference[a]	777	72.0	936	86.8
Moderate [b]	84	7.8	54	5.0
Heavy exposure[c]	218	20.2	89	8.2
in total	1079	100	1079	100

[a]Reference: <20 ng/ml, [b]Moderate exposure: 20–50 ng/ml, [c]Heavy exposure: >50 ng/ml

Table 23. Association between maternal serum cotinine (three-class categorical variable) and offspring ADHD.

Maternal cotinine levels (ng/ml)	Association with maternal serum cotinine		
	OR	95% CI	*P* value
Unadjusted			
Reference[a]	1.00		
Moderate [b]	**1.92**	**1.33–2.77**	**<.001**
Heavy exposure[c]	**2.95**	**2.25–3.88**	**<.001**
Model 1*			
Moderate exposure[b]	1.27	0.84–1.92	.25
Heavy exposure[c]	**2.21**	**1.64–2.99**	**<.001**
Model 2**			
Moderate exposure[b]	1.31	0.87–1.96	.20
Heavy exposure[c]	**2.27**	**1.69–3.07**	**<.001**

*Model 1: Adjusted for birth weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse, paternal age and paternal psychopathology
** Model 2: Adjusted for birth weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse and paternal age
a Reference: <20 ng/ml, b Moderate exposure: 20–50 ng/ml, c Heavy exposure: >50 ng/ml

The analyses by deciles showed that the strongest association was in the highest decile (90%–100%). The odds for offspring ADHD in the highest decile in the unadjusted analyses was 4.90 (95%CI 3.10–7.76). In the adjusted analyses the OR was 3.34 (95% CI 2.02–5.52). For the second highest decile (80–89%) the association in the unadjusted analysis yielded an OR of 2.71 (95% CI 1.70–4.31) and in the adjusted analyses an OR of 1.91 (95% CI 1.15–3.18). The difference between the deciles (80–89% vs. 90–100%) was statistically significant showing that the risk of ADHD was higher with a higher level of nicotine exposure. The distribution of cotinine exposure in deciles by case-control status is presented in Figure 4 and the odds ratios in Table 24.

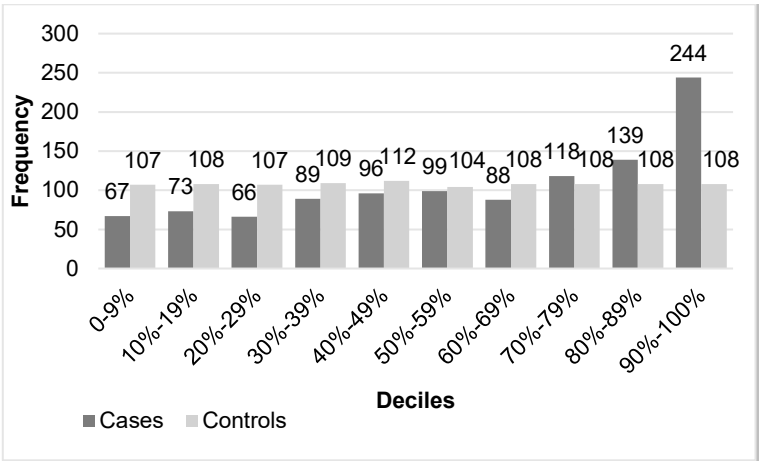

Figure 4. Distribution of cases and controls by maternal cotinine by deciles. Cut-off points based on maternal cotinine levels in the control group.

Table 24. Association between maternal serum cotinine categorized into deciles and offspring ADHD by conditional logistic regression.

Deciles	Range (ng/ml)	OR	95%CI	*P* value	OR[a]	95%CI	*P* value
<10 %	<0.008	reference					
10%–19%	00.9–0.011	1.15	0.71–1.85	.56	1.18	0.71–1.96	.53
20%–29%	0.012–0.014	1.19	0.72–1.95	.50	1.07	0.63–1.83	.81
30%–39%	0.015–0.019	1.58	0.97–2.58	.07	1.67	0.98–2.84	.06
40%–49%	0.020–0.024	**1.79**	**1.09–2.93**	**.02**	1.60	0.94–2.72	.09
50%–59%	0.025–0.033	**2.09**	**1.27–3.44**	**.004**	2.01	1.18–3.44	.01
60%–69%	0.034–0.052	**1.92**	**1.15–3.2**	**.013**	1.71	0.98–2.98	.06
70%–79%	0.053–0.165	**2.78**	**1.66–4.68**	**<.001**	**2.38**	**1.35–4.21**	**.003**
80%–89%	0.166–41.08	**2.71**	**1.70–4.31**	**<.001**	**1.91**	**1.15–3.18**	**.01**
≥90%	≥41.08	**4.90**	**3.10–7.76**	**<.001**	**3.34**	**2.02–5.53**	**<.001**

OR[a] Adjusted for birth weight for gestational age, maternal SES, maternal age, maternal psychopathology, maternal substance abuse, paternal age and paternal psychopathology.

5.6 Maternal 25(OH)D levels and offspring ADHD

The median maternal 25(OH)D level among cases was 29.2 nmol/L (range: 8.9–115.6 nmol/L) and 32.2 nmol/L (range: 7.5–132.5 nmol/L) among controls. The mean gestational week of maternal blood draw was 10.7 (SD: 3.7) for cases and 10.6 (SD: 3.1) for controls. The gender distribution was 85.5% male and 14.5% female in cases as well as and in controls. The distribution of maternal 25(OH)D (nmol/L) and log-transformed maternal 25(OH)D (nmol/L) in cases and controls are presented in Figure 5.

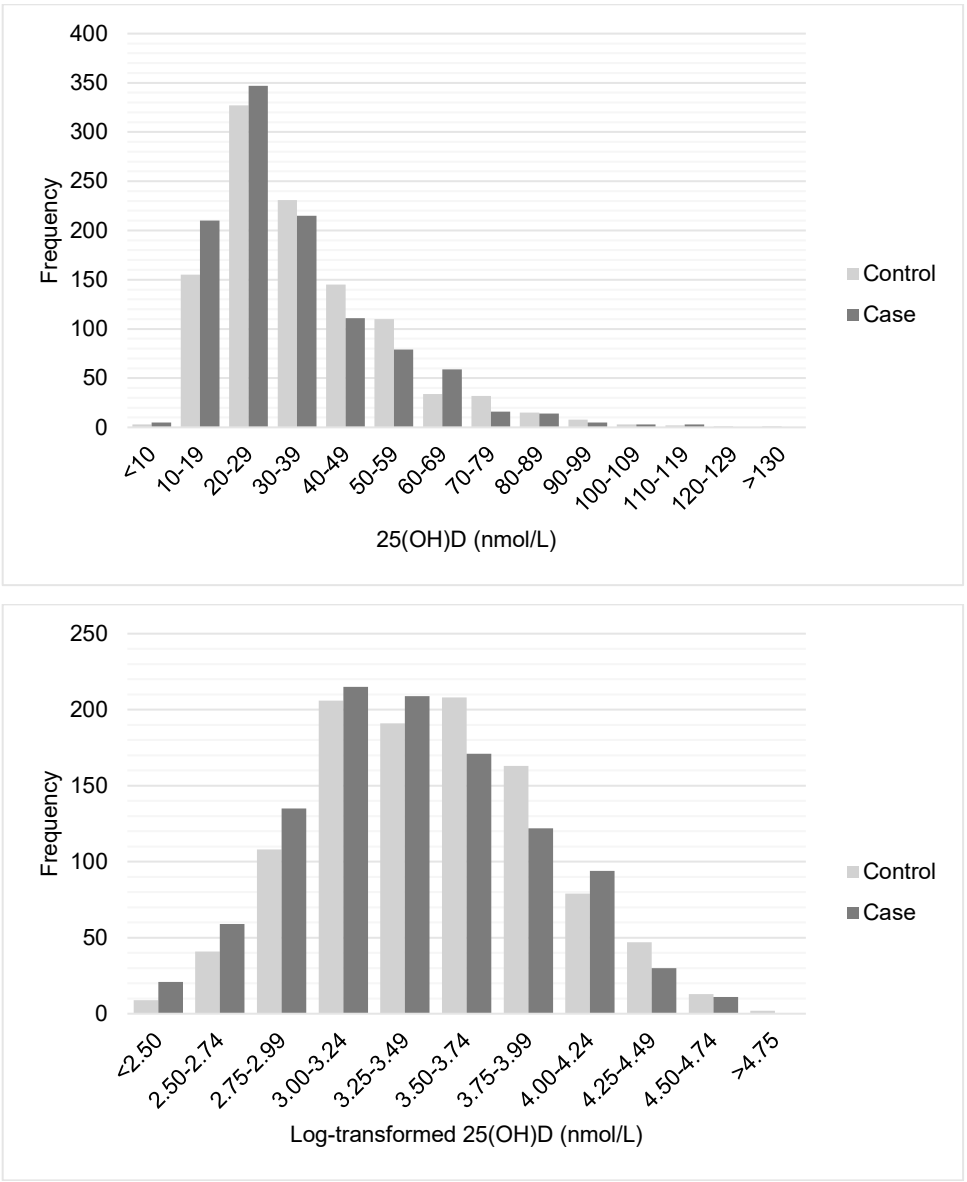

Figure 5. Distribution of 25(OH)D (nmol/L) and log-transformed 25(OH)D (nmol/L) in cases and controls subjects in the given intervals.

There was a significant association between decreasing log-transformed maternal 25(OH)D levels and increasing risk of offspring ADHD both in the unadjusted (OR 1.65, 95% CI 1.33–2.05, *P*<.001) and adjusted analyses (OR 1.45, 95% CI 1.15–1.81, *P*=.002). These results are shown in Table 25. To test for possible mediation by the child's weight for gestational age (WGA) or maternal cotinine levels, or for

confounding by maternal psychiatric history, we ran additional analyses with WGA, maternal psychiatric history and maternal biomarker-based smoking-status added to the adjusted model. The associations remained significant in these analyses. Furthermore, an additional analysis adjusting for maternal immigrant background (mother born / not born in Finland) also did not change the results (OR 1.44, 95% CI 1.14–1.81, *P*=.002). In order to further rule out a potential effect of any confounders, we also ran additional analyses adjusting for the remaining covariates associated with offspring ADHD and the results remained significant in all analyses.

The season of blood collection did not differ between the cases and the controls (P=.86). The mean gestational week of maternal drawn blood did not differ between the cases and the controls (*P*=.54). The cases and the controls were originally also matched on the date (and place) of birth hindering any potential effect of season.

Table 25. Association between maternal serum 25-hydroxyvitamin D (25[OH]D) and ADHD in offspring, modified from original article IV.

	Cases N= 1067	**Controls N=1067**	
Maternal 25(OH)D level (nmol/L)	Median (IQR) 29.20 (21.47–41.68)	Median (IQR) 32.20 (23.21–45.43)	
	Association with maternal 25(OH)D levels		
Log-transformed analysis*	Odds Ratio	95% CI	p-value
Unadjusted	**1.65**	**1.33–2.05**	**<.001**
Adjusted model A[a]	**1.45**	**1.15–1.81**	**.002**
Adjusted model B[b]	**1.40**	**1.11–1.77**	**.005**
Adjusted model C[c]	**1.46**	**1.16–1.83**	**.001**
Adjusted model D[d]	**1.35**	**1.07–1.71**	**.011**

*For one unit decrease, continuous model, IQR= interquartile range
[a]Adjusted for maternal SES and maternal age
[b]Adjusted for maternal SES, maternal age and maternal psychiatric history (ICD-8 (291-308), ICD-9 (291-316) or ICD-10 (F10-99), excluding mental retardation (F70-79), excluding ADHD diagnosis (ICD-10: F90.X or ICD-9: 314.X) and excluding substance abuse diagnosis (ICD-8: 291, 303, 304, ICD-9: 291, 292, 303,304,305 or ICD-10: F10-19)
[c]Adjusted for maternal SES, maternal age and child's weight for gestational age
[d]Adjusted for maternal SES, maternal age and maternal cotinine (<20 or ≥20 ng/ml)

The distribution of maternal 25(OH)D in quintiles is presented in Table 26. The odds ratio for ADHD among offspring of mothers in the lowest vitamin D quintile compared to the highest quintile was 1.83 (95% CI 1.34–2.51, *P*<.001) in the unadjusted model and 1.53 (95% CI 1.11–2.12, *P*=.010) in the adjusted model.

Table 26. Association Between Maternal Serum 25-hydroxivitamin D (25[OH]D) Categorized into Quintiles and Offspring ADHD, modified from original article IV.

Maternal 25(OH)D by quintiles[a]	Range of 25(OH)D in nmol/L	Cases (N=1067) n	Controls (N=1067) n	Unadjusted OR (95% CI)	P-Value	Adjusted[a] OR (95% CI)	P-Value
0–19%	7.5–21.9	277	210	**1.83 (1.34–2.51)**	**<.001**	**1.53 (1.11–2.12)**	**.010**
20%–39%	22.0–27.6	213	208	**1.36 (1.01–1.89)**	**.046**	1.30 (0.94–1.79)	.11
40%–59%	27.7–36.4	221	221	1.30 (0.97–1.76)	.08	1.21 (0.89–1.65)	.23
60%–79%	36.5–49.4	172	214	1.00 (0.75–1.33)	>.99	0.99 (0.73–1.33)	.92
80%–100%	49.5–132.5	184	214	Reference		Reference	

[a]Adjusted for maternal age and maternal SES

When maternal 25(OH)D levels were classified into three clinical categories, maternal vitamin D deficiency (25(OH)D<30 nmol/L) was associated with offspring ADHD in the unadjusted analyses (OR 1.51, 95% CI 1.15–1.99, *P*=.003) as well as when adjusted for maternal age and SES (OR 1.34, 95% CI 1.008–1.78 *P*= .044). (Table 27).

Table 27. Association between maternal serum 25-hydroxyvitamin D (25[OH]D) and ADHD in offspring in clinical categories.

25(OH)D level nmol/L	ADHD Cases, total N= 1067 n (%)	Controls, total N= 1067 n (%)	unadjusted OR (95% CI)	P-Value	Adjusted OR* (95% CI)	P-Value
<30	562 (52.7)	485 (45.5)	**1.51 (1.15–1.99)**	**0.003**	**1.34 (1.008–1.78)**	**0.044**
30–49.9	326 (30.6)	376 (35.6)	1.08 (0.83–1.40)	0.57	1.05 (0.80–1.37)	0.75
≥50	179 (16.8)	206 (19.3)	reference			

*Adjusted for maternal age and maternal SES

6 Discussion

6.1 Main findings

This thesis investigated prenatal and perinatal risk factors of ADHD utilizing nationwide register data. The main findings were:

1. First, premature birth was a risk factor for ADHD and each week of gestation decreased the risk of ADHD until term age. Second, poor fetal growth increased the risk of ADHD. The risk for ADHD increased with a decreasing weight for gestational age.
2. This study found associations between several perinatal risk factors and later ADHD. Perinatal adversities leading to lower Apgar scores increased the risk of ADHD. Birth by planned C-section was associated with an increased risk of ADHD. Additionally, breech presentation and induced labor were risk factors of ADHD.
3. Fetal exposure to nicotine measured by cotinine was associated with ADHD and showed a dose-dependent relationship.
4. Low maternal vitamin D levels during early pregnancy were associated with an elevated risk for offspring ADHD diagnosis.

6.2 Methodological discussion

6.2.1 Study design

This thesis utilized a nested case-control design in all four studies. The nested case-control study is based on a defined cohort, which serves as the source population. Out of this defined cohort the cases of a disease that occur, are identified. For each case a specified number of matched controls are selected from the same cohort. By definition, the controls are individuals that have not developed the disease by the time of the case's disease occurrence (Ernster, 1994; Susser, Ezra et al., 2006). In our data, the controls were individuals that did not develop the disease until the end of the follow-up (until the end of 2011).

In studies I and II the source population was all singleton children born in Finland from January 1st 1991 to December 31st 2005. Out of this cohort the individuals who had received a diagnosis of ADHD before December 31st 2011 in the discharge register were identified. Each case was matched with four randomly selected healthy controls. The controls were matched on sex, the date (±30 days) and place of birth. The controls had to be alive and residing in Finland at the time of the case's ADHD diagnosis. This ensured that the control had an equal follow-up for a possible diagnosis to be registered.

For studies III and IV, the individuals born between January 1st 1998 and December 31st 1999 who had a diagnosis of ADHD were selected. Each case was matched with one healthy control. This decision was made due to feasibility of the laboratory analyses. Otherwise the selection and matching of controls was carried out in a similar manner as in studies I and II.

The nested case-control design has several strengths. The design overcomes certain disadvantages of regular case-control studies, but utilizes some of the advantages of a cohort study (Sedgwick, 2014). The strengths of the nested case-control study include the ability to cost-effectively obtain a large number of cases in comparison to a traditional cohort study, which might end up with only few cases with the disease of interest. For example in the case of our biomarker studies (studies III and IV) the nested case-control study allowed laboratory tests to be performed to a smaller number of individuals in order to obtain a large enough amount of data to investigate our research questions. In addition, a traditional cohort study usually suffers from a certain amount of attrition, which in the field of studies on mental health is often unequal attrition. This means that those most at risk might not eventually be willing to participate in later assessments of the cohort follow-up.

Another strength of this design is the prospectively gathered and documented data on the exposures of interest, prior to the diagnosis. This is especially well suited to studying prenatal and perinatal risk factors as it excludes the possibility of a recall bias. Furthermore, in a traditional case-control setting there is always a particular concern about a selection bias, meaning that the recruited controls might not represent the entire population they are supposed to represent. This reduces the generalizability of the findings. However, in a nested case-control the controls are selected from the database and are therefore more representative of the entire population (Sedgwick, 2014).

The nested case-control design comes with limitations as well. The most important limitation is that the setting only enables discovering associations between exposures and outcomes, but as it is an observational setting, it does not allow us to make conclusions about causal inference. In this thesis study, we were able to show significant associations between many of the studied exposures and ADHD, our outcome of interest, but could naturally not prove causal relationships.

In order to reduce the effect of confounding factors or random associations, the study questions were based on scientific hypotheses and the results were adjusted for potentially confounding factors. However, there will always remain some background variables that are impossible to control or adjust for that might have influenced the observed findings. As the information in our study (excluding the cotinine and 25(OH)D analyses) was gathered from the pre-recorded register information, despite information on a broad range of potential confounding factors, we possibly initially lacked information regarding some potentially important cofounding variables. As an example, we had no information on maternal pre-pregnancy BMI, breastfeeding, nor information on psychiatric care given in the primary care to either the parents or the children. However, the nested case-control setting provides a suitable study design for the research questions of this thesis study bearing in mind that the observed findings should be interpreted with appropriate caution.

6.2.2 Data sources

The data for this thesis was obtained from the Finnish nationwide registers. The Finnish health registers, as well as other Scandinavian health registers, are perceived as reliable sources containing comprehensive, nationwide data. The ADHD diagnoses were obtained from the Care Register for Health Care (previously called the Finnish Hospital Discharge Register, FHDR), the perinatal data from the Finnish Medical Birth Register and the Finnish Population Register Centre was used to identify the controls, obtain information about family relations and information on the place of birth. The sera samples were obtained from the Finnish Maternity Cohort.

The population-based register linkages have several advantages. These include the previously mentioned population-based representative sample, the prospectively collected data, and the ability to obtain a large amount of data and thus increase the statistical power. It is noteworthy that in Finland public health care, both primary care and specialized care, is financed by municipalities and the patient fees are highly subsidized and hence affordable for all citizens. Furthermore, the prenatal check-ups, child health care check-ups and school health care are free of charge altogether. Therefore, the lack of access to health care does not play a significant role in this setting, as it might in some countries where access to health care requires more financial and family resources.

However, while utilizing register data certain limitations must obviously be taken into account. One important limitation in the present study is that the ADHD diagnoses in the registers were only collected from specialized health care. Outpatient diagnoses in the register have been recorded from 1998 onwards. At the

time of this study, the diagnostic evaluations for children suspected of having ADHD have primarily been made in the outpatient units of specialized health care (public outpatient units of child psychiatry and child neurology). These diagnoses are included in this study. However, the register has gathered diagnoses from the primary care outpatient visits only from 2011 onwards (known as Avohilmo) and those were therefore not available in this study.

As the diagnoses are from specialized health care, it is also probably that the ADHD cases in this sample represent patients with more severe phenotypes of ADHD. Those individuals are more likely to have sought care and been admitted into specialized health care than individuals with milder and less impairing symptoms.

In addition, there might be some missed ADHD cases who have been diagnosed in community-based outpatient units administratively under primary care. Furthermore, diagnoses made in the private sector were not recorded in the register during our study period. These limitations could presumably result in some missed cases and possibly also some children ending up as controls although they might have received an ADHD diagnoses elsewhere. These flaws would however have small effects if any, and only attenuate possible connections instead of falsifying the findings towards false positive associations.

The same limitations apply to the parental diagnoses. The discharge register was used to obtain the psychiatric diagnoses of the parents. Of note, there were very little parental ADHD diagnoses in this data since ADHD was not yet a widely recognized diagnosis in the parental generation in Finland. This is a clear limitation of the study, although we did adjust for psychiatric diagnoses of the parents in general.

As for the common limitations of utilizing register data, there is the question of the accuracy and validity of the ADHD diagnoses in the registers. As there are clinicians throughout the country involved in the diagnostic processes, there may be differences in the accuracy of recording diagnoses. A systematic review published in 2012 found that the completeness and accuracy of the information in the Finnish Hospital Discharge Register varied from satisfactory to very good. The main weakness was the poor recording of subsidiary diagnoses (Sund, 2012). An older study found that the accuracy of the diagnoses in the FHDR was good for the diagnoses of mental disorders (Keskimäki & Aro, 1991). In addition, a previous validation study on the data utilized in this thesis has been conducted. In this study a small subsample (n=69) of ADHD cases were interviewed by telephone in order to evaluate the validity of the registered ADHD diagnoses. The study found that 88 % of the examined children met the DSM-IV criteria (Joelsson et al., 2016).

As previously mentioned, an obvious limitation is that the registers might lack some important information that has simply not been documented and can therefore not be included in the register study. Two examples concerning the Finnish Medical

Birth Register are that we did not have data on 5 minute Apgar scores and that the information on the umbilical artery pH was available only in about half of the sample.

6.2.3 Study sample

From the perspective of the study sample, this thesis is composed of two entities. Studies I and II are composed of ADHD cases and controls that were born between January 1st 1991 and December 31st 2005. Study I included 10 321 cases and 38 355 controls and study II included 10 409 cases and 39 124 controls. For studies III and IV the study sample is composed of ADHD cases and controls that were born between January 1st 1998 and December 31st 1999. In study III there were 1079 cases and 1079 controls, and in study IV there were 1067 and 1067 controls. In both samplings the ADHD diagnoses registered until the end of 2011 were included.

Thereby in studies I and II the study population were in the age range of 6 to 20 years at the end of 2011. In studies III and IV the study population were between 12 to 13 years old at the end of 2011. As the mean age of the ADHD diagnoses was 7.6 years (SD 2.3) in studies I and II and 7.3 years (SD 7.3) in studies III and IV, it seems that the age range was sufficient and reasonable. In studies I and II the youngest individuals were only 6 years old, so it is therefore possible that some individuals included as healthy controls would later in their life became ADHD cases.

A previous study on the same data has shown that the cumulative incidence of ADHD in children born in 1991–1993 at age 21 years (the oldest participants) was 2.3% (CI 95% 2.2–2.4%). However, the cumulative incidence of ADHD referred to special healthcare increased in the later born birth cohorts compared to the oldest cohorts (Joelsson, Chudal, Gyllenberg et al., 2016).

Individuals who had received a diagnosis before the age of two years but not after that, were excluded from the data. This decision was made while gathering the initial data, before the preparation of the articles in this thesis commenced. It is reasonable to question the rationale behind the age limit of 2 years as it seems quite young. A retrospective evaluation of the data revealed that there were 31 cases of a registered ADHD diagnoses before the age of three years and 124 diagnoses between three and four years. This means that there were 155 ADHD diagnoses before the age of four years. It is possible that some of these diagnoses are erroneously recorded but some might be intentionally diagnosed ADHD cases at an exceptionally young age. The American Academy of Pediatrics has stated in their guidelines that children from 4 years onwards could be diagnosed and managed for ADHD (Subcommittee on Attention-Deficit/Hyperactivity Disorder et al., 2011). As the entire study sample in this thesis investigation is large, this fault presumably has no significant effect on the observed results.

It is noteworthy that the diagnoses used in this study were of those diagnosed with the ICD-10 code F90. This is the diagnosis of hyperkinetic disorder. During the study period individuals presenting with attention deficit without hyperactivity, in other words the ADD subtype, were not diagnosed with F90 and are thus lacking from this sample. During the study period the diagnosis F98.8 (Other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence) was used for attention deficit disorder without hyperactivity. Later on however, and despite the specific codings listed in the ICD, the national clinical guidelines in Finland (Käypä Hoito) have started to recommend the use of F90 also for the inattentive subtypes without hyperactivity due to the heterogenic nature of the disorder and the variations in the symptoms' spectrum with age.

Another way of identifying the ADHD cases could have been through the purchase of ADHD medications. This approach would have perhaps also identified those cases that had been treated in units whose diagnoses were not reported to the CRHC i.e. the private sector. However, a substantial proportion of ADHD patients are not treated with medication. A combination of searching for diagnoses and drug purchases might have been an option.

The study population included only singleton children in both the ADHD cases and the controls. This is reasonable as the prenatal circumstances of children born from multiple pregnancies (twins, triplets etc.) differ substantially from singleton pregnancies in relation to growth, the risk of premature birth and other obstetric conditions. Another limitation of our study sample is, that in this study we did not utilize sibling or cousin data. That could have allowed us to control for some unmeasured confounding family factors that might have an effect on some of our findings.

6.2.4 Information on the exposures

6.2.4.1 Register information

For studies I and II the information on the exposures were merely based on information from the Finnish Medical Birth Register. These included data on the gestational age and the weight for gestational age. It is possible that some of the information was incorrect. First, it is possible that the evaluated gestational age was initially inaccurate. In Finland the gestational age information is based on the last menstrual period but it has been verified and corrected if needed, with a first-trimester ultrasound examination since the late 1980s (Pihkala et al., 1989). Second, there can also be false recordings in the registers based on mistakenly typed numbers or other obvious errors. However, there is no reason to believe that this possible

inaccuracy would have affected the cases and the controls in a different manner and would therefore have an effect on the findings.

Out of the 10 409 ADHD cases identified, the information on the gestational age or birthweight was unavailable for 87 children. In addition, one observation was excluded as an implausible outlier. Out of the control population of 39 124, there were 452 controls with lacking information on gestational age or birthweight and one clearly incorrect recording that was excluded.

In study II, all other variables were extensively available from the Finnish Medical Birth Register. An exception to this was the umbilical artery pH measurements. The pH measurements were available for 4569 cases out of the 10 409 cases (44%) and for 16 339 controls out of the 39 124 controls (42%). Measuring the umbilical artery pH gradually became routine in Finland during the study years as an increasing number of hospitals started documenting the umbilical artery pH values. The measurements were equally missing for the cases and the controls and therefore an unlikely source for selection bias.

6.2.4.2 Analyses from the FMC samples

For studies III and IV, the ADHD cases born between 1998 and 1999 were selected. Each case was matched with one healthy control. A total of 1320 case-control pairs were identified. Out of these sufficient sera was available for 1079 case-control pairs for study III and 1067 case-control pars for study IV. This means that for study III, there were 241 missing samples and for study IV there were 253 missing samples. It is possible that not all women gave their informed consent to use the sera sample for later scientific research. It is also possible that some women enrolled in the prenatal care so late in their pregnancy that they did not undergo the normal prenatal screenings.

We tested for the distribution of the covariates between the included and the unavailable cases. For study III, there was no difference in covariates between 1079 cases included in the analysis and 241 cases not included due to insufficient serum in all other variables except for paternal age. The mean paternal age among cases not included was 1.2 (SD 6.9) years older than that of included cases (p=0.02). Therefore all models in study III included adjustment for paternal age. Furthermore, there is no reason to suspect that the diffrenece in paternal age of the missing and included ADHD cases would have an effect on the results. For study IV there was no difference between the 1067 included cases and the 253 without available sera.

We only had one sera sample for each pregnancy. The mean gestational week for drawing blood was 10 weeks (interquartile range 8–12 weeks). It is possible that the cotinine levels measured at this phase of the pregnancy did not remain at a similar level later throughout the pregnancy. The same applies to the vitamin D levels.

However, the time of drawing blood did not differ between the cases and the controls, so both groups had an equal time for possible changes in the levels of cotinine and 25(OH)D during the pregnancies.

In addition, the samples were stored and frozen at -25 °C in the Biobank Borealis in Oulu. It is of course possible that melting of the samples and other phases of processing might have affected the values. This, however, would have presumably affected the cases and controls in a similar manner, since the cases and controls were matched on the date of birth and had an equal time of freezing for example. One study analyzing maternal 25(OH)D from FMC samples has evaluated the possible degradation of 25(OH)D during storage. The authors compared samples that had been stored for 10–13 and 14–17 years and found no difference in mean 25(OH)D concentrations (Miettinen et al., 2012).

All the laboratory analyses were conducted in the same laboratory in Oulu. The laboratory analyses were conducted blind to case/control status.

6.3 Discussion of the results

6.3.1 Prematurity and ADHD

The study found that premature birth was a risk factor for ADHD. As a novel finding, our study showed that each declining week of gestation increased the risk of ADHD. A moderately increased risk was also seen in late-preterm infants and even in early-term infants.

Our findings are in line with the majority of research data on the topic. Four population-based studies from the Nordic countries have also shown an increased risk of ADHD associated with preterm birth (D'Onofrio et al., 2013; Halmoy et al., 2012; Lindstrom et al., 2011; Linnet et al., 2006). Furthermore, the risk seen in late-preterm infants was consistent with these studies. Our finding on the slight risk increase among early-term infants is supported by studies from Denmark, Sweden and Australia (Lindstrom et al., 2011; Silva et al., 2014). There are however also contradicting results such as no observed association between late preterm infants and ADHD in a study from the United States (Harris et al., 2013) and no association between prematurity and ADHD after all adjustments in an Australian register study (Silva et al., 2014).

The health care systems in the Nordic countries are quite similar and provide follow-up for all children regardless of family background, which may explain consistent results from Nordic studies compared with studies from Australia and the United States. In addition, in Finland and the other Nordic countries the socioeconomic differences in perinatal health and preterm births are low, unlike in many other countries in the world where access to prenatal health care and child

follow-up are influenced by family resources (Gissler et al., 2009). The public health care system in Finland with its regular child check-ups before school age and in the school health care, is likely to detect many children with ADHD. However, in addition the very preterm children undergo more specified follow-up in their first years of life. This may potentially lead to a higher alertness to neurodevelopmental problems and perhaps enable higher rates of diagnoses or sooner recognition of ADHD at a younger age. This more specified follow-up, however, does not include late preterm infants.

Our findings showed only a minor impact after adjustment due to confounding factors related to family background such as maternal SES, marital status, parental age or smoking during pregnancy. This is in line with the findings from a large Swedish study that found that the associations of gestational age and ADHD were mainly independent of familial factors shared by siblings (D'Onofrio et al., 2013). Many other associations have attenuated in sibling-matched analyses in large register studies. It is therefore unlikely that the association between prematurity and ADHD would be attributed to potentially uncontrolled social background factors. This supports that prematurity could be a causal factor in the etiology of ADHD. In addition, the observation that the risk of ADHD increased by each declining week of gestation in a dose-dependent manner, also supports the role of prematurity as a causal factor in the etiology of ADHD.

It is noteworthy that although the ADHD odds were much higher in the very preterm infants, the modest risk increase among the late preterm infants accounts for a much larger population of children. Approximately 72% of children who are born prematurely, are born in the late preterm period meaning between gestational weeks 34 and 36 (Shapiro-Mendoza & Lackritz, 2012). Therefore, even a slight risk increase in this group results in a remarkable number of ADHD cases at the population level. The same applies to the small increased ADHD risk among early term born infants (37–38 weeks). In this group, some of the births typically take place earlier due to iatrogenic reasons and a chosen earlier timing of birth.

Preterm birth is not simply an abrupt termination of pregnancy. It can be considered as an abnormal, stressful and inflammatory event for both the mother and the fetus (Gotsch et al., 2009). Preterm birth may be initiated by various mechanisms such as infection, uteroplacental ischemia or hemorrhage, immunologically mediated processes or even stress (Goldenberg et al., 2008). These underlying mechanisms may play a role in the pathogenesis of ADHD in the preterm infants.

The fetal brain maturation and development are still in progress when a very premature birth occurs. Brain folding, neurogenesis and neuronal migration continue until the end of the second trimester and are thus vulnerable to disorganization and injuries (Ment, Hirtz, & Huppi, 2009). Premature birth may disrupt the growth and development of crucial brain networks and result in aberrant networks associated

with ADHD (James et al., 2018). Specific impairments in cognitive and brain function among preterm-born individuals have been shown to relate to their increased ADHD symptoms. These include lack of malleability in attention allocation, impairments in speed and variability of reaction times and in response preparation (James et al., 2018).

Inflammation and its consequences play an indisputable role in a substantial proportion of premature births. Examples include a chorioamnionitis of the mother, a sepsis or necrotizing enterocolitis of the newborn or an inflammatory cascade initiated by lung injury (O'Shea et al., 2013). Maternal and neonatal infections might associate with perinatal brain damage and poorer neurodevelopmental prognosis. Animal designs have shown that chronic inflammation mediated by cytokines and chemokines inhibits brain development and results in cerebral damage (O'Shea et al., 2013; Wang, Rousset, Hagberg, & Mallard, 2006). Inflammation and infections may also contribute to the connection between prematurity and attention problems. There appears to be a correlation between systemic inflammation and a corresponding brain injury and the development of ADHD (O'Shea et al., 2013; Rogers & Hintz, 2016).

It is possible that genetic factors could modify associations between inflammation and ADHD in individuals genetically susceptible to the disorder. As an example, genetic factors such as polymorphisms in the regulation of interleukin-6 expression have been linked to a role in protecting against serious infections and also protecting the brain development of premature infants (Reiman et al., 2008). However, the strong inherited component of ADHD in the overall population seems to be less important among preterm-born individuals who develop ADHD (Johnson & Marlow, 2011; O'Shea et al., 2013).

It has also been suggested that the ADHD of preterm individuals may be a somewhat different kind of phenotype than the ADHD of term born individuals. It has been proposed that the phenotype associated to prematurity is characterized more by inattention than hyperactivity, has a more even gender distribution, and is less often related to risk-taking behavior and comorbid disorders (Strang-Karlsson et al., 2008). Therefore, the underlying biological mechanisms might also be different.

In addition, the mother's psychological preparation for the infant's birth is interrupted by the unexpected preterm delivery (Korja, Latva, & Lehtonen, 2012). Preterm-born individuals also face a different kind of postnatal disease burden due to the possible prematurity-associated illnesses, which may create stress and anxiety in parents. The postnatal environment including treatment in the NICU can affect the early bonding and parental psychological well-being, which may have independent effects on child behavioral outcomes in some individuals. Some studies have shown an association between insecure attachment and childhood ADHD (Storebø, Rasmussen, & Simonsen, 2016). Modern solutions in hospital planning aim to

diminish separation between the infant and the mother and new interventions have been developed to increase parents' participation in the infant care (Ahlqvist-Björkroth, Boukydis, Axelin, & Lehtonen, 2017). It is also likely that early intervention in the form of parent training may prevent development of attachment problems (Storebø, Rasmussen, & Simonsen, 2016).

6.3.2 Fetal Growth and ADHD

Our study found that poor fetal growth increased the risk of ADHD. The increased risk was seen already when the birth weight for gestational age was 1 SD below the mean, so before the –2 SD cutoff limit for SGA. We showed that the risk increased further as the weight for gestational age decreased. In addition an increased risk for ADHD was seen when the weight for gestational age was 2 SD above the mean, meaning the LGA children. The odds ratios showed a U-shaped curve for the association.

There are only a few population-based studies examining the weight for gestational age and ADHD. Our results are in line with a Norwegian population-based register-study that found that being SGA both at term or preterm, increased the risk of a diagnosed ADHD (Halmoy et al., 2012). The same was found in a Danish population-based study of term infants (Linnet et al., 2006). Furthermore, large questionnaire-based cohort studies have shown similar associations from the UK and Brazil (Murray et al., 2016). However two large studies from Australia have failed to show statistically significant associations between SGA status and ADHD in their adjusted models or for both genders (O'Keeffe et al., 2003; Silva et al., 2014).

In addition to population-based studies, there are cohort studies following preterm born individuals. These studies have shown associations between SGA-status and the risk of ADHD (Guellec et al., 2011; Heinonen et al., 2010; Strang-Karlsson et al., 2008). Finnish cohort studies have found that the SGA status rather than prematurity or low birth weight, increased ADHD symptoms in children and young adults (Heinonen et al., 2010; Strang-Karlsson et al., 2008). Our study examined weight for gestational age as a separate exposure and gestational age as a separate exposure. Based on our findings and according to the available literature, we can however speculate, that the infants with both poor fetal growth *and* prematurity are at the greatest risk for ADHD, as for many other neurodevelopmental outcomes.

There are far more studies that report the association between birth weight and ADHD. However, many of them have not reported the gestational ages of the infants. Therefore the same birth weight categories may include well grown premature infants as well as severely growth-restricted term infants. These two represent very

different kinds of newborn phenotypes that have experienced very different kinds of prenatal environments.

Some interesting twin studies have examined the difference in the birth weight of the twins and its association to ADHD symptoms (Hultman et al., 2007; Lim et al., 2018; Pettersson et al., 2014). All of them have reported that the lighter-born twin has had more ADHD-symptoms compared to the heavier-born twin. These studies suggest that fetal growth restriction could have a causal pathway leading to ADHD.

The possible explanations for the association between poor fetal growth and later ADHD are based on the biological programming of the non-optimal fetal environment. The developing brain may be disturbed by inappropriate placental-fetal circulation and inadequate supply of oxygen and important nutrients such as glucose and amino acids (McMillen et al., 2001; Tolsa et al., 2004). Neurostructural studies have shown that SGA-born children have reduced brain volumes and differences in brain structure (Martinussen et al., 2005; Tolsa et al., 2004). Abnormal fetal blood flow patterns, suggesting placental insufficiency, have been shown to lead to reduced brain volumes and poorer cognitive functioning at two years of corrected age (Maunu et al., 2007; Maunu et al., 2011). Interestingly, a study on adults born SGA at term identified smaller volumes in brain structures (frontal lobe volume and surface area and temporal lobe surface area) correlated to attention/executive functions deficits (Suffren et al., 2017). ADHD has been associated with reduction in total brain volume and several brain structures such as the frontal lobe, the cerebellum and the basal ganglia are involved in ADHD (Krain & Castellanos, 2006; Hoogman et al., 2017). There seem to be abnormal interactions between brain networks in ADHD (De La Fuente, Xia, Branch, & Li, 2013). It is possible that the non-optimal fetal circumstances mold brain development towards these aberrant connections through changes in brain structure and imbalance in brain functioning.

Our findings were based on analyzing the birth weight for gestational age. As stated before, we did not differentiate between poor growth among term and preterm born children in our analyses. It is also worth noting that we could not observe intrauterine growth trends, so therefore we could not distinguish between those infants who had suffered from intrauterine growth restriction and those who were SGA due to other reasons, such as genetic factors. In addition the effect of smoking and nicotine exposure on the growth was adjusted for based on maternal self-reported smoking information, which might suffer from under-reporting. Our data showed an increased risk for ADHD already for those infants whose weight for gestational age was 1 SD below the mean. This seems biologically rational as the children with milder growth disturbances seem also to suffer from fetal disturbances

compared to optimally grown infants. As the growth restriction becomes worse and further from the optimal measures, the risk for ADHD increases even more.

Interestingly also gestational overgrowth was associated with ADHD in our data. Children born over 2 SD above the mean had an increased risk for ADHD. Being LGA is most often associated with maternal diabetes or maternal obesity. Maternal obesity has been shown to increase the risk of ADHD (Edlow, 2017; Sanchez et al., 2018). A study based on Finnish register data found that among severely obese mothers without pre-gestational diabetes the risk for ADHD was slightly elevated, but the risk markedly increased further if the obese mother also suffered from pre-gestational diabetes (Kong, Norstedt, Schalling, Gissler, & Lavebratt, 2018). A U.S. study examined different types of pre-gestational and gestational diabetes compared to no diabetes during pregnancy. They found that the risk for offspring ADHD was highest among the mothers with type 1 diabetes, followed by type 2 diabetes, and lowest but still observable among mothers with gestational diabetes requiring medication compared to children with no exposure to maternal diabetes (Xiang et al., 2018). These findings suggest that the metabolic disturbances related to diabetes and obesity as well as the inflammation related to obesity could disturb the fetal environment and lead the neurodevelopment towards ADHD. Maternal diabetes, maternal obesity or macrosomia of the child also increase the risk of obstetric complications.

6.3.3 Obstetric and perinatal risk factors

Our study identified several obstetric and perinatal risk factors for ADHD. In our final model birth by planned C-section, lower Apgar scores, breech presentation and induced labor were shown to be associated with an increased risk for ADHD. Treatment at the NICU, which showed a significant association in our adjusted model, was not included in the final model as it represents a consequence of all perinatal adversities. Our adjusted model included adjusting for gestational age and weight for gestational age, maternal age, psychiatric history, substance use, smoking, SES and parity.

The association of lower Apgar scores and ADHD was confirmed in our data by using one-minute Apgar scores. The finding is in line with previous Nordic population-based studies that have examined five-minute Apgar scores (Gustafsson & Kallen, 2011; Halmoy et al., 2012; Li et al., 2011). We did not have access to the five-minute Apgar scores, as they were not comprehensively documented in the FMBR during our study period. However, the one-minute Agar scores reflect more prenatal well-being whereas the five-minute Apgar scores also reflect effectiveness of resuscitation. Furthermore, a large Finnish study with more recent register data

showed that both one-minute and five-minute Apgar scores were associated with long-term neurological morbidity (Leinonen et al., 2018).

In our data the Apgar scores seemed to have a trend for a dose-response type of effect with a higher ADHD risk as the Apgar scores decreased. Furthermore, the lower Apgar scores were consistently associated with an increased ADHD risk also in our additional analyses for different gestational age groups. However, prematurity was a stronger risk factor; the very preterm infants with the best Apgar scores had much higher odds for ADHD than the term infants with the lowest Apgar scores. Moreover, among the late and moderately preterm infants a similar finding was seen, but to a lesser extent: the infants born between weeks 32–36 with the best Apgar scores showed higher ORs for ADHD than the term infants with the lowest Apgar scores.

The finding between lower Apgar scores and a higher risk for ADHD seems biologically reasonable, since the Apgar scores are a general indicator of newborn well-being. Various kinds of perinatal adversities leading to lower Apgar scores can explain the link to an increased risk for ADHD. In addition to birth asphyxia, an infant may receive low Apgar scores because of maternal medications or anesthesia, congenital malformations or trauma and immaturity and slower adaptation to extrauterine life (AAP, 2015; Li et al., 2011). The Apgar scores are known to be affected by interobserver variability and even cultural aspects such as national scoring practices (Rüdiger & Rozycki, 2020). The Apgar scores were not originally developed for the prediction of long-term consequences. However, in our data they appeared to have a clear and plausible association to later ADHD.

Interestingly, no association was observed between the umbilical artery pH and later ADHD in our data. The previous studies on this topic are few and have yielded contradictory results. Our results are in line with a Dutch and a German study, but in contrast with one previous study utilizing Finnish register data (Mikkelsen et al., 2017; Schwenke et al., 2018; Wildschut et al., 2005).

A recent Finnish register study found that the umbilical artery pH was not a good predictor for neurodevelopmental morbidity such as cerebral palsy, epilepsy, intellectual or sensorineural impairment (Leinonen et al., 2019). However, the same authors did find a connection between Apgar scores and these neurodevelopmental morbidities (Leinonen et al., 2018). This is consistent to our observations concerning ADHD; the Apgar scores showed a connection but the umbilical artery pH did not. The low umbilical pH value indicates that the fetus is in a state of biochemical decompensation at birth (Vandenbussche, Oepkes, & Keirse, 1999). This means that a lack of adequate tissue oxygen has resulted in metabolic acidosis in the fetus. There is a well-acknowledged connection between low umbilical artery pH values and short-term morbidity and infant mortality. However, those infants with a low umbilical artery pH at birth, but who appear well during the neonatal period, have a

good long-term outcome (Hafström et al., 2012; Leinonen et al., 2019; Nagel et al., 1995). This appears to be true also in the light of our findings concerning ADHD; the umbilical pH value was not associated with later ADHD, but the Apgar scores were.

Interestingly, birth by planned C-section was associated with an increased risk of ADHD in our data. The association remained at the same level in all models and showed a 15 % increased risk in our final model compared to birth by vaginal birth. Birth by urgent or emergency C-section showed an association to ADHD in the adjusted model, but became statistically insignificant in our final model. In our additional analyses by gestational age groups, we showed that birth by planned C-section showed an increased risk for ADHD in all categories. However, as for the additional analyses for Apgar scores, prematurity was a stronger risk factor for ADHD than the mode of delivery.

Birth by C-section has been shown to increase the risk of many childhood diseases such as asthma, celiac disease, diabetes, leukemia, and juvenile arthritis (Darabi, Rahmati, HafeziAhmadi, Badfar, & Azami, 2019; Kristensen & Henriksen, 2016; Sevelsted, Stokholm, Bonnelykke, & Bisgaard, 2015). Disturbed immune function is thought to play a role in these associations. The previous literature concerning the mode of delivery and ADHD has yielded inconclusive findings. In some studies the observed associations have attenuated in sibling analyses (Axelsson et al., 2019; Curran et al., 2016). We did not have the possibility to conduct sibling analyses, but had access to a wide spectrum of confounding factors such as maternal mental health diagnoses, socioeconomic status, parity, age, and smoking during pregnancy, and newborn characteristics such as gestational age and weight for gestational age.

Our finding between birth by planned C-section and ADHD may be explained by several potential mechanisms. One hypothesized mechanism involves the gut microbiome and the so-called gut-brain axis. A birth by a planned C-section differs substantially from a normal vaginal birth in this respect. During a vaginal birth, the newborn is colonized with the mother's vaginal microbiota, and adopts a resembling gut microbiome. In contrast, infants born by C-section are colonized by the mother′s skin microbiota. Studies have shown that infants born by C-section had a decreased gut microbiota diversity (Bull-Larsen & Mohajeri, 2019; Huurre et al., 2008). There is some literature demonstrating that the ADHD population has a different gut microbial composition compared to healthy controls and further, that probiotic interventions could possibly even reduce the risk of ADHD (Bull-Larsen & Mohajeri, 2019; Pärtty, Kalliomäki, Wacklin, Salminen, & Isolauri, 2015). The possible role of early antibiotic exposure on later ADHD is unclear (Bull-Larsen & Mohajeri, 2019). In addition, birth by C-section has been shown to decrease the success of breastfeeding and there are some studies showing an association with

breastfeeding and a lower prevalence of ADHD (Mimouni-Bloch et al., 2013; Park et al., 2014). Furthermore, it may be hypothesized that the differential release of oxytocin after a C-section may have some effect on early postpartum behavior and attachment (Swain et al., 2008). These speculated links with ADHD are far from proven connections, but add to the interesting pool of data that show, that a normal vaginal birth and successful breastfeeding provide the infant with the best elements for later well-being and a lower risk for many illnesses.

Second, in addition to medical indications, a planned C-section may be chosen for psychosocial reasons. In some countries with a higher C-section rate, a large part of C-sections are performed because of a mother's request for C-section without a medical reason. In Finland, the rate of these procedures is substantially lower, but does exist. Nordic studies have shown that women who request a planned C-section without medical indication more often have underlying trauma, fear, anxiety, depression or history of abuse (Ryding et al., 2016; Sydsjö et al., 2015). Although we adjusted for maternal mental health diagnoses available from specialized health care, it is possible that the effect of psychological factors not recorded in the mother's medical history can contribute to the link between C-sections and ADHD.

In our data, maternal hypertension caused a slightly increased risk for ADHD in the adjusted analyses, but lost statistical significance in our final model. The maternal hypertension included both preeclampsia and other hypertensive disorders. Most of the previous literature has investigated preeclampsia and ADHD and meta-analyses have yielded a positive association. This seems biologically plausible through the mechanisms of placental insufficiency and abnormal fetal blood flow patterns affecting the developing fetal brain. It is possible that the heterogeneity of the various hypertensive disorders in our category explains the difference and our final model incorporating multiple risk factors attenuates some significant associations.

We also found an association between breech presentation and ADHD in our study. However, vaginal breech delivery was not a risk factor for ADHD. The number in the vaginal breech delivery group was very low, approximately one tenth of the individuals in the breech presentation category. The breech presentation is a common reason for a planned C-section. The fetus may remain in the breech position because of reduced fetal movements, and this may be due to neurological abnormalities. Moreover, the delivery itself may be more difficult. Our finding is in line with a meta-analysis on the topic (Zhu, T. et al., 2016).

In addition the induction of labor showed a slight statistically significant association with ADHD in our data. The previous literature on the topic has shown inconclusive results (Kurth & Haussmann, 2011; Silva et al., 2014; Wiggs et al., 2017). This might be explained by the induction of labor acting as an indicator of other prenatal or maternal risk factors.

Admission to NICU was also associated with an increased risk of later ADHD despite adjusting for confounding factors (such as gestational age and weight for gestational age). This is not surprising as the admission to NICU serves also as an indicator of various neonatal morbidities and a need for monitoring and treatments. A previous study has shown associations between neonatal seizures, hypoglycemia, and sepsis, with a later ADHD risk (Atladottir et al., 2015). Additionally, the treatment at NICU involves separation from the mother, which may disturb early bonding and affect later parental psychological well-being. These factors may influence parenting practices and might play a role in later child behavior. The treatment at NICU might also involve the use medications, medical procedures, pain and distress for the infant, that are not yet well understood. We did not examine the reasons for NICU admission nor the length of stay, which might elucidate the association further. It is also noteworthy, that the study population in our data was born during times when modern family-centered NICU practices were not yet established.

6.3.4 Exposure to maternal smoking and ADHD

Our study examining fetal exposure to nicotine measured by maternal cotinine levels showed an association between prenatal nicotine exposure and an increased risk of offspring ADHD. We also observed a dose-dependent relationship between the cotinine levels and the risk of ADHD supporting the hypothesis of a possible causal relationship. The association persisted in all analyses after adjusting for potential confounders such as maternal SES, parental psychopathology, parental age, child weight for gestational age and gestational age. This was the first published study investigating prenatal cotinine levels and diagnosed offspring ADHD, as previous studies were based on maternal self-reports of smoking.

Our findings between prenatal cotinine levels and offspring ADHD add to the evidence of the complex association between smoking during pregnancy and later ADHD. A number of population-based studies have reported consistent associations between self-reported prenatal smoking exposure and child ADHD (Gustavson et al., 2017; Joelsson et al., 2016; Lindblad & Hjern, 2010; Obel et al., 2016; Silva et al., 2014; Skoglund et al., 2014; Zhu, J. L. et al., 2014). However, lately many studies have found that the observed associations have attenuated in sibling comparisons or when analyzing the effect of paternal smoking, and therefore suggested that the association could mostly be explained by familial confounding (D'Onofrio et al., 2008; Gustavson et al., 2017; Langley et al., 2012; Lindblad & Hjern, 2010; Obel et al., 2016; Skoglund et al., 2014).

In addition, our analyses on the correlation of self-reported smoking and measured serum cotinine levels provided interesting results. We found that among

the women who had reported themselves as non-smokers, 8.4 % had cotinine levels in the heavy exposure category (≥ 50 ng/ml). Also in the category of moderate nicotine exposure (20-50 ng/ml) 22.5 % of the women had reported themselves as being non-smokers. The chosen cut-off limit was set at ≤20 ng/ml to clearly distinguish active smokers from women with exposure to passive smoking. Some studies have even used a lower cut-off limit of 11.48 ng/ml to separate active smokers from those exposed to high levels of passive smoking (Minatoya et al., 2019). This Japanese study also showed an association between maternal cotinine levels in the third trimester and child hyperactivity/inattention at age five years measured by an SDQ completed by parents. This underlines the previous notion that due to the socially undesirable stigma, the self-reports of pregnant women may be unreliable for a considerable number of women, and a biomarker based smoking-status provides considerable strength and accuracy over self-reports when examining smoking exposure during pregnancy.

The essential question is, whether maternal smoking is causally associated with offspring ADHD or whether smoking during pregnancy serves as a proxy of some other risk factor that could explain the association. Based on our observational study, we naturally cannot prove causal connections. We unfortunately did not have access to sibling data. However, we did have information of a wide spectrum of possible confounding factors and were able to adjust for maternal SES, age, substance use disorder, psychopathology of both parents and child weight for gestational age. In addition, there are biologically plausible explanations that could support the direct intrauterine effect of nicotine on fetal brain development. Our observation of the dose-dependent relationship between objectively quantified nicotine exposure and the increasing ADHD risk may also imply direct neurotoxic effects.

Nicotine, the primary psychoactive component of tobacco, crosses the placenta during pregnancy and accumulates in human fetal compartments already during the early fetal development (Jauniaux, Gulbis, Acharya, Thiry, & Rodeck, 1999). The same applies for carbon monoxide (Rogers, 2008). Animal studies have shown that nicotine interacts with endogenous acetylcholine receptors in the brain and interferes with normal neurotransmitter functions (Wickström, 2007). Nicotine exposure during critical periods of fetal development has been shown to alter synaptic development, and this may produce permanent changes in synaptic activities that are involved in cognitive and affective functions (Slotkin, 2008). Data on rodents has shown increased locomotor activity in animals exposed to nicotine in utero (Wickström, 2007). Human studies have shown alterations in offspring brain structure and function following exposure to maternal smoking during pregnancy (Bublitz & Stroud, 2012). However, the link between these findings and possible later neurodevelopmental disturbances such as clinical ADHD, remains yet to be investigated in more depth in the future.

Moreover, there is not a clear understanding as to whether there is a critical period for fetal nicotine exposure. At first, it was thought that the developing brain would not be sensitive to disruption by nicotine until the second trimester. However, more recent work has shown that nicotinic acetylcholine receptors are present and biologically active much earlier, and that the developing brain is vulnerable to nicotine already from the early embryonic stage (Slotkin, 2008). The current perception is that there seems to be a progressive sensitivity of the developing brain with the smallest effects from premating exposure, followed by early gestation, and then greatest effects from late gestation (Slotkin et al., 2017).

It is also likely, that gene-environment interactions may play a role in the association between prenatal nicotine exposure and ADHD. There is evidence that prenatal smoking exposure may affect the offspring through epigenetic changes such as altered DNA methylation, microRNA expression and histone modification (Knopik, Maccani, Francazio, & McGeary, 2012; Rzehak et al., 2016). The influence of these epigenetic changes on specific neurobehavioral outcomes and phenotypes in the exposed offspring remains still unclear and requires more research. It is, however, possible that individuals genetically susceptible to ADHD are more prone to the effects –both direct and epigenetic- of prenatal smoking exposure.

Nevertheless, it is also possible that the prenatal smoking exposure acts primarily as a mediator of some other risk factor related to ADHD. It is possible that the women who smoke during pregnancy convey unmeasured traits that increase risk for offspring ADHD. As an example, albeit the dose-response-relationship seen for cotinine is our study, it is possible that the women who suffer more severely from ADHD symptoms themselves, smoke more heavily during pregnancy. An American study showed that females with more ADHD symptoms in adolescence were more prone to initiate smoking early and progress to heavier and more frequent smoking (Elkins et al., 2018). A clear limitation in our study was, that the number of ADHD diagnoses identified in the parents was very low, reflecting the rarity of the ADHD diagnosis in Finland in the parental generation. We did, however, adjust for other psychiatric diagnoses and substance use disorder diagnoses from the specialized health care in our analyses.

Sibling studies from other Nordic countries as well as a novel study utilizing data on children born via assisted reproductive technologies, have suggested the association of smoking and ADHD to be explained mostly by familial confounding (D'Onofrio et al., 2008; Gustavson et al., 2017; Langley et al., 2012; Lindblad & Hjern, 2010; Obel et al., 2016; Skoglund et al., 2014; Thapar et al., 2009). However, not all studies with family designs are in line with this statement. A Finnish sibling study based on self-reported smoking data from >150 000 sibling pairs found evidence for a causal link between smoking exposure and ADHD: if the mother stopped smoking between the pregnancies, the second sibling did not have an

increased risk for externalizing disorders including ADHD. Correspondingly, if the second child was exposed to the mother smoking, the child did have a significantly higher risk (Ekblad et al., 2017).

Another limitation of our study is that we only had one cotinine measurement during the first trimester and did not have information of cotinine levels later during the pregnancy. A Japanese study that measured cotinine in the third trimester reached similar findings, reporting an association between high cotinine levels and increased risk of hyperactivity/inattention in parental reports (Minatoya et al., 2019). It is possible that the women who quit smoking during pregnancy differ between the cases and the controls. It has been studied that women who have a smoking partner, previous children, a high rate of tobacco consumption and attend less prenatal care, are more likely to continue smoking during pregnancy. In contrast pregnant women with a higher social status are more likely to quit smoking (Schneider, Huy, Schütz, & Diehl, 2010).

Despite the lack of solid evidence on the causal role of smoking exposure during pregnancy and ADHD, all women of fertile age should be encouraged to stop smoking already when planning a pregnancy. At the latest, in the first prenatal visits the health care personnel should strongly encourage women to quit smoking. The sufficient, robust data on the other harmful effects of smoking exposure on the fetus provide clinicians with a solid background to support this work. Meanwhile, the scientific community may continue investigating the role of smoking exposure on ADHD in designs that incorporate biomarker measurements, sibling designs and focus on the interplay between environmental, genetic and epigenetic factors.

6.3.5 Maternal vitamin D levels and ADHD

Our study found an association between low maternal vitamin D levels in the first and early second trimester pregnancy and an elevated risk for diagnosed offspring ADHD. This was the first study to investigate the association of early pregnancy vitamin D levels and diagnosed ADHD in the offspring. Previous studies have either had symptom scores as their outcome, vitamin D measurements at birth, or few participants with ADHD in the designs. In our data, the association between low maternal vitamin D levels and higher risk for child ADHD was seen when vitamin D was analyzed as a continuous variable as well as a categorical variable. Multiple additional models as well as adjusting for possible confounders such as maternal age, SES, psychiatric history, cotinine levels and child weight for gestational age did not change the results; the association remained significant.

Recent research activity has linked prenatal vitamin D deficiency to many offspring outcomes such as autism, schizophrenia and MS disease (Eyles et al., 2018; Munger et al., 2016; Vinkhuyzen et al., 2017). Our finding on ADHD is in line with

two studies showing associations between lower early pregnancy maternal vitamin D levels and higher level of ADHD symptoms at 4 to 5 years based on parent- or teacher-ratings (Daraki et al., 2018; Morales et al., 2015). However, two other previous studies on diagnosed ADHD cases and vitamin D levels measurements at birth or late pregnancy did not find this association (Gustafsson et al., 2015; Strom et al., 2014). These studies consisted of considerably fewer participants limiting the statistical power, and lacked important confounding factors such as information on parental psychiatric diagnoses. A recent meta-analysis on the effects of prenatal vitamin D in humans also found that the effects of vitamin D deficiency on offspring outcomes (ADHD, autism and cognitive development) were stronger in studies that analyzed maternal vitamin D concentrations in early to mid-gestation compared to late gestation or at birth (García-Serna & Morales, 2020). The authors suggested that the protective effects of vitamin D most likely occur during early prenatal development when brain structures begin to form and are thus more vulnerable to damage (García-Serna & Morales, 2020; Rice & Barone, 2000).

There are biologically plausible explanations for the link between early pregnancy vitamin D deficiency and offspring ADHD. Recent discoveries have shown, that vitamin D is in fact also a neuroactive steroid capable of regulating multiple pathways in brain development and functions. The vitamin D receptor is expressed in almost all regions of the central nervous system. There is evidence that vitamin D modulates neuronal cell differentiation and maturation, regulates expression of neurotransmitters, and has neuroprotective characteristics (Cui et al., 2013). Furthermore, it has been shown that vitamin D may affect immunological modulation, gene transcription and has anti-inflammatory effects on the brain (Eyles, Burne, & McGrath, 2013; García-Serna & Morales, 2020).

Animal studies have shown that rats who were vitamin D-depleted in utero, developed altered dopamine signaling (Groves et al., 2014). In addition, early vitamin D deficiency in rats has been shown to enhance hyperlocomotion and increased activity (Burne, O'Loan, McGrath, & Eyles, 2006). These mechanisms have been linked mostly to autism and schizophrenia in previous studies, but the alterations in the dopamine systems and disrupted latent inhibition, which is a measure of attentional processing, may well have relevance to ADHD as well (Berridge, 2018; Eyles et al., 2013).

Vitamin D deficiency is a common challenge globally. Many other nutritional deficiencies have now become infrequent in developed countries, but that is not the case with vitamin D. The reasons from vitamin D deficiency include inadequate sun exposure, low vitamin D intake from the diet (such as egg yolks, fatty fish and vitamin D fortified milk products) and physiological factors such as obesity, smoking and skin color (Holick, 2017). There is not a clear consensus as to how vitamin D deficiency should be defined. Most often the serum 25(OH)D

concentration below 30 nmol/l is defined as deficiency and levels between 30 and 50 nmol/l as insufficiency. Other definitions state that deficiency means 25(OH)D levels under 50 nmo/l and levels between 50 and 75 nmol/l as insufficiency (Holick, 2007; Ross et al., 2011).

In our data, the vitamin D levels of the pregnant women were generally very low. The median 25(OH)D value for the mothers of the controls was 32.2 nmol/L and 29.2 nmol/L for the mothers of the cases. Finland is situated as one of the northernmost countries in the world, and therefore the sun light exposure is very limited outside of the summer months. Our data was collected before the national recommendation for the vitamin D supplementation for pregnant women (10 ug per day) began in 2004 based on Nordic guidelines, as the children in our study were born between 1998 and 1999 (Becker, 2005). Moreover, vitamin D fortification of liquid dairy products was initiated in 2003 and further doubled in 2010 (Raulio et al., 2017). It has been showed that these measures in Finland have been effective, and that the concentrations of serum 25(OH)D have increased in the general population as well as among pregnant women (Hauta-Alus et al., 2018; Raulio et al., 2017).

However, there may be certain groups of pregnant women who do not follow the recommendations. Based on Finnish data it has been shown that the women who have a higher education, are older, and have normal weight before pregnancy are more likely to follow the given dietary recommendations and recommendations for the use of supplements (Arkkola et al., 2006). In addition, some immigrant groups are more prone to vitamin D deficiency due to a darker skin color, and therefore require special attention to ensure that the recommendations are followed. In our data, the number of immigrant mothers was very low, restricting the generalizability of our findings to different ethnic groups. However, our additional analyses adjusting for mother's immigrant status did not change the results.

The effect of the season plays a key role in vitamin D intake. As a strength concerning this aspect, the cases and controls in our data were matched on the date of birth as well as the place of birth, so no different effect caused by the season can be expected on the cases compared to the controls. In addition, the season of blood collection did not differ between the cases and the controls nor did the gestational week of drawing blood.

However, despite our efforts to adjust for all possible, available background factors such as maternal age, SES, psychiatric history and cotinine levels, we lacked some factors such as maternal BMI. Furthermore, it is possible that the vitamin D deficiency could be an indicator of other prenatal risk factors such as poor diet or lack of compliance with some other health recommendations or prenatal care. Moreover, it has been shown that the vitamin D concentrations are lower among children and adolescents with ADHD than among healthy controls, but there is a lack

of studies on the vitamin D levels of adults with ADHD (Kotsi, Kotsi, & Perrea, 2018). As mentioned previously, a limitation in our study was, that the number of parental ADHD diagnoses was very low.

We cannot make clinical recommendations based on this register study. Vitamin D is a fat-soluble vitamin meaning that in excessive amounts, it accumulates in the body and may be toxic. It is therefore essential that the clinical recommendations for the use of vitamin D are based on a number of careful clinical trials. Neither can we conclude that the eradication of vitamin D deficiency would substantially diminish the prevalence of ADHD. The effect size of our finding was modest and there are many other environmental risk factors in addition to the considerable genetic liability for ADHD. However, based on our results we may conclude, that this finding adds to the body of literature on the numerous beneficial effects of adequate maternal vitamin D levels during pregnancy on various child outcomes. Our finding also adds to the interesting role of vitamin D on neurodevelopment. We should in clinical practice therefore make sure, that the given recommendations are being followed and pay special attention to individuals at a higher risk for vitamin D deficiency.

6.4 Summary of the limitations

The epidemiologic, observational nature of this thesis study enables discovering associations between exposures and outcomes. We cannot prove definite causal relationships despite our efforts to adjust for a vast number of available confounding factors. We had only access to those variables that were recorded in the registers. For example, parental psychiatric diagnoses were only available from specialized health care and thus lack psychiatric conditions that were treated in the primary care. In particular, the number of parental ADHD diagnoses was very low, as it was not a widely recognized diagnosis in the parental generation. Some of the prenatal and perinatal exposures might be linked with underlying maternal psychiatric conditions such as anxiety or undiagnosed ADHD, which coud not be controlled for by adjusting for the available psychiatric diagnoses. In addition, information on family factors such as parenting style was not available. We did not have access to sibling data that could have better allowed us to control for some unmeasured confounding family factors. In the future, it would beneficial to investigate some of the identified associations, such as cotinine, maternal vitamin D and the mode of delivery, using also sibling analyses.

7 Conclusions

The objective of this population-based study was to investigate and improve understanding of the prenatal risk factors of ADHD. Our study was able to show several interesting associations between prenatal exposures and child ADHD while controlling for a variety of possible confounding factors. Despite the strong inheritable component of ADHD, prenatal risk factors seem to play an important part in the development of ADHD as well. All of the identified risk factors in this thesis study represent somehow unfavorable fetal circumstances. The epidemiological study setting of this thesis cannot prove definite causal inferences or give direct clinical recommendations. The observed findings do, however, point out many interesting associations and raise new research questions.

Out of the identified prenatal and perinatal risk factors, some showed higher odds for later ADHD than others. The strongest risks were observed in very preterm infants yielding the highest odds for ADHD in this whole thesis study. This emphasizes the role of ADHD as a significant possible long-term consequence among the most preterm infants. However, the late preterm infants, who constitute a much larger group of children, showed also a modest risk increase for ADHD. A slight risk was even seen among early term born children. It can thus be concluded, that each gestational week of maturity plays a role in the fetal development and the subsequent risks. In addition, poor fetal growth also increased the risk for ADHD, indicating that suboptimal fetal environment represented by intrauterine growth restriction affects later neurodevelopment as well. Our findings point out the need for a close follow-up of possible ADHD problems among preterm and SGA born children and the need for support interventions for those children and families who develop challenges. Parents of preterm born children may benefit from extra support to implement parenting strategies that can help with the child's behavior.

Prenatal exposure to heavy smoking measured by maternal cotinine levels, also showed high odds for offspring ADHD. Despite the controversies about a possible causal role of prenatal smoking exposure for offspring ADHD, smoking during pregnancy should be strongly discouraged as it is a risk factor that can be avoided, and is associated with many other adverse child outcomes as well.

Our study demonstrated an association between low maternal vitamin D levels and an increased risk for ADHD in the offspring. Based on our study we cannot make clinical recommendations for a suitable intake of vitamin D for pregnant women. We can, however, recommend, that vitamin D deficiency should be avoided during pregnancy as it appears to increase the child's ADHD risk. Clinicians should therefore make sure, that the given recommendations are being followed and pay special attention to individuals at a higher risk for vitamin D deficiency.

Finally, it is possible that prenatal risk factors –such as the ones identified in this study- may lead to an adverse outcome like ADHD if several risk factors accumulate on the same individual. This may in particular affect genetically predisposed individuals or individuals who experience a family environment that mediates the influence. It is possible that if a certain level of prenatal exposures or genetic risks accumulate, and the family environment further reinforces the progression of the symptoms, a threshold is exceeded and leads to the development of ADHD.

7.1 Implications for future research

In the future it would be meaningful to study some of the exposures of this thesis study in sibling designs. For example for our biomarker studies examining cotinine and vitamin D, future studies incorporating biomarker data from the mothers' other pregnancies could further allow us to control for family factors shared by siblings. Obstetric risk factors such as the mode of delivery, would also benefit from sibling analyses.

The current practices of neonatal care have changed considerably since our study population was born, especially concerning the older study participants. It would be interesting to examine whether this change of practice has had an effect on the risk for later ADHD. On the other hand, as an increasing number of immature babies survive the neonatal period without major disabilities, it is possible that the neurodevelopmental outcomes such as inattention plays even a greater role in the later life of preterm-born individuals.

In addition to neonatal care, other iatrogenic factors such as maternal medications may play a role in this complex interplay between genetic risks and prenatal exposures. In the future, is would be interesting to study the effect of maternal medications during pregnancy and their possible effects on the offspring ADHD risk in this cohort, as information on reimbursements for medicine expenses is also possible to obtain using Finnish register data.

Given the very low overall vitamin D levels of our study sample, it would be interesting to examine the effect of prenatal vitamin D in the current situation where vitamin D supplementation is -or at least should be- used by pregnant women. In addition, given the recognized vulnerability of immigrant groups to vitamin D

deficiency in Northern latitudes, it would be important to examine the effect of maternal vitamin D levels in samples with ethnically more diverse samples.

In conclusion, acknowledging the high heritability of ADHD, further study designs that could better take into account the interactions between prenatal exposures, family environment and genetic factors are warranted.

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Appendix

Appendix 1. The diagnostic criteria for hyperkinetic disorder (F90.0) based on ICD-10 (WHO).

At least six symptoms of **attention** have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child.	1. Often fails to give close attention to details, or makes careless errors in school work, work or other activities
	2. Often fails to sustain attention in tasks or play activities
	3. Often appears not to listen to what is being said to him or her
	4. Often fails to follow through on instructions or to finish school work, chores or duties in the workplace (not because of oppositional behavior or failure to understand instructions
	5. Is often impaired in organizing tasks and activities
	6. Often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort
	7. Often loses things necessary for certain tasks and activities, such as school assignments, pencils, books, toys or tools
	8. Is often easily distracted by external stimuli.
	9. Is often forgetful in the course of daily activities
At least three symptoms of **hyperactivity** have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child	1. Often fidgets with hands or feet or squirms on seat
	2. Often leaves seat in classroom or in other situations in which remaining seated is expected
	3. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present)
	4. Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities
	5. Often exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands
At least one of the following symptoms of **impulsivity** has persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child	1. Often blurts out answers before questions have been completed
	2. Often fails to wait in lines or await turns in games or group situations
	3. Often interrupts or intrudes on others (for example, butts into others' conversations or games)
	4. talks excessively without appropriate response to social constraints
Onset of the disorder is no later than the age of 7 years	
The criteria should be met for **more than a single situation**, for example, the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic	
The symptoms cause clinically **significant distress or impairment** in social, academic or occupational functioning	
A mood disorder, mania, anxiety disorder, pervasive developmental disorder or psychosis may not be present	

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