OULU 2024
D 1788

ACTA UNIVERSITATIS OULUENSIS

Jandeh Jallow

EARLY RISK FACTORS FOR ADHD

A NORTHERN FINLAND BIRTH COHORT 1986 STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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JANDEH JALLOW

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A Northern Finland Birth Cohort 1986 study

Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium F202 of the Faculty of Medicine (Aapistie 5 B), on 24 May 2024, at 12 noon

UNIVERSITY OF OULU, OULU 2024

Acta Univ. Oul. D 1788, 2024

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ISBN 978-952-62-4102-9 (Paperback)
ISBN 978-952-62-4103-6 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

PUNAMUSTA
TAMPERE 2024

Jallow, Jandeh, Early risk factors for ADHD. A Northern Finland Birth Cohort 1986 study

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital

Acta Univ. Oul. D 1788, 2024

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Abstract

The aim of this thesis was to explore early risk factors for ADHD within the Northern Finland Birth Cohort 1986 (NFBC1986), and more specifically, to determine whether prenatal maternal inflammation and stress, the duration of breastfeeding, child's own personality and comorbid psychopathology may be associated with an increased risk of ADHD in the offspring.

The NFBC1986 is a population-based birth cohort consisting of 9,479 pregnant women and their 9,432 live-born children, with regard to whom this dissertation utilizes data collected from national registers, clinical examinations, the Borealis Biobank, child health clinics and questionnaires administered at several time points up to 18 years. To study ADHD symptoms, the Rutter Children's Behaviour Questionnaire was used at the age of 8 (n=8,721) and the Strengths and Weaknesses of ADHD symptoms and Normal Behaviours questionnaire at the age of 16 (n=6,622). ADHD was diagnosed by means of a clinical assessment performed at the age of 16 to 18 years (n=457).

Several early life factors were associated with an increased risk of ADHD in the offspring. Unwanted pregnancy and under 3 months of exclusive breastfeeding were associated with hyperactive symptoms at the age of 8 and prenatal maternal fatigue and under 6 months of non-exclusive breastfeeding were markers of an increased risk of ADHD symptoms at the age of 16. Furthermore, the results show that a distinct personality profile was associated with an ADHD diagnosis in adolescence. Adolescents with ADHD were more often novelty seeking and less self-directed, cooperative and persistent than individuals without ADHD.

This is one of the few studies to date that has investigated early life factors in relation to ADHD symptoms in childhood and adolescence, and its most important implications are primarily preventative. The identifying of risk factors for ADHD can enable earlier detection of individuals with ADHD later, which may allow more targeted and timely interventions to prevent the possible impairing outcomes of ADHD. In addition, there are diagnostic challenges regarding ADHD, and it may be over-, under- or misdiagnosed. Identifying the risk factors for ADHD may potentially give rise to new tools for the more accurate diagnosis of ADHD in the future.

Keywords: ADHD, breastfeeding, neurodevelopment, pregnancy, prenatal maternal inflammation, prenatal maternal stress, temperament and character, unwanted pregnancy

Jallow, Jandeh, ADHD:n varhaiset riskitekijät. Pohjois-Suomen syntymäkohorttitutkimus 1986

Oulun yliopiston tutkijakoulu; Oulun yliopisto, lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

Acta Univ. Oul. D 1788, 2024
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Tämän väitöskirjatutkimuksen tarkoituksena oli tutkia ADHD:n varhaisia riskitekijöitä vuoden 1986 Pohjois-Suomen syntymäkohortissa (NFBC1986). Tarkemmin eriteltynä tutkin, liittyykö äidin raskauden aikainen tulehdus ja stressi, imetyksen kesto sekä lapsen oma persoonallisuus ja psykiatriset oheissairaudet lisääntyneeseen ADHD-riskiin lapsuus- ja nuoruusiässä.

NFBC1986 on valikoitumaton, yleisväestöpohjainen kohortti, joka koostuu 9 479 raskaana olevasta naisesta ja heidän 9 432 elävänä syntyneestä lapsestaan. Tässä väitöskirjatutkimuksessa hyödynnettiin tietoja kansallisista rekistereistä, kliinisistä tutkimuksista, Borealis-biopankista, lasten neuvolakorteista ja kyselylomakkeista 18 vuoden seuranta-aikana. ADHD-oireiden tutkimiseksi käytettiin käyttäytymistä kartoittavaa kyselyä (the Rutter Children´s Behaviour Questionnaire) lasten ollessa kahdeksanvuotiaita (n=8 721) ja ADHD-oirekyselyä (the Strengths and Weaknesses of ADHD symptoms and Normal Behaviours) 16-vuotiaina (n=6 622). ADHD diagnosoitiin kliinisillä tutkimuksilla nuorten ollessa 16–18-vuotiaita (n=457).

Tutkimuksen tulokset osoittavat, että useilla varhaiskehityksellisillä tekijöillä on yhteyttä lisääntyneeseen ADHD-riskiin lapsuus- ja nuoruusaikana. Tutkimuksessa osoitimme ei-toivotun raskauden ja alle kolme kuukautta kestäneen täysimetyksen yhteyden yliaktiivisiin oireisiin 8-vuotiaana. Äidin raskauden aikainen stressi ja alle 6 kuukautta kestänyt osittainen imetys olivat merkkejä lisääntyneestä riskistä ADHD-oireisiin 16-vuotiaana. Myös lapsen oma persoonallisuusprofiili liittyi ADHD-diagnoosiin nuoruusiässä. Nuoret, joilla todettiin ADHD, olivat useammin elämyshakuisia sekä vähemmän itseohjautuvia, yhteistyöhaluisia ja sinnikkäitä kuin he, joilla ei diagnosoitu ADHD:ta.

Tämä väitöskirjatutkimus on yksi harvoista, joissa tutkitaan varhaiskehityksen yhteyttä lapsuus- ja nuoruusiän ADHD:seen. Tutkimuksen tärkeimmät vaikutukset ovat ensisijaisesti ennaltaehkäiseviä. ADHD:n riskitekijöiden tunnistaminen voi mahdollistaa ADHD-potilaiden varhaisemman havaitsemisen, joka voi auttaa soveltamaan kohdennettuja ja oikea-aikaisia toimia ADHD:n haittojen ehkäisemiseksi. Lisäksi ADHD:n suhteen on diagnostisia haasteita, se saattaa olla joko ylidiagnosoitu, väärin diagnosoitu tai alidiagnosoitu. Riskitekijöiden tunnistaminen voi tulevaisuudessa tuoda uusia työkaluja ADHD:n tarkempaa diagnostiikkaa varten.

Asiasanat: ADHD, ei-toivottu raskaus, imetys, neurologinen kehitys, raskaus, raskauden aikainen stressi, raskauden aikainen tulehdus, temperamentti ja luonteenpiirteet

To my dearest Mikko

Acknowledgement

This study took place at the Research Unit of Clinical Medicine, Faculty of Medicine at the University of Oulu. First, my deepest gratitude goes to my supervisors Docent Tuula Hurtig, Anu-Helmi Halt M.D., Ph.D., and Professor Jouko Miettunen. Thank you, Tuula, for your words of encouragement, guidance, and advice, and for trusting me to participate in such an important project and providing guidance along the way. I am grateful that you have pushed me into doing my best to chase the deadlines. Anu-Helmi, thank you for believing in me and for making our meetings fun and exciting. I am grateful to have had you as a role model and as a guide in shaping me as a medical doctor and researcher. Finally, having you, Jouko, as my supervisor has had a considerable impact on my thesis. I am thankful for having had the opportunity to learn about epidemiology, and with your help I have managed to be on time with the practicalities as well. Without your guidance and support this thesis would not have been in the shape it is now.

I started this research with barely any skills, but during my journey you have all three taught me and motivated me when challenges arose and have given me the encouragement I needed. You have always helped me with my questions, whether they were relevant or not. Thank you for always finding time for me, even on Christmas Eve or in the middle of the night. I will be forever grateful for the opportunity to work with you and learn under your guidance.

I would also like to express my gratitude to all my co-authors, especially Martta Kerkelä, Ph.D., to whom I am deeply grateful for the time and effort she spent on this project. Thank you for your constant support and for being patient with me when I understood scarcely anything about statistics. I am very grateful to Malcolm Hicks, M.A., for the linguistic revision of the original papers and the thesis. I also thank Hanna Öhman, Ph.D., for sharing her expertise and wisdom with me, and also Olli Kela M.D. for his time spent on the layout of the thesis, which wouldn´t otherwise have been the way it is.

I was privileged to be able to work with datasets from the Northern Finland Birth Cohort 1986 (NFBC1986), and I feel that I owe a debt of gratitude to Professor Marjo-Riitta Järvelin for making it possible for me to use the NFBC1986's valuable data. I would also like to thank all the participants in the research and those who were involved in planning it, gathering the data and working on these data before me. I am also grateful for the research unit I was able to work in and I thank Professor Juha Veijola for the research facilities.

I thank the preliminary examiners, Docent Pekka Tani and Professor Henrik Larsson, for their well-thought and insightful comments, which all helped considerably to improve my thesis. I am also grateful for Professor Eeva Aronen for accepting to be my opponent and for Professor Sami Räsänen and Professor Mirka Hintsanen for being in my follow-up group.

Without the support of sources of funding, this research would, of course, have been impossible. I am grateful for the financial support received from the following institutions: the Emil Aaltonen Foundation, the Finnish Brain Foundation, the Finnish Cultural Foundation, the Finnish Psychiatric Research Foundation, the Foundation for Paediatric Research, the Jalmari and Rauha Ahokas Foundation, the Orion Research Foundation, the Päivikki and Sakari Sohlberg Foundation, the Stiftelsen Alma and K. A. Snellman Foundation and the University of Oulu Graduate School.

Lastly, I want to express my gratitude to the people closest to me. Thank you to my ever-supporting family – my parents, Laura and Momar, and my siblings Alagie, Saffie, Marie and Antonia – who believed in my academic abilities and encouraged me to aim high in all fields of life. Thank you, Saffie, for your time spent on organizing my dissertation day. A huge thank you also goes to my other family, Erja, Mika and Ella, who have endlessly helped me to pursue all my dreams. I am also grateful to my friends for long conversations, laughs and moments spent free of stress.

Mikko, I will always appreciate everything you do for me. Thank you for sharing your life with me and helping me through all the hopeless moments. Thank you for braiding my hair in the mornings and slow dancing with me in our kitchen in the evenings. I love you.

April 2024 Jandeh Jallow

Abbreviations and definitions

ADHD	Attention-deficit/hyperactivity disorder
ANCOVA	Analysis of covariance
ASD	Autism spectrum disorders
CD	Conduct disorder
CI	Confidence interval
CO	Cooperativeness
CRP	C-reactive protein
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed.
HA	Harm avoidance
IL-6	Interleukin 6
IQ	Intelligence quotient
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version
MCP-1	Monocyte chemoattractant protein-1
NDD	Neurodevelopmental disorder
NFBC1986	Northern Finland Birth Cohort 1986
NS	Novelty seeking
ODD	Oppositional defiant disorder
OR	Odds ratio
P	Persistence
p, p-value	Significance probability
RD	Reward dependence
SD	Self-directedness
sd	Standard deviation
ST	Self-transcendence
SWAN	Strengths and Weaknesses of ADHD symptoms and Normal Behaviours
TCI	Temperament and Character Inventory
TNF-a	Tumor necrosis factor alpha
$\chi 2$	Pearson's chi-square test

Original publications

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

I Jallow, J., Halt, A.H., Öhman, H., & Hurtig, T. (2020). Prenatal inflammation does not increase the risk for symptoms of attention deficit hyperactivity disorder (ADHD) in offspring. *European Child & Adolescent Psychiatry*, 30(11), 1825–1828. doi:10.1007/s00787-020-01580-x.

II Jallow, J., Hurtig, T., Kerkelä, M., Miettunen, M., & Halt, A.H. (2024). Prenatal Maternal Stress, Breastfeeding and Offspring ADHD symptoms. *European & Child Adolescent Psychiatry*. https://doi.org/10.1007/s00787-024-02451-5.

III Jallow, J., Halt, A.H., Kerkelä, M., Hurtig, T., & Miettunen, J. (2023). Association of temperament and character traits with ADHD and its comorbidities. *Nordic Journal of Psychiatry*, 29, 1–7. doi: 10.1080/08039488.2023.2262994.

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1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioural disorders. It is a multifactorial disorder defined by age-inappropriate symptoms of inattention, hyperactivity and impulsivity leading to functional impairments in at least two operational environments, including education and social relationships (APA, 2013; Faraone et al., 2021). ADHD has an estimated childhood prevalence of 4% to 7% (Sayal et al., 2018) with increasing evidence pointing to its continuation into adulthood for between 15% and 65% of individuals, with an estimated prevalence of 2.5% (Katzman et al., 2017).

While it is well accepted that the disorder is highly heritable (>70%) (Faraone & Larsson, 2019), not all the risk is genetic. ADHD appears early in life, and there is significant interest in the potential role that the prenatal environment might play in its development. It is estimated that between 10 and 40% of the variance associated with ADHD is likely to be accounted for by environmental factors (Sciberras et al., 2017), and studies have identified numerous pre- and postnatal risk factors which appear to be associated with ADHD, including prematurity, low birth weight (Franz et al., 2018), maternal substance use (Knopik et al., 2019) and environmental toxins (Goodlad et al., 2013).

On the other hand, findings have been inconsistent as to whether there is a relationship between ADHD and early risk factors such as prenatal maternal inflammation, prenatal maternal stress, unwanted pregnancy, breastfeeding and the temperament and character profiles of the offspring. No large longitudinal studies have been able to answer the question of whether these factors increase the risk of ADHD. In other words, not enough evidence has been presented to provide reliable information on the risk factors for ADHD, in view of the fact that a considerable number of studies have been conducted in early childhood, i.e. prior to the age of 6. Also, the outcomes of these studies are difficult to evaluate because many young children cannot avoid being hyperactive.

To address such issues, the present work was aimed at investigating the relationship between ADHD and its early risk factors, focusing on prenatal maternal inflammation, prenatal maternal stress, breastfeeding and the temperament and character profiles of the offspring. The population consisted of the Northern Finland 1986 Birth Cohort (NFBC1986), an unselected general population based on a prospective mother-child birth cohort of 9,432 live births that occurred between 1st July 1985 and 30th June 1986 (Järvelin et al., 1993; University of Oulu, 1986).

With its observational character, this work aims to satisfy practical clinical needs and to generate ideas for future research. Treating ADHD is a complex matter and requires effective strategies for coping with the related symptoms, since Personnel working in medical fields such as family doctors lack information on how to guide families with the risk factors for ADHD and how to address earlier problems in the recognition and diagnosis of this condition. Moreover, prevention or treatment of ADHD may also reduce a child's risk of developing comorbid psychiatric problems.

2 Review of the literature

2.1 Attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a non-episodic pattern of inattentive and/or hyperactive-impulsive symptoms occurring more frequently than expected for the patient's age (APA, 2013; Austerman, 2015).

2.1.1 An overview of ADHD and its prevalence

At present ADHD is considered a complex, multifactorial disorder that is caused by the confluence of various genetic and environmental risk factors, each of which makes a small contribution to the individual's increasing sensibility to the disorder. The risk factors interact with each other and if the causal pathways together exceed the threshold of an individual's cumulative vulnerability, an ADHD phenotype emerges (Sciberras et al., 2017).

ADHD is considered a debilitating disorder and is known to impact many aspects of the individual's life including academic and professional achievements, interpersonal relationships and daily functioning (Posner et al., 2020; Seppä et al. 2023). ADHD can lead to poor self-esteem and impaired social function when not appropriately treated (Harpin et al., 2016), and children with ADHD may have difficulties in sitting still, waiting their turn and paying attention, thus becoming fidgety and acting impulsively (Posner et al., 2020). These symptoms lead to significant suffering and cause problems at home, at school or work, and in personal relationships, but they are not the result of the individual being defiant or unable to understand tasks or instructions. Furthermore, adults with ADHD may experience poor self-esteem, sensitivity towards criticism, and increased self-criticism, possibly stemming from the higher levels of criticism received throughout life (Beaton et al., 2022).

ADHD has an estimated childhood prevalence of 4% to 7% (Sayal et al., 2018), while its prevalence in Finland in 2022 was 8.3% and 3.3% for boys and girls aged 7 to 17, respectively (THL, 2024). Of these, ADHD medication was provided for 5% of the boys aged 7–15 and 1.2% of the girls (Vuori, 2020). The onset of hyperactivity typically occurs at the age of 3 or 4 years, with combined hyperactivity and inattention usually occurring from 5 to 8 years onwards

(Austerman, 2015). In practise, however, ADHD is often first identified in school-aged children, when it leads to disruption in the classroom or problems with schoolwork (Harpin, 2016). Essentially, the clinical course of ADHD is chronic, and the evolution of symptoms is progressive and constant. Earlier studies have suggested that around 80–85% of pre-teen ADHD cases continue to experience symptoms in their adolescent years (Brahmbhatt et al., 2016) and according to reported findings, the incidence of ADHD in adolescents aged 12 to 18 is 5.6% (Salari et al., 2023). Moreover, there is increasing evidence pointing to the continuation of ADHD into adulthood in between 15% and 65% of cases, with an estimated prevalence of 2.5% (Katzman et al., 2017).

The estimated prevalence rates for attention disorders quoted in epidemiological research vary according to factors such as the informant concerned, the diagnostic threshold, the time frame, the gender of each subject and the population studied. There is also a preponderance of males in the prevalence of ADHD, the male-to-female ratio in population-based studies being approximately 3:1 and varying from 5:1 to 9:1 in clinical samples (Skogli et al., 2013). Regardless of the ratio, this does not inevitably mean that boys are more likely to have ADHD. Boys tend to present with hyperactivity and other externalizing symptoms, whereas girls tend to react with inactivity (Katzman et al., 2017).

2.1.2 Diagnostics of ADHD

The diagnosis of ADHD is largely based on two criteria. That mainly used in Europe is the International Classification of Diseases, 11th edition (ICD-11) (World Health Organization, 2019), whereas diagnosis in America is based on the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) (APA, 2013). In Finland we still use the 10th edition of the International Classification of Diseases (ICD-10) (World Health Organization, 1993). These criteria do not substantially differ from each other, however.

The evaluation of ADHD in children and adolescents includes a history and physical examination, a review of information applying to home and community settings, and application of the DSM-5 or ICD-10 criteria (Austerman et al., 2015, Posner et al., 2020). No specific test can diagnose ADHD, and both criteria require the presence of a sufficient number of core symptoms. The diagnosis in children requires six or more of the symptoms of inattention and/or six or more symptoms of hyperactivity-impulsivity (APA, 2013; World Health Organization, 1993). The physician should ask about the presence and duration of ADHD symptoms and the

degree of functional impairment from the perspective of the patient, family and school. The diagnosis should be based on the presence of persistent symptoms (see Table 1) that have occurred over a period of time and have been noticeable over the past six months (APA, 2013).

Although ADHD can be diagnosed at any age, the disorder begins in childhood. When considering a diagnosis according to DSM-5 the symptoms must have been present before the individual was 12 years old, while in the use of ICD-10 implies that the symptoms should have been visible before 7 years of age (APA, 2013; World Health Organization, 1993). In both criteria the symptoms must have caused difficulties in more than one setting, i.e. they shouldn't occur only at home, for instance (Felt et al., 2014). The diagnostic criteria for ADHD in DSM-5 are shown in Table 1. The physician should also look for other possible conditions that may mimic or coexist with ADHD. For instance, sleep problems can affect daytime functioning and account for mild ADHD symptoms (Posner et al., 2020). Medical, social and family histories should be reviewed for medical, contextual, environmental or genetic risk factors.

Many children diagnosed with ADHD will continue to meet the criteria for the disorder later in life and may show impairments requiring ongoing treatment. Sometimes, however, a diagnosis of ADHD may be missed during childhood, so that a comprehensive evaluation of an adult should typically include a review of past and current symptoms, a medical examination and history and the use of adult rating scales or checklists (Austerman et al., 2015). In contrast to childhood diagnosis, which ADHD diagnosis in adults requires only five or more symptoms of inattention and/or five or more of the following symptoms of hyperactivity or impulsivity (APA, 2013).

Table 1. Diagnostic criteria for ADHD in children and adolescents according to the DSM-5.

Inattentive symptoms	Hyperactive-impulsive symptoms
1. Makes a lot of careless mistakes	1. Fidgets
2. Difficulty sustaining attention on tasks	2. Difficulty remaining seated
3. Does not listen	3. Runs or climbs excessively
4. Difficulty following instructions	4. Difficulty playing quietly
5. Difficulty organizing tasks	5. Driven by motor
6. Dislikes/avoids tasks	6. Talks excessively
7. Loses things	7. Blurts out answers
8. Easily distracted	8. Difficulty waiting turn
9. Forgetful in daily activities	9. Interrupts or intrudes

Other criteria for ADHD diagnosis

- symptoms are present before the age of 12
- symptoms are displayed in at least two different settings
- symptoms make life considerably more difficult on a social, academic or occupational level
- symptoms are not just part of a developmental disorder or difficult phase, and are not better accounted for by some other condition

2.1.3 Characteristics of ADHD presentations

Three main nominal presentations of ADHD are identified in DSM-5: predominantly inattentive presentation, predominantly hyperactive/impulsive presentation and combined presentation (APA, 2013). Each type of ADHD is tied to one or more characteristics. Generally, persons of the inattentive type get distracted and have poor concentration and organizational skills. In addition, they can have difficulty in organizing their thoughts and processing new information. The predominantly hyperactive/impulsive symptoms never seem to slow down and they involve interrupting, taking risks and difficulties in pursuing a task consistently. Children with hyperactive/impulsive type ADHD can cause disruption in a classroom and can make learning more difficult for themselves and other pupils. Combined presentation implies that a combination of symptoms from both categories will have been exhibited (Salvi et al., 2019).

The predominantly inattentive type is diagnosed if at least six of the nine inattentive symptoms are present, the predominantly hyperactive-impulsive type if at least six of the nine hyperactive/impulsive symptoms are present and the

combined type in the presence of at least six inattentive symptoms and six hyperactive-impulsive symptoms (see Table 1) (APA, 2013). Enumerating the number of ways an individual can meet the criteria illustrates the potential heterogeneity of the diagnosis: the number of different combinations of 6 drawn from 9 is 504. The heterogeneous nature of ADHD is one cause of its multifactorial aetiology which is reflected in its diversity of clinical profiles and psychiatric comorbidities (Katzman et al. 2017).

According to evidence from worldwide research, the predominantly inattentive type is the most common of the three nominal presentations of ADHD in children aged 4–18, followed by the hyperactive/impulsive type and then the combined type, with prevalences of 2.95%, 2.77% and 2.44%, respectively (Ayano et al., 2020). Epidemiological evidence also suggests that ADHD is more prevalent among boys in all three presentations. Inattentive presentation is the most prevalent type in girls (Simon et al., 2009), and inattentive symptoms remain relatively consistent over time whereas hyperactive/impulsive symptoms are developmentally sensitive and tend to decline gradually and are therefore more prevalent in children (Ayano et al., 2020).

2.1.4 Psychiatric comorbidity with ADHD

Around two-thirds of individuals with ADHD have at least one psychiatric comorbid diagnosis (Katzman et al., 2017; Seo et al. 2022). In addition, 18% of children and adolescents aged 6–17 with ADHD have three or more comorbidities (Cuffe et al., 2020). The comorbidity prevalences vary, while clinical samples show slightly greater numbers than population-based samples. The psychiatric disorders that co-occur with ADHD in the NFBC1986 cohort are shown in Figure 1. It is necessary in the differential diagnosis of ADHD to assess whether the symptoms can be explained by other diseases or disorders. Many disorders that are essential for differential diagnosis can also occur simultaneously with ADHD (Katzman et al., 2017). The most frequent comorbid psychopathologies comprise externalizing disorders, including substance use disorders, behavioural disorders and internalizing disorders, including mood and anxiety disorders and bipolar disorder. Recent studies have found that the hyperactive/impulsive type of ADHD has a higher frequency of anxiety disorders than is found in patients with the combined type of presentation (Salvi et al., 2019). Furthermore, combined presentation shows more behavioural problems and emotional lability (Wu et al., 2022).

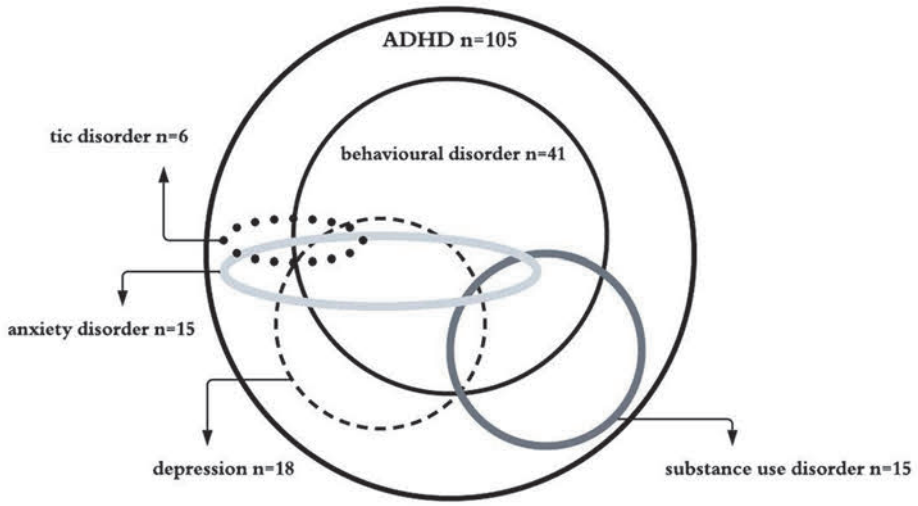

Fig. 1. Co-occurring psychiatric disorders in 16–18-year-olds diagnosed with ADHD in the Northern Finland Birth Cohort 1986. (Modified from ADHD: Käypä hoito -suositus, 2019).

Comorbidity between ADHD and externalizing behaviour disorders such as oppositional defiant disorder (ODD) and conduct disorder (CD) has been found in epidemiological studies of children, (Ercan et al., 2013), the prevalences of ODD and CD co-occurring with the combined type of ADHD being 50.7% and 27%, respectively (Elia et al., 2008; Larson, 2011). In clinic-referred samples, ADHD and comorbid CD appear to be related to greater symptom severity of ADHD (Kessler et al., 2014). Although genetic and environmental factors are associated with both ADHD and behavioural disorders, the largest contributions to comorbid ADHD and CD/ODD are made by shared familial factors such as disturbances in the family, disrupted parent-child relationships and high levels of parenting stress (Cuffe et al., 2020).

ADHD and depression frequently co-occur in both children and adults, with reported prevalence rates for depression in individuals with ADHD ranging from 18.6% to 53.3%, while children show lower prevalences (Katzman et al., 2017). Individuals with comorbid ADHD and depression have a high disease burden, including lower self-reported quality of life than in those with depression alone (Riglin et al., 2021). In addition, the risk of anxiety disorders is higher in individuals with ADHD than in the general population, with rates approaching 50%

(Katzman et al., 2017). Individuals with anxiety disorders who have comorbid ADHD tend to have more severe anxiety symptoms, an earlier age of onset of anxiety, and more frequent additional comorbid psychiatric diagnoses than those who do not have ADHD (Gair et al., 2021).

Possibly the most common condition found to be comorbid with ADHD in adults is substance use disorder, particularly alcohol and/or nicotine, cannabis and cocaine (Spijkerman et al., 2021). Substance abuse or dependence is approximately twice as common in individuals with ADHD as it is in the general population (Katzman et al., 2017). The burden of comorbid ADHD with substance use disorder is substantial, as ADHD has been found to be associated with an earlier onset of substance use, an increased likelihood of suicide attempts, more hospitalizations and less likelihood of achieving abstinence. Overall, the co-occurrence of ADHD and substance use disorder can result in a more severe course of both substance use and psychiatric symptoms and their outcomes (Cuffe et al., 2020).

Adult ADHD also has a high prevalence of comorbidity with bipolar disorder. Rates of comorbid bipolar disorder in ADHD cases have been estimated at 5.1% and 47.1% (Katzman et al., 2017), and several studies have suggested that comorbid ADHD expedites an earlier age of onset of bipolar disorder. In one report, 65% of the individuals with ADHD had an early onset of bipolar disorder compared with only 20% of those who did not have comorbid ADHD (Tamam et al., 2008). In addition to an earlier age of onset, bipolar individuals with comorbid ADHD have demonstrated poorer overall course of the illness with shorter periods of health and more frequent episodes of mania and depression (Salvi et al., 2021).

Although there are strong familial links between ADHD and psychiatric comorbidities, it has been demonstrated that similar regions of the brain are involved in ADHD as in psychiatric disorders (Bond et al., 2012). Neuroimaging studies have implicated differences in the volume and activity of the frontal lobe, which is responsible for attention, behaviour selection and emotion. The overlapping symptoms between ADHD and its comorbid psychopathologies represent challenges for their recognition, diagnosis and management. Symptoms of depression and anxiety may naturally overlap with some ADHD symptoms, such as poor concentration or restlessness, which may be symptoms of all these disorders. Consequently, ADHD may not be the primary disorder. The guidelines recommend that when ADHD coexists with other psychopathologies in adults it is the most seriously impairing condition that should generally be treated first (APA, 2013). Early recognition and treatment of ADHD and its comorbidities has the potential to change the trajectory of psychiatric morbidity later in life (Katzman et al., 2017).

2.1.5 Comorbidity of ADHD with other neurodevelopmental disorders

There is substantial comorbidity of ADHD with other neurodevelopmental disorders (NDDs), i.e. early onset disorders originating in the central nervous system with impairments generally lasting into adulthood (Thapar et al., 2017). The DSM-5 classifies NDDs into six main groups: intellectual disability, communication disorders, autism spectrum disorder (ASD), ADHD, neurodevelopmental motor disorders and specific learning disorders (APA, 2013).

Intellectual disabilities are defined by the DSM-5 as deficits in general mental abilities, which includes impairments in intellectual functioning and the skills of everyday life (APA, 2013). These core characteristics are often accompanied by ADHD. The prevalence rate for ADHD in people with intellectual disability has been estimated to be around 20% (Sawhney et al., 2021). One study showed that children with mild intellectual disability and ADHD appear to be clinically typical ADHD children except that they present with more conduct problems (Ahuja et al., 2013).

ASD is characterized by persistent deficits in social interaction and social communication in multiple contexts and restricted, repetitive patterns of stereotyped behaviour, interests, or activities (Fernell & Gillberg, 2023). A meta-analysis in 2022 found that over one fourth of adolescents with ASD had concurrent ADHD (Mutluer et al., 2022), while conversely, approximately 1 in 8 adolescents with ADHD will also have ASD (Antshel & Russo, 2019). The pattern of behaviour including inattention and hyperactivity-impulsivity may overlap between the two conditions, which complicates differential diagnosis, so that adolescents with ADHD, for example, are diagnosed as having ASD approximately two years later than children with ASD without pre-existing ADHD (Kentrou et al., 2019). Children with ASD and concurrent ADHD show more impairments in activities of daily living and in social adaptation than children with ASD without comorbid ADHD (Fernell & Gillberg, 2023).

The prevalence of motor problems in children with ADHD ranges from 30 to 52% depending on the method of measurement and the manner of ADHD presentation, i.e. the predominantly inattentive and combined types of ADHD have been found to show more fine motor problems than the predominantly hyperactive presentation type (Mokobane et al., 2019). Furthermore, ADHD and learning disorders often co-occur and it is estimated that 20 to 60% of individuals with ADHD also present with learning disorders (Langberg et al., 2011; Pliszka, 1998). A meta-analysis published in 2013 found that children under the age of 10 with

ADHD symptoms showed around three times more dyslexia and dyscalculia than children without ADHD symptoms (Czamara et al., 2013). Language problems are also common and it is reported that nearly half of all children with ADHD have a learning problem (Staikova et al. 2013).

All NDDs share at least partially the same underlying process, risk factors and characteristics which cause diagnostic challenges. Accurate identification is challenging for ADHD because it is often enmeshed with other neurodevelopmental disorders (Thapar et al., 2017). Moreover, the presence of other NDDs together with ADHD not only increases the heterogeneity of phenotypes but also tends to disguise or alter the ADHD symptoms so that children are more likely to be misdiagnosed and their ADHD diagnosis delayed (Askri et al., 2023). What makes it even more challenging is that the previous disease classifications (ICD-9 and ICD-10) conceptualized most NDDs as separate, exclusive categories, so that a diagnosis of ASD excluded ADHD, for example (World Health Organization, 1993). In conclusion, the accurate diagnosis of NDDs in early childhood is vital for timely effective treatment, which will alleviate the severity of the symptoms and the long-term impacts of the disorder (Hus & Segal, 2021).

2.2 Early risk factors for ADHD

This section will provide an overview of the types of risk factors for ADHD, some of which are well-known, while others have been studied only to a limited extent.

2.2.1 Known risk factors for ADHD

It is well accepted that ADHD is highly heritable (>70%) (Faraone & Larsson, 2019) but to date no single gene has been discovered that plays a major role in this. In particular, the genetic basis is likely to be held in common with other NDDs and to involve many genes which have a small individual effect (Thapar et al., 2013). The suspected ADHD genes are thought to be involved in the creation of dopamine, which when normally produced is in charge of the brain´s ability to maintain regular and consistent attention (Alonso-Gonzalez et al., 2019).

Despite the high heritability of ADHD, not all the risk involved is genetic. ADHD appears early in life, and significant interest has been shown in the potential role that the pre- and postnatal environment might play in the development of this disorder. It is estimated that between 10 and 40% of the variance associated with

ADHD is likely to be accounted for by environmental factors (Sciberras et al., 2017). Still, it should be noted that in addition to the purely environmental risk, estimates of heritability should also include an element of dynamic genetic, epigenetic and environmental interactions (Faraone & Larsson, 2019).

Numerous pre- and postnatal risk factors have been identified which appear to be associated with ADHD, and in addition, these risk factors partially overlap in all NDDs and are not specific to ADHD. Prenatal development is one of the most critical windows during which adverse conditions and exposures may influence the development of the fetal brain and its future postnatal health (Sciberras et al., 2017). Well recognized prenatal risk factors predicting ADHD include prematurity, low birth weight (Franz et al., 2018), maternal substance use (Knopik et al., 2019) and environmental toxins (Goodlad et al., 2013).

Prematurity (born at 22–37 weeks' gestation), especially extreme prematurity (<28 weeks' gestation), has the strongest relationship with ADHD of all the prenatal risk factors that have been implicated (Franz et al., 2018), while the evidence for an effect of low birth weight (<2500 g) is less clear, although there is some evidence to support an increased risk of ADHD, independent of prematurity, in those that are small for gestational age (Aarnoudse-Moens et al., 2009). This implies that being born early or having a low birth weight can disrupt the normal sequence of brain development processes. While improvements in perinatal care have resulted in increased survival rates for extreme preterm neonates and/or those with a very low birthweight (<1500 g), there is a growing awareness that many of these children encounter neurodevelopmental problems such as behavioural problems and deficits (Montagna et al., 2020).

Maternal prenatal substance use is widely recognized as a risk factor, and has been linked to numerous adverse health consequences for both the developing fetus and the mother (Sciberras et al., 2017). Yet a considerable proportion of women in Europe continue their substance use while pregnant. The most frequently used substance is tobacco, followed by alcohol, cannabis and other illicit substances (Forray & Foster, 2015). The European Region has the highest estimated prevalence of smoking during pregnancy, 8.1% (Lange et al., 2018). Nicotine intake can damage the developing fetal brain by interfering with its dopaminergic activity (Shiberras et al., 2017), and the findings also suggest that there are a variety of placental complications linked to prenatal exposure to substance use which could effectively translate into neurodevelopmental complications (Einarson & Riordan, 2009). An umbrella review in 2020 linked prenatal exposure to tobacco with later ADHD (Kim et al., 2020), and furthermore, a Finnish study revealed a dose-

response relationship between nicotine exposure during pregnancy and ADHD in the offspring (Sourander et al. 2019). In addition to drugs, the same study linked maternal acetaminophen and SSRI exposure during pregnancy to a higher risk of offspring ADHD, and similar associations have been demonstrated with maternal pre-pregnancy obesity and gestational diabetes and with pre-eclampsia (Kim et al., 2020).

Postnatal environmental toxins are also a widely identified risk factor for ADHD, and in particular environmental lead and PCB exposures have been associated with higher rates of inattention and impulsivity (Donzelli et al., 2019). Numerous neurotransmitter systems, such as dopamine, are sensitive to endocrine disruption (Braun et al., 2006), and exposure to even small doses of endocrine disruptors such as lead can cause subtle or even serious damage to the endocrine system. The early factors suggested as affecting the risk of ADHD are summarized in Table 2.

Table 2. Early risk factors for ADHD and their risk estimates.

Risk factor	Risk estimate	Reference
Genes (both parents´ ADHD)	Pooled prevalence 0.38, 95% CI 0.08–0.68	Uchida et al., 2021 (meta-analysis)
Male gender	Male to female ratio 3:1	Barkley, 2006 (original publication)
Preterm birth or low birthweight	Odds ratio 3.04 95% CI 2.19–4.21	Franz et al., 2018 (meta-analysis)
Maternal smoking during pregnancy	Odds ratio 1.60 95% CI 1.45–1.76	Kim et al., 2020 (umbrella review)
Acetaminophen exposure during pregnancy	Odds ratio 1.25 95% CI 1.17–1.34	Kim et al., 2020 (umbrella review)
SSRI exposure during pregnancy	Odds ratio 1.37 95% CI 1.16–1.63	Kim et al., 2020 (umbrella review)
Maternal pre-pregnancy obesity	Odds ratio 1.49 95% CI 1.14–1.94	Bitsko et al., 2022 (meta-analysis)
Gestational diabetes	Odds ratio 2.10 95% CI 1.42, 2.81	Kim et al., 2020 (umbrella review)
Pre-eclampsia	Odds ratio 1.26 95% CI 1.09, 1.46	Bitsko et al., 2022 (meta-analysis)

Risk factor	Risk estimate	Reference
Environmental lead	Odds ratio 1.73 95% CI 1.09, 2.73	Ji et al., 2018 (original publication)

2.2.2 Prenatal maternal inflammation

Maternal health during pregnancy plays a major role in shaping health and disease risks in the offspring. In general, inflammation and infections are common events during pregnancy. Inflammation is part of the biological response of body tissues to harmful stimuli such as pathogens or damaged cells (Furman et al., 2019), and pathogens, such as viruses and bacteria, can be explanatory factors for infections, which in turn typically cause acute inflammation (Ginsberg et al., 2019). More harmful still, however, is chronic inflammation, which usually appears in the form of low-grade inflammation and is increasingly being recognized as a cause or consequence of many common problems, including obesity, stress, depression, pollution and disease states such as autoimmunity, asthma and infection (Furman et al., 2019).

Maternal immune activation, triggered by both acute and systemic chronic inflammation, has been hypothesized to be one of the mechanisms implicated in the pathogenesis of neurodevelopmental disorders. Thus, our current evidence on the association between maternal inflammation during pregnancy and the subsequent risk of neurodevelopmental disorders pertains primarily to conditions such as schizophrenia, autism and cerebral palsy (Han et al., 2021; Werenberg Dreier et al., 2016). Although the mechanisms through which maternal inflammation causes brain impairment are not well understood (Werenberg Dreier et al., 2016), one potential explanation may lie in elevated maternal interleukin-6 (IL-6) levels, leading to an anatomically larger and more functionally connected amygdala in the offspring. The amygdala is responsible for emotional responses and deformities in it may be linked to poorer impulse control at the age of two years (Graham et al., 2018).

Only a few studies to date have assessed the impact of inflammation on pregnancy and the risk of ADHD in the child, and the results have been inconsistent as to whether prenatal maternal inflammation and ADHD are connected or not. Most of the previous studies have used maternal respiratory infections and genitourinary infections as markers of inflammation, but where three studies published between 2007 and 2014 support an association between prenatal maternal infections and ADHD in the offspring (Mann et al., 2011; Pineda, 2007;

Silva, 2014), more recent ones have not found any such association (Ginsberg et al., 2019; Werenberg Dreier et al., 2016).

There have only been two previous studies in which C-reactive protein (CRP) has been used as a blood marker for inflammation when exploring the association between prenatal maternal inflammation and ADHD in the offspring, and these were inconsistent (Chudal et al., 2020, Rosenberg et al. 2023). In addition, to the present author's knowledge there has been only one study with clinical evaluations that has investigated maternal inflammation during pregnancy in relation to childhood ADHD, and this reported that higher levels of cytokines (IL-6, TNF-a and MCP-1) were associated with increased severity of ADHD symptoms in children at 4–6 years of age (Gustafsson et al., 2020).

2.2.3 Prenatal maternal stress

The prevalence of prenatal maternal stress, i.e. a low or negative state of well-being during pregnancy, has been estimated at 31% (McDonald et al., 2013). Stress in this context includes negative life events, anxiety and depressive symptoms, and can be either chronic, linked to ongoing events in the woman's life, or acute, linked to sudden changes in her daily routine or environment.

Research findings have associated stress levels with negative consequences in fetal and infant development. The pituitary-adrenal axis, for example, is thought to play a key role in mediating the effects of maternal stress on the fetus, so that when a pregnant woman is exposed to an event that is perceived as stressful, the brain triggers a cascade of events on the pituitary-adrenal axis ultimately leading to the release of stress hormones such as cortisol (Seckl & Holmes, 2007), which can pass from the mother to the fetus via the placenta. Exposure to these high cortisol levels may then have a negative effect on the developing fetus (Zhu et al., 2015). Furthermore, in utero exposure to high levels of cortisol may also affect postnatal development (Van den Bergh et al., 2020).

There is a growing literature examining the health consequences for the offspring of exposure to high stress hormone levels in utero. Epidemiological studies have shown that prenatal stress increases the rate of spontaneous abortions, fetal malformations, and preterm births (Coussons-Read, 2013). In addition, earlier studies have shown that exposure to stress is associated with the development of common somatic and psychiatric diseases such as mental disorders and cardiovascular diseases (Evans et al., 2020). Along with these, research has suggested that prenatal stress will disturb the neurobehavioural development of the

offspring, and consequently a few studies have shown that prenatal maternal stress increases the risk of the offspring developing ADHD (Manzari et al., 2019; Okano et al., 2019), although in some instances this association has been found only in boys (Li et al., 2010; Rodriguez et al.; 2005 Shao et al., 2020; Zhu et al., 2015).

In contrast, not all the studies have found an association between maternal stress and the risk of ADHD in the offspring (Rice et al., 2010; Rosenqvist et al., 2018), preferring to suggest that the association is largely explained by familial factors (Rosenqvist et al., 2018). Furthermore, there are limitations in the literature on prenatal maternal stress and ADHD. To this day, there have been only a few prospective studies, while the majority of those reporting adjusted results are case–control studies, which may be subject to recall bias. In addition, most reports do not adjust for key potential confounders such as gender, parents' psychiatric disorders, maternal age and socio-economic status. Another alternative is to use fatigue to determine prenatal maternal stress, since there is evidence to suggest a clear bidirectional association between fatigue and stress (Kop & Kupper, 2016).

Apart from prenatal maternal stress, unwanted pregnancy is a major risk factor for maternal depression, anxiety (Biaggi et al., 2016) and pregnancy complications (Eftekhariyazdi et al., 2021), but unlike stress during pregnancy, the role of unwanted pregnancy in the risk of offspring ADHD has only been studied once before, when a positive association was established (Golmirzaei et al., 2013).

2.2.4 Breastfeeding

Breastfeeding is one of the most widely studied and important postnatal influences not only on infant health but also on early cortical development, and thus probably on self-regulation, emotional development and neurodevelopmental conditions (Krol et al., 2018). A lack of breastfeeding has been linked with offspring mortality caused by infectious diseases, child obesity, both type 1 and type 2 diabetes mellitus, leukaemia and sudden infant death syndrome (Stuebe, 2009). As for the importance of breastfeeding, the Finnish Institute of Health and Welfare recommends exclusive breastfeeding for the first 4 to 6 months, with continued breastfeeding along with the introduction of appropriate complementary foods up to one year of age (THL, 2023).

Furthermore, the outcomes of breastfeeding have been examined with respect to neurodevelopmental diseases. In relation to ADHD, initiation and duration of breastfeeding may be expected to be particularly important among the neonate's early experiences for several reasons. Firstly, the occurrence of ADHD is in theory

based on the child's early neural development (Faraone & Larsson, 2019). The early postnatal period is characterized by continued developmental plasticity, and as nutrition is among the most important supports for such development, suboptimal infant nutrition can induce adaptations that may be detrimental to brain development (Herba et al., 2013). Secondly, ADHD is associated with higher-order cognitive delays, including a subtle reduction in the intelligence quotient (IQ) (Polderman et al., 2010). Consistent with the above, breastfeeding has been associated with better intellectual function in children and the effect is understood as being dose-dependent in relation to the duration of breastfeeding, as noted in a meta-analysis published over two decades ago (Anderson et al., 1999).

Thirdly, the duration of breastfeeding has been associated directly with brain white matter development in infants and toddlers (Herba et al., 2013; Tawia, 2013), and it was subsequently found in eight-year-old children that the duration of breastfeeding was associated with increased white matter development in key brain tracts, including the superior longitudinal fasciculus, the cingulum, the body of the corpus callosum and the posterior thalamic radiations (Ou et al., 2014). These brain regions are similar to those in which altered white matter development had been noted previously in eight-year-olds with ADHD (Nagel et al., 2011).

Although no association of breastfeeding with ADHD has yet been firmly established, a recent meta-analysis showed that ADHD is more common in children with lower rates of breastfeeding (Tseng et al., 2019). On the other hand, the mechanism by which breastfeeding affects a child´s health has not yet been determined, although it has been thought to be either biological (protective effects of breastmilk) or psychological (mother-child contact). Some studies have also suggested that ADHD children are simply harder to breastfeed and that this alone may explain the association (Stadler et al., 2016). Contrary to the recent meta-analysis, several studies have found no association between maternal breastfeeding and offspring ADHD (Boucher et al., 2017; Schwenke et al., 2018).

In addition, the varying targets of exclusive or non-exclusive breastfeeding might account for the differing results. For example, in one recent study the rate of exclusive breastfeeding for a duration of over 12 months did not differ significantly between children with ADHD and controls (Say et al., 2015). However, Stadler et al., focusing on non-exclusive breastfeeding, suggested that the children with ADHD had a significantly lower rate of breastfeeding for a duration of over 12 months than did the controls (Stadler et al., 2016).

2.2.5 Temperament and character profiles

Given the centrality of emotional processes for normative social and cognitive development, research has increasingly become focused on the significance of stable internal factors such as personality for the development of neurobehavioural disorders. Personality is viewed as being composed of temperament and character, both of which have been implicated in developmental psychopathology and together encompass both biological and environmental influences (Cloninger et al., 1993). Temperament describes an individual's profile of biological response patterns to external stimuli, which is reflected in individual differences in emotional responses to the environment (Cloninger et al., 1993). These may play a central role in determining individual differences among young people with or without ADHD, especially regarding emotional and behavioural functioning as well as comorbidity concerns.

Various models have been used to describe personality. The Big Five personality model allows the evaluation of five main factors: Openness to experience, Conscientiousness, Extraversion, Agreeableness and Neuroticism (Costa & McCrae, 1992). Meanwhile, Cloninger describes a psychobiological model for the structure and development of personality that accounts for the dimensions of both temperament and character (Cloninger et al., 1993). In this model temperament is determined by neurobiological and genetic factors and can be divided into four independent dimensions: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P). According to Cloninger's theory, these dimensions are associated with the brain´s neurotransmitters, high novelty seeking being associated with high dopamine levels (Costa et al., 2014) and high harm avoidance with low serotonin levels (Lin et al., 2013). Also, there have been findings that associate high noradrenaline with reward dependence (Nagy et al., 2022). In general, people with high novelty seeking tend to react to new stimuli and allusions that point to reward or experience. They try to avoid uninflected and dull situations. In addition, curiosity and impulsivity are associated with high novelty seeking. Harm avoidance is defined as the avoidance of stimuli that are felt to be obnoxious or indeterminate. Reward dependence is a dimension that covers persons who tend to maintain pleasant and previously rewarded actions, especially in social situations. People with lower persistence are typically unable to maintain good behaviour in the face of frustration (Hansenne, 1999).

Furthermore, character refers to self-concepts and individual differences in goals and values which may influence people's voluntary choices, intentions and the meaning and salience of what they experience in life. Differences in character are moderately heritable and moderately influenced by socio-cultural learning. Character may be divided into three dimensions: Self-Directedness (SD), Cooperativeness (CO) and Self-Transcendence (ST) (Cloninger et al., 1993). People with poor teamwork and supporting skills usually have lower scores for cooperativeness, while self-directedness is a personality trait of self-determination, and it describes the ability to regulate one's behaviour according to the demands of the situation. In addition, self-transcendence is a personality trait that involves the expansion of one's personal boundaries. In general, there is no universal consensus about differentiating between temperament and character, but it is thought that temperament involves a greater element of genetic determination, whereas character can be more shaped via environmental stimuli (Ando et al., 2004; Cloninger et al., 1993). The personality dimensions and traits observable in high and low scorers are shown in Figure 2.

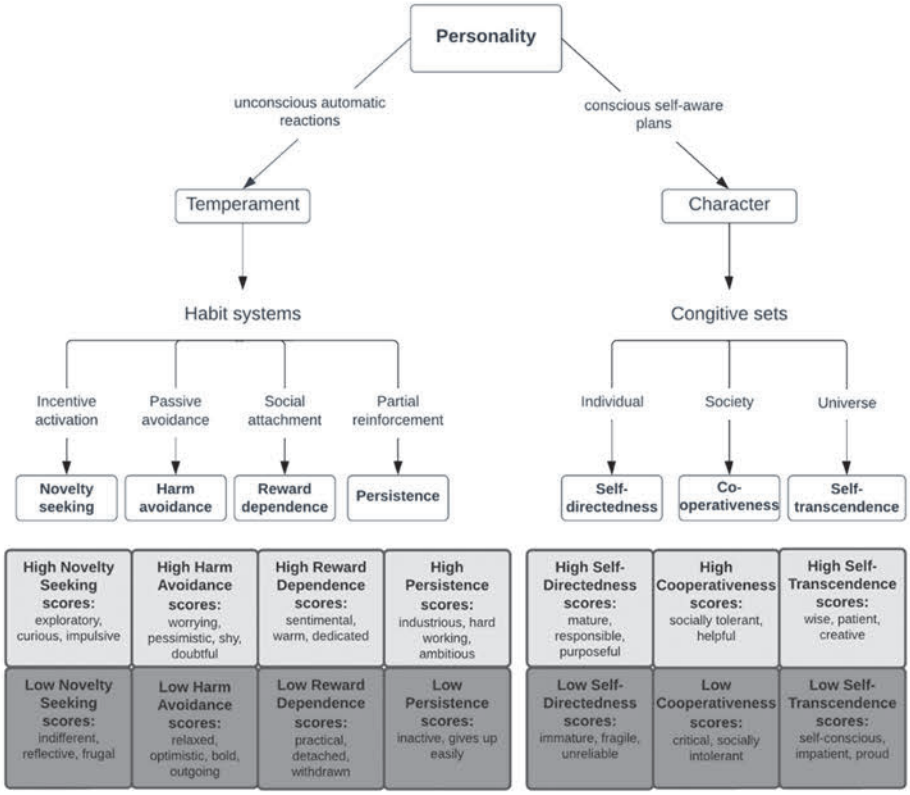

Fig. 2. Temperament and character traits for high and low scorers according to Cloninger's model.

Despite its importance, the evidence for an adolescent's temperament structure is highly inconsistent in the literature and studies tend to use different models to predict psychopathology, which may lead to inconclusive results. One recent meta-analysis showed that there are extensive, complex and distinct relationships between the various temperament and character traits and the different types of mental disorders (Komasi et al., 2022). The most important finding of this meta-analysis was that harm avoidance and self-directedness play a fundamental role in psychopathology. As far as ADHD is concerned, a meta-analysis in 2019 showed that it has come to be associated with higher novelty seeking and lower persistence and cooperativeness scores (Pinzone et al., 2019). In contrast, the same study did not associate ADHD with reward dependence. Intriguingly, current studies have yielded contradictory results concerning the association between ADHD and harm

avoidance and two of the character traits: self-directedness and self-transcendence (Melegari et al., 2015; Pinzone et al., 2019). A review of the associations between ADHD and temperament and character found in recent studies using Cloninger's personality dimensions is provided in Table 3.

Table 3. Association of ADHD with temperament and character profiles. The arrows indicate an association between ADHD and the personality profile as compared to healthy controls.

Study	Study Design	Study Population	NS	HA	RD	P	SD	CO	ST
Anckarsäter et al., 2006	Case-Control	240	↑	↑	-	-	↓	↓	-
Cho et al., 2008	Case-Control	102	↑	-	-	-	↓	-	-
Faraone et al., 2009	Case-Control	370	↑	↑	↓	↓	↓	↓	↑
He et al., 2019	Case-Control	329	↑	↑	↓	↓	↓	↓	↑
Kim et al., 2017	Case-Control	429	↑	↑	-	-	↓	↓	↑
Melegari et al., 2015	Case-Control	120	↑	-	↓	↓	-	↓	↓
Merwood et al., 2013	Case-Control	886	↑	↑[1]	↓	↓↑[2]	-	-	-
Perroud et al., 2016	Case-Control	522	↑	↑	-	↓	↓[1]	↓[3]	↑[3]
Pinzone et al., 2019	Systematic review	15 articles using TCI	↑	↑	-	↓	↓	↓	↑
Rapinesi et al., 2018	Case-Control	98	-	↑	-	-	↓	-	-

↑; Higher in individuals with ADHD. ↓; lower in individuals with ADHD. -; no statistically significant association

[1]Only in inattentive ADHD

[2]Higher points in hyperactive-impulsive ADHD, lower points in inattentive ADHD

[3]Only in hyperactive-impulsive ADHD

Abbreviations: NS: Novelty Seeking, HA: Harm Avoidance, RD: Reward Dependence, P: Persistence, SD: Self-Directedness, CO: Cooperativeness, ST: Self-Transcendence, TCI: Temperament and Character Inventory

2.2.6 Summary of the literature on the risk factors for ADHD

Genes and male gender determine the risk for ADHD (Skogli et al., 2013; Uchida et al., 2021). Furthermore, previously well recognized prenatal risk factors for ADHD include prematurity, low birth weight (Franz et al., 2018) and maternal substance use (Knopik et al., 2019), including tobacco, alcohol (Einarson & Riordan, 2009), acetaminophen and SSRI exposure (Kim et al., 2020). In addition, there are findings that associate maternal pre-pregnancy obesity, gestational diabetes and pre-eclampsia with ADHD in the offspring (Kim et al., 2020). Postnatal environmental toxins are also widely identified risk factors for ADHD (Donzelli et al., 2019).

There is still very little research evidence available, however, and results are inconsistent regarding the direct causal connections between offspring ADHD and prenatal maternal inflammation, prenatal maternal stress, the duration of breastfeeding and the child´s own personality. The well identified risk factors and those possibly associated with ADHD are summarized in Figure 3.

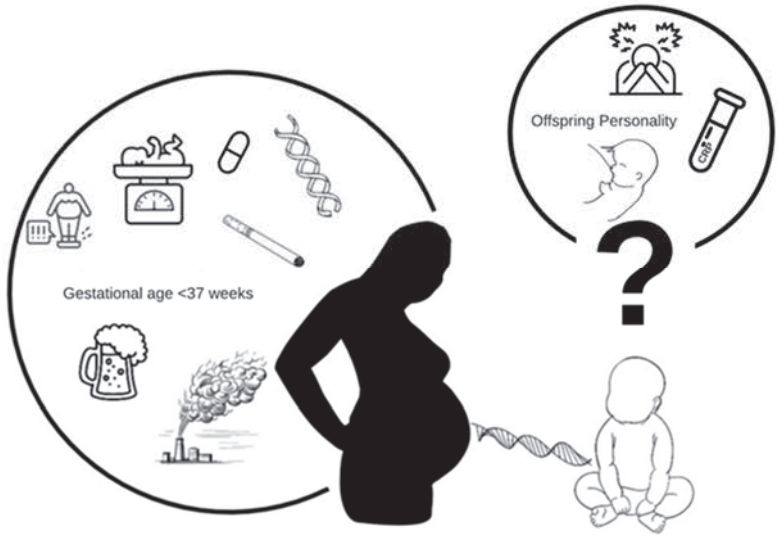

Fig. 3. The reliably identified early risk factors for ADHD include genetic basis, maternal pre-pregnancy obesity, maternal prenatal substance use, gestational diabetes, pre-eclampsia, prematurity, low birth weight, and environmental toxins. This study focuses on whether prenatal maternal inflammation and stress, duration of breastfeeding and personality are associated with offspring ADHD.

3 Aims of the research

This work carried out using prospectively collected data from the Northern Finland Birth Cohort 1986 (NFBC1986) was aimed at detecting early risk factors for ADHD, which are as yet not fully understood. These factors include prenatal inflammation, prenatal maternal stress, breastfeeding and child's own temperament and character profiles.

The aims of this work were to study

1. Whether prenatal maternal inflammation is associated with offspring ADHD (I),
2. Whether prenatal maternal stress and unwanted pregnancy are associated with offspring ADHD (II),
3. Whether the duration of maternal breastfeeding is associated with offspring ADHD (II),
4. Whether there are differences in temperament and character between adolescents with and without ADHD (III), and
5. How internalizing and externalizing psychiatric comorbidities of ADHD are associated with temperament and character (III).

4 Materials and Methods

4.1 Population and procedure

The population analysed here consisted of the Northern Finland Birth Cohort 1986 (NFBC1986), a prospective mother-child cohort that includes 99 percent of all births that took place in the area concerned in the interval 1.7.1985–30.6.1986 (n=9,479, live births 9,432) (Järvelin et al., 1993; University of Oulu, 1986). In the first trimester of their pregnancy 8,785 mothers completed a questionnaire including information on fatigue (i.e. stress) during pregnancy and the desirability of the pregnancy. At the same time 7,094 of the mothers had their CRP analysed. When the offspring reached the age of one, their health clinic cards were collected and their mothers were asked to fill in a questionnaire concerning the duration of breastfeeding (n=3,255).

To study hyperactivity in the children, their teachers were asked to fill in the Rutter Children's Behaviour Questionnaire (Rutter B2, Rutter, 1967) at the age of 8 (n=8,721) (Taanila et al., 2004). Then, when the children reached the age of 16, their parents filled in the Strengths and Weaknesses of ADHD symptoms and Normal Behaviours (SWAN) questionnaire (Swanson et al., 2001) to detect possible ADHD symptoms (n=6,622). The capacity of the Rutter B2 for screening child psychiatric disturbances has been shown by Kresanov et al. (1998). Burton et al. (2019) has shown that SWAN scores distinguish ADHD participants with high sensitivity and specificity.

When NFBC1986 itself conducted a clinical ADHD study in which the participants for ADHD assessment were selected on the basis of the SWAN score, the probable ADHD cases invited to take part in the clinical examination (scoring above the 95th percentile of SWAN scores) and a random sample of adolescents scoring below the 90th percentile and matched with them as a group for gender, place of birth and age amounted to 261 cases, and 196 controls, 457 in total (Smalley et al., 2007). The clinical assessment included the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kaufman et al., 1997) to determine the adolescents' ADHD and other psychopathology. During the visit to the clinic the adolescents also filled in the Temperament and Character Inventory (TCI) designed to assess their personality dimensions (n=402). The whole NFBC1986 data collection process is illustrated in Figure 4.

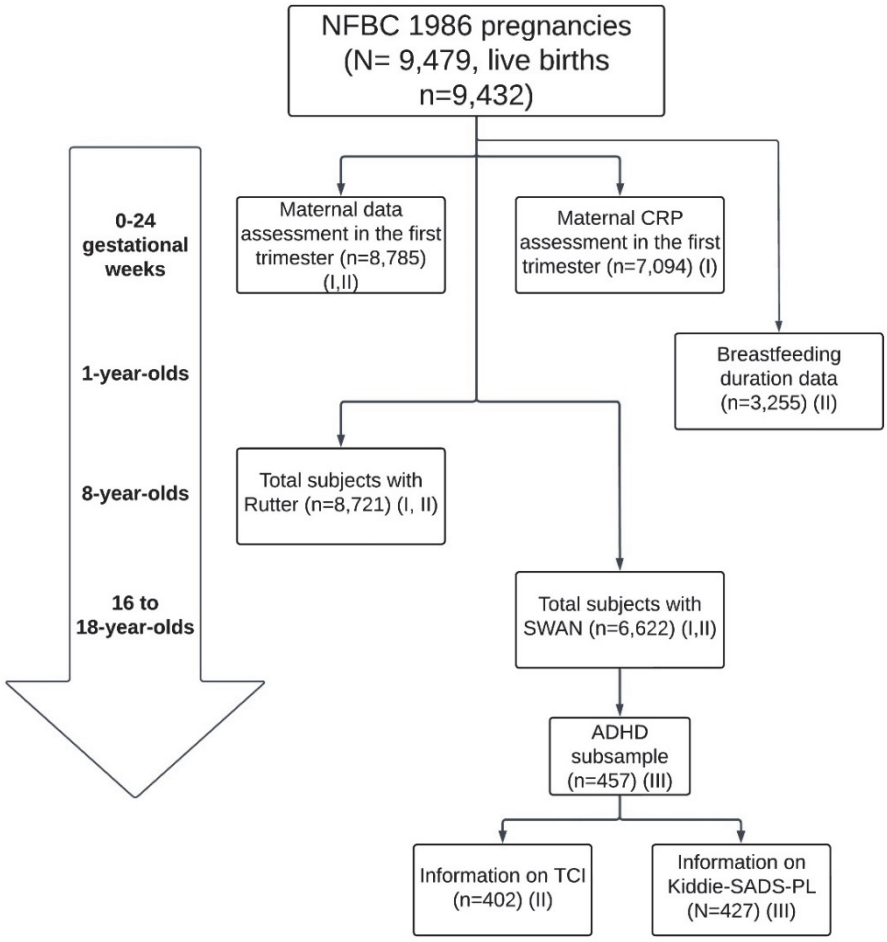

Fig. 4. Data collection for the Northern Finland 1986 Birth Cohort and the ADHD subsample.

4.2 Instruments and measures

4.2.1 Maternal data

The pregnancy and delivery data collected from the antenatal clinics covered 99% of all births in the area (n=9,479), and questionnaires for background information were given to all the mothers at their first antenatal visit and returned by them in

the 24th gestational week at the latest. The questionnaires included items concerning maternal age, occupation, education, BMI before pregnancy, marital status, and the desirability of the pregnancy. Maternal age was assigned to three categories in Study II: under 20 years, from 20 to 35 years and over 35 years. The educational status replies were also divided into two categories: parents without a high school diploma and parents with a high school, college, or university qualification, and the desirability of the pregnancy was similarly divided into two categories: “planned pregnancy” and “not planned or planned for later”. For Study I the mothers’ occupations were assigned to five categories: professional, skilled worker, unskilled worker, farmer or other/missing.

A questionnaire concerning information on the pregnancy was filled in by local midwives at the mother's last visit to the antenatal care unit or during the first home visit after the delivery. This questionnaire gathered information on maternal smoking and stress during pregnancy. The answers to the question concerning how stressed the mother had felt during the pregnancy were categorized in Study II into “ordinary or better than before” and “depressed”. Information on the delivery and the sex of the child was forwarded by the delivery clinics to the child health clinics, which entered the data in their files (Järvelin et al., 1993).

Data on maternal C-reactive protein (CRP) were available from the Finnish Maternity Cohort of Northern Finland Biobank Borealis. One serum sample was obtained during the first or early second trimester of each pregnancy and stored as a single aliquot at -25C. CRP was measured on an Architect c8200 clinical chemistry analyser (Abbott Laboratories, Abbott Park, IL, USA) using a latex immunoassay. The coefficient of variation (mean ± SD) of the test was 5.1% ± 2.3% and the assay sensitivity 0.10 mg/dL. CRP was used as both a continuous and a categorized variable (classification: <3, 3–10 and >10, with <3 mg/L as the reference level). This cut-off was chosen based on the American Heart Association and Centre for Disease Control and Prevention recommendations, which defined CRP levels of <3 mg/L as their reference level (Pearson et al., 2003). CRP measurements above 3 mg/L but below 10 mg/L were taken to represent low-grade inflammation and those over 10 mg/L a high inflammatory state (Rifai et al., 2003).

4.2.2 1-year data and child health clinic data

Data concerning the children's growth, health and development were collected from the child health clinics at about one year of age, when their health clinic cards were collected and their mothers were asked to fill in a questionnaire on the duration of

breastfeeding. Information from these sources, prioritizing the child health clinic card data, was used to determine the duration of exclusive and non-exclusive breastfeeding, after which two duration categories were formed: exclusive breastfeeding for under three months and three months or more and non-exclusive breastfeeding for under six months or six months or more. These categories were selected based on breastfeeding recommendations from the 1980's and previous studies that had used the same time points (Hasunen et al., 1989; Tseng et al. 2018).

4.2.3 The Rutter Children´s Behaviour Questionnaire

The Children's Behaviour Questionnaire developed by Rutter measures emotional and behavioural problems in childhood (Rutter, 1967). Symptoms of childhood hyperactivity were evaluated by the child's main teacher at eight years of age, when the teachers filled in a questionnaire that included the official Finnish translation of the Rutter scale B2 with 26 items. Three of the items measure hyperactivity, which was assessed for the present purposes in terms of the sum scores of these hyperactivity items (item 1, the child is restless, does not have the patience to sit down for a longish period of time, item 3, wriggles and is restless and item 16, is not able to concentrate on anything for a longish period of time). The items were scored as 0 (does not apply), 1 (applies somewhat) or 2 (certainly applies). Thus, the total score of the present hyperactivity items ranged from 0 to 6 and children were categorized as hyperactive if they scored more than 3 points (Taanila et al. 2004).

4.2.4 Strengths and Weaknesses of ADHD symptoms and Normal Behaviours (SWAN)

Strengths and Weaknesses of ADHD symptoms and Normal Behaviours (SWAN) is a questionnaire that measures problems in attention and hyperactivity (Swanson et al., 2001). The SWAN questionnaire is a modification of the Swanson, Nolan and Pelham (SNAP-IV) rating scale for ADHD and includes 18 items: 9 concerning hyperactive-impulsive symptoms and 9 concerning inattentive symptoms as described in DSM-5 (see Table 1) (APA, 2013). The symptoms are translated into statements which are rated on a 7-point scale anchored to average behaviour in the middle, rated as 0. Thus, each item is scored on a scale from −3 to +3. Strengths are rated as –1 (slightly above average), -2 (above average) and –3 (well above average) and problematic forms of behaviour as 1 (slightly below average), 2

(below average) and 3 (far below average). The ratings can be summed to yield summary scores, which can be used to determine the cut-off point for problems, for which Swanson recommends the highest 5th percentile (Swanson et al., 2012).

4.2.5 Temperament and Character Inventory (TCI)

The Temperament and Character Inventory (TCI) is an instrument for personality assessment that was developed by C. Robert Cloninger (Cloninger et al., 1993). Cloninger describes a psychobiological model for the structure and development of personality that accounts for dimensions of both temperament and character (see Figure 2). It divides personality into seven dimensions: four for temperament and three for character. The dimensions can vary widely in the general population, rather than focusing only on pathology or abnormal traits.

The original TCI comprises 226 self-reported true-false items, and the number is increased to 240 in later versions. Also, Cloninger (1999) developed a new TCI-R version in which 240 items are answered on a five-point Likert scale (Farmer & Goldberg, 2008). The present NFBC1986 subsample participants filled in a TCI with 125 items during a visit to the clinic. This version of the Temperament and Character Inventory is a recognised, valid and reproducible tool used to measure seven components of personality (Svrakic et al., 1993), described in the following terms (abbreviation, number of items); novelty seeking (NS, 20), harm avoidance (HA, 20), reward dependence (RD, 15), self-transcendence (ST, 15), self-directedness (SD, 25), cooperativeness (CO, 25) and persistence (P, 5).

4.2.6 Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)

The semi-structured diagnostic interview that is most commonly used in child psychiatry is the K-SADS-PL which is designed to correspond to the DSM-IV-TR. The interview is administered to both a parent and the child or adolescent and assesses current and past episodes of psychopathology in children and adolescents between ages of 6 and 18. The primary diagnoses assessed with the K-SADS-PL instrument include major depression, dysthymia, mania, hypomania, cyclothymia, bipolar disorders, schizoaffective disorders, schizophrenia, schizophreniform disorder, panic disorders, separation anxiety disorder, specific phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, ADHD, conduct disorder, oppositional defiant disorder, enuresis, encopresis, anorexia nervosa,

bulimia, Tourette's syndrome, motor or vocal tic disorder, substance abuse and dependence, post-traumatic stress disorder and adjustment disorders (Kaufman et al., 1997).

K-SADS-PL has been shown to be valid for DSM-IV-TR-based ADHD diagnosis among adolescents (Faraone et al., 2002), and the symptoms of DSM-5 ADHD are identical to those of DSM-IV-TR except for additional examples of how they may manifest themselves in adolescence and adulthood, and the reduction in of the minimum number of symptoms in either symptom domain from six to five in older adolescents and adults (Epstein & Loren, 2013). The adolescent diagnosis of ADHD was reached in accordance with the current ADHD symptoms of the adolescent and with the other criteria in the DSM-IV-TR (see Table 1) and the childhood diagnosis of ADHD in accordance with the parents' and children's retrospective recall of their childhood symptoms (from early childhood to the age of 12) and other criteria based on the interview. The diagnoses obtained in the interviews were classified in terms of ADHD and its presentations (inattentive, hyperactive/impulsive or both), depressive disorders, anxiety disorders, tic disorders, substance abuse disorders and behavioural disorders.

The original interviews and re-ratings in NFBC1986 had been performed with the personnel blinded to the SWAN diagnostic status, and the inter-site reliability, determined from the initial Best Estimate diagnosis established by the Finnish team and the final consensus diagnosis, was 0.87 for childhood ADHD (based on symptoms occurring by the age of 12) and 0.90 for current ADHD (age 16–18). The average kappa for the other psychiatric diagnoses was 0.94 (range 0.82–0.96) (Smalley et al., 2007).

4.2.7 Other assessments and study variables

The sociodemographic factors at the age of 16 were determined by means of a further questionnaire in which the parents, for instance, were asked to describe the adolescent's behaviour and to answer questions on their marital (family structure) and social status and their education and work. Also, data from the national registers (Care Register for Health Care, CRHC) of maternal and parental psychiatric disorders (ICD-8 codes 290-315, ICD-9 codes 290–319 and ICD-10 F-codes) were included in Study II. These disorders were taken into account provided they had been diagnosed after 1972 and before the offspring reached the age of 8 in the 8-year follow-up or 16 in the 16-year follow-up. In addition, we extracted any diagnosed NDDs from the CRHC (ICD-8 codes 306.0, 306.2, 308.0 and 311–

319, ICD-9 codes 2990, 3072–3073, 3153 and 3170–3199 and ICD-10 codes F70–F79, F80, F84 and F95). CRHC is a national social and healthcare data collection and reporting system, and its data form a significant part of the national social and healthcare database. The information is used in many ways to guide and monitor social and healthcare activities (THL, 2023).

4.3 Statistical methods

4.3.1 Study I

Associations between prenatal maternal inflammation and offspring ADHD symptoms were investigated by means of logistic regression modelling (odds ratios (OR) with 95% confidence intervals (CI)). The association was then evaluated using CRP as a continuous and categorized variable and four domains of ADHD symptoms: hyperactive symptoms on the Rutter scale, inattentive symptoms, hyperactive/impulsive symptoms, and combined symptoms on the SWAN scale. After assessing the crude models, adjustments were made using information on the mother's BMI and occupation before pregnancy and smoking during pregnancy (yes/no) and the sex of the child at birth.

4.3.2 Study II

Associations between unwanted pregnancy, prenatal maternal fatigue, duration of breastfeeding and offspring ADHD symptoms were investigated using logistic regression and odds ratios (OR) were reported with 95% confidence intervals (CI). In the analyses of prenatal maternal fatigue and unwanted pregnancy the ADHD symptoms were divided into four categories: hyperactivity symptoms at the age of 8 and hyperactive-impulsive, inattentive and combined ADHD symptoms at the age of 16. The analyses of breastfeeding employed the Rutter B2 scale for hyperactivity symptoms at the age of 8 and the SWAN symptom category for 16-year-olds with inattentive and/or hyperactive-impulsive symptoms. In then further analyses, i.e. those of the associations between unwanted pregnancy, prenatal maternal fatigue and continuance of the ADHD symptoms, these symptoms were divided into three categories: positive ADHD symptoms (hyperactivity symptoms) only at the age of 8, positive ADHD symptoms only at the age of 16 (inattentive and/or hyperactive-impulsive symptoms) and positive ADHD symptoms at both time points.

Both the crude models those adjusted with reference to the gender of the offspring, the mother´s high school education, the mother´s age at the time of the pregnancy and maternal psychiatric disorders. In addition, the model was adjusted for the desirability of the pregnancy and maternal prenatal fatigue, and the adjusted supplementary tables also included the parents' marital status. The frequencies of the sociodemographic factors in the offspring grouped by ADHD symptoms were reported and comparisons made using Pearson's chi-square test ($\chi 2$).

4.3.3 Study III

The associations between the ADHD and TCI subscales, types of psychiatric comorbidity and TCI subscales in the ADHD cases and controls, ADHD presentations and TCI subscales were tested with Analyses of covariance (ANCOVAs). All the ANCOVA analyses were adjusted for gender and F-values with their p-values are reported. Tukey's post-hoc pairwise comparisons were also made between the types of psychiatric comorbidity and the TCI subscale and significant differences are reported. In addition, standardized mean differences (Cohen's d) were calculated for the comparisons between the ADHD and TCI subscales, the results of which were reported together with 95% CIs.

The frequencies of the sociodemographic factors and comorbidities in adolescence with or without ADHD are reported and comparisons are made using Pearson's chi-square test ($\chi 2$). Means with standard deviations (SD) on each TCI subscale were reported for the ADHD cases and controls, for each type of psychiatric comorbidity and for each mode of ADHD presentation.

4.4 Ethical considerations and personal involvement

The NFBC1986 cohort study was approved by the Ethical Committee of the Ostrobothnia Hospital District in Oulu. After receiving a complete account of the research, all the non-neonate participants gave their written informed consent to the epidemiological and clinical examinations. All the cohort members have the right to refuse to allow their data to be used at any time, and those who denied permission in this way were excluded from the population.

The author of this thesis joined the research group in 2019 in order to write a licentiate thesis in medicine and was accepted as a member of the University of Oulu Graduate School in late 2020. She participated in designing the use of the statistical methods in the three original studies included here and was responsible

for all the presentations of the methods and results and for writing the three original studies and this thesis. In addition, the author has been the first and corresponding author of all the original publications, wrote the first and final drafts of the manuscripts and coordinated the submissions, revisions and resubmissions of the original publications.

5 Results

5.1 Characteristics of the samples

The samples varied to some extent between the three studies. In the 8-year follow-up 630 subjects met the criteria for hyperactive symptoms, representing 7.4% of the offspring with Rutter B2 questionnaire information available, and 27% of these also showed ADHD symptoms at the age of 16. Overall, 579 cases (8.0%) were identified by the SWAN instrument in the 16-year follow-up, 150 with combined ADHD symptoms, 130 with inattentive ADHD and with 299 hyperactive-impulsive symptoms. Based on the SWAN scores, 261 cases had completed the clinical assessment and 105 had been diagnosed with ADHD.

The results of this study showed that males more often had hyperactive symptoms at the age of 8 (boys 13.3%, girls 3.0%, $p<0.001$), and they similarly, showed more ADHD symptoms in all of the symptom domains at the 16-year follow-up than did the females. The percentages of males and females among the diagnosed ADHD cases were 60.6% and 39.4%, respectively ($p=0.081$). Moreover, the ADHD cases showed more depressive, behavioural and substance abuse disorders than the controls, but there was no significant difference with respect to anxiety disorders.

The prevalence of NDDs was low in this population. as 27 cases in the control group (0.3%) met the criteria for intellectual disability in the 8-year-follow-up, 23 (0.3%) for ASD, 43 (0.6%) for language impairment and 8 (0.1%) for tic disorders. Taken together, these represented 1.2% of the offspring meeting the criteria for further analyses. The group showing hyperactive symptoms had more NDDs than did the control group (4.9%), and the results were similar in the 16-year-follow-up: 1.0% of the control group, 4.7% of the group with combined ADHD symptoms, 6.9% of those with inattentive symptoms and 3.7% of those with hyperactive-impulsive symptoms had NDDs.

Comparing the parental factors, the ADHD case and control groups did not differ in terms of their parents' marital status ($p=0.153$), but the parents of the control cases were better educated than those of the ADHD cases, as they more often had a high school or college education. Also, the children whose mothers had given birth under the age of 20 more often had hyperactive symptoms at the age of 8 and inattentive symptoms at the age of 16 ($p<0.001$). The mothers of the adolescents aged 16 with combined ADHD symptoms ($p=0.013$) or inattention

symptoms ($p<0.001$) presented with more psychiatric disorders than those in the control group. Paternal psychiatric disorders were not associated with any ADHD symptoms in either follow-up.

5.2 Prenatal maternal inflammation and offspring ADHD

In the 8-year follow-up of 5,998 participant mothers 3,612 (60.2%) were found to have had a CRP level under 3, 1,819 (30.3%) a level from 3 to 10 and 567 (9.5%) a level over 10 early in their pregnancy. Similarly, 2,920 of the 4,832 participant mothers in the 16-year follow up (60.4%) had had a CRP level under 3, 1,466 (30.3%) had had a level from 3 to 10 and 446 (9.2%) had had a level over 10 during the pregnancy.

The results show that there was no association between maternal exposure to elevated CRP in pregnancy and the occurrence of ADHD symptoms in the offspring. We further tested for independent associations between these findings by adjusting for the sex of the offspring and the mother's occupation, smoking during pregnancy and BMI before pregnancy. The associations between maternal CRP and offspring ADHD symptoms on the Rutter hyperactive scale at the age of 8 and the SWAN scales at the age of 16 are shown in Table 4.

Table 4. Logistic regression analyses examining the association between maternal CRP as a continuous variable and ADHD symptom domains. (Modified from study I © Springer Nature.)

CRP	Hyperactive symptoms at age 8	Inattentive ADHD symptoms at age 16	Hyperactive-impulsive ADHD symptoms at age 16	Combined ADHD symptoms at age 16
Crude OR (CI)	0.99 (0.97–1.01)	0.97 (0.95–1.00)	0.99 (0.97–1.01)	0.98 (0.96–1.01)
Adjusted OR[a] (CI)	0.99 (0.97–1.00)	0.97 (0.95–1.00)	0.99 (0.96–1.01)	0.98 (0.96–1.01)

[a]Adjusted for sex, mother's occupation, mother's smoking during pregnancy and mother's BMI before pregnancy. OR=Odds ratio, CI=Confidence interval

We further investigated whether there was any difference between maternal low-grade inflammation (CRP value from 3 to 10) and high-grade inflammation (CRP value over 10) in relation to ADHD in the offspring, but there was no evidence of any association. The results of the logistic regression are shown in Figure 5.

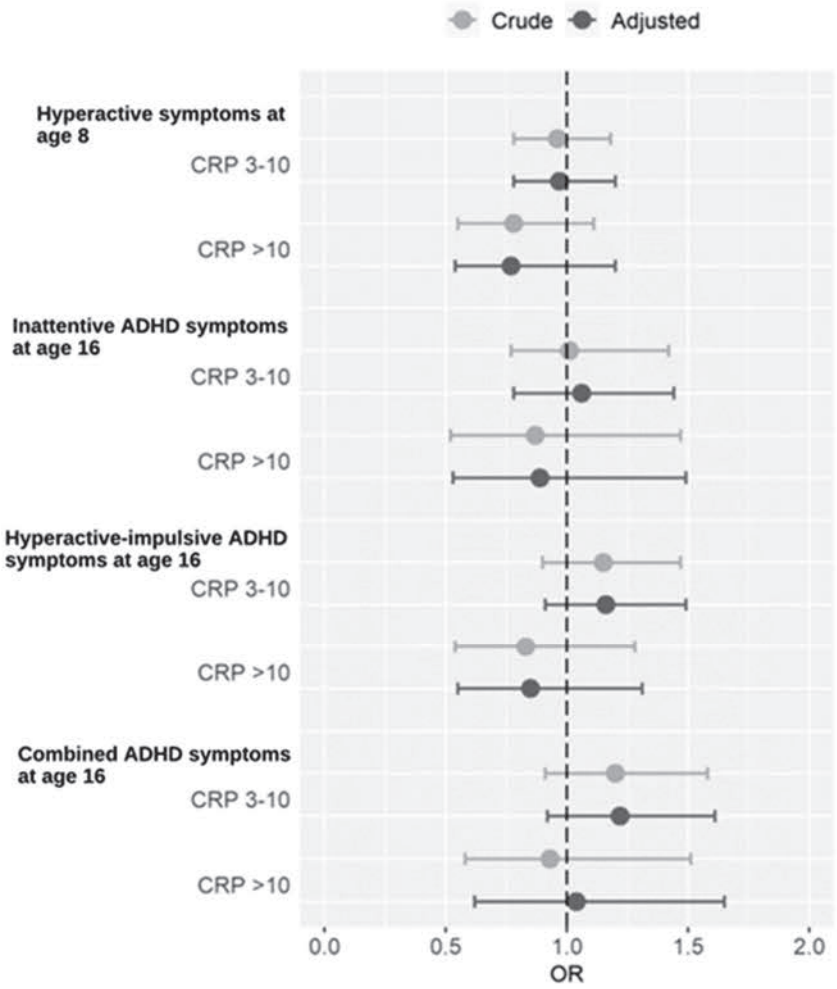

Fig. 5. Logistic regression analyses showing the association (odds ratios (OR) with 95% confidence intervals) between high and low maternal CRP and ADHD symptom domains. (From study I © Springer Nature.)

5.3 Prenatal maternal stress and offspring ADHD

The findings showed an association between prenatal fatigue and an increased risk of combined ADHD symptoms at the age of 16, although fatigue was not associated with any specific ADHD symptom. This association was evident from the crude model and remained significant after adjustment (OR 1.88, 95% CI 1.26–2.77). Similarly, a history of unwanted pregnancy was significantly more frequent among the children with hyperactivity than in the control subjects (OR 2.08, 95% CI 1.55–2.77). The groups defined by the desirability of the pregnancy did not differ in 16-year follow-up, however. These pregnancy-related factors are shown in Table 5.

Table 5. Logistic regression analyses examining the associations between unwanted pregnancy, prenatal maternal fatigue, and ADHD symptoms at the ages of 8 and 16 in the crude and adjusted models. (Modified from study II © Springer Nature.)

Risk factors	Hyperactive symptoms at age 8	Inattentive ADHD symptoms at age 16	Hyperactive-impulsive ADHD symptoms at age 16	Combined ADHD symptoms at age 16
Unwanted pregnancy				
Crude OR (95% CI)	2.17 (1.67–2.78)**	1.51 (0.76–2.72)	0.90 (0.52–1.44)	1.13 (0.57–2.02)
Adjusted OR (95% CI)	2.08 (1.55–2.77)**	1.43 (0.65–2.80)	0.74 (0.39–1.30)	1.01 (0.47–1.94)
Fatigue				
Crude OR (95% CI)	0.87 (0.69–1.08)	1.09 (0.67–1.71)	1.00 (0.72–1.35)	1.95 (1.34–2.80)**
Adjusted OR (95% CI)	0.78 (0.61–1.00)	1.34 (0.97–1.84)	1.02 (0.73–1.41)	1.88 (1.26–2.77)*

* p-value<0.05 **p -value<.001

Adjusted for the desirability of the pregnancy, maternal prenatal fatigue, gender of the offspring, mother´s education level, mother´s age at the time of labour, and maternal psychiatric disorders. OR = odds ratio, CI = confidence interval.

Furthermore, the observations regarding maternal age, fatigue and unwanted pregnancies were that mothers aged over 35 years were more often fatigued than those under 35 years and that those aged under 20 years had more unwanted pregnancies than did the older mothers (Table 6).

Table 6. Logistic regression analyses examining the association between maternal age during labour, fatigue, and unwanted pregnancy. (Modified from study II © Springer Nature.)

Risk Factors	yes/no	Maternal age during labour			χ2
		<20	20–35	>35	p–value
n		239	5783	751	
fatigue (%)	no	147 (79.9)	3764 (78.8)	431 (70.2)	<0.001
	yes	37 (20.1)	1011 (21.2)	183 (29.8)	
n		239	5783	751	
unwanted preg. (%)	no	142 (70.6)	4743 (93.5)	595 (93.3)	<0.001
	yes	59 (29.4)	330 (6.5)	43 (6.7)	

5.4 Breastfeeding and ADHD

Of the 3,255 mothers who exclusively breastfed their child, 578 (21.8%) did so for less than three months and 2,072 (78,2%) for over three months, the corresponding values for non-exclusive breastfeeding under and over six months being 970 (43.6%) and 1,257 (56.4%), respectively. Over three months of exclusive breastfeeding was associated with less frequent symptoms of pronounced hyperactivity in the 8-year follow-up, even after adjustment (OR 0.58, 95% CI 0.40–0.85), but there was no significant association in the case of non-exclusive breastfeeding (OR 0.76, 95% CI 0.54–1.06). In addition, less than six months of non-exclusive breastfeeding was associated with a small but statistically significant increase in ADHD symptoms in the 16-year follow-up (OR 0.65, 95% CI 0.44–0.95). The relevant crude and adjusted breastfeeding models are shown in Table 7.

Table 7. Logistic regression analyses examining the associations of exclusive and non-exclusive breastfeeding with ADHD symptoms at the ages of 8 and 16 years. (Modified from study II © Springer Nature.)

Breastfeeding	Hyperactive symptoms at age 8	Any ADHD symptoms at age 16
	OR (95% CI)	OR (95% CI)
Exclusive breastfeeding		
Crude models		
Breastfeeding ≥ 3 months	0.65 (0.46–0.92)*	1.00 (0.66–1.55)
Adjusted models		
Breastfeeding ≥ 3 months	0.58 (0.40–0.85)*	1.17 (0.73–1.94)
Non-exclusive breastfeeding		
Crude models		

Breastfeeding	Hyperactive symptoms at age 8	Any ADHD symptoms at age 16
	OR (95% CI)	OR (95% CI)
Breastfeeding ≥ 6 months	0.76 (0.54–1.06)	0.68 (0.48–0.95)*
Adjusted models		
Breastfeeding ≥ 6 months	0.79 (0.54–1.16)	0.65 (0.44–0.95)*

* p-value<0.05 **p -value<.001

Adjusted for gender of the offspring and mother´s high school (HS) education. OR = odds ratio, CI = confidence interval

Further analyses comparing the difference between the outcomes of ADHD symptoms in both follow-ups with sociodemographic factors, prenatal maternal fatigue, unwanted pregnancy and the duration of breastfeeding showed that prenatal maternal fatigue and female gender were risk factors for developing ADHD symptoms later in life and for showing such symptoms only at the age of 16 as compared with the individuals who showed ADHD symptoms in both follow-ups or only at the age of 8 (Table 8).

Table 8. Logistic regression analyses examining associations between positive ADHD symptoms in both 8- and 16-year-olds in relation to positive ADHD symptoms only at the age of 8 or 16. (Modified from study II © Springer Nature.)

Risk factors	Positive ADHD symptoms only at age 8	Positive ADHD symptoms only at age 16
	OR (95% CI)	OR (95% CI)
Crude models		
Unwanted pregnancy	1.21 (0.62–2.51)	0.58 (0.28–1.22)
Fatigue	1.24 (0.70–2.30)	1.68 (0.97–3.04)
Adjusted models		
Unwanted pregnancy	1.84 (0.79–4.80)	0.83 (0.35–2.14)
Fatigue	1.27 (0.67–2.49)	1.91 (1.04–3.70)*
Gender (female ref.)	0.96 (0.49–1.80)	0.36 (0.19–0.63)*
Only primary education	1.03 (0.59–1.84)	1.32 (0.76–2.35)
Married	2.14 (0.62–7.09)	1.78 (0.53–5.59)
Mother's age		
<20	1.36 (0.45–3.78)	1.84 (0.63–4.98)
>35	1.44 (0.41–4.99)	1.18 (0.34–4.06)

* p-value<0.05

Adjusted for the desirability of the pregnancy, maternal prenatal fatigue, gender of the offspring, mother´s education, mother´s age at the time of labour, parents' marital status, and maternal psychiatric disorders. OR = odds ratio, CI = confidence interval.

Furthermore, an association was found between non-exclusive breastfeeding and prenatal maternal fatigue. Pregnant women who experienced fatigue were more likely to breastfeed non-exclusively for a shorter duration than those who did not experience fatigue. When the combined effect of prenatal maternal fatigue, unwanted pregnancy and breastfeeding on ADHD symptoms was examined, non-exclusive breastfeeding was no longer associated with ADHD symptoms at the age of 16. These results are shown in Table 9.

Table 9. Logistic regression analyses examining the combined effect of prenatal maternal fatigue, unwanted pregnancy and breastfeeding duration on hyperactivity symptoms at the age of 8 and ADHD symptoms at the age of 16. (Modified from study II © Springer Nature.)

Risk factors	Any ADHD symptoms at age 16	Hyperactive symptoms at age 8
	OR (95% CI)	OR (95% CI)
Exclusive breastfeeding		
Crude models		
Breastfeeding ≥ 3 months	1.00 (0.66–1.55)	0.65 (0.46–0.92)*
Adjusted models		
Breastfeeding ≥ 3 months	1.32 (0.78–2.37)	0.62 (0.41–0.95)*
Gender (female ref.)	1.81 (1.19–2.78)*	3.56 (2.33–5.59)**
Unwanted pregnancy	1.00 (0.38–2.19)	1.83 (0.94–3.31)
Fatigue	1.35 (0.82–2.16)	0.97 (0.58–1.55)
Mother without a HS diploma	1.69 (1.05–2.66)*	0.76 (0.47–1.21)
Non-exclusive breastfeeding		
Crude models		
Breastfeeding ≥ 6 months	0.68 (0.48–0.95)*	0.76 (0.54–1.06)
Adjusted models		
Breastfeeding ≥ 6 months	0.65 (0.42–1.01)	0.78 (0.51–1.19)
Gender (female ref.)	1.77 (1.15–2.79)*	3.76 (2.35–6.25)**
Unwanted pregnancy	1.32 (0.53–2.83)	2.53 (1.33–4.54)*
Fatigue	1.22 (0.73–1.99)	0.60 (0.33–1.04)
Mother without a HS diploma	0.95 (0.55–1.58)	1.09 (0.66–1.75)

* p-value<0.05 **p -value<0.001

Adjusted for gender of the offspring, mother´s education level, and mother's age at the time of labour.

OR = odds ratio, CI = confidence interval, HS = high school.

5.5 Temperament, character, and ADHD

Two temperament traits, high novelty seeking (Cohen's d 0.58, 95% CI 0.34–0.83, p<0.001) and low persistence (Cohen's d -0.36, 95% CI -0.61–-0.12, p=0.003), were associated with ADHD in adolescence, while on the character dimension the ADHD cases were less self-directed (Cohen's d -0.47, 95% CI -0.71–-0.23), p<0.001) and cooperative (Cohen's d -0.66, 95% CI -0.91–-0.41, p<0.001) than the controls. These tendencies were found in both the crude and adjusted models, but no significant differences in harm avoidance, reward dependence or self-transcendence were found between the groups. All the associations are presented in Table 10.

Table 10. Mean associations of the Temperament and Character Inventory subscales and with a diagnosis of ADHD as seen in ANCOVA. (Modified from study III © Taylor & Francis Group.)

Temperament and character dimensions	ADHD in adolescence			
	Cases, n=85	Controls, n=292		
	Mean (sd)	Mean (sd)	Cohen's d (95% CI)	F (P-value) *
Novelty seeking (NS)	12.50 (3.85)	10.33 (3.69)	0.58 (0.34–0.83)	22.47 (<0.001)
Harm avoidance (HA)	8.27 (4.55)	8.25 (4.12)	0.00 (-0.24–0.25)	0.00 (0.969)
Reward dependence (RD)	8.68 (2.53)	9.16 (2.46)	-0.19 (-0.43–0.05)	2.64 (0.105)
Persistence (P)	1.53 (1.37)	2.07 (1.53)	-0.36 (-0.61–-0.12)	9.10 (0.003)
Self-directedness (SD)	14.37 (4.74)	16.58 (4.70)	-0.47 (-0.71–-0.23)	14.6 (<0.001)
Cooperativeness (CO)	15.74 (3.82)	17.85 (3.00)	-0.66 (-0.91–-0.41)	29.09 (<0.001)
Self-transcendence (ST)	4.92 (2.74)	5.42 (2.85)	-0.18 (-0.42–0.06)	2.08 (0.151)

*Adjusted for gender. sd = standard deviation.

Examination of the associations between ADHD presentation and the temperament and character profiles revealed that the ADHD cases of the hyperactive-impulsive type was more persistent than those of the inattentive type (p<0.001) (see Table 11). The remaining temperament and character profiles did not show any significant differences between the ADHD cases and controls.

Table 11. Mean associations of the Temperament and Character Inventory subscales with the modes of ADHD presentations as seen in ANCOVA. (Modified from study III © Taylor & Francis Group.)

Temperament and character dimensions	ADHD presentation			
	Combined, n=21	Inattentive, n=57	Hyperactive, n=7	
	Mean (sd)	Mean (sd)	Mean (sd)	F (P-value)*
Novelty seeking (NS)	12.13 (3.78)	12.60 (3.85)	12.80 (4.54)	0.14 (0.873)
Harm Avoidance (HA)	7.91 (4.60)	8.82 (4.53)	4.86 (3.23)	2.68 (0.075)
Reward dependence (RD)	8.56 (2.05)	8.83 (2.69)	7.86 (2.61)	0.58 (0.565)
Persistence (P)	2.10 (1.51)	1.18 (1.17)	2.71 (1.38)	8.00 (<0.001)
Self-directedness (SD)	14.70 (4.57)	13.88 (4.77)	17.30 (4.41)	1.74 (0.182)
Cooperativeness (C)	15.07 (4.21)	15.92 (3.87)	16.33 (1.82)	0.48 (0.621)
Self-Transcendence (ST)	5.29 (2.85)	4.56 (2.62)	6.71 (2.87)	2.24 (0.113)

*Adjusted for gender, TCI = Temperament and Character Inventory

5.6 Psychiatric comorbidities, temperament and character

Associations of the temperament profiles with internalizing and externalizing psychiatric disorders were found in both the ADHD cases and the controls. The groupings of ADHD cases in terms of psychiatric comorbidity (none, externalizing disorder, internalizing disorder, both) differed in their self-directedness scores (p=0.035), indicating that the ADHD cases with internalizing comorbidity were less self-directed than the other groups. There were no statistically significant differences in the relations of the other temperament and character profiles to psychiatric comorbidity in the ADHD cases, the controls with both externalizing and internalizing disorders were found to be more novelty-seeking and harm-avoiding and less self-directed than the other groups. The results are shown in Table 12.

Table 12. Mean associations of the Temperament and Character Inventory subscales with comorbidities in the ADHD cases and controls as seen in ANCOVA. (Modified from study III © Taylor & Francis Group.)

Temperament and character dimensions	Type of Comorbidity				
	Both n=15	Externalizing n=16	Internalizing n=9	None n=45	
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	F (p-value)*
ADHD cases					
Novelty seeking (NS)	13.60 (3.38)	12.22 (3.76)	10.37 (4.50)	12.66 (3.84)	1.36 (0.261)
Harm avoidance (HA)	7.53 (4.00)	8.56 (3.82)	11.89 (6.15)[a]	7.69 (4.39)	2.59 (0.059)
Reward dependence (RD)	8.56 (2.88)	8.07 (2.51)	9.76 (2.36)	8.73 (2.46)	0.82 (0.486)
Persistence (P)	1.13 (1.41)	1.81 (1.47)	1.11 (1.27)	1.64 (1.33)	0.70 (0.557)
Self-directedness (SD)	12.49 (4.99)	15.97 (4.09)	11.16 (6.51)	15.06 (4.09)	3.01 (0.035)
Cooperativeness (C)	14.59 (4.60)	14.72 (3.57)	18.03 (3.64)	16.03 (3.53)	2.14 (0.102)
Self-transcendence (ST)	5.04 (2.16)	5.00 (3.08)	5.40 (3.27)	4.75 (2.75)	0.14 (0.932)
ADHD controls	n=5	n=27	n=40	n=220	
Novelty seeking (NS)	13.60 (3.58)	11.85 (4.42)	9.80 (3.05)	10.16 (3.65)	3.36 (0.019)
Harm avoidance (HA)	12.00 (3.16)	7.26 (4.47)	10.69 (4.06)[b]	7.84 (3.92)	6,66 (<0.001)
Reward dependence (RD)	8.40 (4.04)	8.89 (2.42)	9.14 (2.23)	9.21 (2.47)	0.56 (0.639)
Persistence (P)	1.20 (1.30)	1.81 (1.80)	2.00 (1.54)	2.14 (1.49)	0.79 (0.501)
Self-directedness (SD)	9.80 (5.54)[c,d]	16.37 (5.22)	14.32 (4.85)[e]	17.17 (4.36)	8.13 (<0.001)
Cooperativeness (CO)	16.40 (3.36)	17.27 (3.29)	17.64 (2.97)	18.00 (2.96)	1.12 (0.343)
Self-transcendence (ST)	4.63 (2.67)	5.19 (2.64)	5.20 (2.78)	5.51 (2.90)	0.32 (0.808)

* Adjusted for gender

Significant post hoc Tukey when comparing the comorbidities:

[a] Comparison between None and Internalizing in the ADHD cases $p<0.05$

[b] Comparison between Internalizing and Externalizing in the controls $p<0.01$

[c] Comparison between Externalizing and Both in the controls $p<0.05$

[d] Comparison between None and Both in the controls $p<0.01$

[e] Comparison between None and Internalizing in the controls $p<0.01$

The results also showed that the ADHD cases with no comorbidities were more novelty seeking ($p<0.001$) and less persistent ($p=0.02$), self-directed ($p=0.003$) and cooperative ($p<0.001$) than the controls with no comorbidities (see Table 13). When comparing the ADHD cases and controls in the presence of comorbidities, the ADHD cases with an externalizing comorbidity showed less cooperativeness than the corresponding control group ($p=0.016$). Otherwise, the results did not show any statistically significant differences in the other temperament and character profiles.

Table 13. Comparisons by ANCOVA of Temperament and Character Inventory subscales between ADHD cases and controls in different comorbidity groups. (Modified from study III © Taylor & Francis Group.)

Temperament and character dimensions	Both	Externalizing	Internalizing	None
	F (p-value)*	F (p-value)*	F (p-value)*	F (p-value)*
Novelty seeking (NS)	0.00 (0.957)	0.07 (0.789)	0.50 (0.485)	18.09 (<0.001)
Harm Avoidance (HA)	4.17 (0.057)	1.79 (0.188)	0.59 (0.446)	0.01 (0.944)
Reward dependence (RD)	0.16 (0.693)	0.81 (0.373)	1.25 (0.270)	0.75 (0.389)
Persistence (P)	0.05 (0.823)	0.23 (0.635)	2.94 (0.093)	5.45 (0.020)
Self-directedness (SD)	0.94 (0.345)	0.42 (0.520)	2.37 (0.131)	8.99 (0.003)
Cooperativeness (C)	0.28 (0.605)	6.36 (0.016)	0.24 (0.629)	14.23 (<0.001)
Self-Transcendence (ST)	0.19 (0.670)	0.08 (0.778)	0.03 (0.861)	2.76 (0.098)

* Adjusted for gender

6 Discussion

6.1 Main findings

The main findings regarding the relations between pregnancy and childhood-related factors and ADHD symptoms at the ages of 8 and 16 years, as summarized in Figures 6–8, point to associations between unwanted pregnancy and exclusive breastfeeding for less than 3 months with hyperactive symptoms at the age of 8. On the other hand, no connection was found between prenatal maternal inflammation, fatigue during pregnancy or non-exclusive breastfeeding for under 6 months and hyperactive symptoms in the 8-year-olds.

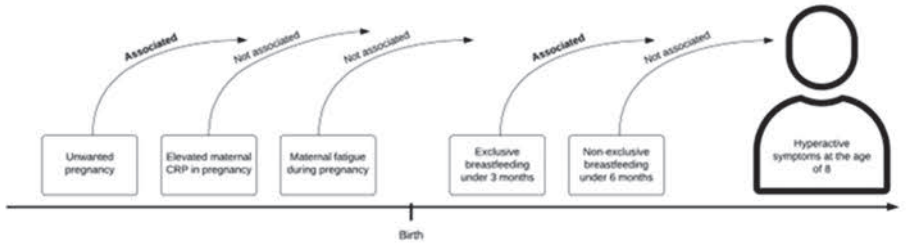

Fig. 6. Associations between hyperactive symptoms and prenatal and postnatal factors at the age of 8.

Using logistic regression, the data showed associations between ADHD symptoms at the age of 16 and prenatal maternal fatigue and non-exclusive breastfeeding for under 6 months, but no such associations for unwanted pregnancy, high prenatal CRP or exclusive breastfeeding for under 3 months. Furthermore, a distinct personality profile for the child was associated with a diagnosis of ADHD in adolescence. The adolescents with ADHD were more often more novelty seeking and less self-directed, cooperative and persistent than the controls, but no differences existed with regard to harm avoidance, self-transcendence or reward dependence. These results are summarized in Figures 7 and 8.

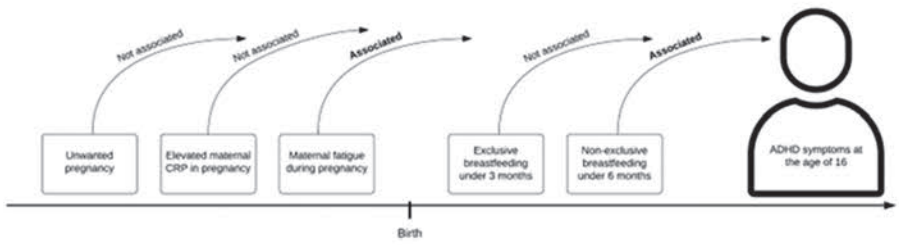

Fig. 7. Associations between ADHD symptoms in adolescence and prenatal and postnatal factors.

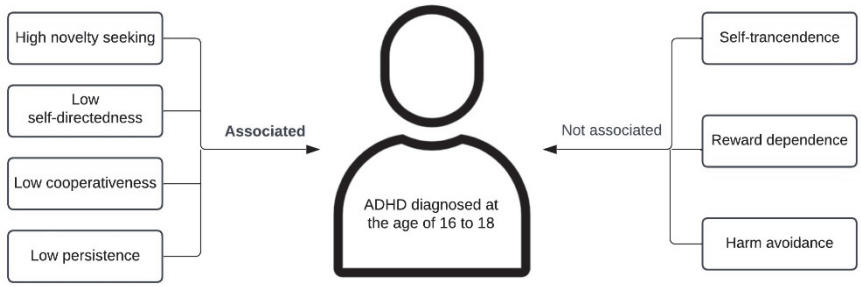

Fig. 8. Associations between ADHD diagnosed in adolescence and the personality dimensions.

6.2 Comparison with previous studies

6.2.1 Prenatal maternal inflammation

No connection was found here between early pregnancy prenatal maternal inflammation and symptoms of ADHD in the offspring at the ages of 8 and 16, not even when the CRP values were grouped into low-grade inflammation (CRP from 3 to 10) and high-grade inflammation (CRP over 10).

These results are in line with those of a large Finnish register study using CRP as a biomarker for inflammation, which did not report any association with the risk of an ADHD diagnosis or with the load of ADHD symptoms (Chudal et al., 2020). That study used a case-control design and serum CRP collection took place at a

median gestational age of 10 weeks, so that the data should be relatively comparable to the sample collection in the present study, which was performed in gestational week 13. On the other hand, our results contrast with those presented in a Danish cohort study performed in 2023, where the CRP was obtained late in the second trimester (Rosenberg et al., 2023). The timing of inflammation could be of importance for the offspring's neurodevelopment, and thus can affect the results. CRP is a valid marker of inflammation and is widely used in clinical settings, but it is known to be an acute-phase reactant primarily synthesized in the liver in response to both infectious and non-infectious inflammation (Gabay, 1999).

Animal studies support a potential causal relationship between prenatal exposure to inflammation and behavioural changes in the offspring that are consistent with ADHD (Dunn et al., 2019), but there have as yet been no other studies in humans that have explored the association of prenatal maternal inflammation with offspring ADHD using CRP as a blood marker for inflammation. To the author's knowledge, only one study with clinical evaluations has investigated maternal inflammation during pregnancy in relation to childhood ADHD, and this reported that higher levels of cytokines (IL-6, TNF-a and MCP-1) were associated with the severity of ADHD symptoms in children at 4–6 years of age (Gustafsson et al., 2020).

Some of the risk factors indirectly suggest a role of prenatal maternal inflammation in the risk of developing ADHD. These include increased maternal body mass index and maternal infections (Han et al., 2021; Sanchez et al., 2018). In addition, previous studies have suggested that the possible association between prenatal maternal inflammation and ADHD offspring may be explained by prenatal maternal tobacco smoking and genitourinary infections, as a large number of studies support associations between these and offspring ADHD (Mann et al., 2010; Pineda, 2007).

6.2.2 Prenatal maternal stress

Our findings showed an association between prenatal fatigue and an increased risk of combined ADHD symptoms at the age of 16, although fatigue was not associated with any other ADHD symptom in 8 or 16-year-olds. These results indicate that prenatal maternal stress is related to more severe forms of ADHD symptoms and may contribute to the development of symptoms that fulfil the diagnostic criteria for this disorder.

Earlier research into the association between prenatal maternal stress and ADHD-like behaviour or ADHD symptoms has not always been in agreement on this matter. Two earlier longitudinal studies support such an association (Huhtala et al., 2015; Ronald et al., 2011), while one large cohort study performed in 2018 refutes these results and suggests that the association between prenatal maternal stress and offspring ADHD may be largely explained by familiar factors (Rosenqvist et al., 2018). A meta-analysis published in 2019 (Manzari et al., 2019) showed that earlier cohort studies have found an association between maternal stress and diagnosed ADHD, but it should be noted that this present work is the first cohort study to find an association of ADHD with self-perceived maternal fatigue during pregnancy, while in previous instances the association has only been significant in male offspring or following maternal stress attributable to bereavement in the form of the unexpected death of a family member (Manzari et al., 2019).

Another risk factor for prenatal maternal mental health, an unwanted pregnancy, has not been widely studied, so that to the author's knowledge this is the first cohort study to include information on unwanted pregnancies. A negative attitude towards the pregnancy, such as the admission that it was unwanted, is a pregnancy-specific stressor that has been connected with poorer neurodevelopment in the offspring (De La Rochebrochard & Joshi, 2013) and psychiatric disorders later in life, including schizophrenia-spectrum and affective disorders (McNeil et al., 2009). There is one case-control study that has associated unwanted pregnancy with childhood ADHD (Golmirzaei et al., 2013).

6.2.3 Breastfeeding

According to the meta-analysis of Tseng et al. (2018), the duration of breastfeeding – an important factor influencing emotional and neurological development – is associated with ADHD and results clearly demonstrate that the rate of ADHD is inversely proportional to the duration of both exclusive and non-exclusive breastfeeding. The present findings were not as definite as this, as an association existed only for a lower duration of exclusive breastfeeding with higher hyperactivity symptoms in 8-year-olds and for a lower duration of non-exclusive breastfeeding with ADHD symptoms in 16-year-olds. Although these findings are not in line with the meta-analysis, they correspond to two earlier observations that the distinction between exclusive and non-exclusive breastfeeding accounts for differences in the results (Say et al., 2016; Stadler et al., 2016).

Even so, most of the earlier literature suggests a clear relationship between ADHD and a lower rate of breastfeeding. If breastfeeding is associated causally with ADHD, its effect is likely to be part of an interplay between genotype and the environment. Several studies of ADHD have suggested that genetic and environmental risk factors may act together, giving rise to the theory that some genes may influence the development of ADHD by affecting the individual's sensitivity to environmental adversity, and that the long-term clinical course of ADHD is influenced by prenatal, biological and psychosocial environmental risk factors (Thapar et al., 2007; Waldman et al., 2007). In the light of these findings, our results indicate that the causal relationship between a short duration of breastfeeding and ADHD is unclear and can be explained by factors that are related to both the child and the mother. In our cohort study, the mothers in the ADHD symptom groups more often had a lower level of education or a diagnosis of a psychiatric disorder, both of which are well-known risk factors connected with ADHD in an offspring (Spencer et al., 2022) and attributable to a short duration of breastfeeding (Demirtas et al., 2012).

6.2.4 Temperament and character

Our data revealed differences in both temperament and character between the adolescent ADHD cases and the healthy controls, in that high novelty seeking, for example, was associated with a diagnosis of ADHD. Novelty seeking is connected with rule violation, impulsivity and unsafe forms of behaviour. Individuals with high novelty seeking tend to be unorganized, impatient and easily agitated (Cloninger et al., 1997). According to previous studies, novelty seeking is associated with ADHD (Anckarsäter et al., 2006; Cho et al., 2008; Faraone et al., 2009; He et al., 2019; Kim et al., 2016; Melegari et al., 2015; Merwood et al., 2013; Perroud et al., 2016; Pinzone et al., 2019) and is the present findings are in line with this. In particular, hyperactivity presentation is known to be specifically associated with novelty seeking (Rettew et al., 2004; Salgado et al., 2009), although not all studies support such a difference between the ADHD presentations (Merwood et al., 2013). We did not, however, find any differences in novelty seeking between the hyperactive-impulsive and inattentive types of ADHD.

The low persistence level shown by the individuals diagnosed with ADHD was to be expected on the basis of findings in previous studies (Faraone et al., 2009; He et al., 2019, Melegari et al., 2015; Perroud et al., 2016; Pinzone et al., 2019), and when comparing the ADHD presentations, we were inclined to associate lower

persistence scores with inattentive rather than hyperactive ADHD, consistent with the observation of Merwood et al. (2013). This emphasizes the fact that adolescents with attention problems tend to give up easily on the tasks that are given to them.

The observation that the self-directedness and cooperativeness levels of the ADHD group were significantly lower than those of the control group concur with those of Melegari et al. (2015) and Pinzone et al. (2019). Individuals with high self-directedness are goal-oriented and constructive, while cooperativeness is a tendency to be sympathetic to and cooperative with other people (Cloninger et al., 1997).

On the other hand, we did not find any association between ADHD and high harm avoidance or self-transcendence. Harm avoidance is a tendency to inhibit or discourage dangerous acts (Cloninger, 1993). There have been a few previous reports of high harm avoidance and/or self-transcendence in connection with ADHD in early childhood or in adulthood (Anckarsäter et al., 2006; He et al., 2019; Kim et al., 2016; Melegari et al., 2015; Perroud et al., 2016), and the setting for the present study differed in this respect, a fact that may have played a vital role regarding comparison of the results. Children may be more hyperactive in early childhood but their character tends modify with age, making evaluation of the outcomes difficult in different age settings. Furthermore, earlier authors have speculated that higher harm avoidance seems to be due to higher rates of comorbid anxiety, affective disorders, or substance use disorders (Marquez-Arrico et al., 2016). It was also possible to take comorbidity concerns into account in the present work.

6.2.5 Psychiatric comorbidity, temperament, and character

Research has increasingly become focused on the significance of internalizing symptoms and externalizing behaviour in ADHD, and it has been speculated that the presence of such problems may be an indicator of potentially different aetiological risk factors as well as different outcomes (Gillberg et al., 2004). It was found above that the ADHD cases had depressive, behavioural and substance abuse disorders and either externalizing disorders or both internalizing and externalizing disorders, more often than did the controls, and previous studies are in line with these findings, as internalization problems and externalizing behaviour, in particular substance use and behavioural disorders, have proved to be frequent in adolescent ADHD patients (Katzman et al., 2017).

One recent study concerning the association between personality profiles and internalizing and externalizing symptoms in adolescents with ADHD concluded that the combination of ADHD and specific personality traits explained a significant proportion of the variance between coexisting internalizing and externalizing disorders (Deotto et al., 2022), observing that young people who ranked high on internalizing symptoms were significantly higher in harm avoidance and lower in self-directedness, while those who were high on externalizing behaviour were significantly lower in cooperativeness. The present findings point to similar results as well, as the comorbidity types differed in their novelty seeking and harm avoidance scores in controls and in their self-directedness scores in a similar manner in both the ADHD cases and the controls. Personality traits and characteristics, especially low self-directedness, have been linked to functional impairments even after controlling for ADHD symptoms, executive function deficits and current psychiatric comorbidities (He et al., 2019). It may be said that personality traits give rise to unique associations with the quality of life and functional impairment in adolescents with and without ADHD across the whole span of major life domains.

Furthermore, the results presented here have shown that, when comparing personality traits and psychiatric comorbidities in the ADHD cases, those with no comorbidities were more novelty seeking and less persistent, self-directed and cooperative than those with any comorbidity. These findings indicate that comorbidities do not show any particular association with temperament and character profiles in ADHD cases, but rather that distinct personality traits separate the ADHD cases from the healthy controls and from persons with the other psychiatric disorders considered here. This could have implications for modifying intervention efforts based on these profiles in adolescents with ADHD, and, since temperament is fairly consistent throughout life, these results can be applied to earlier diagnoses of ADHD.

6.3 Methodological discussion

6.3.1 Strengths of the study

This work has a number of evident strengths. NFBC1986 is one of the largest birth cohorts with high genetic and ethnic homogeneity, allowing diagnostic variables to be elucidated by valid methods. It includes all the births in the area, contrary to

register-based studies, which take into account only those who seek treatment for impairing symptoms of ADHD. In addition, being a large general population-based birth cohort with excellent participation rates, the results are widely generalizable to white-Caucasian populations and largely free of recall and selection biases.

Also, it was possible to use the symptom domains of ADHD as well as the numbers of diagnosed ADHD cases when assessing the associations between the early risk factors and ADHD, which enabled us to determine whether the inattentive and hyperactive-impulsive types of ADHD accounted for different outcomes. This is a major strength, since only a few previous studies have been able to consider the ADHD symptom domains.

The choice of the NFBC1986 cohort enabled the use of reliable child health clinic data for extracting information on breastfeeding and the inclusion of information on unwanted pregnancies in Study II. This is to the author's knowledge the first cohort study to include information on unwanted pregnancies.

Another strength lay in the inclusion of covariates. Altogether it became possible to include information on maternal age, BMI before pregnancy, smoking during pregnancy, maternal education, mother's occupation, parental marital status, parental and the offspring's psychiatric disorders and the gender of the offspring. These are all important factors that can increase the risk of the offspring developing ADHD.

6.3.2 Limitations

The limitations of this study were the following. Firstly, as the sample was homogeneous, it may not be generalizable to other populations of a different kind. Secondly, information on parental ADHD symptoms was lacking, whereas ADHD is known to be a highly heritable disorder. Thirdly, only hyperactivity symptoms could be measured at the age of eight, and these may have be mingled with other symptoms besides those of ADHD, although it was admittedly found that the ADHD hyperactivity symptoms identified at the age of 8 correlated with all the ADHD symptom domains observed at the age of 16. Fourthly, participants with NDDs were not excluded, although it must be said that there were only a few participants with diagnosed NDD and excluding them would not have affected the results.

In addition, there were some limitations that applied separately to each of the studies. The first study lacked information on maternal infection and CRP in the last trimester and on the birthweight of the child, and in the second we were unable

to include those infants who had not been breastfed at all. In addition, fatigue is not the best estimate for stress, and it should be noted that it is distinct from stress even though strongly associated with it (Kop & Kupper, 2016). Unwanted pregnancy is also highly loaded for impulsivity and hence the genetic risk for the mother with respect to the outcome. Furthermore, the experience of fatigue for pregnant women in the 1980's may have been different from what is experienced in contemporary society and the reports of fatigue from that time may have been underestimated. Lastly, more than 10% of the data on variables related to unwanted pregnancy, fatigue and maternal education were missing, possibly as a result of some questionnaires being lost. This loss is probably coincidental and its effect on the results is small. In the case of Study III, many of the tests performed on the clinical features of ADHD involved the use of relatively small samples, which would have greatly reduced the possibility of detecting small influences.

7 Conclusions

7.1 Main conclusions

The research reported here represents one of the first, and to date the most representative, of the investigations carried out into the early risk factors for ADHD. Its conclusions indicate that prenatal maternal fatigue and unwanted pregnancy can increase the risk of ADHD symptoms in the offspring and suggest that prenatal maternal fatigue is related to more severe forms of ADHD symptoms and may contribute to the development of symptoms that fulfil the diagnostic criteria for ADHD. One negative conclusion to arise is that prenatal maternal inflammation via an increase in CRP is not a risk factor for ADHD symptoms in the offspring.

As for postnatal risk factors, it can be assumed that the duration of breastfeeding is associated with ADHD symptoms but that its effect is not direct but rather part of an interplay with genotype and the environment. Also, the research revealed differences in both temperament and character between the adolescent ADHD cases and the healthy controls. Low persistence, cooperativeness and self-directedness scores and high novelty seeking scores were associated with a diagnosis of ADHD in adolescence. The findings further indicated that comorbidities do not particularly show an association with the temperament and character profiles of ADHD cases, but rather that distinct personality traits separate the ADHD cases from the healthy controls and from the other psychiatric disorders considered in this context.

Considering the overall situation, the task of protecting fetal, infant and early childhood growth provides a window of opportunity for preventing ADHD in the offspring, and the factors mentioned above may play a role in the diagnosis of ADHD in the future.

7.2 Early risk factors for ADHD and the implications of the results

ADHD is associated with functional and psychosocial disability, leading to personal and societal costs. Its most prominent feature is attentional dysfunction, which is associated especially with impairment where sustained and focused attention is required (Bálint et al., 2009). Individuals with ADHD also experience neuropsychological difficulties associated with deficient inhibition, memory and decision making as well as with emotional dysregulation (Katzman et al., 2017).

ADHD is associated with educational difficulties and higher rates of academic suspension and dropouts (Jangmo et al., 2019). Later in life, adult ADHD has been associated with poorer driving and a higher incidence of traffic citations and motor vehicle accidents (Curry et al., 2017). This said, individuals with ADHD have been shown in Denmark to have a lower life expectancy and more than double the risk of untimely death than adults without ADHD (Dalsgaard et al., 2015). This was mostly attributed to accidental deaths and characteristics associated with ADHD, such as risk-taking behaviour.

The overlapping symptomology between ADHD and other neurodevelopmental, mood, anxiety, or substance use disorders poses certain barriers to diagnosis and treatment. Physicians are often more familiar with mood and anxiety disorders, which may contribute to misdiagnosis and delays in treating ADHD (Furzer et al., 2022). It has in fact been suggested that stress, depression and anxiety could manifest themselves because of undiagnosed and untreated ADHD (Alexander et al., 2013). In any case, the result is that many individuals with ADHD do not receive treatment for ADHD, but for comorbid mood disorders. Overall, these challenges have contributed to an under-diagnosis and under-treatment of ADHD in Europe (Sayal et al., 2018). Identifying risk factors for ADHD might be the most viable avenue for reducing the burden that it places on society.

The numbers of diagnoses of ADHD and the amounts of medication provided for it have increased significantly in Finland over recent years (THL, 2024), in addition to which there are clear regional differences in the prevalence of ADHD. This raises the question of how reliable its diagnosis currently is.

The most important clinical implications of the research reported here are primarily preventative. Identifying the risk factors for ADHD should allow for early detection of individuals with this condition, which may in turn enable us to apply targeted and timely interventions. In addition, these risk factors can guide the diagnosis of ADHD, which is still under-, over-, or misdiagnosed in different parts of the world (Thomas et al., 2015). The findings presented in this thesis suggest that interventions to protect prenatal maternal mental health and encourage mothers to accept to notion of breastfeeding may reduce individual ADHD risks in the offspring. Special attention should also be paid to children born from unwanted pregnancies. The second important implication is to guide future research and help narrow the wide field of study focused on risk factors in the early years of life.

Although ADHD is substantially a genetic disorder, the present results may help us understand more about the reasons for the risk factors underlying it. It is to

be hoped that these findings will be beneficial when developing the diagnostics of ADHD and/or primary preventative measures.

7.3 Future research

This work has revealed that several developmental factors present in childhood may be markers for an increased risk of developing ADHD symptoms and of the diagnosis of this disorder during childhood or adolescence. For this reason it is crucial that there should be increased interest in research into prenatal and postnatal risk factors for ADHD in the future.

The present findings prompt further questions regarding the risk factors for ADHD. What parts do genetics, epigenetics and environmental aspects play in the accumulated risk for the individual? Does a causal pathway exist between the duration of breastfeeding and ADHD? What are the neurodevelopmental mechanisms behind the risk factors identified for ADHD? The results presented in this thesis highlight the need for future research to elucidate the pathways behind these observations. A better understanding of the relationship between pre- and postnatal development and ADHD may provide tools for targeting primary preventative measures for individuals who are particularly at risk. Also, some of the already known risk factors, including environmental lead and male gender, have not yet been meta-analysed and would undoubtedly yield additional information in the future.

Finally, one future research target would be to find better means of diagnosing ADHD. The present results arouse speculations regarding the use of the temperament and character dimensions of ADHD for this purpose, since these are strongly associated with ADHD.

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I Jallow, J., Halt, A.H., Öhman, H., & Hurtig, T. (2020). Prenatal inflammation does not increase the risk for symptoms of attention deficit hyperactivity disorder (ADHD) in offspring. *European Child & Adolescent Psychiatry*, 30(11), 1825–1828. doi:10.1007/s00787-020-01580-x.

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Original publications are not included in the electronic version of the dissertation.

1772. Aitavaara-Anttila, Mia (2024) Clinical pathway of the critically ill patient in Oulu University Hospital district

1773. Lipponen, Joonas (2024) MitAtax : hereditary ataxias in Northern Finland

1774. Pramila-Savukoski, Sari (2024) Hybridikoulutusintervention kehittäminen terveystieteiden geneerisen osaamisen varmistamiseksi

1775. Heikkinen, Anna-Leena (2024) Evaluation of cognitive complaints and neuropsychological performance in early-onset cognitive impairment and dementia

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1778. Nätynki, Antti (2024) Autoimmunization against collagen XVII in patients with high risk for bullous pemphigoid and the effect of vildagliptin on the mouse skin proteome

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1781. Tissarinen, Pinja (2024) Human placental and serum proteins in spontaneous preterm birth

1782. Mattila, Suvi (2024) Multiplex polymerase chain reaction diagnostic testing for respiratory pathogens in acutely ill children

1783. Silvén, Heidi (2024) Incidence and etiologic factors of premature ovarian insufficiency : register-based nationwide study

1784. Karjula, Topias (2024) Treatment and histopathological prognostic factors of colorectal cancer pulmonary metastases

1785. Kamau, Suleiman (2024) Organisational integration of culturally and linguistically diverse nurses : a hypothetical model

1786. Jarva, Erika (2024) Digital health competence of healthcare professionals in healthcare settings

1787. Tuovinen, Timo (2024) Investigating BOLD signal variability and its physiological signal sources in Alzheimer's disease, behavioral variant frontotemporal dementia, and schizophrenia

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ISBN 978-952-62-4102-9 (Paperback)
ISBN 978-952-62-4103-6 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)