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DEVELOPMENTAL ORIGINS OF MENTAL HEALTH

HUMAN OBSERVATIONAL STUDIES OF PRETERM BIRTH, ANTENATAL SYNTHETIC GLUCOCORTICOID EXPOSURE, AND MATERNAL DEPRESSIVE SYMPTOMS DURING PREGNANCY

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ACADEMIC DISSERTATION

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To my husband Jason,
and my darling nephew Ohto and niece Kerttu.

ABSTRACT

Mental disorders are a considerable factor in the global burden of disease, with population growth and aging increasing the prevalence of the disorders. While interventions and treatment to ameliorate the burden of mental disorders is important, another critical goal is to find possible risk factors for optimal mental health. According to the Developmental Origins of Health and Disease hypothesis, environmental factors during pregnancy and fetal life may have adverse programming effects on offspring mental health. However, observational human studies on the long term effects of an adverse fetal life are still needed.

The aim of this work was to study the developmental origins of mental health focusing on three important risk factors: preterm birth (birth before 37 weeks of gestation), exposure to antenatal synthetic glucocorticoids (sGC), and maternal depressive symptoms during pregnancy. Specifically, to study the long term effects of preterm birth at very low birth weight (VLBW; birth weight <1,500g) (1) on self-reported mental health problems in young adulthood, and (2) on the association between and cumulative effect of autism spectrum disorder (ASD)-related traits and visual processing skills in young adulthood. Additionally, the goal was to study (3) the association between antenatal synthetic glucocorticoid exposure and early childhood mental health and psychological development, and (4) the association between maternal depressive symptoms during pregnancy and early childhood attention-deficit/hyperactivity disorder (ADHD) symptoms.

The participants for the studies on young adulthood outcomes after preterm birth came from the Adults Born Preterm International Collaboration (APIC) combining six cohorts from five different countries. The participants for the studies on childhood outcomes after antenatal synthetic glucocorticoid and maternal depressive symptom exposure came from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) Study.

The APIC study groups consisted of 747 young adults born preterm at VLBW and 1,512 controls born at term (birth ≥ 37 weeks of gestation) at ages 19 to 29 years, born between 1977-1988 with data on self-reported mental health problems (Study I). The original HeSVA cohort (included in APIC) consisted of 335 discharged infants born preterm at VLBW between 1978-1985 and matched term-born controls. Altogether 101 young adults born preterm at VLBW and 104 controls had data on visual processing skills and self-reported autism spectrum disorder (ASD)-related traits (Study II).

The PREDO study comprises altogether 4,777 mothers who gave birth to a singleton live-born offspring in Finland between 2006-2010. Maternal depressive symptoms were reported throughout pregnancy and information on synthetic glucocorticoid treatment was extracted from medical records

and/or the Finnish Medical Birth Register. In 2011-2012, 4,586 women from the original sample were invited to participate in a follow-up with their children. The follow-up included questionnaires for the mothers on their depressive symptoms as well as their children's age-appropriate developmental milestones and psychiatric problems (n=2,640; Study III), and child behavioural symptoms of ADHD (n=1,779; Study IV). Diagnoses of child mental and behavioral disorders were identified from the Finnish Hospital Discharge Register from the child's birth to December 31st, 2016 (n=4,708 ; Study III).

We found that young adults born preterm at VLBW continue to report long term mental health problems revealing a characteristic preterm behavioral phenotype that includes a heightened risk for internalizing problems and avoidant personality problems in combination with a lowered risk for externalizing problems (Study I). Young adults born preterm at VLBW were also shown to have a risk of cumulative social and cognitive problems as higher levels of ASD-related traits were associated with slower performance in visual processing tasks requiring global visual processing skills (Study II).

In Study III, antenatal exposure to sGC was shown to be associated with problems in early childhood mental health and psychological development regardless of whether the child was born preterm or at term. Children who were exposed to sGCs had nearly three times higher odds of having any mental and behavioral disorder, higher scores on mother-reported total, internalizing, and externalizing problems, and higher odds of failing to meet the development that is typical for the child's age in personal social skills regardless of being born preterm or at term.

Furthermore, in Study IV, maternal depressive symptoms throughout pregnancy were shown to be associated with child ADHD symptoms in early childhood, with children of mothers who experienced consistently high depressive symptoms throughout pregnancy having almost three times higher odds for clinically significant ADHD symptoms in early childhood.

Our observational human studies support the Developmental Origins of Health and Disease hypothesis by showing that environmental factors during pregnancy and fetal development are associated with long term harmful mental health outcomes. Preterm birth constitutes an early vulnerability factor with long-term consequences on the individual into adulthood. In addition, being exposed to sGCs during pregnancy is another risk factor for mental health problems even in children who end up being born at term, emphasizing the need to extend clinical follow-up of child mental health beyond the preterm group to the group exposed to antenatal sGCs and born at term. Finally, early pregnancy screening and preventive interventions focusing on maternal depressive symptoms during pregnancy may benefit not only maternal, but offspring wellbeing.

TIIVISTELMÄ

Mielenterveyden ongelmat ovat lisääntyneet maailmanlaajuisesti liittyen väestön kasvuun ja ikääntymiseen. Vaikka interventioiden ja hoitomuotojen kehittäminen on tärkeää, on lisäksi olennaista tunnistaa riskitekijöitä mielenterveyden ongelmien kehittymiselle. Raskaudenaikaiset haitalliset ympäristötekijät voivat vaikuttaa sikiön kehitykseen sikiöaikaisen ohjelmoitumisen kautta, mutta ihmistutkimuksia sikiöaikaisen haitallisen kasvuympäristön pitkäaikaisista vaikutuksista yksilön kehitykselle tarvitaan edelleen.

Tässä väitöskirjassa tutkitaan mielenterveyden kehityksellistä alkuperää keskittyen kolmeen tärkeää riskitekijään: ennenaikaiseen syntymään (syntymä ennen 37. raskausviikkoa), sikiöaikaiseen glukokortikoidialtistukseen ja äidin raskaudenaikaisiin masennusoireisiin. Erityisesti keskitytään tutkimaan ennenaikaisen syntymän ja pienipainoisuuden pitkäaikaista vaikutusta (1) itseraportoituihin mielenterveyden ongelmiin varhaisaikuisuudessa ja (2) autismikirjon häiriön piirteiden ja visuaalisen prosessoinnin taitojen yhteyteen sekä näiden kumulatiiviseen vaikutukseen varhaisaikuisuudessa. Lisäksi keskitytään tutkimaan (3) sikiöaikaiselle glukokortikoidihoidolle altistumisen yhteyttä varhaislapsuuden mielenterveyteen ja psykologiseen kehitykseen, sekä (4) äidin raskaudenaikaisten masennusoireiden yhteyttä lapsen tarkkaavaisuus- ja yliaktiivisuushäiriön (ADHD) oireisiin.

Tämä väitöskirja pohjautuu useaan tutkimuskohorttiin. Ennenaikaisen syntymän, eli keskosuuden, pitkäaikaisia vaikutuksia on tutkittu APIC (Adults Born Preterm International Collaboration)-yhteistyössä, johon kuuluu kuusi eri tutkimuskohorttia viidestä eri maasta. Sikiöaikaisen glukokortikoidialtistuksen ja äidin raskaudenaikaisten masennusoireiden vaikutusta lapsen kehitykselle on tutkittu PREDO (engl. Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction Study)-tutkimuksessa.

APIC-yhteistyössä oli mukana 747 nuorta aikuista, jotka olivat syntyneet pienipainoisina (syntymäpaino alle 1500g) keskosina sekä 1512 täysiaikaisena syntynyttä (syntymä raskausviikosta 37 lähtien) verrokkia. Osallistujat olivat syntyneet vuosina 1977-1988 ja täyttivät kyselylomakkeita omista mielenterveyden ongelmista 19-29-vuotiaina (tutkimus I). Alkuperäinen Pikku-K-kohortti, joka kuuluu APIC-yhteistyöhön, koostui vuosina 1978-1985 syntyneistä 335 pienipainoisista keskosista ja heidän täysiaikaisena syntyneistä normaalipainoisista verrokeistaan. Yhteensä 101 pienipainoisella keskosella sekä 104 verrokilla oli varhaisaikuisuudessa tietoa visuaalisen prosessoinnin taidoista ja itsearvioiduista autismikirjon häiriön piirteistä (tutkimus II).

PREDO-tutkimuksessa oli alun perin mukana 4777 äitiä, jotka synnyttivät elävän yksösen vuosina 2006-2010. Äidit raportoivat masennusoireitaan läpi raskausajan ja tieto sikiöaikaisesta glukokortikoidihoidosta saatiin sairaskertomuksista ja syntymärekisteristä. Vuosina 2011-2012, 4586 naista alkuperäisestä otoksesta kutsuttiin lastensa kanssa osallistumaan seurantatutkimukseen. Seurantatutkimus sisälsi äidin täyttämiä kyselylomakkeita omista masennusoireista, lapsen kehityksestä ja lapsen psykiatrisista oireista (n=2640, tutkimus III) sekä lapsen ADHD-oireista (n=1779, tutkimus IV). Lapsen mielenterveyden ja käyttäytymisen häiriön diagnoosit heidän syntymästä joulukuun 31. päivään vuonna 2016 mennessä määriteltiin poistoilmoitusrekisteristä (n=4708, tutkimus III).

Tulokset osoittivat, että pienipainoisena keskosena syntyneet nuoret aikuiset raportoivat edelleen mielenterveyden ongelmia (tutkimus I). Heille tyypillisiä vaikeuksia olivat sisäänpäin suuntautuneet oireet ja estyneet persoonallisuusoireet yhdistettynä vähäisempään ulospäin suuntautuneiden oireiden riskiin. Lisäksi nuorilla aikuisilla, jotka olivat syntyneet pienipainoisina keskosina, oli suurempi riski kasautuville sosiaalisille ja kognitiivisille vaikeuksille (tutkimus II). Mitä enemmän he raportoivat autismikirjon häiriön piirteitä, sitä hitaampaa heidän prosessointi oli kokonaisuuden hahmottamista vaativassa visuaalisen prosessoinnin tehtävässä.

Sikiöaikainen altistus glukokortikoidihoidolle oli tutkimuksessa III yhteydessä varhaislapsuuden mielenterveyteen ja psykologiseen kehitykseen. Niillä lapsilla, jotka olivat altistuneet glukokortikoidihoidolle, oli lähes kolminkertainen riski saada mielenterveyden ja käyttäytymisen häiriön diagnoosi, heillä oli enemmän äidin raportoimia sisään- ja ulospäin suuntautuneita oireita ja heillä oli suurempi riski olla saavuttamatta omalle ikätasolle tyypillistä kehitystä omissa ja sosiaalisissa taidoissa riippumatta siitä, olivatko he syntyneet keskosena vai täysiaikaisena.

Äidin raskaudenaikaiset masennusoireet olivat tutkimuksessa IV yhteydessä lapsen ADHD-oireisiin varhaislapsuudessa. Lisäksi niillä lapsilla, joiden äidit raportoivat läpi raskauden vahvoja masennusoireita, oli lähes kolminkertainen riski kliinisesti merkitseville ADHD-oireille varhaislapsuudessa.

Tämän väitöskirjan löydökset tukevat käsitystä siitä, että sikiöaikaisella haitallisella kasvuympäristöllä on pitkäaikaisia vaikutuksia mielenterveydelle ja yksilön kehitykselle. Ennenaikainen syntymä on erityinen riskitekijä mielenterveyden haitalliselle kehitykselle jatkuen jopa aikuisuuteen asti. Lisäksi sikiöaikainen altistuminen glukokortikoidille on lisäriskitekijä jopa niiden lasten kohdalla, jotka syntyvät täysiaikaisena. Kehitysseuranta on siis oleellista keskosten kohdalla, mutta myös kaikkien niiden lasten kohdalla, jotka altistuvat sikiöaikana glukokortikoidihoidolle. Lopuksi, äidin masennusoireiden aikainen seulonta raskausaikana sekä interventioiden kehittäminen raskausajalle on erityisen tärkeää. Näillä keinoilla voidaan mahdollisesti lisätä sekä äidin että kasvavan lapsen hyvinvointia.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I   Pyhälä, R., Wolford, E., Kautiainen, H., Andersson, S., Bartmann, P., Baumann, N., Brubakk, A.-M., Evensen, K. A. I., Hovi, P., Kajantie, E., Lahti, M., Van Lieshout, R. J., Saigal, S., Schmidt, L. A., Indredavik, M. S., Wolke, D., Räikkönen, K. Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-analysis. *Pediatrics*. 2017; 139(4):e20162690.

II   Wolford, E., Pesonen, A.-K., Heinonen, K., Pyhälä, R., Hovi, P., Andersson, S., Kajantie, E. and Räikkönen, K. The Association between Autism Spectrum Traits and Visual Processing in Young Adults with Very Low Birth Weight: The Helsinki Study of Very Low Birth Weight Adults. *Journal of Developmental Origins of Health and Disease*. 2017; 8(2):161-167.

III   Wolford, E., Lahti-Pulkkinen, M., Girchenko, P., Lipsanen, J., Tuovinen, S., Lahti, J., Savolainen, K., Heinonen, K., Hämäläinen, E., Kajantie, E., Pesonen, A-K., Villa, P. M., Laivuori, H., Reynolds, R. M. & Räikkonen, K. Associations of antenatal glucocorticoid exposure with mental health in children. *Submitted to Psychological Medicine*.

IV   Wolford, E., Lahti, M., Tuovinen, S., Lahti, J., Lipsanen, J., Savolainen, K., Heinonen, K., Hämäläinen, E., Kajantie, E., Pesonen, A-K., Villa, P. M., Laivuori, H., Reynolds, R. M. & Raikkonen, K. Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3-to 6-year-old children. *PLoS One*. 2017;12(12): e0190248.

The publications are referred to in the text by their roman numerals. All original publications have been reprinted with the kind permission of the copyright holders.

ABBREVIATIONS

11β-HSD	11 beta hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit/hyperactivity disorder
AGA	Appropriate-for-gestational age
ALSPAC	Avon Longitudinal Study of Parents and Children
APIC	Adults Born Preterm International Collaboration
AQ	Autism-Spectrum Quotient
ASD	Autism spectrum disorder
ASQ	Ages and Stages Questionnaire
AVP	Arginine vasopressin
BDI	Beck Depression Inventory
BLS	Bavarian Longitudinal Study
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CBCL	Child Behavior Checklist
CES-D	Center for Epidemiological Studies Depression Scale
CHI	Conners' Hyperactivity Index
CI	Confidence interval
CRH	Corticotropin-releasing hormone
DOHaD	Developmental Origins of Health and Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELBW	Extremely low birth weight
EPT	Extremely preterm
ESTER	Preterm Birth and Early Life Programming of Adult Health and Disease
FDR	False detection rate
GDM	Gestational diabetes mellitus
GR	Glucocorticoid receptor
HDR	Finnish Hospital Discharge Register
HeSVA	Helsinki Study of Very Low Birth Weight Adults
HPA	Hypothalamic-pituitary-adrenal
ICD	International Classification of Diseases
IGF	Insulin-like growth factor
IQ	Intelligence quotient
IUGR	Intrauterine growth restriction
IVH	Intraventricular hemorrhage
LBW	Low birth weight
LPT	Late preterm
MBR	Finnish Medical Birth Register
MD	Mean difference
MPT	Moderately preterm

MR	Mineralocorticoid receptor
mRNA	Messenger ribonucleic acid
n	Number of cases
NBW	Normal birth weight
NICU	Neonatal intensive care unit
OR	Odds ratio
PGDM	Pre-gestational diabetes mellitus
PREDO	Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction study
PVL	Periventricular leukomalacia
RCT	Randomized controlled trials
RDS	Respiratory distress syndrome
ROCF	Rey-Osterrieth Complex Figure Test
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SES	Socioeconomic status
SGA	Small-for-gestational age
sGC	Synthetic glucocorticoid
VLBW	Very low birth weight
VPT	Very preterm
vs	Versus
WAIS	Wechsler Adult Intelligence Scale
WCC	Weak central coherence
YABCL	Young Adult Behavior Checklist
YASR	Young Adult Self-Report

1 INTRODUCTION

Across the world, one in five adults experience a mental disorder every year, and almost one in three adults will experience a mental disorder during their lifetime (Steel et al., 2014). With regard to the global burden of disease, as education, fertility rates, and economic status have improved in the recent decades across the world, there has been a shift from communicable, maternal, neonatal, and nutritional to non-communicable diseases being the leading causes of global disease burden (Abajobir et al., 2017). Recently, the disease burden of mental disorders has been proposed to be even greater than previously estimated, levelling with, or even surpassing, cardiovascular and circulatory diseases as the leading cause of global disease burden (Vigo, Thornicroft, & Atun, 2016). Focus in the field of mental health treatment has traditionally been set on treatment of, or prevention of the progression of severity in, established mental disorders, while preventative actions to combat risk factors have received less attention (Arango et al., 2018). Risk factors of adverse mental health include genetic, biological, family-related and societal risk factors, which can occur at any time point from conception to adulthood (Arango et al., 2018). Even though the complex interplay between risk factors makes the identification of specific risk factors challenging (Arango et al., 2018), identifying those specific risk factors may help to plan targeted interventions and public health policies to promote mental health.

In the recent decades, findings from a large amount of studies have suggested that cardiovascular, metabolic, endocrine, and even cognitive and mental health function and dysfunction may have developmental origins (Heindel & Vandenberg, 2015). There are multiple different terms for this phenomenon: 'programming' (Lucas, 1991), 'the thrifty phenotype hypothesis' (Hales & Barker, 1992), 'phenotypic' or 'developmental plasticity' (West-Eberhard, 1989, 2003), and the 'Developmental Origins of Health and Disease (DOHaD) hypothesis' (Barker, 2007). According to these hypotheses, internal and external stimuli affect the fetus during critical periods of development and thus alter the trajectories of subsequent development of health and disease with permanent lifelong consequences on the individual (Barker, 1998a). This framework, thus, provides a possibility to identify specific risk factors for optimal later life mental health and cognitive development.

In this thesis, I will focus on the developmental origins of mental health from the perspective of human observational studies. The term mental health, in this thesis, covers physician diagnosed mental disorders as well as subthreshold symptoms of internalizing problems (including depressive, anxious, withdrawn problems), externalizing problems (including aggressive, rule-breaking, attention deficit/hyperactivity problems), and autism-spectrum disorder traits. I will also address behavioral and cognitive development in this work. The developmental exposures, this work is based

on, are preterm birth, antenatal synthetic glucocorticoid exposure, and maternal depressive symptoms during pregnancy.

2 REVIEW OF THE LITERATURE

2.1 THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE FRAMEWORK

In the latter part of the 20th century, the hypothesis of an association between adverse early life influences and coronary heart disease started to gain support. After multiple studies established that poorer living conditions in childhood and adolescence were associated with an increased risk of coronary heart disease later on in life (Kaplan & Keil, 1993), the focus started to shift towards studying the effects of intrauterine life on later coronary heart disease risk. The landmark papers by Barker and Osmond in 1986 and Barker et al. in 1989 were essential in establishing the beginning of the Developmental Origins of Health and Disease (DOHaD) hypothesis. Barker and Osmond studied the geographical differences of death rates from coronary heart disease in England and Wales and found that the differences were associated with previous differences in both neonatal and postnatal mortality (Barker & Osmond, 1986) . Later Barker and colleagues found that the risk of death by coronary heart disease increased with decreasing birth weight and weight at one year (Barker, Osmond, Winter, Margetts, & Simmonds, 1989) suggesting that lower weight as a proxy for poor fetal and infant growth is a risk factor for later coronary heart disease. These findings launched a new wave of research trying to entangle the associations between lower birth weight or other adversities during the fetal and infant stage and later life health. In addition to the association between low birth weight and coronary heart disease, two major risk factors of coronary heart disease, hypertension and type II diabetes mellitus, have been associated with lower birth weight and preterm birth (birth before 37 weeks of gestation) (Beaumont, Horikoshi, McCarthy, & Freathy, 2017; de Jong, Monuteaux, van Elburg, Gillman, & Belfort, 2012; Hales et al., 1991; Harder, Rodekamp, Schellong, Dudenhausen, & Plagemann, 2007; Hovi et al., 2016; S. Li et al., 2014; Mi, Fang, Zhao, & Zhong, 2017; Parkinson, Hype, Gale, Santhakumaran, & Modi, 2013; Whincup et al., 2008).

Later on, the DOHaD framework has extended from aging-related diseases to also cover the developmental origins of mental health, behaviour, and cognition (Pesonen & Räikkönen, 2012; Räikkönen, Pesonen, Roseboom, & Eriksson, 2012). As the DOHaD hypothesis gained support, interest in studying the effect of birth weight and shorter length of gestation on mental health and cognitive development in later life also started to emerge. The first studies on the association between low birth weight (LBW; <2,500g) and lower intelligence quotients (IQ) came out in the late 1970s (Aylward, Pfeiffer, Wright, & Verhulst, 1989), and soon after that came the first reports of more behavioural and psychiatric problems in very low birth weight (VLBW;

<1,500g) children (Breslau, Klein, & Allen, 1988; Marlow, Roberts, & Cooke, 1989).

Since reliably measuring the fetal environment is practically impossible in human studies, birth weight, intrauterine growth restriction (IUGR), and preterm birth have been extensively studied in relation to later outcomes as markers of an adverse intrauterine environment. However, it is important to remember that these are only crude markers. Especially in older studies using birth weight as a marker of an adverse fetal environment, it was often not specified whether the lower birth weight was a result of being born preterm or growth restriction. Even when including measures of gestational age or IUGR, they do not provide information about the etiology of these adverse birth outcomes. However, whatever the cause of their size or preterm birth, it is still important to identify these individuals, because they are at an increased risk of adverse outcomes later in life (Barker, 1998b).

In addition to studying birth weight and shorter length of gestation as markers of an adverse fetal environment, already in the mid 20th century, studies were showing that complications during pregnancy and delivery were associated with behaviour disorder in school-aged children, as well as tics, epilepsy, speech disorders, and cognitive disability (Acheson, 1964). In the 1960s the idea that maternal stress might affect the fetus and subsequent emotional development through the endocrine system, was introduced (Acheson, 1964). Research has started to focus more on maternal stress during pregnancy in the last three decades with the first studies reporting more increased arousal in fetuses and more cognitive, behavioural, and emotional regulation problems in children of mothers who were stressed or anxious during pregnancy (Van Den Bergh, Mulder, Mennes, & Glover, 2005).

Another line of research, where the developmental origins of offspring development can be seen, is research on the effects of exposure to synthetic glucocorticoids (sGC) in the fetal stage. The first signs of the programming effects of sGC exposure on offspring development came from observations of altered cognitive ability, inattention, and fearfulness in girls with congenital adrenal hyperplasia, who had been exposed to synthetic glucocorticoids in low levels early on in fetal life (Drake, Tang, & Nyirenda, 2007). The effects of sGC exposure have mostly been studied in experimental animal models. These studies have shown adverse effects of antenatal sGC exposure on offspring brain development as well as subsequent behavior (Damsted, Born, Paulson, & Uldall, 2011).

The mechanisms underlying the associations between an adverse fetal and early life environment and later life health and development are not very well known. However, developmental programming is one of the key mechanisms suggested to explain the developmental origins of health and disease. During fetal development, there are critical or sensitive periods when tissues and organs go through rapid cell division (Godfrey & Barker, 2001). These sensitive periods are also characterized by developmental plasticity, where the system is genetically susceptible to different environmental effects enabling

the development of different morphological or physiological states (West-Eberhard, 1989). Sensitive periods are followed by a reduction of plasticity which then results in fixed functional capacity (Barker, 2007). An insult or an environmental disturbance, such as malnutrition or exposure to exogenous or endogenous glucocorticoids, during these sensitive periods thus programs the organs and systems and may have lasting effects on the individual (Kwon & Kim, 2017). Some changes may be beneficial for the individual to adapt to their environment, however, these changes may also lead to harmful and non-adaptive long term consequences, especially when the environment is not matched with the predicted environment of what the fetus has adapted to (Bateson et al., 2004). These concepts of developmental or fetal programming and developmental plasticity are the basis of the DOHaD framework.

2.2 MECHANISMS OF DEVELOPMENTAL PROGRAMMING

Multiple environmental factors during pregnancy have been found to affect fetal development. Among them are maternal nutrition, infection, smoking, alcohol consumption, toxins, stress during pregnancy (Schlotz & Phillips, 2009), and pregnancy disorders (Fraser & Lawlor, 2014; Howell & Powell, 2017; Villar et al., 2006). The effects can occur indirectly by alteration of oxygen and nutrition supply to the fetus or directly through transfer of glucocorticoids (Schlotz & Phillips, 2009). These factors can influence the development of hormonal systems that control fetal growth and development. Specifically the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the insulin-like growth factors (IGF), which mediate the stress response, have been of interest (Schlotz & Phillips, 2009). By changing the stress response system, the person may be more prone to chronic stress and further the neurodevelopmental changes caused by chronic stress leading to structural changes in brain areas important for cognitive and emotional functions. These environmental influences may also affect fetal brain development directly causing structural and functional changes in important brain areas for emotional and cognitive development (Lupien, McEwen, Gunnar, & Heim, 2009). Fetal development is an interactive process where the fetus is not just a passive target for environmental effects, but can also respond in different ways to environmental stimuli. When facing an adverse environment, the fetus can conserve nutrients by reducing growth or accelerate its maturation by elevating its glucocorticoid levels (Gluckman & Hanson, 2004).

Since the beginning of the DOHaD framework, fetal and early life nutrition have been thought to be the major mechanism through which fetal programming occurs. Barker first hypothesized in 1986, that

> *"The association of ischaemic heart disease with neonatal mortality suggests that the childhood influences predisposing to it are related to nutrition during prenatal and early postnatal life."*
>
> *(Barker & Osmond, 1986)*

While first emphasizing the effects of undernutrition, the effects of over-nutrition have lately come into focus, as well, with worldwide obesity rates rising. Gluckman et al. (2008) introduced the idea of fetal programming operating across the range of under- to over-nutrition, with a U-shaped association curve between prenatal nutrition and adult metabolic disease (Gluckman, Hanson, Cooper, & Thornburg, 2008). Hence it is more accurate to define adverse nutrition as malnutrition, rather than undernutrition.

Another mechanism through which prenatal environmental factors may affect fetal programming is overexposure to endogenous or exogenous glucocorticoids. The first signs of the fetal programming effects of glucocorticoids came from animal studies showing the association between maternal stress during pregnancy, which causes overproduction of endogenous glucocorticoids, or the administration of exogenous synthetic glucocorticoids during pregnancy and offspring birth weight and later disease risk and behavioral problems (Drake et al., 2007).

In the following section, I will go through these two mechanisms through which fetal programming operates, in more detail.

2.2.1   MATERNO-FETAL MALNUTRITION

Fetal nutrition does not equal maternal nutrition, as maternal energy and macronutrient intake have just a relatively small impact on birth weight, even at the extremes of maternal nutritional intake (Gillman, 2002; Harding, 2001). Further maternal diet quality during pregnancy has only a small effect on child cognitive and emotional development when children with VLBW are excluded (Borge, Aase, Brantsæter, & Biele, 2017). The nutritional *supply line,* starting from maternal nutrient intake through the maternal metabolic and endocrine status into the uterine blood flow and further through the placental transport and metabolism into the umbilical blood flow and finally to the fetal metabolic and endocrine status, is long and protects the fetus from an adverse diet consumed by the mother (Harding, 2001). However, there is evidence of nutrition during fetal life having an effect on birth size and later disease susceptibility for example from animal studies where nutrition intake has been reduced, as well as natural experiments such as the Dutch famine, where pregnant women were exposed to severe hunger during the winter of 1944-45 at the end of World War II (Harding, 2001)

Undernutrition can affect fetal growth by causing metabolic changes, redistribution of blood flow, or endocrine changes in the developing fetus (Barker, 1998a). When maternal supply of nutrients is restricted, the fetus will

consume its own substrates to provide energy, which may lead to lowering of the metabolic rate (Barker, 1998a). The fetus may also direct the distribution of blood flow to the most critical organs for survival, such as the brain, resulting in restricted blood flow in other less essential organs, such as the liver (Barker, 1998a). Fetal insulin and IGF regulate a large proportion of fetal growth and respond fast to changes in available nutrient supplies (Barker, 1998a). When maternal nutrition is restricted, fetal insulin, IGF, and glucose concentrations fall, which results is reduction of fetal growth due to reduced transfer of amino acids and glucose from the maternal side to the fetus (Barker, 1998a). Another mechanism through which undernutrition programs the developing fetus is the rise of maternal cortisol concentrations, which affect cell differentiation and can thus program fetal development (Barker, 1998a).

2.2.2   FETAL OVEREXPOSURE TO GLUCOCORTICOIDS

Glucocorticoids (cortisol) are hormones that are produced in the adrenal gland and are part of the stress response system. They are critical in the development of fetal organs, especially the brain, kidney, and lungs. During gestation, the levels of maternal endogenous glucocorticoids provide a developmental trigger for the appropriate timing of fetal organ development (Moisiadis & Matthews, 2014a). However, inappropriate timing or levels of exposure to glucocorticoids may have harmful effects on the maturation of fetal organs (Harris & Seckl, 2011; Lupien et al., 2009; Moisiadis & Matthews, 2014a). Maternal stress or malnutrition during pregnancy, as well as fetal stress or placental dysfunction may increase the levels of endogenous glucocorticoids the fetus is exposed to (Harris & Seckl, 2011; Lupien et al., 2009; Moisiadis & Matthews, 2014a).

In addition to endogenous glucocorticoids, in some cases the fetus may be exposed to exogenous glucocorticoids. Synthetic glucocorticoids such as betamethasone or dexamethasone are routinely administered at late gestation to pregnant women at risk of imminent preterm delivery to enhance fetal lung maturation. There are also instances where lower levels of sGCs are administered in early pregnancy or throughout pregnancy, such as with fetal congenital adrenal hyperplasia (CAH) (Nimkarn & New, 2007), maternal asthma (Murphy, 2015), or some autoimmune diseases (Adams Waldorf & Nelson, 2008).

Under normal circumstances, the placenta acts as a barrier to protect the fetus from overexposure to maternal endogenous glucocorticoids. The placental glucocorticoid barrier enzyme, 11 beta hydroxysteroid dehydrogenase (11β-HSD2) (Benediktsson, Calder, Edwards, & Seckl, 1997; Edwards, Benediktsson, Lindsay, & Seckl, 1993; Seckl & Meaney, 2004) converts 80-90% of active maternal cortisol to its inactive form, cortisone (Benediktsson et al., 1997; Edwards et al., 1993). However, the placenta metabolizes sGCs poorly, so they easily cross to the fetal side (Seckl & Meaney,

2004) and pass the blood-brain barrier (Damsted et al., 2011). In addition, in some instances placental dysfunction may expose the fetus to excessive amounts of glucocorticoids: for example maternal depression during pregnancy has been shown to increase placental glucocorticoid sensitivity (R M Reynolds et al., 2015) and consuming licorice during pregnancy can inhibit the function of the placental enzyme 11β-HSD2, because licorice is high in glycyrrhizin, an inhibitor of 11β-HSD2 (Monder et al., 1989).

Glucocorticoids affect the brain directly by binding to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) which are abundant especially in the hippocampus (Reul & De Kloet, 1985) and in the human fetus they are expressed already at 24 weeks of gestation (Noorlander, de Graan, Middeldorp, Van Beers, & Visser, 2006). Synthetic glucocorticoids only bind to GRs but not MRs, whereas endogenous glucocorticoids bind to both GRs and MRs. As the GRs in the brain and pituitary are occupied, the maternal and fetal HPA axes are feedback inhibited and this leads to reduction in the levels of cortisol. When this happens, the MRs in the developing hippocampus become "starved" of ligand and respond by upregulating the expression of MRs (McCabe, Marash, Li, & Matthews, 2001). Glucocorticoids affect brain growth (Huang et al., 1999; Moss et al., 2005), alter myelination (Huang, Harper, Evans, Newnham, & Dunlop, 2001; Raschke, Schmidt, Schwab, & Jirikowski, 2008), cell proliferation (Scheepens, van de Waarenburg, van den Hove, & Blanco, 2003), and neuronal migration (Fukumoto et al., 2009) as well as axonal and dendritic development and synaptogenesis (Moisiadis & Matthews, 2014b).

Glucocorticoids also have indirect effects on the fetal brain through promoting the maturation of different organs, including the thyroid and liver (Moisiadis & Matthews, 2014b). Thyroid hormone has a critical role in brain development (Bernal, 2007), and the liver, on the other hand, produces high levels of 11β-HSD1 (Chapman, Holmes, & Seckl, 2013), which can have a direct effect on local and circulating concentrations of bioactive cortisol in the fetus. Hence, glucocorticoids may influence the development of the fetal HPA axis indirectly by influencing these critical organs (Moisiadis & Matthews, 2014b).

The HPA axis regulates the production and secretion of corticosteroids under basal and stress conditions and plays a key role in the regulation of homeostasis and the stress response system. During a stress response, first, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This, in turn, leads to the production and release of glucocorticoids (cortisol) from the adrenal cortex. The released glucocorticoid binds to the GRs in the pituitary and the hypothalamus, as well as the GRs and MRs in the hippocampus to further activate the HPA axis. Feedback loops from the adrenal cortex to the hypothalamus, hippocampus and frontal cortex are triggered once the perceived stressor has subsided to signal shutting down of the HPA axis and returning to a homeastatic state. The dysregulation of the

HPA axis is associated with cardiovascular, metabolic, cognitive, and mental health problems (Moisiadis & Matthews, 2014a).

2.3 HUMAN PLATFORMS TO STUDY DOHAD

Animal studies have mostly been used to study the mechanisms through which developmental programming occurs, however, in human studies, the associations between prenatal factors and later life mental health and cognitive development have mostly been studied in observational studies. In this thesis, I will focus on three human platforms to study developmental origins of mental health and cognitive development: preterm birth, antenatal synthetic glucocorticoid exposure, and exposure to maternal depressive symptoms during pregnancy.

2.3.1 PRETERM BIRTH AND LOW BIRTH WEIGHT

Preterm birth is defined as birth before 37 completed weeks of gestation. Preterm birth is further divided into extremely preterm (EPT; <28 weeks of gestation), very preterm (VPT; 28 to <32 weeks of gestation), moderately preterm (MPT; 32 to <34 weeks of gestation), and late preterm (LPT; 34 to <37 weeks of gestation) birth (March of Dimes, PMNCH & WHO, 2012). In addition to using definitions of preterm birth according to gestational weeks, studies also use measures of birth weight to define immaturity at birth. Low birth weight (LBW) is defined as birth weight of less than 2,500 grams, very low birth weight (VLBW) as less than 1,500 grams, and extremely low birth weight (ELBW) as less than 1,000 grams (World Health Organization, 2004). Further, studies will often use measures of the appropriateness of birth weight in relation to gestational weeks to determine intrauterine growth restriction (IUGR). Small-for-gestational age (SGA) is often defined as either the 10th percentile of less than two standard deviations (SD) below the population mean birth weight when taking into account gestational weeks and sex, while appropriate-for-gestational age (AGA) is defined as within two SDs from the population mean birth weight (P. A. Lee, Chernausek, Hokken-Koelega, Czernichow, & for the International SGA Advisory Board, 2003).

Preterm birth occurs in one in every ten deliveries worldwide, the equivalent of 15 million births per year (Blencowe et al., 2012), and it is one of the current leading causes of perinatal mortality and morbidity (Liu et al., 2012). The incidence of preterm birth in Finland, however, is smaller than the worldwide average, with only 5.3% of births in the year 2017 being preterm (available at: https://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/synnyttajat-synnytykset-ja-vastasyntyneet/perinataalitilasto-synnyttajat-synnytykset-ja-vastasyntyneet, retrieved on 24.10.2018). Even though most of the individuals born preterm grow up to be healthy and function well, there is still a significant amount of

individuals who suffer from neurologic, personality, mental health, cardiovascular, and metabolic problems (Raju, Buist, Blaisdell, Moxey-Mims, & Saigal, 2017). This is not surprising, as at birth the brain of an infant born preterm is still very immature and therefore vulnerable to immaturity-associated complications and adversities. At 34 weeks of gestation the brain weighs only about 65% of its term weight (Kinney, 2006). Also, cortical volume increases by 50% between 34 and 40 weeks of gestation and significant changes in gray and white matter volumes take place as well (Kinney, 2006).

Preterm birth is associated with structural and functional brain abnormalities, such as periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) grades III or IV, and despite advances in the treatment of preterm infants, the morbidity rates due to these conditions are persistently high, especially in the most vulnerable preterm infants (Glass et al., 2015). In addition to these major abnormalities, preterm individuals often have more subtle microstructural abnormalities, such as white matter abnormalities, which persist into adulthood (K. Li et al., 2015). These perinatal injuries may underlie the developmental sequelae of cognitive, behavioral, and mental health problems in preterm individuals.

2.3.1.1 Preterm birth and cognitive development

Lower birth weight and preterm birth have been associated with lower cognitive functioning later in life in multiple studies. The first meta-analysis on the association between low birth weight (LBW; <2,500g) and cognitive ability was conducted by Aylward et al. (1989) and it included studies with children born between 1960 and 1983 (Aylward et al., 1989). Despite multiple methodological issues and differences between the different studies, children with LBW had statistically significantly lower intelligence quotients (IQ) than controls (97.77 vs. 103.78, respectively) (Aylward et al., 1989). Later Ornstein et al. (1991) reviewed 25 studies of children who were born VLBW or ELBW, and concluded that even though their IQs were in the normal range, they were lower than those of controls' (Ornstein, Ohlsson, Edmonds, & Asztalos, 1991). The studies also reported more incidence of learning difficulties, special education need, language delay and articulation deficits, visual-motor dysfunction, and motor performance in children born VLBW or ELBW (Ornstein et al., 1991). These studies were not able to take into account gestational age of the children at birth, or whether they were born preterm or not.

Later meta-analyses have been able to use more stringent criteria and they have focused more on prematurity than birth weight. These studies have continued to show significantly lower cognitive ability in children and adolescents born preterm or at lower birth weights than their term-born and NBW peers. Bhutta et a. (2002), conducted a meta-analysis of children aged 5 to 14 years, who were born preterm between 1975-1988 and compared their IQs to term-born controls (Bhutta, Cleves, Casey, Cradock, & Anand, 2002).

The meta-analysis showed that term-born controls had almost 11 points higher IQ scores than preterm children, and the mean cognitive scores were directly proportional to their gestational age and birth weight (Bhutta et al., 2002). Kerr-Wilson et al. (2011) added to the findings by including births until the year 2000, and the finding were similar with preterm participants having 12 points lower IQ scores at 3 to 16 years of age compared to term-born controls (Kerr-Wilson, MacKay, Smith, & Pell, 2012). In a recent meta-analysis including only VPT and EPT participants born in the era of antenatal corticosteroids and surfactants, the difference in IQ scores assessed at age 5 to 20 years between controls and the VPT/EPT participants was comparable, 0.86 SD scores, which is equivalent to almost 13 points (Twilhaar et al., 2018).

In addition to lower general cognitive ability, individuals born preterm show more specific difficulties in multiple areas of cognitive development. Commonly reported problems in children include problems in motor skills (Allotey et al., 2018; de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009), visuo-motor integration and visuo-spatial abilities (Geldof, van Wassenaer, de Kieviet, Kok, & Oosterlaan, 2012), memory (Anderson, 2014), language (Barre, Morgan, Doyle, & Anderson, 2011; van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012), attention (Mulder, Pitchford, Hagger, & Marlow, 2009; van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008), executive function (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Mulder et al., 2009), and academic skills (Aarnoudse-Moens et al., 2009; Allotey et al., 2018). Studies have also found impairments to some extent in global form perception (Atkinson & Braddick, 2007; N. M. Taylor, Jakobson, Maurer, & Lewis, 2009) and specifically in processing global and biological motion (Atkinson & Braddick, 2007; N. M. Taylor et al., 2009; Williamson, Jakobson, Saunders, & Troje, 2015). One of these studies found that difficulties in biological motion processing were associated with a higher incidence of autism spectrum disorder (ASD)-related traits in preterm children, but not their term-born peers (Williamson et al., 2015).

As cohorts born at LBW have been followed further, findings from later meta-analyses have found that the cognitive impairments associated with LBW do indeed extend beyond childhood and adolescence into early adulthood (Gu et al., 2017; Kormos, Wilkinson, Davey, & Cunningham, 2014). Even in the NBW range, cognitive ability in adulthood has been shown to decrease in relation to decreasing birth weight (Grove, Lim, Gale, & Shenkin, 2017). However, findings differ on whether the difference in cognitive abilities decreases (Grove et al., 2017; Kormos et al., 2014) or remains the same (Gu et al., 2017) over time. Specifically problems in attention (Pyhälä, Lahti, et al., 2011), executive function (Allin et al., 2008; Nosarti et al., 2007; Pyhälä, Lahti, et al., 2011), processing speed (Hallin, Hellström-Westas, & Stjernqvist, 2010; Strang-Karlsson et al., 2010), visual memory (Pyhälä, Lahti, et al., 2011; Strang-Karlsson et al., 2010), visuospatial processing (Pyhälä, Lahti, et al., 2011), visuomotor integration and motor coordination (Sripada et al., 2015)

academic achievement (Hack et al., 2002; Hallin et al., 2010), and need for special support in school (Pyhälä, Lahti, et al., 2011) have been reported.

2.3.1.2 Preterm birth and mental health

In addition to cognitive abilities, lower birth weight and preterm birth have been associated with mental health problems later in life. The risk of developing severe psychiatric disorders is higher in individuals born preterm than in those born at term (D'Onofrio et al., 2013; Nosarti et al., 2012). These include non-affective psychotic disorders and bipolar affective disorders, depressive disorders, ADHD and ASD (D'Onofrio et al., 2013; Nosarti et al., 2012). Individuals diagnosed with a psychiatric disorder in childhood are at a highly increased risk for adverse health, legal, financial, and social outcomes in adulthood (Copeland, Wolke, Shanahan, & Costello, 2015). However, these adverse outcomes are not restricted to those with diagnosed disorders, but also pertain to those individuals with subthreshold psychiatric symptoms (Copeland et al., 2015). Hence, it is important not only to investigate if individuals born preterm are at an increased risk for diagnosed mental disorders, but also self-reported subclinical mental health problems.

The first studies came out in the late 1980s with reports of more behavioural problems in VLBW children at age 6 compared to their NBW peers (Marlow et al., 1989) and more psychiatric problems in 9-year-old boys born at VLBW compared to their NBW peers (Breslau et al., 1988). However, there were also reports of no differences in behavioural problems between ELBW and NBW children at the age of 5 years (Portnoy & Gamsu, 1988). The first meta-analysis of childhood behavioural outcomes was conducted by Bhutta et al. (2002) and included 5 to 14-year-olds, who were born preterm and at least with LBW between 1975-1988 (Bhutta et al., 2002). They concluded that children born preterm had increasing internalizing and externalizing problems and an over 2.5-times higher risk of having attention-deficit/hyperactivity disorder (ADHD) (Bhutta et al., 2002). Another meta-analysis of VPT and/or VLBW individuals confirmed the association between preterm birth and internalizing and attention problems, but found no differences between VPT and/or VLBW individuals and their term-born peers in externalizing problems at the age of 5 to 20 years (Aarnoudse-Moens et al., 2009). The prevalence of any diagnosis of a psychiatric condition, and more specifically anxiety or depressive disorder, was shown to be significantly higher in preterm and LBW individuals compared to their term-born peers (Burnett et al., 2011). This meta-analysis included individuals between the ages of 10 and 25 years, and indicated that the mental health problems evident in children born preterm may extend through adolescence into young adulthood (Burnett et al., 2011).

However, evidence of more subtle mental health and behavior problems in adults born preterm at VLBW remain still somewhat mixed. While childhood studies use parent- or teacher-reports to assess subclinical or more subtle

mental health and behavior problems, adult studies mostly rely on self-reports and occasionally on parent-reports. The first report of young adult mental health and behavioral outcomes of individuals born at VLBW came from a hospital-based cohort study in Cleveland, Ohio, of 241 VLBW subjects (46 SGA) and 232 NBW control subjects (Hack et al., 2004). They studied gender specific outcomes of self- and parent-reported mental health problems, and found that parents of VLBW women reported more internalizing problems in in their offspring than parents of NBW women, and the rates of internalizing problems above the borderline clinical cutoff reported by VLBW women was higher than for NBW control women (Hack et al., 2004). In another study using both self- and parent-reports of mental health problems in a nationwide population based cohort of 656 VPT and/or VLBW young adults (243 SGA) in the Netherlands, parent-reports showed more internalizing, externalizing, and total problems compared to the normative population data in both women and men (Hille et al., 2008). In this study, VLBW women reported more internalizing and total problems than the normative data (Hille et al., 2008). There were no differences between VLBW and control men in internalizing, externalizing, or total problems in self-reports or parent-reports (Hack et al., 2004), and reports of internalizing, externalizing or total problems did not differ significantly from the Dutch normative data (Hille et al., 2008). Hack et al. (2004) also found that parents reported more inattention in men, even though there were no differences in the self-reports compared to the controls (Hack et al., 2004).

In a study conducted by Boyle and colleagues, self-reported mental health problems were assessed in a Canadian cohort of ELBW adults (Boyle et al., 2011). They compared self-reported internalizing and externalizing problems of 142 ELBW subjects (35 SGA) to 133 NBW control subjects, and found that internalizing problems were elevated compared to controls, but there were no differences in externalizing problems (Boyle et al., 2011). There was a sex x group interaction, such that being male muted the risk for externalizing problems among the ELBW group (Boyle et al., 2011). They also found that the internalizing problems in the ELBW group were most noticeable among those born SGA (Boyle et al., 2011). Correspondingly, in a Finnish VLBW cohort study, Räikkönen and colleagues found that among adults born preterm at VLBW, those born AGA reported fewer depressive symptoms, and those born SGA reported more depressive symptoms than term-born controls (Räikkönen et al., 2008).

In a Norwegian longitudinal study of individuals born at VLBW, self-reported mental health problems of 43 preterm VLBW subjects (11 SGA) were compared to 74 control subjects (Lund et al., 2012). The VLBW group reported more internalizing problems than the controls, but the groups did not differ in externalizing or total problems (Lund et al., 2012). The VLBW group also reported more ASD-related problems in social skills and attention switching (Lund et al., 2012). ASD-related problems especially in social interaction have also been reported elsewhere in adults born preterm at VLBW (Pyhälä et al.,

2014) and VLBW adults have been shown to report higher levels of problems related to social and emotional functioning (Westrupp, Northam, Doyle, Callanan, & Anderson, 2011).

The mixed results in previous cohort studies may be due to small sample sizes and limited power to detect subtle differences between groups, or varying degrees of prematurity and intrauterine growth restriction between samples. The differences in the results could also reflect cultural differences between cohorts. It has been shown in studies with children that results can differ according to the country of origin of the sample (Hille et al., 2001).

2.3.2 SYNTHETIC GLUCOCORTICOID TREATMENT IN PREGNANCY

Synthetic glucocorticoids such as betamethasone or dexamethasone, to enhance fetal maturation, are a standard treatment when preterm birth before 34 gestational weeks is imminent to enhance fetal lung maturation. Up to 10% of women in Europe and North America at risk of preterm delivery are administered sGCs (Rebecca M. Reynolds & Seckl, 2012). In Finland, the recommended course is two doses of 12mg of betamethasone intramuscularly 24 hours apart to all women at risk of preterm birth before 35 completed weeks of gestation (Uotila et al., 2011). Regular repeated courses are not recommended, however, if preterm birth is still imminent after 7 days of the previous course, a repeated course of one or two doses can be administered (Uotila et al., 2011). The treatment has been found to carry benefits for infants born before 34 weeks of gestation with the incidence of respiratory distress syndrome, intraventricular hemorrhage, and neonatal mortality going down substantially (March of Dimes, PMNCH & WHO, 2012). Some evidence suggests that also those born late preterm (births between 34-36 weeks of gestation) may gain similar respiratory benefits of antenatal sGCs (Gyamfi-Bannerman et al., 2016), and that also those born early-term (births between 37-39 weeks of gestation) after caesarean sections (P. Stutchfield, 2005) may benefit from antenatal sGS in short-term as they have been reported to have less respiratory complications as well (Kamath-Rayne, Rozance, Goldenberg, & Jobe, 2016; Saccone & Berghella, 2016; Sweet et al., 2017; The American College of Obstetricians and Gynecologists, 2016). In Finland, in high-risk situations, such as when the risk of respiratory difficulties is large or in planned caesarean sections, the treatment is also recommended for women giving birth between 35-36 weeks of gestation (Uotila et al., 2011).

In 1972 Liggins and Howie published the first findings from their controlled trial of the effect of antenatal synthetic glucocorticoid treatment on the prevention of respiratory distress syndrome (RDS) in preterm infants (Liggins & Howie, 1972). Later, in the 1990s it became routine to administer sGCs, such as betamethasone or dexamethasone, to pregnant women at risk of imminent preterm delivery to enhance fetal lung maturation and prevent RDS (The American College of Obstetricians and Gynecologists, 2016). Even though sGC treatment has significant benefits for children born preterm,

including reduction of RDS, IVH, and neonatal mortality, and it has been shown to have no effect on neurodevelopment delay in childhood (Roberts, Brown, Medley, & Dalziel, 2017), prediction of preterm birth is uncertain, and many infants exposed to sGCs end up being born at term. The programming quality of glucocorticoids has raised questions on the possible harmful effects of being exposed to sGCs in fetal life. It remains unclear whether the benefits related to sCGs equally outweigh the potential harms in individuals born at term (Rebecca M. Reynolds & Seckl, 2012).

Experimental animal models have shown adverse effects of antenatal sGC exposure on offspring brain development, including reduced brain growth (Huang et al., 1999; Moss et al., 2005), altered myelination (Huang et al., 2001; Raschke et al., 2008) and cell proliferation (Noorlander et al., 2014; Scheepens, van de Waarenburg, van den Hove, & Blanco, 2003), and retardation of neuronal migration (Fukumoto et al., 2009). In addition, the adverse effects of antenatal sGCs have also been evident in subsequent behavior, such as in signs of hyperactivity (Owen & Matthews, 2007), and cognitive skills, such as in spatial learning (Noorlander, Visser, Ramakers, Nikkels, & de Graan, 2008).

2.3.2.1 Effects of antenatal synthetic glucocorticoid exposure on child development

Synthetic glucocorticoid treatment effects have been studied in preterm children with an emphasis on comparing the effects of single and repeated courses of sGCs. Repeated courses have been shown to significantly reduce morbidity in preterm children (Crowther, Haslam, Hiller, Doyle, & Robinson, 2006; French, Hagan, Evans, Mullan, & Newnham, 2004), but also to increase attention problems (Crowther et al., 2007) and aggressive or hyperkinetic behavior problems (French et al., 2004). When comparing just a single course of sGC treatment to no exposure, studies have shown that in young adults who were born preterm, the ones exposed to sGCs were more likely to show internalizing problems (Savoy et al., 2016; van der Voorn, Wit, Van Der Pal, Rotteveel, & Finken, 2015). Since preterm birth is associated with psychiatric symptoms (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Twilhaar et al., 2018), associations between sGC treatment and psychiatric symptoms in preterm individuals may be confounded by other factors related to being born preterm. Hence, studies with term-born individuals are needed to exclude the confounding effect of being born preterm.

Studies on the effect of sGCs on child psychiatric symptoms in term-born children are still scarce. Two randomized controlled trials (RCT) have examined the effects of sGCs on mental health and psychological development in term-born children. In one of these studies, term-born children exposed prenatally to multiple (up to 4) courses (n=201) of either betamethasone or dexamethasone had no more neurobehavioral problems at 5 years compared to peers exposed to a single course (n=236) of sGCs (Asztalos et al., 2014).

They had a higher rate of and more severe neurosensory disabilities, but no more abnormally elevated levels of attention and memory problems compared to the children who were exposed to a single course of sGCs (Asztalos et al., 2014). Asztalos and colleagues did not, however, have a control group of children not exposed to sGCs. The other RCT found no differences in parent-reported Strengths and Difficulties Questionnaire (SDQ) behavior problems between 8-15-year-old children born from elective term caesarian sections, who exposed prenatally to a single course of betamethasone (n=217) and those not exposed to sGCs (n=190) (P. R. Stutchfield et al., 2013). In addition, there were no differences in academic achievement, however, schools did report more learning difficulties in those exposed to betamethasone (P. R. Stutchfield et al., 2013).

In addition, there are some observational studies examining the effect of antenatal exposure to a single course of betamethasone or dexamethasone in term-born children. Khalife et al. (2013) studied preterm and term-born children at ages 8 (n=37 exposed to sGCs/n=6,079 not exposed) and 16 years (29 exposed to sGCs/n=4,950 not exposed), and found that 8-year-old children exposed to sGCs had higher teacher-rated Rutter scale total, neurotic, and inattention scores (Khalife et al., 2013). Findings at 16 years of parent-reported inattention and hyperactivity problems and self-reported total problems showed a similar trend, but did not reach significance (Khalife et al., 2013). However, even though they adjusted the analyses for gestational age, they did not study the effects separately in preterm and term-born children. In another observational study, there were no differences between exposed (n=18) and non-exposed (n=36) term-born children in the levels of parent-reported affective problems measured by the Child Behavior Checklist (CBCL) at the age of 6 to 10 years (Davis, Sandman, Buss, Wing, & Head, 2013). Alexander et al. (2016) studied term-born 6 to 11-year-olds exposed to a single course of either betamethasone or dexamethasone and compared the exposed group to a non-treated group and a control group with no pregnancy complications. There were no differences between the sGC group and the non-treated group in IQ scores, however, both groups had lower IQ scores than the control group with no pregnancy complications (Alexander et al., 2016). They also showed that the children exposed to antenatal sGCs have an increased cortisol reactivity to acute psychosocial stress, which was more pronounced in females effects (Alexander et al., 2012). Lastly, in one study, newborn term-borns exposed to sGCs (n=30) displayed higher salivary cortisol stress reactivity to the painful stress of a heel-stick blood draw than their non-exposed term-born peers (n=60) (Davis, Waffarn, & Sandman, 2011).

The mixed findings may result from different study designs, differences in the number of sGC courses administered, and the use of varying measures of psychiatric symptoms and cognitive development at ages that vary in developmental stage. Further, only one of these previous studies has examined the possible confounding of maternal obesity and common pre-pregnancy and pregnancy disorders (Alexander et al., 2016). These disorders often underpin

the risk of preterm birth (Goldenberg, Culhane, Iams, & Romero, 2008; Rosenberg, Garbers, Lipkind, & Chiasson, 2005), and hence co-occur with antenatal sGC treatment.

2.3.3 MATERNAL DEPRESSION DURING PREGNANCY

Maternal stress during pregnancy includes psychological distress, such as depressive mood, anxiety, psychosocial stress or pregnancy-related stress, major life events during pregnancy, or exposure to disasters during pregnancy. Stress can be measured in terms of subjective, perceived stress, and objective stress. Although some effects of maternal stress during pregnancy on both fetal programming and child outcomes are to some extent comparable, there is evidence of somewhat different effects and underlying mechanisms with different forms of stress (Barker, Jaffee, Uher, & Maughan, 2011; Dunkel Schetter & Tanner, 2012; Ibanez et al., 2015; O'Donnell et al., 2012). Maternal depression during pregnancy was chosen as a focus for this thesis because of the high disease burden of depressive disorders compared to other mental disorders worldwide (Murray et al., 2015). The prevalence of perinatal depression in women, i.e. a major depressive episode during pregnancy or in the four weeks following delivery, is nearly 12% (Woody, Ferrari, Siskind, Whiteford, & Harris, 2017) and up to 20% of women experience clinically significant levels of depressive symptoms at some point during pregnancy (M. Lahti et al., 2017; Molyneaux, Poston, Ashurst-Williams, & Howard, 2014). Hence, maternal depression or depressive symptoms during pregnancy are a major health concern for both the expectant mother and the unborn child.

2.3.3.1 *Associations between maternal depression and child development*

The effects of maternal depression either during or after pregnancy on child cognitive development has been studied in multiple settings. The findings are to some extent mixed with some studies finding harmful effects (El Marroun et al., 2017; Evans et al., 2012; Hay, Pawlby, Waters, & Sharp, 2008; Koutra et al., 2013; Lin et al., 2017; Tuovinen et al., 2018; van der Waerden et al., 2017), some finding no effects (Nulman et al., 2012), and some even finding beneficial effects (DiPietro, Novak, Costigan, Atella, & Reusing, 2006; Keim et al., 2011; Plamondon et al., 2015). Many studies have shown that the harmful effects are more evident in boys (Gerardin et al., 2011; Hay et al., 2008; Kurstjens & Wolke, 2001; van der Waerden et al., 2017) and when maternal depression is persistent and chronic (Comaskey et al., 2017; Evans et al., 2012; Kurstjens & Wolke, 2001; Tuovinen et al., 2018; van der Waerden et al., 2017).

It is now widely agreed upon that maternal depression during pregnancy can have adverse effects on offspring emotional and behavioral development (M. Lahti et al., 2017; Van den Bergh et al., 2017). Even though findings have

been mixed on whether the effect of maternal depression during pregnancy is independent of maternal mood after pregnancy (Van den Bergh et al., 2017), a recent study found that maternal depressive symptoms after pregnancy partially mediated the prenatal effects and also added to child internalizing, externalizing, and total problems, but antenatal depressive symptoms also had independent effects (M. Lahti et al., 2017).

In addition to broad scale psychiatric symptoms, depression during pregnancy has been associated more specifically with offspring symptoms of ADHD. Mothers of children with diagnosed ADHD have been shown to be more likely to be diagnosed with depression before pregnancy (Ray, Croen, & Habel, 2009) or report having a depressive mood during pregnancy (Say, Karabekiroğlu, Babadağı, & Yüce, 2015). Also, in prospective cohort studies, there has been a significant association between depression during pregnancy and child ADHD symptoms in early childhood (Foulon et al., 2015; Leis, Heron, Stuart, & Mendelson, 2014; Van Batenburg-Eddes et al., 2013).

Even though there is evidence of depression during pregnancy being associated with child ADHD symptoms, it is still unclear whether the association is independent of postnatal maternal depression. There are, to my knowledge, three prospective cohort studies to date that consider the effect of depression after pregnancy on the association between depression during pregnancy and child ADHD symptoms. In the Generation R Study (n=2,280), maternal depressive symptoms during gestational week 20 were associated with a higher risk of mother-reported child attention problems at 3 years (Van Batenburg-Eddes et al., 2013). Also, in the Avon Longitudinal Study of Parents and Children (ALSPAC), maternal depressive symptoms at gestational week 18 and 32 were associated with a higher risk of mother-reported child attention and hyperactivity problems at 4 (n=3,442) and 11 years (n=2,891) (Leis et al., 2014; Van Batenburg-Eddes et al., 2013). Foulon et al. (2015) studied the developmental sequence of risk factors for inattention-hyperactivity symptoms in 1,311 3-year-olds in the EDEN study. They found that low family socioeconomic status (SES) before pregnancy was associated with higher maternal depression and anxiety during pregnancy, which in turn was associated with higher maternal and child distress during the first year after birth, and finally with higher levels of inattention-hyperactivity (Foulon et al., 2015). In the ALSPAC, the association between depression during pregnancy and child ADHD symptoms remained significant after adjusting for postnatal maternal depressive symptoms (Leis et al., 2014; Van Batenburg-Eddes et al., 2013). However, in the Generation R Study, the association was no longer significant (Van Batenburg-Eddes et al., 2013) and in the EDEN study the significant association between maternal depressive symptoms during pregnancy and child ADHD symptoms disappeared in the multivariate model including maternal and child distress and dysregulation (Foulon et al., 2015).

These contradictory findings could partly be explained by differing assessment measures and time points. The Generation R Study is the only one

where maternal depressive symptoms were only measured at the same time as child behavior was assessed (Van Batenburg-Eddes et al., 2013). In the ALSPAC study, maternal postnatal depressive symptoms were measured multiple times after pregnancy, with measures coinciding with (Leis et al., 2014), and predating rating child behavior (Van Batenburg-Eddes et al., 2013). In the EDEN study, maternal depressive symptoms were measured two years prior to rating child behavior (Foulon et al., 2015). Hence, it still remains unclear whether the mother's concurrent mood at the time of rating child behavior accounts for, mediates or adds to the effect of depressive symptoms during pregnancy. In addition, the previous studies have only included one or two assessments of maternal depressive symptoms during pregnancy, and the assessments have been conducted at varying gestation stages. Therefore, it remains unknown if some developmental periods during pregnancy are more vulnerable than others to the effects of maternal depressive symptoms, and if feeling depressed throughout pregnancy is more harmful for the offspring than feeling depressed only for a week or two in one or two arbitrary time-points. In addition, while two of these studies accounted for maternal depression after pregnancy (Leis et al., 2014; Van Batenburg-Eddes et al., 2013), none of the studies tested if maternal depression after pregnancy added to or mediated either fully or partially the prenatal effects. Furthermore, ADHD in childhood is associated with higher levels of depression in adulthood (Meinzer et al., 2016) and ADHD is highly heritable (Larsson, Chang, D'Onofrio, & Lichtenstein, 2013). Hence, maternal ADHD problems could underlie both maternal depressive symptoms and child ADHD symptoms, yet, no previous study has controlled for maternal ADHD problems when studying the association between maternal prenatal depression and child ADHD symptoms.

2.3.3.2 *The effect of pregnancy disorders*

Pregnancy disorders, such as hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia), diabetic disorders (gestational diabetes mellitus [GDM] and disorders already occurring before pregnancy, or pre-gestational diabetes mellitus [PGDM] including type 1 diabetes and type 2 diabetes), and maternal pre-pregnancy obesity, often co-occur with depressive symptoms during pregnancy (Hu, Li, Zhang, & Yan, 2015; Molyneaux et al., 2014). There is evidence of both depressive symptoms during pregnancy and pregnancy disorders being associated with child ADHD symptoms, hence, it is important to take pregnancy disorders into account especially when studying the effects of depressive symptoms during pregnancy. So far, these effects are largely unknown, however, a recent study reported that pregnancy disorders did not affect the associations between maternal depressive symptoms during pregnancy and child psychiatric symptoms (M. Lahti et al., 2017). Previous studies have reported contradictory findings on the association between pregnancy disorders and child ADHD symptomatology. A meta-analysis on

the association between pre-eclampsia and offspring ADHD found a 31% increased risk of offspring ADHD (Zhu et al., 2016). However chronic hypertension has not been shown to be associated with a risk of ADHD (Instanes et al., 2015). Both GDM and PGDM have been associated with an increased risk of ADHD or symptoms related to ADHD (Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015). A recent review also concluded that maternal obesity in pregnancy is associated with an increased risk of ADHD in the child, however, racial differences have been found in relation to the risk of ADHD, and when controlling for familial factors, the associations have been lost (Edlow, 2017; Rivera, Christiansen, & Sullivan, 2015). In addition, a prospective study combining almost 7,500 mother-child pairs from two large cohorts found no association between maternal pre-pregnancy overweight and child attention problems rated by the mothers at three to four years-of-age (Brion et al., 2011).

3   AIMS OF THE STUDY

The overall aim of this work is to study the developmental origins of mental health focusing on three important risk factors: preterm birth, exposure to antenatal synthetic glucocorticoids, and maternal depressive symptoms during pregnancy.

The specific aims of the individual studies are:

To study the long term effects of preterm birth at very low birth weight on self-reported mental health problems by conducting an individual participant data meta-analysis (Study I). The sample size allows additional examination of group differences by sex or by the pattern of intrauterine growth restriction as reflected in SGA and AGA births. The APIC cohorts included in this meta-analysis are from different countries and regions allowing us to additionally examine whether variations in findings arise from cross-cultural differences.

To study the association between and cumulative effect of autism spectrum disorder traits and visual processing skills in young adults born preterm at VLBW and if the associations vary between the preterm VLBW and term groups (Study II). We also studied if the degree of intrauterine growth restriction as reflected in SGA and AGA births modified any potential associations in the preterm VLBW group.

To study the association of antenatal betamethasone exposure with early childhood mental and behavioral disorders and mother-reported psychiatric problems and developmental milestones (Study III). We examined if these associations varied by whether the children were born preterm or at term. We also took into account pregnancy disorders, and tested if the association of antenatal betamethasone exposure with early childhood mental and behavioral disorders and mother-reported psychiatric problems and developmental milestones varied by sex.

To study if maternal depressive symptoms, measured biweekly during pregnancy, are associated with child attention-deficit/hyperactivity disorder symptoms (Study IV). The biweekly assessments allowed us to address gestation-week and trimester-specific effects, and maternal re-ratings of depressive symptoms at the time of rating the 3- to 6-year-old child allowed us to address if any effects were specific to the prenatal stage. Our study also tested if maternal depressive symptoms after pregnancy added to or mediated any of the prenatal effects. Finally, we tested if maternal pregnancy disorders or maternal ADHD symptoms accounted for any observed effects.

4 METHODS

4.1 PARTICIPANTS

4.1.1 ADULTS BORN PRETERM INTERNATIONAL COLLABORATION (STUDY I)

The Adults Born Preterm International Collaboration (APIC) is a group of researchers around the world studying adults who were born preterm by conducting individual-participant meta-analyses on different aspects of health and well-being. Within APIC, our research group led the meta-analysis on mental health problems of adults born preterm at VLBW.

All research groups known to have followed up a cohort of young adults born preterm at ELBW or VLBW, and who had data on self-reported mental health problems using the Achenbach Adult Self-Report (ASR) (Achenbach & Rescorla, 2003) or the Achenbach Young Adult Self-Report (YASR) (Achenbach, 1997) were contacted. Each cohort was required to have a control group born at term. Gathering of new cohorts with ongoing follow-up studies was discontinued according to an a priori plan in May, 2013. The cohorts included in the meta-analysis were the McMaster cohort (Boyle et al., 2011), the Helsinki Study of Very Low Birth Weight Adults (HeSVA) (Pyhälä, Lahti, et al., 2011), the Preterm Birth and Early Life Programming of Adult Health and Disease (ESTER) Study (Sipola-Leppänen et al., 2015), the Bavarian Longitudinal Study (BLS) (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2016), the Trondheim cohort (Lund et al., 2012), and the Cleveland cohort (Hack et al., 2004). The study groups consisted of altogether 747 young adults born preterm at ELBW or VLBW and 1,512 controls born at term (from here on called preterm and control groups, respectively) at ages 19 to 29 years. Data on the original ASR and YASR raw scores, perinatal information, and other important covariates from all the participating cohorts were provided and data were harmonized to compute commensurate variables and pooled across the cohorts.

Table 1. *Characteristics of the very low birth weight cohorts with data on self-reported mental health problems included in the meta-analysis.*

Cohort	Country	Born	Preterm VLBW/ELBW	Control
		Years	n (%)	n (%)
HeSVA	Finland	1978-85	108 (50.7)	105 (49.3)
Cleveland	USA	1977-79	241 (51.0)	232 (49.0)
McMaster	Canada	1977-82	142 (51.6)	133 (48.4)
Trondheim	Norway	1986-88	42 (25.1)	125 (74.9)

| ESTER | Finland | 1985-89 | 46 (6.1) | 703 (93.9) |
| BLS | Germany | 1985-86 | 168 (44.0) | 214 (56.0) |

4.1.2 HELSINKI STUDY OF VERY LOW BIRTH WEIGHT ADULTS (STUDIES I AND II)

The Helsinki Study of Very Low Birth Weight Adults (HeSVA) is a follow-up study aimed at studying the long-term effects of being born preterm at VLBW (Figure 1). The original cohort consisted of 335 discharged (survival rate 70.7%) infants born preterm at VLBW between 1978 to 1985 and treated in the neonatal intensive care unit at Helsinki University Central Hospital in Finland. A term-born control group, not born SGA according to the Finnish birth weight charts (Pihkala et al. 1989) was group-matched for sex, age, and birth hospital. The study protocol included two clinical follow-ups, with the first follow-up including cardiovascular and metabolic assessments, as well as questionnaires on the participants' medical history, socioeconomic characteristics, physical activity, and mental health. During the second clinical follow-up when the participants were approximately 25 years old, their neurocognitive abilities, including visual processing skills (Study II) were assessed and they were asked to rate their mental health problems (Study I) and ASD-related traits (Study II).

4.1.3 PREDICTION AND PREVENTION OF PRE-ECLAMPSIA AND INTRAUTERINE GROWTH RESTRICTION STUDY (STUDIES III AND IV)

The Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study comprises altogether 4,777 mothers who gave birth to a singleton live-born offspring in Finland between 2006 and 2010 (Figure 2) (Girchenko et al., 2016; Reynolds et al., 2015; Räikkönen et al., 2014). The women were recruited to the study in antenatal clinics at one of the ten study hospitals in Southern and Eastern Finland at their first ultrasound screening between 12+0-13+6 weeks+days of gestation. To enrich the number of women with pre-eclampsia and IUGR in the PREDO sample, 969 of the recruited women had one or more risk factors for pre-eclampsia (Girchenko et al., 2017).

In 2011-2012, 4,586 women from the original sample were invited to participate in a follow-up with their children. The follow-up included a postal questionnaire on multiple aspects of the mothers' wellbeing, as well as the children's behavior.

	VLBW	**Term-born controls**
Clinical visit I (2004-2006) Young adults residing in the greater Helsinki area were invited to participate in the study	**n = 166** 65.1% of the 255 invited)	**n = 172** (54.8% of the 314 invited)
Not invited: Not traced, n = 2 Lived abroad, n = 11 Refused to be contacted, n = 4 Developmental deficit, n = 1 Not eligible for intravenous glucose tolerance test, n = 7		
Not participating: Did not respond, n = 29 Refused to participate, n = 66		
Clinical visit II (2007-2008) Participants of the first clinical visit were invited to participate in the study	**n = 113** 71.1% of the 159 invited)	**n = 105** (68.2% of the 154 invited)
Study I Self-reported mental health problems	**n = 108**	**n = 105**
Study II ASD-related traits and visual processing	**n = 101**	**n = 104**

Figure 1   Flowchart of the Helsinki Study of Very Low Birth weight Adults.

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**Baseline
(2006–2010)**
Women with liveborn singleton children enrolled at their first ultrasound visit

4,753 children had neonatal data from Finnish Medical Birth Register (FMBR) and follow-ups

4,728 children had data on antenatal betamethasone exposure

3,410 women completed prenatal psychological well-being questionnaires during pregnancy

**Follow-up of child mental and behavioral disorder diagnoses
(2006–2016)**
Information identified from the Finnish Hospital Discharge Register (HDR)

Study III
Analytic sample with data on antenatal betamethasone exposure and child mental and behavioral disorder diagnoses

**Follow-up of mother and child wellbeing
(2011–2012)**
Women and their children were invited to participate in a follow-up.

Mother-reported information:

2,312 with data on child ADHD symptoms

2,594 with data on child psychiatric problems

2,500 with data on child developmental milestones

Study III
Analytic sample with data on antenatal betamethasone exposure and mother-reported psychiatric problems and developmental milestones of the child

Study IV
Analytic sample with mother-reported depressive symptoms during pregnancy and child ADHD symptoms

n = 4,777

n = 4,753
(99.5% of the original baseline sample)

n = 4,708

n = 2,667
(58.2% of the 4,586 invited)

n = 2,640

n = 1,779

24 children's data was not recovered from the Finnish Hospital Discharge Register
2 mothers withdrew consent later in the follow-up

3 children died
33 did not have data in the Finnish Medical Birth Register
55 had declined participation
100 addresses were not traceable

Figure 2   Flowchart of the Predo study

4.1.4 ETHICAL CONSIDERATIONS

For all participating cohorts, ethical approvals were provided by local ethics committees. All participants gave their informed consent. In Study I, all data were de-identified before pooling.

4.2 MEASURES

4.2.1 PRETERM BIRTH, VERY LOW BIRTH WEIGHT, SMALL FOR GESTATIONAL AGE (STUDIES I AND II)

In Studies I and II, gestational length in weeks+days and birth weight in grams were derived from hospital records. In Study I, due to dissimilar national standards used in previous publications, birth weight in relation to gestational age SD scores were calculated based on uniform criteria for both sexes separately (Olsen, Groveman, Lawson, Clark, & Zemel, 2010). SGA was defined as birth weight for gestational age ≤ -2 SD, and AGA as birth weight for gestational age > -2 SD and < +2 SD. SGA and AGA status could not be calculated for controls in the McMaster and Cleveland cohorts, because data on exact length of gestation were not available for term controls (Boyle et al., 2011; Hack et al., 2004, 2005). For Study II, Finnish growth charts (Pihkala, Hakala, Petri, & Raivio, 1989) were used to define birth weight SD scores.

4.2.2 SYNTHETIC GLUCOCORTICOID EXPOSURE (STUDY III)

Information on betamethasone treatment (yes vs. no) was extracted from medical records and/or the Finnish Medical Birth Register (MBR). For a subset of women who were recruited based on their risk factor status for pre-eclampsia and IUGR, information on the number of courses (n = 43; mean = 1, SD = 0.4, range 0.5-2 courses of 2x12mg per course) and the timing of the exposure (n = 45; mean = 3.5, SD = 3.9, range 0-13 weeks before delivery) were available. However, given the small sample size of these cases, analyses were not carried out to study the effect of timing or number of courses. According to Finnish National Current Care Guidelines (Uotila et al., 2011) during the time our cohort was born, repeated betamethasone courses were not recommended, unless the risk of neonatal respiratory distress syndrome was considered high, more than 7 days had passed after treatment, and delivery was imminent within 1-7 days.

4.2.3 PREGNANCY DISORDERS (STUDIES III AND IV)

In Studies III and IV, maternal pre-pregnancy obesity (body mass index; BMI, ≥ 30 kg/m²), GDM (yes vs. no) and hypertensive disorders of pregnancy (pre-

eclampsia, gestational hypertension; yes vs. no) were extracted from the MBR, the Finnish Hospital Discharge Register (HDR), and/or from medical records independently verified by a clinical jury.

4.2.4   CHILD MENTAL AND BEHAVIORAL DISORDERS (STUDY III)

Diagnoses of child mental and behavioral disorders were identified from the HDR from the child's birth between 2006-2010 to December 31st, 2016. The HDR includes primary and subsidiary diagnoses of all inpatient and outpatient visits (data on both visits available since the child's birth) coded using International Classification of Diseases-10 (ICD-10) during the study period and is a valid tool for research (Sund, 2012; Tolonen et al., 2007). We included in the analyses only those disorders which included children in the betamethasone-exposed and non-exposed groups born preterm and at term. Children with no disorders were used as the referent in all analyses.

4.2.5   PSYCHIATRIC SYMPTOMS QUESTIONNAIRES

4.2.5.1   Childhood mother-reported questionnaires (Studies III and IV)

Mothers rated their child's behavioural symptoms of ADHD at the child's age of 3 to 6 years (Study IV) using the Conners' Hyperactivity Index (CHI) (Conners, 2001). The CHI comprises ten questions on the child's hyperactivity and impulsivity on a scale of "not at all" (0) to "very much" (3) (Conners, 2001). A sum-score of 10 or above indicates clinically significant ADHD symptoms (Landgren, Pettersson, Kjellman, & Gillberg, 2008). The scale has good internal consistency (Parker, Sitarenios, & Conners, 1996; Westerlund, Ek, Holmberg, Näswall, & Fernell, 2009) and discriminant validity (Parker et al., 1996; Westerlund et al., 2009). In this sample, it showed high internal consistency (α=.91). I used both the continuous sum score and the cutoff score as outcomes in the analyses (Study IV).

   The mothers also rated their child's psychiatric problems at the child's age of 1.9 to 5.9 years using the CBCL 1½-5 years comprising 99 problem items rated on a scale of "not true" (0) to "very or often true" (2) (Achenbach & Rescorla, 2000). The CBCL yields three main scales (internalizing, externalizing, and total problems), seven syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior), and five Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-IV)-oriented scales (affective, anxiety, pervasive developmental, attention-deficit/hyperactivity, and oppositional defiant problems) (Achenbach &

Rescorla, 2000). In the main analyses, we used the three main psychiatric problem scales T scores as outcomes (Study III).

4.2.5.2 Adulthood self-reported questionnaires (Studies I-IV)

In Study I, mental health problems during the past six months were self-reported in young adulthood using the ASR (Achenbach & Rescorla, 2003) in HeSVA, Trondheim, and ESTER, and the YASR (Achenbach, 1997) in Cleveland, McMaster, and BLS). The ASR is composed of 123 and YASR of 116 items that are self-rated on a scale of "not true" (0) to "very or often true" (2). The Ratings to Scores software by ASEBA (Achenbach, 2005) was used to compute raw scores and T scores for scales according to the ASR form for both the ASR and YASR data. Thus, all scale scores across the study cohorts were based on the same items independent of the form version that was originally used.

The scales yield three main scales (internalizing, externalizing, and total problems), eight syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive behaviour), six DSM-IV-oriented scales (depressive, anxiety, somatic, avoidant personality, attention deficit/hyperactivity, and antisocial personality problems), and one scale measuring critical items (a clinician-based sum of items referring to problems clinicians may typically be particularly concerned about) (Achenbach & Rescorla, 2003). T scores of the scales were used in all analyses as outcomes.

In Study II, the Autism-Spectrum Quotient (AQ) was used to assess ASD-related traits. The AQ is a self-rated questionnaire, which comprises 50 questions on a four-point dichotomized scale of "definitely agree" and "slightly agree" (1) to "slightly disagree" and "definitely disagree" (0) in half of the items, while in the other half the scoring is the opposite (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Total sum score combines all scores (ranging from zero to 50), and a higher score indicates stronger ASD-related traits. In addition to the Total sum score we used a two-factor model, first introduced by Hoekstra et al., of the AQ scale yielding a Social interaction subscore, which combines 40 items relating to social and communication skills, imagination and attention switching abilities, and an Attention to detail subscore, which combines 10 items. The AQ scale and its two-factor model have been shown to have good discriminant validity (Hoekstra, Bartels, Cath, & Boomsma, 2008). In this sample, internal consistency (Cronbach's alpha) for the Total, Social interaction, and Attention to detail sum scores were 0.78, 0.81, and 0.58, respectively. The Total sum score and Social interaction and Attention to detail subscores were used as continuous outcome variables.

In Study III and IV, maternal depressive symptoms were reported biweekly up to 14 times throughout pregnancy starting from 12+0-13+6 to 38+0-39+6 weeks+days gestation or delivery using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The CES-D has 20 questions rated

on a scale of "none of the time" (0) to "all the time" (3) during the past week, with higher scores indicating more frequent symptoms of depression, and a sum score of ≥ 16 indicating a risk for clinical depression (Radloff, 1977). The continuous sum score was used as the predictor in Study IV and as a covariate in Study III.

In the follow-up, depressive symptoms were reported using the Beck Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996). This scale comprises 21 four-statement sets (scored from 0 to 3) with each statement reflecting increasing severity of depressive symptoms during the past two weeks (Beck et al., 1996). A sum-score of ≥ 14 indicates at least mild depressive symptoms (Beck et al., 1996). The continuous sum score was used as a covariate in Studies III and IV, and also as a mediator in Study IV.

Both depression scales have good psychometric properties (Beck et al., 1996; Erford, Johnson, & Bardoshi, 2016; Nast, Bolten, Meinlschmidt, & Hellhammer, 2013; Radloff, 1977; Stockings et al., 2015), and the CES-D has been used extensively and validated also in pregnant populations (Nast et al., 2013). It has been shown previously that in our sample the CES-D (Cronbach`s α=.88 to .92 in the 14 biweekly measurement points) and the BDI-II (α=.91) have high internal consistency (M. Lahti et al., 2017).

4.2.6 COGNITIVE DEVELOPMENT MEASURES

4.2.6.1 *Childhood developmental milestones questionnaire (Study III)*

Mothers filled in the Ages and Stages Questionnaire-3 (ASQ) (Squires, Bricker, & Potter, 1997) which measures age-appropriate developmental milestones in five domains (communication, fine motor, gross motor, problem solving ability, and personal-social functioning). Six questions in each domain indicate whether the child has mastered ("yes", 10 points), partly/inconsistently mastered ("sometimes", 5 points), or not yet mastered the milestone ("not yet", 0 points) (Squires et al., 1997). Mild developmental delay was defined as scoring between -1 and -2 SD below the age-specific mean and failure to meet the development that is typical for the child's age as scoring -2 SD or more below the age-appropriate mean for each domain (Squires et al., 1997). The ASQ has been validated in the general population and is a reliable screening tool for determining children in need of further developmental assessment (Charkaluk et al., 2017; Filgueiras, Pires, Maissonette, & Landeira-Fernandez, 2013; Kerstjens et al., 2009; Steenis, Verhoeven, Hessen, & van Baar, 2015).

4.2.6.2 Adulthood cognitive and neuropsychological tests (Studies I and II)

In Study II, visual processing skills were assessed using The Rey-Osterrieth Complex Figure Test (ROCF), which comprises three different test conditions: copy, immediate recall, and delayed recall (Rey, 1941). The ROCF is a standardized, highly used method for assessing visual processing skills in adults. The participants were introduced with a complex figure and first asked to copy it, then after copying the figure, they were immediately asked to draw the figure from recall (immediate recall) and approximately 35 minutes later to draw the figure again from recall (delayed recall). Raw scores on the accuracy of the reproduction of the figure were derived using the 18-point scoring system (E. M. Taylor, 1959) and reproduction times were measured from all three conditions respectively. These were used as continuous outcomes. Visuospatial cognitive ability was assessed using the Block Design subtest of the Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler, 2005) and the raw sum score was used as a continuous outcome.

4.2.7 COVARIATES

The covariates in the different adjustment models for Studies I and II are shown in Table 2. Both studies used parental education as a proxy of socioeconomic position of the childhood family. For Study I, the highest education of either parent as reported by the parent(s) at participant's birth was used in the Cleveland and BLS cohorts, in childhood in the McMaster cohort, and in adolescence in the Trondheim cohort. In the HeSVA (also for Study II) and ESTER cohorts the highest education of either parent was reported by the participant in young adulthood. Parental education was classified into lower secondary or less, higher secondary education, lower tertiary education, or higher tertiary education. In Study I, multiple birth was extracted from hospital records and neurosensory impairments were determined as cerebral palsy (CP), severe hearing or visual deficit, or IQ<70. Data on CP, hearing or visual deficit were based on clinical assessments in childhood (HeSVA, Cleveland, McMaster, Trondheim, BLS), and/or self-reports in young adulthood (HeSVA, ESTER). Data on estimated IQ were available from clinical assessments in childhood (McMaster), or young adulthood (HeSVA, Trondheim, BLS). In Study II participants with neurosensory impairments were excluded from the analytic sample (n = 6). In Study II, information on head circumference (cm) at birth was extracted from hospital records and converted into SD scores by sex in relation to gestational age (Pihkala et al., 1989). Adult head circumference (cm) was measured during the clinical visit. Full scale IQ was estimated using WAIS-III subscales Block Design, Vocabulary, Similarities and Digit Span using the Finnish norms (Wechsler, 2005) (this was adjusted for only in the ROCF analyses).

Table 2. *Different adjustment models in Studies I and II.*

	Study I	Study II		
	Models			
	I	I	II	III
Sex	+	+	+	+
Age at assessment	+	+	+	+
Multiple birth	+			
Parental education	+		+	+
Neurosensory impairments	+			
Current head circumference			+	+
Head circumference SD score at birth			+	+
Full Intelligence Quotient				+

The covariates in the different adjustment models for Studies III and IV are shown in Table 3. In the Predo study (Studies III and IV) maternal age at delivery (years), family structure (cohabitating/married vs. single), parity (primiparous vs. multiparous), delivery mode (vaginal vs. caesarian section), premature rupture of membranes (yes vs. no), smoking during pregnancy (did not smoke/ quit during the first trimester/ smoked throughout pregnancy), antidepressant use (yes vs. no), psychotropic medication use (yes vs. no), birth weight (g) adjusted for sex and gestation length in Study IV, birth weight standardized by sex and gestational age (Pihkala et al., 1989) in Study III (SD units), gestational age, and child's sex were extracted from the MBR and/or from medical reports. Maternal alcohol use during pregnancy (yes vs. no), past or present physician-diagnosed asthma (yes vs. no), past or present physician-diagnosed depression (yes vs. no), and education (secondary or less, upper secondary, lower tertiary, upper tertiary) were mother-reported during pregnancy. Questions on maternal ADHD problems were embedded in the ASR (Achenbach & Rescorla, 2003), which the mothers completed in the follow-up (T-score ≥ 65 points indicates borderline significant problems). The mothers also reported the child's age the follow-up.

In Study III, maternal any mental disorder diagnoses were identified from the HDR based on inpatient and outpatient visits (any vs. no DSM-III-R diagnosis of mental disorder or ICD-10 diagnosis of mental and behavioral disorder). Inpatient data were available between 1987 and December 31st 2016 and outpatient data were available between 1998 and December 31st 2016. Birth year of the mothers varied from 1959 to 1977, hence the mothers were 10-28 years old at the start of the HDR inpatient registration and 19-39 years old at the start of the HDR outpatient registration in our study.

Table 3. *Different adjustment models in Studies III and IV.*

	Study III			Study IV				
	Models			Models				
	I	II	III	I	II	III	IV	V
Child characteristics								
Sex	+	+	+	+	+	+	+	+
Age at assessment	+	+	+	+	+	+	+	+
Birth year	+							
Gestational age					+	+	+	+
Birth weight adjusted for sex and gestational age		+	+	+	+	+	+	+
Maternal characteristics								
Age at childbirth		+	+		+	+	+	+
Parity		+	+		+	+	+	+
Family structure					+	+	+	+
Education level		+	+		+	+	+	+
Delivery mode		+	+					
Premature rupture of membranes		+	+					
Type 1 diabetes		+	+		+	+	+	+
Gestational diabetes		+	+			+	+	+
Chronic hypertension		+	+		+	+	+	+
Gestational hypertension		+	+			+	+	+
Pre-eclampsia		+	+			+	+	+
Early-pregnancy BMI		+	+					
Early-pregnancy obesity						+	+	+
History of depression					+	+	+	+
History of asthma		+	+					
Antidepressant use					+	+	+	+
Other psychotropic medication use					+	+	+	+
Alcohol use during pregnancy		+	+		+	+	+	+
Smoking during pregnancy		+	+		+	+	+	+
Maternal ADHD problems							+	+
Depressive symptoms during pregnancy			+					
Depressive symptoms at follow-up			+					+
Any mental disorder diagnosis			+					

4.3 STATISTICAL ANALYSES

4.3.1 STUDY I

All statistical analyses were performed with Stata, version 14.0 (StataCorp, College Station, TX). A two-step individual participant data random-effects meta-regression analysis was conducted, in which analyses were first run separately for each cohort, and the results from the individual cohorts were then combined in a meta-analysis. First, we tested if those born preterm differed from term controls on the sum scales (internalizing, externalizing and total problems) by using multiple linear regression models. Then, we tested if the groups differed in the syndrome, DSM-IV-oriented and critical items scales by using Tobit regressions. Tobit models are designed to estimate linear relationships between variables when there exists either left- or right-censoring in the outcome variable. Pooled effects and 95% confidence intervals (CI) were then computed using the random-effects method with DerSimonian and Laird technique (DerSimonian & Laird, 1986). In all meta-analyses, between-study heterogeneity was tested using the Cochran's Q statistic and quantified by the I2-value. Low heterogeneity was defined as an I2-value of 0–25%, moderate heterogeneity as an I2 of 25–75%, and high heterogeneity as an I2 of 75–100%. The two-step meta-analyses were then run by restricting the preterm group to ELBW births and comparing them to the term controls. Analyses contrasting the preterm and term groups were subsequently rerun after excluding individuals with neurosensory impairments (199 preterms and 21 controls). We also tested if the group-differences varied by sex, and if those born preterm differed in the mental health problems according to SGA or AGA birth weight.

4.3.2 STUDY II

Linear regression analyses were run to test associations between AQ scores and visual processing scores, first, in the VLBW and control groups separately, and then to test if the associations varied between the groups in a regression model that included VLBW vs term*AQ score interactions. We controlled the associations between AQ Total sum score and all visual processing scores for inflation of Type II error rate due to multiple testing with a false detection rate (FDR) procedure (Benjamini & Hochberg, 1995) setting the false detection rate across 7 tests at 0.05. We did not apply the FDR procedure to the AQ Social interaction and Attention to detail subscores, because the AQ Total sum score is a composite of these scores with subscores being highly correlated with the Total score (r=.94 and .37, both *P*-values<.001, respectively).

We also explored if the associations were different in the VLBW SGA (n=37) and AGA (n=64) groups, and then included the AGA vs SGA*AQ score -interaction term to the models to test if the associations between the groups were significantly different.

4.3.3 STUDY III

Since the PREDO study was not originally designed to study the effects of betamethasone treatment on child developmental outcomes, we used propensity score weighing (Austin, 2011) to account for the differences in baseline characteristics associated with betamethasone treatment. We determined the propensity score weights by logistic regression to estimate the probability of receiving betamethasone treatment conditional on the observed covariates. We then trimmed the highest propensity score weights downwards with a cutpoint of 95th percentile (B. K. Lee, Lessler, & Stuart, 2011). The resulting propensity score weights were used in all analyses. Because the sample size differed between the child disorders (n=4,708) and mother-reported child outcomes (n=2,640), we calculated the propensity score weights separately for these two samples.

Using logistic regression analysis, we tested the associations between antenatal betamethasone exposure and child main category diagnoses of mental and behavioral disorders, and multinomial logistic regression to test associations with having just one or two to four co-morbid mental and behavioral disorders compared to no disorders. If associations with the main category disorders were significant, we specified the effects by analyzing the disorders in the specific disorder category.

We then tested the associations between antenatal betamethasone exposure and mother-reported child total, internalizing, and externalizing psychiatric problems (converted into SD units) by using generalized linear models with Gaussian reference distribution. Associations between antenatal betamethasone exposure and mother-reported child developmental milestones (scores >-1SD contrasted with scores between -1SD and -2SD and with scores ≤-2SD) were tested by using multinomial logistic regression analysis.

We entered an interaction term 'betamethasone exposure/non-exposure x preterm/term birth' into the equations to study if the betamethasone effects varied by preterm/term status, and an interaction term 'betamethasone exposure/non-exposure x girl/boy' into the equations to study if the betamethasone effects varied by child's sex.

4.3.4 STUDY IV

We used MPLUS and SPSS 24 data packages for the analyses. We first examined maternal depressive symptom profiles during pregnancy with a latent profile analysis and compared solutions with two to eight clusters, and identified the most optimal one by using Akaike Information Criterion, sample size-adjusted Bayesian Information Criterion, and Vuong-Lo-Mendell-Rubin Likelihood Ratio Test and Lo-Mendell-Rubin Adjusted Likelihood Ratio Tests. We then tested if the child ADHD symptom scores, treated as a continuous outcome variable, and the proportion of children with clinically significant ADHD symptoms, treated as a dichotomous variable using the ADHD

symptom score 10 or above as a clinical cutoff (Landgren et al., 2008), differed between the groups of mothers with different depressive symptom profiles during pregnancy. These group differences are presented as mean differences (MD) and odds ratios (OR) and their 95% CIs from linear (continuous ADHD symptom scores) and logistic regression analyses (ADHD symptom scores dichotomized at clinical cutoff), respectively.
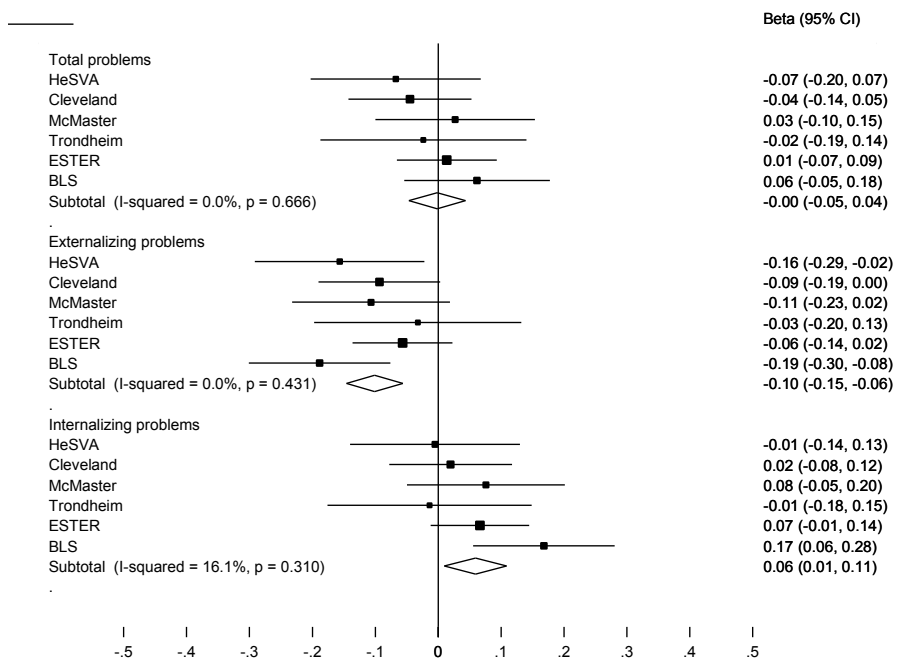
We if the associations between maternal depressive symptoms during pregnancy and child ADHD symptoms were gestation-week- or trimester-specific. In these tests, we used linear regression analysis when treating child ADHD symptoms as continuous and logistic regression analysis when using dichotomized child ADHD symptom scores at the clinical cutoff. Further, in these analyses maternal depressive symptom scores (biweekly values; first trimester value, mean values of the second and third trimester values; trimester-weighted mean value) were square root transformed to improve linear model fitting.

We also tested if maternal depressive symptoms after pregnancy added to the prenatal effects with an interaction term of maternal trimester-weighted mean depressive symptoms during pregnancy*maternal depressive symptoms after pregnancy that was added to the linear (continuous ADHD symptom scores) and logistic regression models (ADHD symptoms scores dichotomized at the clinical cutoff). In addition, we tested if maternal depressive symptoms after pregnancy mediated the effects of maternal trimester-weighted mean depressive symptoms during pregnancy using the PROCESS macro for mediation in SPSS 24 with 5000 bootstrapping re-samples with bias-corrected CIs (Hayes & Preacher, 2014; Preacher & Hayes, 2008). Finally, we conducted sensitivity analyses by running the linear regression analyses separately in groups according to maternal pre-pregnancy obesity and pregnancy disorders, child's sex, maternal history of physician-diagnosed depression, and maternal ADHD problems.

5 RESULTS

## 5.1 PRETERM BIRTH AND SELF-REPORTED MENTAL HEALTH PROBLEMS IN ADULTHOOD (STUDY I)

In the pooled individual participant data meta-analyses, young adults born preterm reported more internalizing problems (p = 0.02) and less externalizing problems (p < 0.001) than controls (Figure 3).

	Beta (95% CI)
Total problems	
HeSVA	-0.07 (-0.20, 0.07)
Cleveland	-0.04 (-0.14, 0.05)
McMaster	0.03 (-0.10, 0.15)
Trondheim	-0.02 (-0.19, 0.14)
ESTER	0.01 (-0.07, 0.09)
BLS	0.06 (-0.05, 0.18)
Subtotal (I-squared = 0.0%, p = 0.666)	-0.00 (-0.05, 0.04)
Externalizing problems	
HeSVA	-0.16 (-0.29, -0.02)
Cleveland	-0.09 (-0.19, 0.00)
McMaster	-0.11 (-0.23, 0.02)
Trondheim	-0.03 (-0.20, 0.13)
ESTER	-0.06 (-0.14, 0.02)
BLS	-0.19 (-0.30, -0.08)
Subtotal (I-squared = 0.0%, p = 0.431)	-0.10 (-0.15, -0.06)
Internalizing problems	
HeSVA	-0.01 (-0.14, 0.13)
Cleveland	0.02 (-0.08, 0.12)
McMaster	0.08 (-0.05, 0.20)
Trondheim	-0.01 (-0.18, 0.15)
ESTER	0.07 (-0.01, 0.14)
BLS	0.17 (0.06, 0.28)
Subtotal (I-squared = 16.1%, p = 0.310)	0.06 (0.01, 0.11)

The black boxes and corresponding numbers represent betas, and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in young adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

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Figure 3   Associations between preterm birth at VLBW or ELBW and self-reported total, externalizing, and internalizing problems in young adulthood.
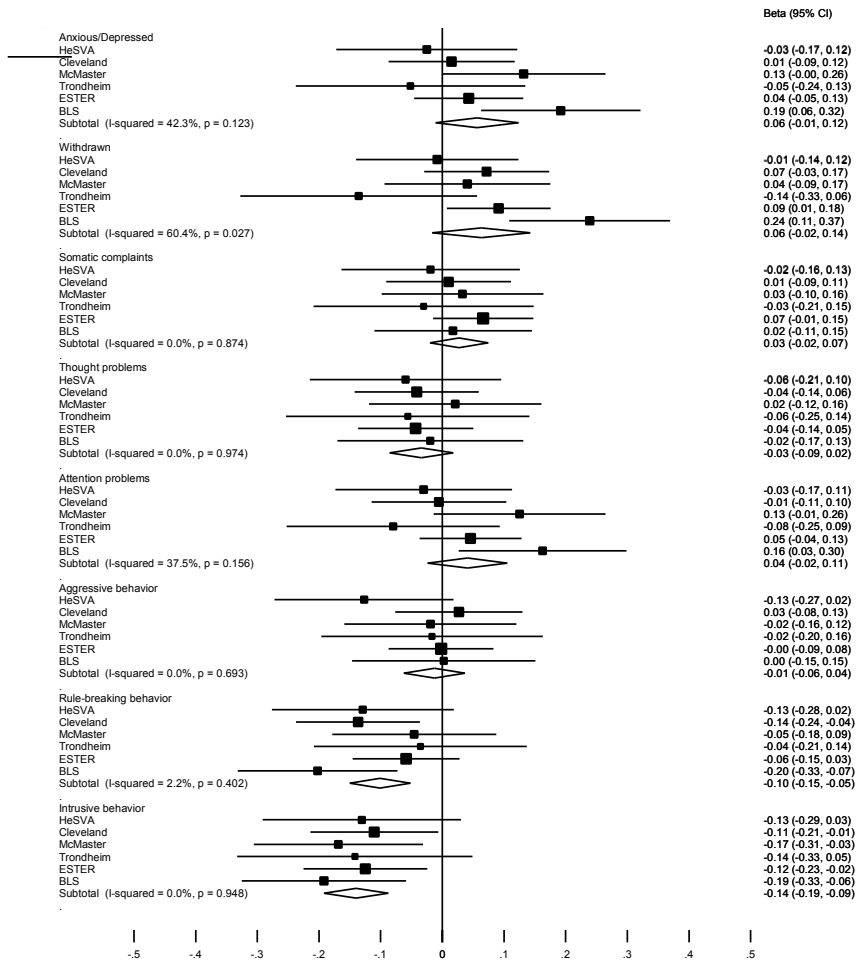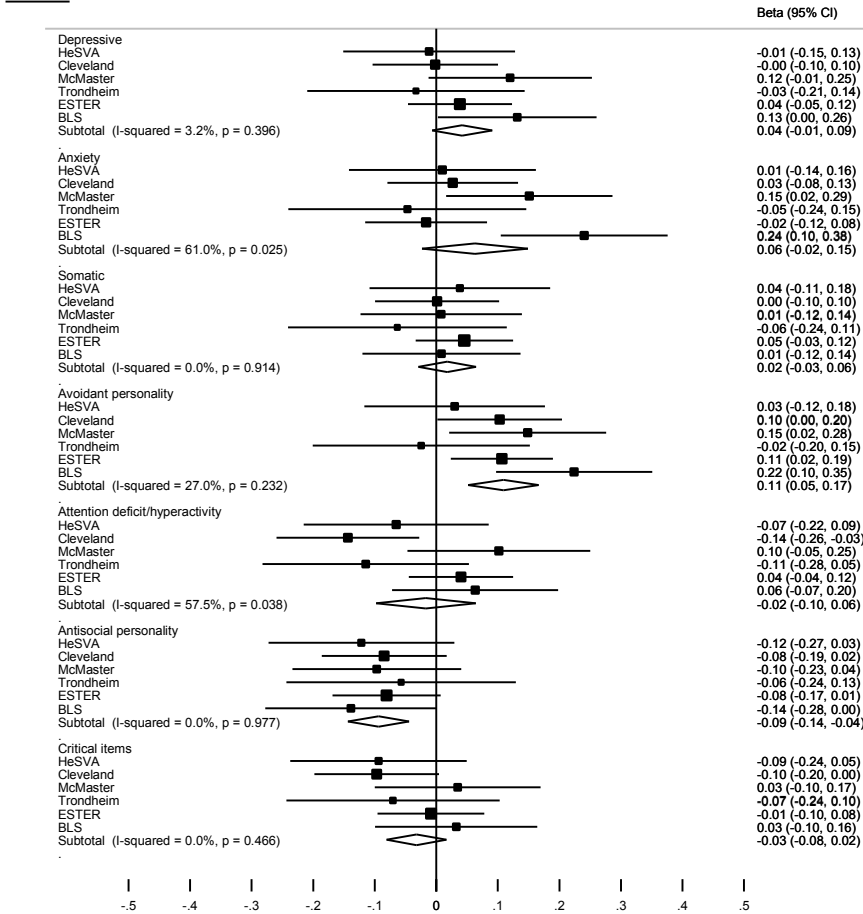
The black boxes and corresponding numbers represent betas, and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in young adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

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Figure 4   Associations between preterm birth at VLBW or ELBW and mental health problems on the Achenbach Adult Self-Report syndrome scales in young adulthood.

On the syndrome scales preterms reported less rule-breaking behavior and intrusive behavior (Figure 4) and on the DSM-IV-oriented scales they reported more avoidant personality and less antisocial personality problems (Figure 5)

than controls (*p*-values < 0.001). No statistical heterogeneity existed between the study cohorts in these analyses (*I²* < 27.0% in all analyses, *p*-values > 0.23) (Figures 3-5).

The black boxes and corresponding numbers represent betas, and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in young adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

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Figure 5   Associations between preterm birth at VLBW or ELBW and mental health problems on the Achenbach Adult Self-Report DSM-IV-oriented scales and critical items in young adulthood.

When we excluded individuals with neurosensory impairments from the analyses, the significant findings remained virtually identical (pooled meta-analysis p-values < 0.005; data not shown), except for two: in the pooled meta-analysis the difference between preterms and controls on internalizing problems became non-significant (p = 0.052), and the previously marginally significant difference in the withdrawn problems, with preterms reporting higher levels, became significant (p = 0.01).

When we restricted the comparisons to those preterms who were born at ELBW, they reported less externalizing problems than controls (pooled beta = -0.07; 95% CI = -0.14, -0.01, p = 0.04). There was no significant heterogeneity between the study cohorts in this analysis (I^2=36.6%, p > 0.13), and no other significant differences between the groups (p-values > 0.07).

Sex*preterm *vs*. control interactions were significant in the analyses of intrusive behavior (p = 0.02) and avoidant personality problems (p = 0.03). Separate meta-analyses for men and women revealed, that both preterm men (beta = -0.02; 95% CI = -0.04, -0.00; p = 0.03) and women (beta = -0.10; 95% CI = -0.17, -0.03; p = 0.005) reported less problems on intrusive behaviors than controls. Further, both preterm men (beta = 0.02; 95% CI = 0.00, 0.04; p = 0.02) and women (beta = 0.18; 95% CI = 0.11, 0.25; p < 0.001) reported more avoidant personality problems than controls. However, the differences between preterms and controls were more pronounced in women.

Finally, we tested if those born preterm at SGA and AGA differed from each other in mental health problems. The SGA group reported less thought problems than the AGA group (beta = -3.00; 95% CI = -4.45, -1.55; p < 0.001). Otherwise these groups were similar (p-values > 0.05; data not shown).

5.2 PRETERM BIRTH AND THE ASSOCIATION BETWEEN ASD-RELATED TRAITS AND VISUAL PROCESSING IN ADULTHOOD (STUDY II)

Young adults born preterm had lower ROCF Immediate and Delayed recall, Block Design and Full scale IQ scores, and they performed slower on the ROCF Immediate recall task than controls. Preterms also had higher AQ Social interaction subscores (indicating higher ASD-related traits) and lower Attention to detail subscores (indicating lower ASD-related attention to detail traits), but there were no significant differences between the SGA and AGA groups in these scores.

Figure 6 shows that among preterms, higher AQ Total sum score was associated with slower performance in all three ROCF time conditions (Copy, Immediate recall and Delayed recall) (models 1-3), and higher AQ Social interaction subscore was associated with slower performance in ROCF Immediate and Delayed recall time conditions (models 1-3). However, the association between AQ Total sum score and ROCF Copy time score did not survive the FDR correction. The effects were of small to medium size (Cohen's

f^2 ranges from 0.05 to 0.16). These associations were not significant in the control group.

Associations between ASD-related traits and visual processing in very low birth weight and term-born young adults
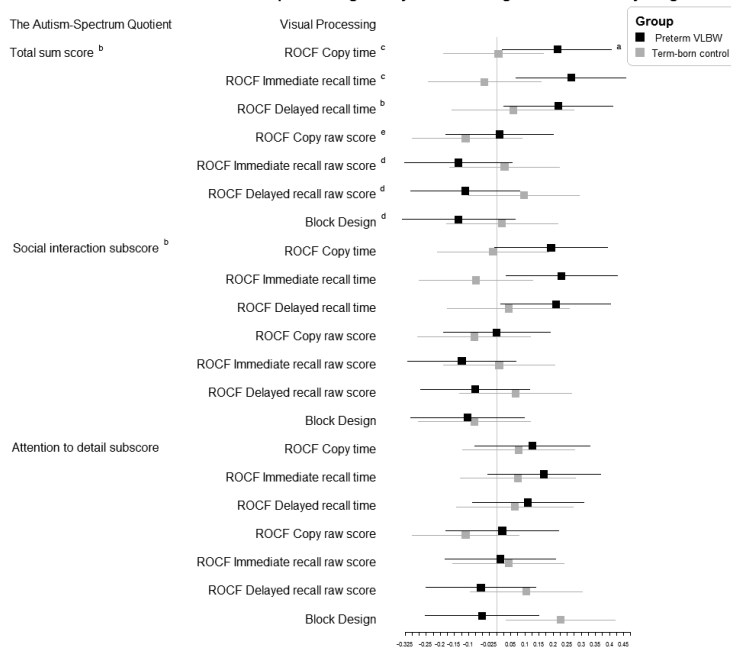
Unstandardized regression coefficients (B) and their 95% confidence intervals (CI) indicating the increase in AQ scores in SD units per each ROCF and Block Design SD unit score increase in a model adjusting for sex and age at assessment (Model 1).

When adjusting further for highest education of either parent, current head circumference, and head circumference S.D. score at birth (Model 2), and further, for full IQ (Model 3; only in ROCF analyses), all associations stayed statistically significant (P-values<0.05).

(a) Not significant after controlling for inflation of Type II error rate due to multiple testing with a false detection rate (FDR) procedure setting the false detection rate across 7 tests at 0.05.

Variables were transformed to attain normality and improve linear model fitting using (b) square-root, (c) logarithmic, or (d) square transformations, or were e rank-normalized using Blom's formula.

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Figure 6   The associations between Autism-Spectrum Quotient (AQ) scores and Rey-Osterrieth Complex Figure Test (ROCF) time and raw scores and Block Design score in the VLBW and control groups. Unstandardized regression coefficients (B) and their 95% confidence intervals (CI) indicating the increase in AQ scores in SD units per each ROCF and Block Design SD unit score increase.

In order to investigate the clinical significance of the effect sizes of AQ Total sum score on the ROCF Immediate and Delayed recall time scores, we reran the analyses of model 1 using unstandardized transformed variables. Then,

using the unstandardized regression coefficients, we back-transformed the ROCF time scores to conclude how many seconds slower the performance was per each 1-point increase in AQ Total sum score. On the Immediate recall condition, the performance time was 1.4 seconds slower, and on the Delayed recall condition, it was 3.1 seconds slower for every 1-point increase in the AQ Total sum score (range of scores 0-50). Hence, the participants drew the ROCF figure from recall immediately 1.4 seconds and when being delayed 3.1 seconds slower for each AQ Total sum score they reported more.

Interaction analyses revealed that the associations between AQ Total sum score and Immediate recall time condition ($F (1,196) = 4.79$ $p = 0.03$ for preterm vs. control*AQ Total sum score interaction in model 1; p-values < 0.03 for models 2-3), and the association between AQ Social interaction subscore and Immediate recall time condition ($F (1,196) = 4.39$ $p = 0.04$ for preterm vs. control*AQ Social interaction interaction in model 1; p-values < 0.04 for models 2-3) were statistically significantly different between the preterm and control groups. Other interaction estimates with the time variables showed a similar trend, but they were not statistically significant (p-values > 0.07 for preterm vs. control x AQ score interactions). There were no significant associations between AQ scores and ROCF raw scores in the preterm or control group, and no significant interactions (p-values > 0.10 for preterm vs. control *AQ score interactions).

In the control group higher scores in AQ Attention to detail subscore were associated with better performance in Block Design (models 1-2). This association was not significant in the preterm group, and preterm vs. control *AQ Attention to detail subscore interaction showed the same trend (p-values > 0.06, models 1-2).

In the preterm AGA group, higher AQ Total score and Social interaction subscore was associated with slower performance in ROCF time conditions (Copy, Immediate recall and Delayed recall, p-values < 0.05 in models 1-3 except the AQ scores and Copy time score p-values > 0.07 in models 2-3). In the preterm SGA group none of these associations were significant (p-values > 0.63). P-values for interactions between AGA vs. SGA*AQ Total score were 0.58, 0.06, and 0.12, and for AGA vs. SGA*AQ Social interaction subscore 0.90, 0.74, 0.08, for the three ROCF time conditions, respectively. In the preterm SGA group, higher AQ Social interaction subscore was associated with lower Delayed recall raw scores ($p = 0.047$, model 1, p-values > 0.26, models 2-3), in the preterm AGA group this association was not significant ($p = 0.97$). P-value for interaction between AGA vs. SGA*AQ Social interaction subscore was 0.62.

5.3 SYNTHETIC GLUCOCORTICOID EXPOSURE AND EARLY CHILDHOOD MENTAL HEALTH AND PSYCHOLOGICAL (STUDY IV)

Compared to non-exposed children, betamethasone-exposed children had lower gestational age, were more often born preterm, had lower birth weight, length, and head circumference, as well as lower birth weight and length SD scores, and were more often born small-for-gestational age in birth weight and birth length. They were more often delivered by caesarean section and were more often born from pregnancies complicated by pre-eclampsia, type 1 diabetes, obesity, and premature rupture of membranes.

In comparison to betamethasone non-exposed children, children who were exposed to betamethasone had higher odds of any mental and behavioral, psychological development, and behavioral and emotional disorder (Table 5). They also had higher odds of having two to four co-morbid disorders from the main diagnosis categories. Adjustments for the covariates did not change the significant findings (models 1-3 in Table 5).

Of the specific disorders of psychological development, betamethasone-exposed compared to non-exposed children had higher odds of having specific developmental disorders of speech and language (6.8% vs 2.9%, OR=2.57, 95% CI=1.25 to 5.30, $p \leq 0.05$ across all adjustment models 1-3) and other disorders of psychological development (4.3% vs 0.7%, OR = 7.26, 95% CI = 2.83 to 18.62, $p < 0.001$ across all adjustment models 1-3). Of the specific behavioral and emotional disorders, betamethasone-exposed compared to non-exposed children had higher odds of having hyperkinetic disorders (6.0% vs 1.4%, OR = 4.70, 95% CI = 2.11 to 10.49, $p < 0.02$ across all adjustment models 1-3). When replacing birth weight SD score with birth length or head circumference SD scores in the analyses with mental and behavioural disorders in models 2-3, the results were similar to those in the original analyses (all p-values < 0.01; data not shown).

The interaction analyses 'betamethasone-exposure vs. non-exposure* preterm vs. term birth' (all p-values>0.27) or 'betamethasone exposure vs. non-exposure*girl vs. boy' did not reveal any significant interactions (all p-values > 0.07; data not shown).

Betamethasone-exposed, in comparison to non-exposed children, had higher scores on total, internalizing, and externalizing psychiatric problems (Table 6). These differences survived all covariate adjustments (models 1-3 in Table 6).

The odds of failing to meet the development that is typical for the child's age in communication, problem solving, and personal social skills was higher in betamethasone-exposed children compared to non-exposed children (model 1 in Table 7). The association with personal social skills survived adjustments for all covariates (models 2-3 in Table 7). When replacing birth

weight SD score with birth length or head circumference SD scores in models 2-3, the results were similar to those in the original analyses (data not shown).

The interaction analyses 'betamethasone-exposure vs. non-exposure*preterm vs. term birth' did not reveal any significant interactions (all p-values > 0.12; data not shown).

Further, we found only one significant betamethasone exposure vs. non-exposure*girl vs. boy interaction on externalizing problems (p = 0.04) which showed that betamethasone-exposed boys scored higher than non-exposed boys on externalizing problems (B = 0.66, 95% CI = 0.28 to 1.04, p = 0.001) while exposed and non-exposed girls did not differ on this scale (p = 0.33).

Table 4. *The prevalence of child main category diagnoses of mental and behavioral disorders according to the International Classification of Diseases-10 and associations with antenatal betamethasone exposure.*

International Classification of Diseases, tenth revision (ICD-10) diagnoses	BM-exposed No. (%)	BM non-exposed No. (%)	Model 1 Odds Ratio (95% Confidence Interval)	p	Model 2 Odds Ratio (95% Confidence Interval)	p	Model 3 Odds Ratio (95% Confidence Interval)	p
Any mental and behavioral disorder (F00-F99)	24 (20.5)	386 (8.4)	2.76 (1.76, 4.32)	<0.001	2.56 (1.50, 4.38)	<0.001	2.58 (1.50, 4.42)	<0.001
ICD-10 main diagnosis categories								
Disorders of psychological development (F80-F89)	19 (16.2)	238 (5.2)	3.61 (2.19, 5.95)	<0.001	3.59 (1.96, 6.59)	<0.001	3.57 (1.94, 6.59)	<0.001
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90-F98)	14 (12.0)	184 (4.0)	3.29 (1.86, 5.82)	<0.001	2.61 (1.28, 5.31)	0.008	2.66 (1.30, 5.46)	0.007

Only disorders which included children in the betamethasone-exposed and non-exposed groups born preterm and at term were included in the analyses.

Model 1: adjusted for child sex and birth year.

Model 2: adjusted for model 1 + maternal early pregnancy body mass index (kg/m²), hypertensive (gestational hypertension, pre-eclampsia, chronic hypertension) and diabetic (gestational diabetes, type 1 diabetes) pregnancy and pre-pregnancy disorders, delivery mode (vaginal/caesarian section), premature rupture of membranes (yes/no), mother's age (years), education (tertiary/other), parity (primiparous/multiparous), maternal smoking during pregnancy (no/quit or smoked throughout), maternal alcohol use during pregnancy (yes/no), maternal history of physician-diagnosed asthma (yes/no), child's gestational age (weeks), birth weight standardized by sex and gestational age according to Finnish growth charts (Pihkala et al., 1989) (SD units).

Model 3: adjusted for model 2 + maternal mental and behavioral disorder (any diagnosis/no diagnosis).

Table 5. *The mean differences between betamethasone-exposed and non-exposed children in mother-reported psychiatric problems.*

Psychiatric problems	Model 1 Mean difference (95% Confidence Interval) (n=2,581)	p	Model 2 Mean difference (95% Confidence Interval) (n=2,581)	p	Model 3 Mean difference (95% Confidence Interval) (n=2,257)	p
Total Problems	0.39 (0.15, 0.64)	0.002	0.35 (0.09, 0.61)	0.008	0.31 (0.05, 0.56)	0.02
Internalizing Problems	0.33 (0.09, 0.58)	0.008	0.29 (0.03, 0.55)	0.03	0.28 (0.03, 0.54)	0.03
Externalizing Problems	0.38 (0.13, 0.62)	0.003	0.34 (0.08, 0.60)	0.01	0.29 (0.03, 0.55)	0.03

Differences are in standard-deviation units.

Model 1: adjusted for child sex (boy/girl) and age (months)

Model 2: model 1 + maternal early pregnancy body mass index (kg/m^2), hypertensive (gestational hypertension, pre-eclampsia, chronic hypertension) and diabetic (gestational diabetes, type 1 diabetes) pregnancy and pre-pregnancy disorders, delivery mode (vaginal/caesarian section), mother's age (years), education (tertiary/other), parity (primiparous vs. multiparous), premature rupture of membranes (yes/no), maternal smoking during pregnancy (no/quit or smoked throughout), maternal alcohol use during pregnancy (yes/no), maternal history of physician-diagnosed asthma (yes/no), child's gestational age (weeks), birth weight standardized by sex and gestational age according to Finnish growth charts (Pihkala et al., 1989) (SD units).

Model 3: model 2 + trimester-weighted mean score of maternal depressive symptoms during pregnancy and maternal depressive symptoms at the time of rating the child behavior.

Table 6.   *The associations between antenatal betamethasone exposure and child developmental milestones.*

Developmental milestones domains	No developmental delay (>-1SD as reference group) vs.							
	Mild developmental delay (-2SD > - ≤ -1SD)				Fails to meet development typical for child's age (≤-2SD)			
	No. (%)		Odds Ratio (95% Confidence Interval)	p	No. (%)		Odds Ratio (95% Confidence Interval)	p
	Exposed	Non-exposed			Exposed	Non-exposed		
Communication skills								
Model 1 (n=2,470)	4 (6.6)	129 (5.0)	1.54 (0.56, 4.21)	0.40	5 (8.2)	96 (3.7)	2.64 (1.06, 6.56)	0.04
Model 2 (n=2,470)	4 (6.6)	129 (5.0)	1.26 (0.42, 3.79)	0.68	5 (8.2)	96 (3.7)	1.69 (0.57, 5.04)	0.35
Model 3 (n=2,146)	4 (7.8)	115 (5.2)	1.28 (0.41, 4.00)	0.68	5 (9.8)	90 (4.1)	1.63 (0.54, 4.94)	0.38
Fine motor skills								
Model 1 (n=2,455)	6 (9.8)	208 (8.1)	1.44 (0.61, 3.39)	0.40	4 (6.6)	117 (4.5)	1.75 (0.64, 4.81)	0.28
Model 2 (n=2,455)	6 (9.8)	208 (8.1)	1.08 (0.42, 2.76)	0.88	4 (6.6)	117 (4.5)	1.27 (0.40, 4.03)	0.69
Model 3 (n=2,139)	5 (9.8)	181 (8.2)	1.15 (0.42, 3.17)	0.79	3 (5.9)	109 (4.9)	0.99 (0.27, 3.72)	0.99
Gross motor skills								
Model 1 (n=2,469)	4 (6.6)	177 (6.9)	1.01 (0.38, 2.74)	0.98	5 (8.8)	128 (5.0)	1.77 (0.71, 4.42)	0.22
Model 2 (n=2,469)	4 (6.6)	177 (6.9)	1.00 (0.34, 2.92)	1.00	5 (8.8)	128 (5.0)	0.69 (0.22, 2.20)	0.53
Model 3 (n=2,144)	4 (7.8)	151 (6.8)	1.11 (0.37, 3.31)	0.85	4 (7.8)	112 (5.0)	0.68 (1.19, 2.40)	0.54
Problem solving skills								
Model 1 (n=2,447)	5 (8.2)	159 (6.2)	1.69 (0.68, 4.18)	0.26	8 (13.1)	113 (4.4)	3.74 (1.76, 7.94)	<.001
Model 2 (n=2,447)	5 (8.2)	159 (6.2)	1.61 (0.60, 4.33)	0.34	8 (13.1)	113 (4.4)	3.24 (1.37, 7.69)	0.008
Model 3 (n=2,133)	5 (9.8)	142 (6.4)	1.67 (0.61, 4.52)	0.32	7 (13.7)	103 (4.6)	2.45 (0.93, 6.46)	0.07

Personal social skills

|							
Model 1 (n=2,479)	6 (9.8)	1.44 (0.62, 3.34)	0.39	6 (9.8)	92 (3.6)	3.70 (1.56, 8.81)	0.003
Model 2 (n=2,479)	6 (9.8)	1.13 (0.45, 2.83)	0.80	6 (9.8)	92 (3.6)	3.56 (1.32, 9.58)	0.01
Model 3 (n=2,152)	6 (11.8)	1.43 (0.56, 3.64)	0.45	6 (11.8)	87 (3.9)	3.76 (1.35, 10.43)	0.01

Model 1: adjusted for child sex (boy/girl) and age (months)

Model 2: model 1 + maternal early pregnancy body mass index (kg/m²), hypertensive (gestational hypertension, pre-eclampsia, chronic hypertension) and diabetic (gestational diabetes, type 1 diabetes) pregnancy and pre-pregnancy disorders, delivery mode (vaginal/caesarian section), mother's age (years), education (tertiary/other), parity (primiparous vs. multiparous), premature rupture of membranes (yes/no), maternal smoking during pregnancy (no/quit or smoked throughout), maternal alcohol use during pregnancy (yes/no), maternal history of physician-diagnosed asthma (yes/no), child's gestational age (weeks), birth weight standardized by sex and gestational age according to Finnish growth charts (Pihkala et al., 1989) (SD units).

Model 3: model 2 + trimester-weighted mean score of maternal depressive symptoms during pregnancy and maternal depressive symptoms at the time of rating the child behavior.

5.4 DEPRESSIVE SYMPTOMS DURING PREGNANCY AND CHILD ADHD SYMPTOMS (STUDY III)

Maternal biweekly, trimester-specific and trimester-weighed mean values of depressive symptoms during pregnancy were significantly correlated (Pearson r's ranged from 0.51 to 0.92, all *p*-values < 0.001) and were also significantly correlated with depressive symptoms after pregnancy (Pearson r's ranged from 0.36 to 0.46, all *p*-values < 0.001) (M. Lahti et al., 2017). The median number of consecutive depressive symptom measurements during pregnancy in the entire sample was 13 and the interquartile range was 12 to 14. There were altogether 879 (49.4%) women with data on all 14 measurement points during pregnancy and only 334 (18.8%) women had more than two missing values during pregnancy.
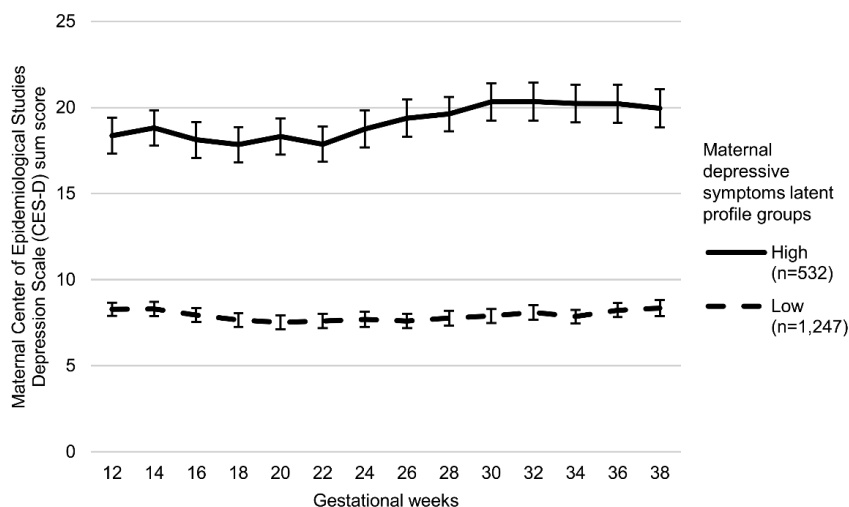
Figure 7   Latent profile analysis showing the most optimal, two group, solution of mothers with consistently low and high scores on the Center of Epidemiological Studies Depression Scale (CES-D) throughout pregnancy.

Figure 7 shows that the most optimal latent profile solution (in comparison to solutions with three to eight groups) identified two groups of women with consistently low and high levels of depressive symptoms throughout pregnancy (Akaike Information Criterion = 147821.10, sample-size-adjusted Bayesian Information Criterion = 147920.30, Vuong-Lo-Mendell-Rubin LRT and Lo-Mendell-Rubin-adjusted likelihood ratio test *p*-values < 0.001). For

the two latent profile groups, the percentage of women with data on all 14 measurement points compared to the ones with at least one missing value was not significantly different (50.9% in the low and 45.9% in the high depressive symptom level group had all 14 measurement points, $p = 0.051$ for group difference). Figure 8 also shows that child ADHD symptoms and the proportion of and odds of children with clinically significant ADHD symptoms were higher in the group of women who had consistently high depressive symptoms throughout pregnancy compared to the group with consistently low depressive symptoms.
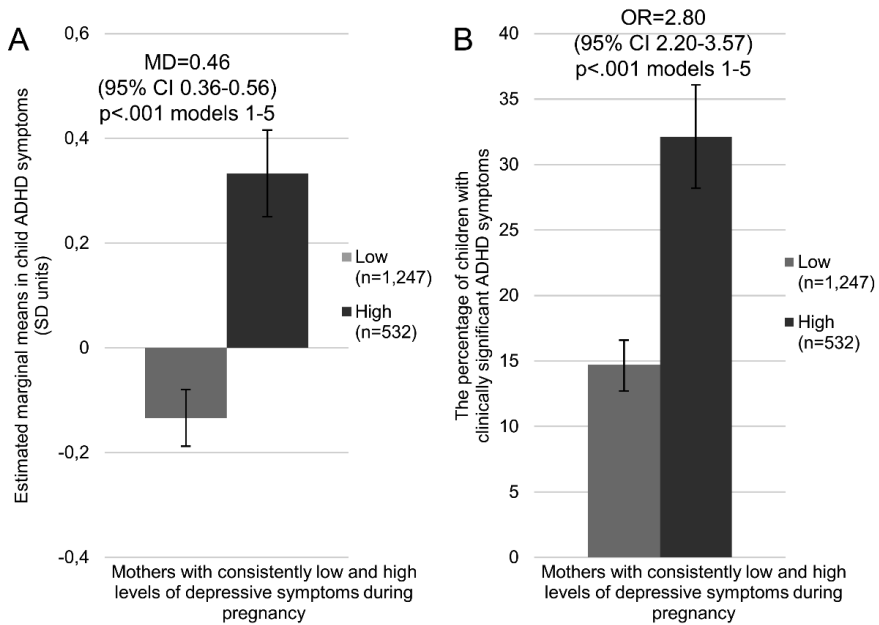
Figure 8 Child's behavioural symptoms of attention-deficit/hyperactivity disorder on the Conners' Hyperactivity Index (CHI) estimated marginal mean scores (A), and proportion of children with scores above the clinical cutoff (10) in the CHI (B) according to whether the mother had consistently low or high scores on the Center of Epidemiological Studies Depression Scale (CES-D) throughout pregnancy.

Further, higher maternal biweekly, trimester-specific and trimester-weighted mean depressive symptom scores were significantly associated with higher ADHD symptom scores and higher odds for clinically significant ADHD symptoms in children (Table 4). These associations were significant across all adjustment models with all covariates, including maternal ADHD symptoms.

Table 7. *Association between maternal depressive symptoms during pregnancy and child behavioural symptoms of attention-deficit/hyperactivity disorder on the Conners' Hyperactivity Index at age 3.5 years.*

Maternal Center of Epidemiological Studies Depression Scale trimester-weighted mean score during pregnancy	Child's Conners' Hyperactivity Index Sum score		Child's Conners' Hyperactivity Index Sum score≥10	
	B (95%CI)	p	OR (95%CI)	p
Model 1	0.26 (0.22, 0.31)	<0.001	1.83 (1.62, 2.08)	<0.001
Model 2	0.25 (0.21, 0.30)	<0.001	1.85 (1.62, 2.11)	<0.001
Model 3	0.26 (0.21, 0.30)	<0.001	1.86 (1.63, 2.12)	<0.001
Model 4	0.24 (0.20, 0.29)	<0.001	1.77 (1.55, 2.03)	<0.001
Model 5	0.15 (0.10, 0.20)	<0.001	1.49 (1.29, 1.73)	<0.001

Figure 9 shows that maternal depressive symptoms after pregnancy added to the effect of maternal depressive symptoms during pregnancy (both *p*-values for interactions = 0.03 for depressive symptoms during pregnancy*depressive symptoms after pregnancy interaction on child continuous and clinically significant ADHD symptoms scores). Across all adjustment models, child ADHD symptom scores and proportion of children with clinically significant symptoms were the highest if the mother reported depressive symptoms above the clinical cutoff both during and after pregnancy (Figure 9).
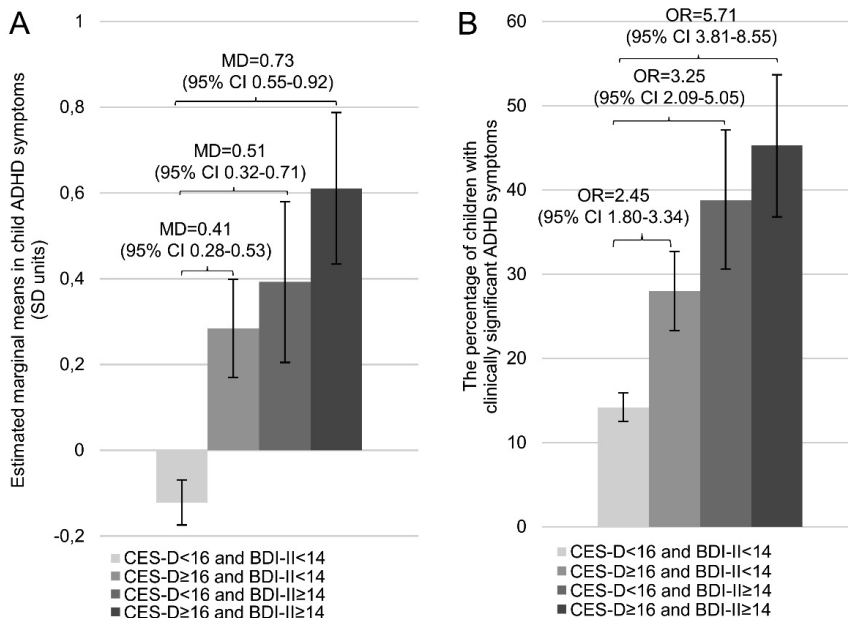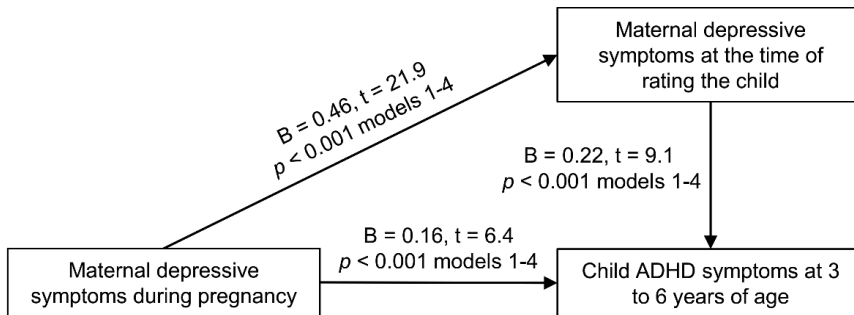
Error bars refer to 95% Confidence Intervals (95% CI), and numbers to mean differences (MD) (A) and odds ratios (OR) (B) and their 95% CIs in model 1. Women who scored below the clinical cutoff in both the CES-D during pregnancy and in the BDI-II after pregnancy were used as the comparison group.

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Figure 9   Estimated marginal means (A) of the child's behavioural symptoms of attention-deficit/hyperactivity disorder on the Conners' Hyperactivity Index (CHI) and proportion of children with scores above the clinical cutoff (≥10) in the CHI (B) according to the maternal Center of Epidemiological Studies Depression Scale (CES-D) trimester-weighted mean score (≥16) during pregnancy and Beck Depression Inventory-II (BDI-II) sum score (≥14) after pregnancy above and below the clinical cutoffs.

Figure 10 shows, that the effect of maternal depressive symptoms during pregnancy on child ADHD symptoms was partially mediated via maternal depressive symptoms after pregnancy. The model also shows that maternal depressive symptoms during pregnancy still had a direct and significant effect on child ADHD symptoms after adjusting for depressive symptoms after pregnancy. Together, depressive symptoms during and after pregnancy accounted for 11.4% of the variation of the child's ADHD symptoms.

Indirect effect B = 0.10, 95% Confidence Interval 0.08 – 0.13, p < 0.001 models 1-4

Numbers refer to unstandardized regression coefficients (B) and their 95% Confidence Intervals from models adjusted for child's age and sex.

Figure 10   Mediation model of the effects of maternal depressive symptoms during pregnancy on child's behavioural symptoms of attention-deficit/hyperactivity disorder on the Conners' Hyperactivity Index via maternal depressive symptoms after pregnancy.

Finally, maternal pre-pregnancy obesity and pregnancy disorders, child's sex, maternal history of physician-diagnosed depression, or maternal ADHD problems had no effects on the findings: across all groups, the associations between maternal depressive symptoms during pregnancy and child ADHD symptoms were significant.

6 DISCUSSION

The overall aim of this work was to study developmental origins of mental health from early childhood to adulthood. Specifically, I focused on three important risk factors: preterm birth, exposure to antenatal synthetic glucocorticoids, and maternal depressive symptoms during pregnancy.

First, it was shown that individuals born preterm at VLBW continue to report long term mental health problems in young adulthood revealing a characteristic preterm behavioral phenotype that includes a heightened risk for internalizing problems and avoidant personality problems in combination with a lowered risk for externalizing problems (Study I). Young adults born preterm at VLBW were also shown to have a higher risk of cumulative social and cognitive problems as higher levels of ASD-related traits were associated with slower performance in visual processing tasks requiring global visual processing skills (Study II).

Thirdly, antenatal exposure to betamethasone was shown to be associated with problems in early childhood mental health and psychological development. Children who were exposed to betamethasone had nearly three times higher odds of having any mental and behavioral disorder, higher scores on mother-reported total, internalizing, and externalizing psychiatric problems, and higher odds of failing to meet the development that is typical for the child's age in personal social skills (Study III).

Furthermore, maternal depressive symptoms throughout pregnancy were shown to be associated with child ADHD symptoms, with children of mothers who experienced consistently high depressive symptoms throughout pregnancy having almost three times higher odds for clinically significant ADHD symptoms in early childhood (Study IV).

I will further discuss the individual study findings in relation to previous evidence below.

6.1 ASSOCIATION BETWEEN PRETERM BIRTH AND YOUNG ADULTHOOD MENTAL HEALTH AND COGNITION (STUDIES I AND II)

6.1.1 SELF-REPORTED MENTAL HEALTH PROBLEMS (STUDY I)

Study I showed that, across six longitudinal birth cohort studies from five countries, individuals born preterm at VLBW reported more internalizing problems and avoidant personality problems in young adulthood compared to their term-born peers. Further, they also reported less externalizing, rule-breaking, intrusive, and anti-social personality problems than term-born

controls. Additionally, Study II found that young adults born preterm at VLBW reported more social interaction problems. These findings suggest that there is a universal phenotype of mental health problems in young adults born preterm at VLBW characterized by internalizing, avoidant personality, and social interaction problems. This indicates that young adults born preterm at VLBW may worry more, be more anxious, shy and withdrawn, and lack self-confidence in social relationships. Additionally, results from Study II suggest cumulative social and cognitive problems in preterm VLBW individuals.

Previous individual studies on self-reported mental health problems in adults born preterm have also shown more internalizing and social problems, but they have been less consistent in their findings on externalizing problems (Boyle et al., 2011; Hack et al., 2004; Hille et al., 2008; Lund et al., 2012; Vederhus et al., 2015). In addition, previous studies on personality traits have shown more withdrawal, social avoidance and anxiousness (Eryigit-Madzwamuse, Strauss, Baumann, Bartmann, & Wolke, 2015; Hertz, Mathiasen, Hansen, Mortensen, & Greisen, 2013), and less extraversion, hostility and assertiveness (Allin et al., 2006; Pesonen et al., 2008; Pyhälä, Räikkönen, et al., 2011) in preterm VLBW adults. Further, these behavioral characteristics of preterm VLBW adults are reflected in their reports of lesser risk-taking behavior and fewer romantic partners (Eryigit-Madzwamuse et al., 2015; Kajantie et al., 2008; Strang-Karlsson et al., 2008).

Meta-analyses conducted on children who were born preterm have demonstrated more internalizing and attention problems, but mixed findings on externalizing problems (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Franz et al., 2018). Thus, our findings suggest that problems in internalizing and social behaviors may persist into young adulthood. The absence of self-reported attention problems in preterm VLBW young adults in our meta-analysis may reflect a change in the symptom manifestation from childhood to adulthood. However, speculation on developmental change should be treated with caution, because the age-dependent decline in ADHD problems seems to be even greater in the general population (Breeman et al., 2016), and different measures and/or informants have been used to measure symptomatology in childhood and in adulthood.

Apart from studies using self-reports of mental health, nationwide registry studies have demonstrated an increased risk for a range of manifest psychiatric disorders, including non-affective psychotic disorders and bipolar affective disorders, depressive disorders, ADHD and ASD (D'Onofrio et al., 2013; Nosarti et al., 2012) in adults born preterm. Other studies using structured psychiatric interviews have also found an increased risk for depression and anxiety disorders (Lund, Vik, Skranes, Brubakk, & Indredavik, 2011; Walshe et al., 2008; Westrupp et al., 2011) and ADHD (Franz et al., 2018; Lund et al., 2011; Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015), and a lower risk for substance-use disorders (Van Lieshout et al., 2015) in adulthood. Childhood studies, which have indicated increased risks for attention and internalizing problems (Aarnoudse-Moens et al., 2009; Bhutta

et al., 2002), as well as externalizing problems (Bhutta et al., 2002), have used parent- or teacher-reports. However, mental health problems were self-reported in the current study. Therefore, direct comparisons with studies that have fused diagnoses of severe mental disorders from nationwide registries, or that have used structured psychiatric interviews or parent- or teacher-reports, are not fully justified. For example, psychotic disorders or autism are not comprehensively assessed in the ASR. It has been estimated that health care services use and expenditure is higher in the preterm group than in term-borns (Petrou, Eddama, & Mangham, 2011), which may also lead to more sensitive diagnosing of psychiatric disorders among them. However, the partially discrepant study findings may also reflect the difference between categorical diagnostic approaches and dimensional self-assessments. Diagnoses represent severe mental disorders while dimensional self-assessments also cover the sub-clinical symptoms. Thus, they supplement each other in adding understanding of mental health problems among adults born preterm. Hence differences in the study findings may arise from the different source of obtaining information and different focus of instruments. In line, previous studies have demonstrated that parent-reports and in-depth psychiatric interviews assign more problems to preterm-born adults' mental health than their self-reports (Hack et al., 2004; Heinonen et al., 2013; Hille et al., 2008; Lund et al., 2012).

Those preterms born SGA reported less thought problems than those born AGA. Also, in both men and women, less intrusive behavior problems and more avoidant personality problems were more characteristic of preterms than of controls, but the group differences were more pronounced among women. These specific associations have not been reported before, although elevated risk of depressive (Räikkönen et al., 2008), internalizing (Boyle et al., 2011), and ADHD (Strang-Karlsson et al., 2008; Van Lieshout et al., 2015) problems for those preterms born SGA, and internalizing problems for preterm women (Hack et al., 2004) have been reported in previous studies. One explanation for the inconsistent pattern of the previous studies and the current meta-analysis may arise from the different sample sizes, but differences may also arise from the different definitions of SGA used in this and the previous studies. It is also noteworthy that previous meta-analyses conducted in preterm children have not studied whether there are differences in mental health problems between those born SGA or AGA and between the sexes (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002).

6.1.2   ASD-RELATED TRAITS AND VISUAL PROCESSING SKILLS (STUDY II)

In Study II, it was shown that a higher level of ASD-related traits was associated with slower performance in visual processing tasks among young adults born preterm at VLBW. This association was characteristic only to preterms as indicated by a statistically significant interaction and no

significant association among term-born adults. However, the accuracy of the copied figure was not associated with ASD-related traits in preterm adults, concurring with a recent meta-analysis (Van der Hallen, Evers, Brewaeys, Van den Noortgate, & Wagemans, 2015). While processing speed in the ROCF has not been studied previously, the significant finding related to the associations between ASD-related traits and slower speed in the ROCF task is in line with previous research on individuals with ASD indicating that they are slower in perceiving global order (Van der Hallen et al., 2015). Prior studies have documented that difficulties in making the developmental shift from a part-oriented approach to drawing the ROCF in childhood to a global approach in adulthood could be associated with ASD (Tsatsanis et al., 2011). This lends credence to suggest that slower performance on the ROCF in association with higher levels of ASD-related traits in our sample of preterm young adults may reflect difficulties in global processing.

It is not surprising that in this group of young adults born preterm at VLBW, we would see associations between global visual processing and ASD-related traits. Although research on atypicalities in non-social visual processing in ASD has focused on the tendency of individuals with ASD to focus on details rather than the whole, some studies have reported that individuals with ASD have problems in global visual processing (Grinter, Maybery, Pellicano, Badcock, & Badcock, 2010; Mammarella, Giofrè, Caviola, Cornoldi, & Hamilton, 2014; Narzisi, Muratori, Calderoni, Fabbro, & Urgesi, 2013), referring to problems in integrating parts to form a whole (Olu-Lafe, Liederman, & Tager-Flusberg, 2014) or being slower in perceiving global order than individuals without ASD (Van der Hallen et al., 2015). Coherent global motion perception (Chen et al., 2012; Greimel et al., 2013; C. E. Robertson, Martin, Baker, & Baron-Cohen, 2012; C. E. Robertson et al., 2014) and biological motion detection (Koldewyn, Whitney, & Rivera, 2011; Pavlova, 2012) problems have also been associated with ASD, but even these results have been contradicted in some studies (Pavlova, 2012; Vandenbroucke, Scholte, van Engeland, Lamme, & Kemner, 2008; Wright, Kelley, & Poulin-Dubois, 2014).

ASD can be considered as a continuum ranging from mild traits in the general population to the severe form of the disorder (Baron-Cohen et al., 2001; A. E. Robertson & Simmons, 2013; Worley & Matson, 2012). Hence, an increasing number of studies on samples of university students have shown that the atypical visual processing style as seen in ASD can also be found in neurotypical young adults in relation to higher levels of ASD-related traits (Grinter, Beek, Maybery, Badcock, & Van Beek, 2009; Laycock, Cross, Dalle Nogare, & Crewther, 2014). A higher level of ASD-related traits has been associated with a higher perceptual capacity and superior visual search (Almeida, Dickinson, Maybery, Badcock, & Badcock, 2013; Bayliss & Kritikos, 2011), an enhanced ability to find embedded targets in a large figure (Almeida, Dickinson, Maybery, Badcock, & Badcock, 2010, 2014; Grinter, Beek, et al., 2009), and a bias toward local visual processing (Grinter, Maybery, et al.,

2009; van Boxtel & Lu, 2013). Also, problems in global visual processing (Grinter, Maybery, et al., 2009) and in quick object recognition (Laycock et al., 2014) have been observed in individuals with higher levels of ASD-related traits.

Similar coherent global motion and biological motion problems have also been found in preterm children (Atkinson & Braddick, 2007; N. M. Taylor et al., 2009) and problems in biological motion processing have been associated with higher ASD-related traits in preterm children (Williamson et al., 2015). Disturbed dorsal stream processing in the visual system has most often been considered the cause of the atypical visual processing style related to ASD (Greimel et al., 2013; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005) and it has also been suggested to underlie visual processing problems in preterm children (Atkinson & Braddick, 2007).

The weak central coherence (WCC) theory has been proposed to explain the tendency of individuals with ASD to focus on details rather than the whole. WCC theory originally proposed that ASD-related traits associate with both enhanced processing of details and impaired global processing skills. This pattern results in difficulties to combine local information to create a coherent global form (Happé, 1999). The current findings of slower performance in global form visual processing fit the WCC theory. The reason why we saw this association only in the VLBW group may relate to the higher variability of ASD-related traits and visual processing difficulties in the VLBW group, and to the higher quantity of participants scoring above the intermediate cutoff of AQ Total sum score in the VBLW group compared to the control group. Previous studies of global processing difficulties associated with ASD-related traits in samples of university students have not controlled for preterm birth or low birth weight. Because preterm birth occurs in one in every ten deliveries worldwide, 15 million births per year (Blencowe et al., 2012), it is possible that those samples may have included participants who were born preterm or at VLBW. Note that we also had a single observation in the control group of an association between higher attention to detail and better performance on the Block Design task, suggesting better local visual processing (Simmons et al., 2009). This aspect of enhanced local visual processing has previously been shown in studies with university student samples (Grinter, Beek, et al., 2009), and it has specifically been emphasized in later versions of the WCC theory.

Modern theories of intelligence consider processing speed as a component of intelligence (see Deary *et al.*(Deary, Penke, & Johnson, 2010) for review). Slower processing speed has been reported to be associated with higher levels of problems in communication in high-functioning children with ASD, indicating that processing speed may moderate communication skills and deficits in ASD (Oliveras-Rentas, Kenworthy, Roberson, Martin, & Wallace, 2012). Whether the current finding of slower visual processing speed reflects slower processing speed in general, is an intriguing question. Measurement of general processing speed in WAIS-IV does rely on visual stimuli, so other assessment methods would be required to investigate this option further.

Our hypothesis was that the SGA group would be more susceptible to ASD-related traits and a stronger association between ASD-related traits and visual processing would be observed. However, our hypothesis was not supported. The degree of intrauterine growth restriction in the preterm group did not modify any associations between ASD-related traits and visual processing tasks, though our sample size which enabled us to detect main effects, may have been under-powered to detect significant interaction effects.

6.1.3 MECHANISMS

Potential underlying mechanisms for our findings are multiple, including neurobiological, endocrinological and psychosocial processes, which may individually affect or interact resulting in the outcomes found in our meta-analysis (Montagna & Nosarti, 2016). Being born preterm impacts brain development causing reductions in total brain volume, and disruptions in specific regional structures, structural connectome, and functional connectivity (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012; Karolis et al., 2016; Sølsnes et al., 2015), with neuroinflammation possibly contributing to the disruption of neural development (Hagberg et al., 2015; Pataky, Howie, Girardi, & Boardman, 2016). Further, potential abnormalities in brain development and function may directly be associated with behavioral, mental and social problems (Nosarti, 2013; Papini et al., 2016), or the association may be mediated by executive function problems (Loe, Feldman, & Huffman, 2014; Loe, Lee, & Feldman, 2013; Østgård et al., 2016; Wolfe, Vannatta, Nelin, & Yeates, 2015). In relation to endocrinological pathways, preterm birth, together with periods of treatment in the neonatal intensive care unit (NICU), parental separation and distress may alter the HPA-axis functioning of the developing infant (Brummelte et al., 2015, 2011; Habersaat et al., 2014; Kaseva et al., 2014; Winchester, Sullivan, Roberts, & Granger, 2016), and predispose preterm children to stress-related problems. Furthermore, there is increasing evidence that preterm children may be more the target of peer victimization (bullying) which may as well contribute to emotional and social problems through increased psychosocial stress and marginalization (Montagna & Nosarti, 2016; Wolke, Baumann, Strauss, Johnson, & Marlow, 2015). In addition, although studies on parenting sensitivity with preterm children are varied (Bilgin & Wolke, 2015), prematurity may cause long-term challenges for the development of parent-child relationship that fosters the emotional and behavioral development of the child (Brummelte et al., 2011; Huhtala et al., 2012). Naturally, genetic mechanisms cannot be ruled out either. However, at least part of the association between preterm birth and mental health problems is found to be independent of familial confounding (D'Onofrio et al., 2013). While sociodemographic factors have also been shown to differ between preterm and term populations (Smith, Draper, Manktelow, Dorling, & Field, 2007) and to

affect mental health outcomes (Hall & Wolke, 2012), our findings persisted after controlling for parental education.

6.2 THE ASSOCIATION BETWEEN SYNTHETIC GLUCOCORTICOID EXPOSURE AND EARLY CHILDHOOD MENTAL HEALTH (STUDY III)

Study III showed that antenatal exposure to betamethasone is associated with early childhood mental health and psychological development. Compared to non-exposed children, betamethasone-exposed children had nearly three times higher odds of having any mental and behavioral disorder, as well as over three times higher odds of having a disorder of psychological development (specifically speech and language) and behavioral and emotional disorder (specifically hyperkinetic) in childhood. Compared to non-exposed children, the betamethasone-exposed children also had nearly six times higher odds of co-morbid disorders. Our study findings with mother-reported child outcomes are in alignment with our findings on the child disorders: compared to the non-exposed children, the betamethasone-exposed children had higher scores on total, internalizing, and externalizing psychiatric problems, and higher odds of failing to meet the development that is typical for the child's age in personal social skills. Children who were born preterm or at term did not differ in the effects of betamethasone. Our findings are thus the first to show that sGCs are associated with harmful effects on child development that are robust and consistent across the sources of information; these harms not only relate to child mental and behavioral disorders but also to problems that are sub-threshold as indicated my maternal reports.

Our study findings disagree with the previous observational studies showing null effects of sGCs on affective problems (Davis et al., 2013) and intelligence (Alexander et al., 2016) in term-born children. Our findings also disagree with the RCTs which have reported null effects of sGCs on child behavior problems (Asztalos et al., 2014; P. R. Stutchfield et al., 2013) in term-born children. The RCTs have, however, shown harmful neurosensory effects in those exposed to multiple vs. a single course of sGCs (Asztalos et al., 2014), and harmful effects on learning in those exposed to a single course of sGCs vs. no exposure (P. R. Stutchfield et al., 2013). Our findings agree with a small observational study which combined preterm and term children and found that in comparison to those not exposed to sGCs, those exposed displayed more total psychiatric and inattention problems at age 8 years; These group differences were rendered non-significant at the age of 16 years (Khalife et al., 2013). This latter study did not examine if the effects varied by preterm/term birth. This precludes direct comparisons of our findings with findings of this study; Yet, our study verifies that antenatal sGCs may carry harmful effects on child developmental outcomes that are present, not only in mother-reports,

but also in mental and behavioral disorders. Whether these harmful effects persist in our study as the children age, is a subject of future studies.

None of the observed effects varied significantly between those born preterm and at term. These effects, tested in the presence of propensity score weights, were not explained by a number of important covariates either, including maternal pregnancy and pre-pregnancy disorders or premature rupture of membranes, which increase the risk of preterm birth (Goldenberg et al., 2008; Rosenberg et al., 2005) and hence the risk of exposure to antenatal sGCs, and maternal mental health which increases the risk of child mental and behavioral disorders and suboptimal psychological development. Our findings, thus, additionally also suggest that in term-born children, the potential benefits of antenatal sGCs may not outweigh the longer-term developmental harms.

Betamethasone appeared to exert sex-specific effects on mother-reported externalizing problems. This is of interest as boys in our and in other samples display higher scores on these problems. This may have resulted in a higher variance and statistical power to detect the associations in boys, or suggests that boys may be more susceptible to the harmful effects of sGCs. These findings, however, contradict a previous observational study which showed that the effect of betamethasone on higher salivary cortisol stress-reactivity was present in girls (Alexander et al., 2012). The sex-specific effects of sGC exposure have not been shown in other human studies, and findings from animal studies remain mixed (Kapoor, Petropoulos, & Matthews, 2008). The study by Alexander et al. (2012) comprised both pre-pubertal and pubertal children (Alexander et al., 2012) and our study sample with mother-reported psychiatric problems were pre-pubertal.

The mechanisms through which the sGC betamethasone affects development may relate to the functioning of the placenta. The typical timing of the administration of sGCs in clinical practice corresponds with when GRs and MRs are already expressed in the human fetus (Noorlander et al., 2006). Experimental animal studies have shown, that sGC administration can lead to a decrease in neuronal proliferation, neuronal damage and even neuronal death in the hippocampus (Haynes, Griffiths, Hyde, Barber, & Mitchell, 2001; Kim et al., 2004; Noorlander et al., 2014, 2008). Given the importance of the hippocampus in learning, memory, and spatial functioning (Burgess, Maguire, & O'Keefe, 2002), as well as neuroendocrine function (Lupien et al., 2009) and neurobehavioral problems (Geuze, Vermetten, & Bremner, 2005), it is plausible that hippocampus is the key target of sGC-related harms. However in a small human study, no hippocampal changes associated with exposure to sGCs were found (Modi et al., 2001). Another key target may be the cerebellum which undergoes rapid growth after 24 weeks of gestation (Limperopoulos, 2005). The cerebellum is highly dense in GRs (Pavlík, Buresová, & Burešová, 1984) and plays a role in emotion regulation (Schutter & van Honk, 2009) and neurobehavioral development (O'Halloran, Kinsella, & Storey, 2012). Studies

have found that exposure to sGCs can affect cerebellar development, which subsequently, may affect cognitive development (Noguchi, 2014).

There may be other brain mechanisms through which sGCs affect neurobehavioral development as well. In human studies, exposure to sGCs has been associated with cortical thinning especially in the rostral anterior cingulate cortex (Davis et al., 2013), which is also associated with internalizing problems (Boes, McCormick, Coryell, & Nopoulos, 2008). In addition, exposure to sGCs has been associated with decreased brain surface area and complexity of cortical folding in close to or term infants (Modi et al., 2001). Finally, a recent study found that antenatal sGC exposure is associated with reduced cord blood neurotrophin-3 (NT-3) in late preterm infants (Hodyl et al., 2016). NT-3 mediates neuronal growth, differentiation and synapse formation (Chao, 2003; Park & Poo, 2012), and thus may provide one mechanism through which sGC exposure affects brain development and subsequent neurobehavioral development.

6.3 PRENATAL DEPRESSIVE SYMPTOMS AND CHILD ADHD SYMPTOMS (STUDY IV)

Study IV showed, that maternal depressive symptoms throughout pregnancy are associated with child ADHD symptoms. Maternal depressive symptoms during pregnancy were also shown to be highly stable, and children of mothers with consistently high depressive symptoms during pregnancy showed higher levels of ADHD symptoms at the age of 3 to 6 years. These children also showed a higher proportion (over 32%) and nearly three times higher odds for clinically significant ADHD symptoms. It was therefore not surprising that were no gestation-week or trimester-specific associations between maternal depressive symptoms during pregnancy and child ADHD symptoms.

Our study also showed that higher levels of maternal depressive symptoms after pregnancy were associated with higher child ADHD symptom scores. These higher levels of depressive symptoms after pregnancy only partially accounted for the prenatal effects as maternal depressive symptoms during pregnancy also had a significant direct effect on the child's ADHD symptoms when adjusting for the symptoms after pregnancy. They did, however, add to the prenatal effects, such that child ADHD symptom scores and the proportion and odds of children with clinically significant ADHD symptoms were the highest among those women with clinically significant depressive symptoms both during and after pregnancy.

Our findings correspond with other findings within the DOHaD framework suggesting that prenatal exposure to environmental adversity may carry enduring effects on brain developmental sequelae, including risk for ADHD symptomatology (Barker, 2007; J. Lahti et al., 2006; Strang-Karlsson et al., 2008). Our findings are also in alignment with our own recent study on psychiatric behaviour problems (M. Lahti et al., 2017), and the other two

previous prospective studies based on the ALSPAC and the Generation-R cohorts on child attention and hyperactivity problems (Leis et al., 2014; Van Batenburg-Eddes et al., 2013) showing that maternal depressive symptoms during pregnancy are associated with child ADHD symptoms. Also in alignment with the ALSPAC study, our study showed that maternal depressive symptoms after pregnancy did not entirely account for the effects of maternal depressive symptoms during pregnancy on child's ADHD symptoms. In contrast, in the Generation-R study maternal depressive symptoms after pregnancy rendered the prenatal effects on child attention problems non-significant (Van Batenburg-Eddes et al., 2013). While our study is to our knowledge the first to formally test for mediation, both the ALSPAC and Generation-R findings point to mediation: the ALSPAC findings point to partial and the Generation-R findings point to full mediation of the prenatal depression effects via the depression effects after pregnancy.

A series of sensitivity analyses demonstrated that the associations between maternal depressive symptoms during pregnancy and child ADHD symptoms did not vary by maternal pre-pregnancy obesity, hypertensive disorders of pregnancy, or gestational diabetes. Further, adding these pregnancy disorders as covariates in the analysis had no effect on the effects.

None of the associations between maternal depressive symptoms during pregnancy and child ADHD symptoms varied by the child's sex. The effects were similar in boys and girls.

For a long time, the most commonly hypothesized mechanism linking maternal stress during pregnancy to child outcomes was excessive concentration of maternal cortisol. However, in a systematic review, Zijlmans et al. found that most studies did not find an association between maternal cortisol levels and child outcomes (Zijlmans, Riksen-Walraven, & de Weerth, 2015). However, in studies where a significant association was found, higher levels of maternal cortisol during pregnancy were mostly related to poorer child outcomes (Zijlmans et al., 2015). Another plausible mechanism is placental dysfunction, which could lead to higher placental glucocorticoid sensitivity (R M Reynolds et al., 2015). Yet, another study has shown that the risk of borderline clinically significant ADHD problems was over 3-fold in those offspring who were exposed to high levels of maternal licorice consumption during pregnancy (Räikkönen et al., 2017). Glycyrrhizin, a natural constituent of licorice, is a potent inhibitor of a placental enzyme protecting the fetus from maternal glucocorticoid excess.

An obvious study limitation of Study IV is that we are not able to specify the brain structural or functional nor biological or behavioural underlying mechanisms. Existing literature suggests that higher maternal depressive symptoms and/or salivary cortisol levels during pregnancy are linked with altered offspring brain structure and functional connectivity (Scheinost et al., 2016), and with cortical thinning in the right hemisphere (Buss et al., 2012). Emerging evidence also suggests that inflammatory markers may be involved, as maternal depressive symptoms and pro- and anti-inflammatory cytokines

during pregnancy have been shown to be correlated (Shelton, Schminkey, & Groer, 2014).

6.4   METHODOLOGICAL CONSIDERATIONS

Study I is the first individual participant data meta-analysis of self-reported mental health problems in young adults born preterm. Our sizable sample of 747 young adults born preterm at VLBW and of 1,512 term controls represent data from six longitudinal birth cohort studies from five countries. The several strengths of the study include the large sample size combining individual participant data across six cohorts. We were able to gather comprehensive perinatal, childhood, and young adulthood data, which enabled us to control for various confounders and analyse the results according to subgroups. Additional strength lies in the self-reported mental health problems scales that were comparable across cohorts. Limitations in the study include the lack of data on childhood or adolescent mental health, so that we could not study continuity of mental health in preterm individuals in our meta-analysis. In addition, our findings from exclusively self-reported data should be confirmed by other assessment methods including psychiatric diagnostic interviews and alternative data sources such as ratings by parents or spouses, given the previously demonstrated discrepancy between the self- and parent-assessments (Hack et al., 2004; Heinonen et al., 2013; Hille et al., 2008; Lund et al., 2012).

Study II had several strengths, including a longitudinal case control study design with detailed information on neonatal and birth characteristics. We also used standardized, validated methods to measure visual processing and ASD-related traits, and controlled for possible false positive findings with multiple outcomes. Limitations of Study II include follow-up-related sample attrition. While non-participation was not related to any of the multiple pre-, post- and neonatal factors, we cannot rule out that participants could have been healthier than non-participants or might have differed in some unmeasured way, e.g. in terms of their own cognitive abilities, educational attainment, genetic or behavioral factors.

Both Studies III and IV used data from the Predo study, which is a longitudinal study design and a well-characterized large cohort with detailed information on the maternal pregnancy and mother-child perinatal characteristics and child developmental outcome data from different sources. In Study III, since the coverage of the Finnish HDR is nearly 100% follow-up attrition in our sample with information on mental and behavioral disorders was minimal. A further strength is that the findings were in alignment regardless of the source of information lending validity to our findings.

In Study III, even though our sample size was large, the number of children exposed to betamethasone prenatally was relatively small as our study was not originally designed to test the effects of antenatal betamethasone on child

developmental outcomes. Indeed, the study was designed to examine risk factors for pre-eclampsia and IUGR, and as a result of the recruitment criteria, the prevalence of pre-eclampsia in the PREDO cohort was markedly higher than in the Finnish general population (Girchenko et al., 2017). This may limit the generalizability of our findings. However, the gestational age of the children in the cohort corresponded with the national average (Girchenko et al., 2017). The number of children with mental and behavioral disorders was also relatively small which precluded studying more rare specific disorders. Also, our observational study design precludes conclusion about causality. We did not have information on possible postnatal sGC treatment. A previous study of VPT children showed that postnatal sGC treatment has had an adverse effect (Munck et al., 2010). Finally, we had information on the dose and timing of the antenatal betamethasone treatment only for a small number of study participants, precluding tests of dose- or timing-dependent effects. However, according to Finnish National Current Care Guidelines (Uotila et al., 2011) during the time our cohort was born, repeated betamethasone courses were not recommended, unless the risk of neonatal respiratory distress syndrome was considered high, more than 7 days had passed after treatment, and delivery was imminent within 1-7 days. In the subsample of our study whom dosage and timing information was available, only one mother had received one course (two doses) of 12 mg of betamethasone twice.

In Study IV limitations relate to child ADHD symptoms being reported by the mother only. However, Leis et al. (2014) found that the effect of maternal prenatal depression on child hyperactivity was significant whether the child was rated by the mother or the teacher (Leis et al., 2014). Furthermore, we measured ADHD symptoms dimensionally, and did not use diagnostic criteria, rendering generalizations to ADHD disorder tentative. Since maternal depressive symptoms after pregnancy were self-rated at the time of rating the child's behaviour, and maternal depression and child behaviour may influence each other, we cannot rule out shared method variance. Sample attrition which was not independent of maternal characteristics also limits the external validity of the findings.

6.5   IMPLICATIONS OF THE STUDY

While actions aiming at decreasing the rates of preterm births are warranted, the findings from this work highlight the importance of long term follow-up of individuals born preterm from birth to adulthood. Supporting coping skills and peer relationship skills already in childhood may help pre-empt possible problems in peer relationships and subsequent emotional and social problems. In addition to providing preterm individuals with support, early support for parents is crucial. It is also important to note that not all adults born preterm experience mental health problems and most of them do well. Besides being a vulnerability factor, preterm birth may in fact serve as a

protective factor in some respect as was demonstrated in their lesser amount of externalizing problems in our study.

While preterm birth constitutes an early vulnerability factor with long-term consequences on the individual into adulthood, additionally, being exposed to synthetic glucocorticoids during fetal life is another risk factor for mental health problems even in children who end up being born at term. This observation is important as preterm birth is difficult to predict and a substantial number of the women administered antenatal sGCs, continue to deliver at term. This observation is of importance as antenatal sGCs may be administered in late-preterm deliveries and early term caesarean section deliveries as a result of observations of their short-term respiratory benefits. Hence, it is important to also understand the possible harms that being exposed to sGCs may carry on the neurodevelopment of children born at term. Our findings show that term-born sGC-exposed children have similar problems in mental health than the sGC-exposed children who are born preterm. At the moment, there is no systematic clinical follow-up of children exposed to sGCs who end up being born at term. These findings thus carry a public health message suggesting the need to extend clinical follow-up of child mental health beyond the preterm group to the group exposed to antenatal sGCs and born at term.

Finally, the current findings suggest that early pregnancy screening and preventive interventions focusing on maternal depressive symptoms may benefit not only maternal, but offspring wellbeing. As maternal depressive symptoms were shown to be highly stable throughout pregnancy, it is crucial to identify those women who are most at risk early on in pregnancy.

6.6 DIRECTIONS FOR FUTURE RESEARCH

The findings from this work show that while individuals born preterm have a higher risk of internalizing and social problems, as well as comorbid cognitive problems in young adulthood, they also have less externalizing behaviour problems. Therefore, finding the key features to plan timely and targeted preventive interventions to promote long-term resilience in all areas of psychological wellbeing among preterm individuals is an important goal for future research. Since our study is only limited to young adulthood, and some evidence of possible changes in evident mental health problems from childhood to adulthood were seen, it is important to continue following up these preterm-born cohorts as they age. Our results challenge previous research by showing that the associations between visual processing and ASD-related traits might be restricted to individuals born preterm. Further studies will tell whether this result repeats in relation to developmental programming in other contexts than premature birth, or whether this is a specific prematurity-related finding. This observation is also important in terms of future studies, since they should take better into account the role of

prematurity and low birth weight when examining the relations between ASD-related traits and visual processing.

Additionally, future studies should investigate whether the harmful associations found in our study between exposure to antenatal sGCs and early childhood mental health persist as the children age. Our findings suggested that at least pre-pubertal boys may be more susceptible to the harmful effects of sGCs. However, future studies are warranted to unravel if the sex-specificity of the antenatal sCG exposure differs according to the child's developmental stage. Further, even in preterm individuals, antenatal sGCs may have different effects on neurodevelopment depending on individual tissue-sensitivity to sGCs. It has been shown that individual genetic variations in glucocorticoid sensitivity and exposure to antenatal sGCs are associated with IQ and behavior in young adults born preterm (van der Voorn, Wit, van der Pal, Rotteveel, & Finken, 2015). Future studies should further examine the possibility of more tailor-made approaches in sGC dosing.

Our findings highlight the need to develop preventive interventions, suited for pregnancy. A recent meta-analysis demonstrated null to very small benefits of existing techniques in decreasing maternal distress during pregnancy (Fontein-Kuipers, Nieuwenhuijze, Ausems, Budé, & de Vries, 2014), hence, suitable interventions during pregnancy should be further studied.

As this work is in its entirety observational, it is not possible to make causal inferences and discussion of mechanisms is purely speculation. Clearly, further studies delineating the underlying mechanisms of the associations between the prenatal adversities and mental health outcomes studied in this thesis are needed.

6.7   OVERALL CONCLUSIONS

Our observational human studies support the Developmental Origins of Health and Disease hypothesis by showing that environmental factors during pregnancy and fetal development are associated with long term harmful mental health outcomes. Preterm birth constitutes an early vulnerability factor with long-term consequences on the individual into adulthood. In addition, being exposed to synthetic glucocorticoids during pregnancy is another risk factor for mental health problems even in children who end up being born at term, emphasizing the need to extend clinical follow-up of child mental health beyond the preterm group to the group exposed to antenatal sGCs and born at term. Finally, early pregnancy screening and preventive interventions focusing on maternal depressive symptoms during pregnancy may benefit not only maternal, but offspring wellbeing.

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