

Department of Psychology and Logopedics

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**OBESITY AND CO-MORBID HYPERTENSIVE AND
DIABETIC DISORDERS IN PREGNANCY AND
EARLY MANIFESTATIONS OF
NEURODEVELOPMENTAL ADVERSITY IN THE
OFFSPRING**

PREDICTION AND PREVENTION OF PRE-ECLAMPSIA AND
INTRAUTERINE GROWTH RESTRICTION (PREDO) STUDY

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ACADEMIC DISSERTATION

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ABSTRACT

The prevalence of women entering pregnancy with overweight and obesity is growing worldwide reaching epidemic proportions. Apart from the risks of maternal and fetal morbidity associated with overweight and obesity, excessive weight is also an essential risk factor for diabetic and hypertensive disorders occurring before and during pregnancy. Maternal obesity and co-morbid hypertensive and diabetic disorders affect fetal development and have been linked with compromised neurodevelopment of the offspring; however, previous findings are not entirely consistent. Further, due to high co-morbidity between maternal overweight/obesity and hypertensive and diabetic disorders, it is difficult to disentangle their individual effects on child neurodevelopment. In addition, the mechanisms underlying associations between maternal overweight/obesity and co-morbid disorders and child neurodevelopment remain elusive.

This thesis examines the effects of maternal overweight/obesity and co-morbid hypertensive and diabetic disorders on early manifestations of neurodevelopmental adversity and on developmental delay in early childhood. It also examines whether DNA methylation (DNAm) biomarker of gestational age (GA) at birth reflects prenatal exposure to maternal overweight/obesity and co-morbid hypertensive and diabetic disorders, and hence, has a potential to identify individuals at risk for neurodevelopmental adversity already at birth.

This thesis capitalizes on the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) birth cohort comprising 4777 women and their singleton children born in Finland between 2006 and 2010. Data on maternal early pregnancy BMI, pre-pregnancy and gestational hypertension, pre-eclampsia, type 1 diabetes and gestational diabetes mellitus (GDM) were derived from the Finnish Medical Birth Register (MBR). DNAm gestational age (DNAm GA) was calculated using the method based on the methylation profile of 148 selected cytosine-phosphate-guanine (CpG) sites on DNA. Regulatory behavior problems in infancy were measured using Neonatal Perception Inventory (NPI) at the infant's mean age of 16.9

(SD=7.6) days. Developmental milestones were measured using Ages and Stages Questionnaire (ASQ) Third edition at the child's mean age of 42.1 (SD=8.2) months.

In comparison to the infants born to normal weight mothers, infants born to overweight/obese mothers displayed more regulatory behavior problems and were more likely to display regulatory behavior problems in multiple areas of self-regulation. These effects were independent of the co-morbid hypertensive and diabetic disorders (Study II). Children of overweight and obese mothers were more likely to display more severe and pervasive developmental delay in comparison to the children on normal weight mothers. The effects of maternal overweight and obesity on severity and pervasiveness of developmental delay in early childhood were also independent of the co-morbid hypertensive and diabetic disorders (Study III). Infant regulatory behavior problems partially mediated the association between maternal overweight/obesity and child neurodevelopmental milestones (Study II). Maternal pre-eclampsia was marginally associated with infant regulatory problems in multiple areas of self-regulation in normal weight non-diabetic women, but its effect was not significant in overweight/obese women and/or women with GDM (Study II). Maternal pre-eclampsia increased the odds of more severe and pervasive developmental delay in early childhood, and these effects were lower in the presence of overweight/obesity and diabetic disorders (Study III). GDM was not associated with infant regulatory behavior problems (Study II). The effect of GDM on severity and pervasiveness of developmental delay in early childhood was partially driven by maternal overweight/obesity and/or pre-eclampsia (Study III). Gestational and chronic hypertension were not associated with infant regulatory behavior problems and developmental delay (Studies II and III). Maternal BMI was not associated with variation in DNAm GA (Study IV). Maternal pre-eclampsia was associated with DNAm GA acceleration (Study IV). GDM in index pregnancy was not associated with variation in DNAm GA, however, insulin treated GDM in previous pregnancy was associated with DNAm GA deceleration (Study IV).

These study findings suggest that maternal overweight and obesity affect child neurodevelopment independently of the co-morbid hypertensive and diabetic disorders, and that the trajectory of this effect can partially be traced from infant regulatory behavior problems to developmental delay in early childhood. Hence, infant regulatory behavior problems may represent an early manifestation of

neurodevelopmental adversity due to prenatal exposure to maternal overweight/obesity. Pre-eclampsia increases the risk of developmental delay in early childhood independently of maternal overweight, obesity and diabetic disorders and its adverse effects on child neurodevelopment have a potential to be detected already at birth by assessing DNAm GA. Adverse effects of gestational diabetes on child neurodevelopment can be partially accounted for by highly co-morbid maternal overweight/ obesity and pre-eclampsia. Efforts aimed at weight management among women of reproductive age and prevention of pre-eclampsia during pregnancy are likely to reduce the burden of neurological morbidity in the future.

TIIVISTELMÄ

Yhä useampi hedelmällisessä iässä oleva nainen ympäri maailmaa on ylipainoinen tai lihava. Ylipaino on tärkeä diabeteksen ja verenpainesairauksien riskitekijä sekä yleisesti että raskauden aikana, ja näitä häiriöitä voidaankin kuvata ylipainon ja lihavuuden liitännäissairauksiksi. Aiempien tutkimusten perusteella äidin lihavuus ja nämä liitännäissairaudet vaikuttavat sikiön kehitykseen ja voivat mahdollisesti lisätä lapsen käytös- ja tunnehäiriöiden ja muiden kehityksellisten ongelmien riskiä, mutta nämä aiemmat tulokset ovat osin ristiriidassa keskenään. Lisäksi on vaikeaa arvioida, mikä on yksittäisten riskitekijöiden itsenäinen merkitys lapsen kehityksen kannalta, sillä äidin lihavuus ja ylipaino, diabetes ja verenpainesairaudet esiintyvät usein yhdessä. On myös huomattava, että mekanismit, jotka selittävät äidin ylipainon tai lihavuuden ja sen liitännäissairauksien yhteyttä lapsen kehitykseen ovat edelleen varsin epäselviä.

Tässä väitöskirjassa tarkastellaan äidin ylipainon ja lihavuuden sekä diabeteksen ja verenpainehäiriöiden vaikutusta lapsen varhaisiin käytös- ja tunnehäiriöiden ilmentymiin sekä kehitysviivästymiin. Lisäksi väitöskirjassa tarkastellaan vastasyntyneen perimäaineksen epigeneettisiä muutoksia, eli DNA:ssa ennen syntymää tapahtuneita muokkauksia, joiden johdosta emäsjärjestys ei muutu, mutta jotka voivat vaikuttaa solujen toimintaan. Epigeneettisten muutosten osalta selvitetään, ovatko ne yhteydessä äidin raskauden aikaiseen lihavuuteen, ylipainoon ja liitännäissairauksiin. Lisäksi selvitetään, voitaisiinko epigeneettisiä muutoksia tutkimalla auttaa tunnistamaan mahdollisimman varhaisessa vaiheessa ne lapset, joilla on kohonnut kehityksen häiriöiden riski.

Väitöskirja on toteutettu osana suomalaista Predo-tutkimusta. Predo (Pre-eklampsian ennustaminen ja ehkäisy) on seurantatutkimus, johon kuuluu 4777 äitiä sekä heidän lastaan, jotka syntyivät Suomessa 2006-2010. Äidin varhaisraskauden painoindeksiä, diabetesta ja verenpainesairauksia koskeva tieto kerättiin Terveiden ja Hyvinvoinnin laitoksen ylläpitämästä kansallisesta Syntyneiden lasten rekisteristä. Epigeneettisten muutosten osalta tarkasteltiin syntymän yhteydessä otettuja napanuoran verinäytteitä, joista on mahdollista tutkia

vastasyntyneen soluja. Tutkimuksessa valittiin vastasyntyneen DNA:sta 148 sytosiini-fosfaatti-guaaniini-kohtaa, joiden metylaatioaste heijastelee raskauden kestoja, ja näiden kohtien metylaatioastetta tarkasteltiin suhteessa äidin painoon, sairauksiin sekä lapsen kehitykseen. Itsesäätelyvaikeuksia imeväisiässä mitattiin Neonatal Perception Inventory -kyselylomakkeella, jonka vastasyntyneiden äidit täyttivät keskimäärin 17 päivää synnytyksen jälkeen. Kehitysviivästyksiä arvioitiin Ages and Stages -kyselylomakkeella, jonka äidit täyttivät lapsen ollessa keskimäärin 42 kuukauden ikäinen.

Tutkimuksessa havaittiin, että äidin ylipaino ja lihavuus vaikuttavat lapsen kehitykseen riippumatta liitännäissairauksista eli myös silloin, kun diabeteksen ja verenpainesairauksien vaikutus lapseen on huomioitu. Äidin ylipaino ja lihavuus olivat tutkimuksessa yhteydessä sekä vastasyntyneen varhaisiin itsesäätelyvaikeuksiin että kehitysviivästyksiin varhaislapsuudessa. Tutkimuslöydösten perusteella vastasyntyneen itsesäätelyvaikeudet voivat olla äidin ylipainon ja lihavuuden haittavaikutusten varhainen ilmentymä lapsessa. Tutkimuksessa havaittiin lisäksi, että pre-eklampsia – raskaushäiriö, joka aiheuttaa muun muassa verenpaineen nousua ja jota on kutsuttu Suomessa myös raskausmyrkytykseksi – lisää lapsen varhaisen kehitysviivästyksen riskiä riippumatta äidin ylipainosta, lihavuudesta tai diabeteksestä. Tulosten perusteella on mahdollista, että pre-eklampsian haitalliset vaikutukset lapsen kehitykseen voidaan havaita jo varhain tutkimalla vastasyntyneen perimäaineksessa tapahtuneita epigeneettisiä muutoksia. Hedelmällisessä iässä olevien naisten painonhallintaan ja pre-eklampsian ehkäisyyn tähtäävät toimet voisivat vähentää psykiatristen ja neurologisten sairauksien kuormaa tulevaisuudessa.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Girchenko, P., Lahti, M., Tuovinen, S., Savolainen, K., Lahti, J., Binder, E. B., Rebecca M. Reynolds, Sonja Entringer, Buss, C., Pathik D. Wadhwa, PD., Hämäläinen, E., Kajantie, E., Pesonen, AK., Villa, PV., Laivuori, H., Räikkönen, K. Cohort Profile: Prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. *Int J Epidemiol* 2017.
- II Girchenko P, Lahti-Pulkkinen M, Lahti J, Pesonen AK, Hämäläinen E, Villa PM, Kajantie E, Laivuori H, Reynolds RM, Räikkönen K. Neonatal regulatory behavior problems are predicted by maternal overweight/obesity. *Pediatr Res*. 2018.
- III Girchenko P, Tuovinen S, Lahti-Pulkkinen M, Lahti J, Savolainen K, Heinonen K, Pyhälä R, Reynolds RM, Hämäläinen E, Villa PM, Kajantie E, Pesonen AK, Laivuori H, Räikkönen K. Maternal early pregnancy obesity and related pregnancy and pre-pregnancy disorders: associations with child developmental milestones in the prospective PREDO Study. *Int J Obes (Lond)*. 2018.
- IV Girchenko P, Lahti J, Czamara D, Knight AK, Jones MJ, Suarez A, Hämäläinen E, Kajantie E, Laivuori H, Villa PM, Reynolds RM, Kobor MS, Smith AK, Binder EB, Räikkönen K. Associations between maternal risk factors of adverse pregnancy and birth outcomes and the offspring epigenetic clock of gestational age at birth. *Clin Epigenetics*. 2017.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
ASQ	Ages and Stages Questionnaires
BMI	Body mass index
CI	Confidence interval
CpG	Cytosine-phosphate-guanine
GA	Gestational age
GAA	Gestational age acceleration
GAD	Gestational age deceleration
GDM	Gestational diabetes mellitus
DNA	Deoxyribonucleic Acid
DNAm	DNA methylation
DOHaD	Developmental Origins of Health and Disease
HPAA	Hypothalamic pituitary adrenal axis
IUGR	Intrauterine Growth Restriction
IQR	Interquartile range
MBR	Medical Birth Register
M	Median
NPI	Neonatal Perception Inventory
OR	Odds ratio
PAR	Predictive Adaptive Response
PREDO	Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

1. INTRODUCTION

Obesity in pregnancy has become one of the major public health problems. Of the world's adult population of women, including women of the childbearing age, 14% were obese in 2014 (2016). Prevalence of obesity among women is forecasted to increase to 21% by 2025 (2016). The risks of pre-pregnancy obesity for the pregnant woman include gestational diabetes mellitus (GDM) (Weiss, Malone et al. 2004, Chu, Callaghan et al. 2007) and hypertension spectrum pregnancy disorders (gestational hypertension and pre-eclampsia) (Weiss, Malone et al. 2004, Spradley, Palei et al. 2015, Spradley 2017). Furthermore, obese women are at increased risk to enter pregnancy already suffering from chronic hypertension and diabetes, the major health complications associated with obesity (Mokdad, Ford et al. 2003, Re 2009, Kotsis, Stabouli et al. 2010).

Apart from the health risks for the mother and adverse perinatal outcomes, including preterm birth, intrauterine growth restriction (IUGR), macrosomia and related illnesses and complications, stillbirth and congenital anomalies (Leddy, Power et al. 2008, Liu, Xu et al. 2016, Blickstein, Doyev et al. 2017, Catalano and Shankar 2017), growing evidence suggests that maternal pre-pregnancy obesity is also associated with long-term neurodevelopmental adversities and aging-related diseases in the offspring. These include disadvantages in intellectual quotient (Pugh, Richardson et al. 2015, Mina, Lahti et al. 2017) and motor function (Ghassabian, Sundaram et al. 2015, Mina, Lahti et al. 2017), neurodevelopmental disorders (Krakowiak, Walker et al. 2012, Casas, Chatzi et al. 2013, Huang, Yu et al. 2014), and obesity (Gaillard, Steegers et al. 2014, Hemond, Robbins et al. 2016), diabetes (Eriksson, Sandboge et al. 2014, Gaillard, Steegers et al. 2014), cardiovascular diseases (Eriksson, Sandboge et al. 2014), and even cancer (Contreras, Ritz et al. 2016). Existing data suggests that co-morbid hypertensive and diabetic maternal conditions may add to neurodevelopmental disadvantage of the offspring: GDM (Fraser, Nelson et al. 2012, Fraser, Almqvist et al. 2014) and hypertension spectrum pregnancy disorders (Tuovinen, Raikkonen et al. 2012, Tuovinen, Eriksson et al. 2013, Ghassabian, Sundaram et al. 2015, Tearne, Allen et al. 2015) have been

found to carry adverse neurodevelopmental consequences on the offspring that are independent of maternal pre-pregnancy BMI.

Because neurodevelopmental and cardiometabolic and oncological diseases associated with maternal pre-pregnancy obesity and co-morbid conditions occur years or even decades later to the exposure, it is crucial to identify individuals at risk as early in life as possible. Therefore, current work is focused on examining early neurodevelopmental consequences of prenatal exposure to maternal overweight, obesity and co-morbid conditions: chronic and gestational hypertension, pre-eclampsia, and GDM, all of these maternal conditions being among the well documented causes of prematurity and low/high birthweight (Meis, Goldenberg et al. 1998, Roberts, Pearson et al. 2003, Valero De Bernabe, Soriano et al. 2004, Goldenberg, Culhane et al. 2008, Torloni, Betran et al. 2009, Papachatzzi, Dimitriou et al. 2013) and hence representing environmental exposures that may trigger fetal maladaptation. The key overarching objective of this thesis is to identify early life manifestations of prenatal exposure to maternal overweight/obesity and co-morbid diabetic and hypertensive disorders that may indicate increased risk of long-term neurological morbidity. This will also help in the eventual development of timely preventive interventions.

1.1. Epidemiology of pregnancy obesity

Obesity was first classified as a disease in 1948 by the World Health Organization (WHO) (James 2008). Currently, the most conventional approach to define obesity is by assessing body mass index (BMI) measured in kilograms of weight per meter squared of height. Adults with a BMI between 25 and 30 kg/m² are considered overweight and those with a BMI higher than 30 kg/m² are defined as obese (2000).

Over the last few decades, profound changes in the diet combined with a decrease in levels of physical activity among the populations of many developed and developing countries resulted in increase in the prevalence of overweight and obesity (Yach, Stuckler et al. 2006). Worldwide prevalence of obesity has doubled between 1980 and 2008, dramatically increasing the burden on public health (Mitchell and Shaw 2015). The rising prevalence of overweight and obesity in several countries including USA, UK, Germany, Russia, Egypt, Saudi Arabia, Australia, New Zealand,

14 countries in Central and Latin America, Kuwait, Kiribati, the Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa has been described as a global pandemic (Ng, Fleming et al. 2014).

Female sex is associated with higher risk of obesity (Ogden, Yanovski et al. 2007). In 2014, 40% of adult women aged 18 years and older worldwide were overweight and 15% were obese (Devlieger, Benhalima et al. 2016). Current estimates suggest that by 2025 more than 21% of women in the world will be obese (Poston, Caleyachetty et al. 2016).

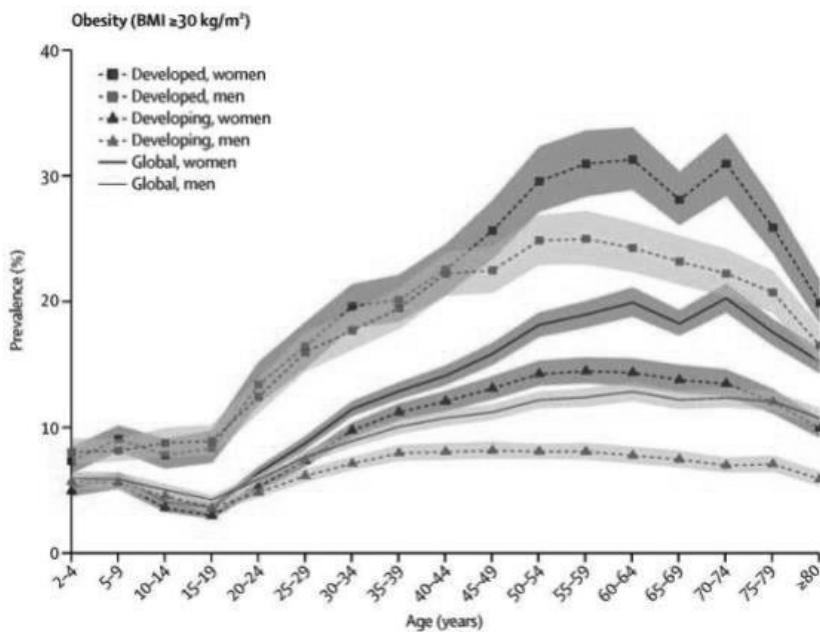


Fig. 1. Prevalence of obesity by age and sex, 2013. (Ng et al. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 384(9945): 766-781).

The epidemic of obesity has proportionally affected women of reproductive age. Pregnancy obesity is increasing in developed countries to almost epidemic proportions (Huda, Brodie et al. 2010). Prevalence of obesity among women aged 20-44 years in the USA is around 33% (Flegal, Carroll et al. 2002, Huda, Brodie et al. 2010). Similar trends are observed in Europe: prevalence of pre-pregnancy

obesity in many European countries including UK, Ireland, Spain, and Hungary exceeded 20% (Devlieger, Benhalima et al. 2016). Prevalence of overweight and obesity among pregnant women in Finland was increasing similarly to the trends observed in the other European countries: in 2010 19% to 22.5% of pregnant women in Finland were overweight and 10% to 12.1% were obese (Devlieger, Benhalima et al. 2016, Metsala, Stach-Lempinen et al. 2016).

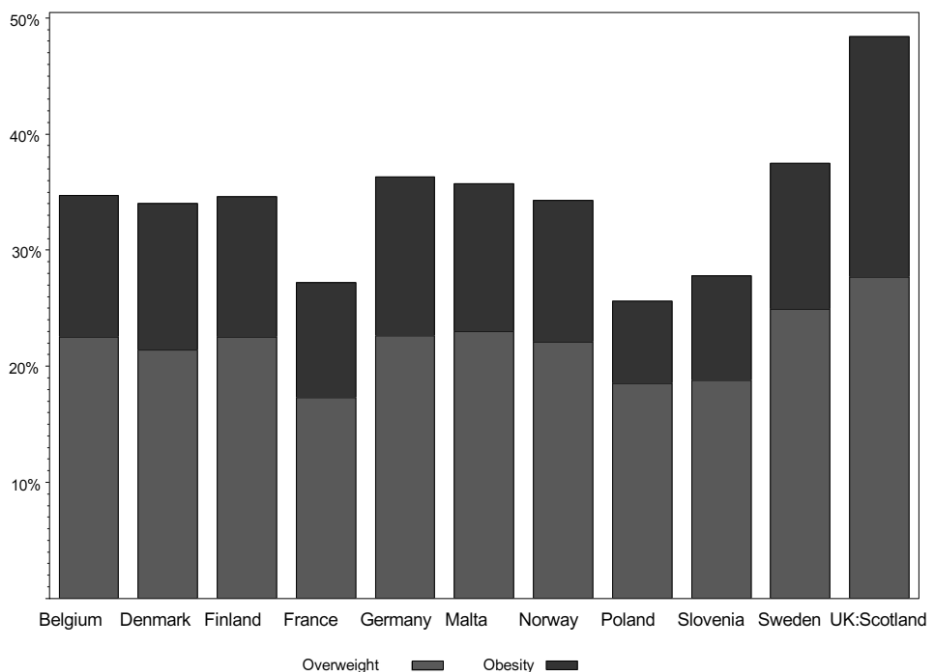


Fig. 2. Distribution of maternal pre-pregnancy overweight and obesity from Euro-Peristat database
 Source: <http://www.europeristat.com/our-indicators/euro-peristat-perinatal-health-indicators-2010.html>

1.2. Pregnancy obesity and woman's health

Obesity is associated with a wide spectrum of health complications, such as cardiovascular disease, diabetes, hypertension, atherosclerosis, depression, non-alcoholic fatty liver disease, gall bladder disease, pancreatitis, osteoarthritis, and cancer (Lean, Gruer et al. 2006, Lykke, Langhoff-Roos et al. 2009, Dixon 2010). In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life-years worldwide (Ng, Fleming et al.

2014). The risks of obesity for pregnant women include gestational diabetes, hypertensive pregnancy disorders, caesarian section delivery, and thromboembolism (Huda, Brodie et al. 2010, Godfrey, Reynolds et al. 2017). Further, overweight and obese women are more likely to enter pregnancy suffering from chronic hypertension and diabetes (Mokdad, Ford et al. 2003). Moreover, maternal obesity is a significant risk factor for maternal mortality with more than 50% of maternal deaths occurring in overweight and obese women (Lewis 2012).

1.2.1. Co-morbid hypertensive and diabetic disorders

Hypertensive and diabetic pregnancy disorders are among the most prevalent complications associated with overweight/obese pregnancy. Findings from the large, prospective population-based study from Sweden demonstrated that weight gain between two consecutive pregnancies was strongly associated with increased risk of hypertensive and diabetic pregnancy disorders, suggesting causal dose-response relationship between maternal overweight/obesity and these disorders (Villamor and Cnattingius 2006).

1.2.1.1. Hypertensive pregnancy disorders

Hypertensive pregnancy disorders are common pregnancy complications affecting up to 10% of all pregnancies (Wagner, Barac et al. 2007, Lazdam, de la Horra et al. 2010, Hutcheon, Lisonkova et al. 2011). Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, and pre-eclampsia.

Chronic hypertension is defined as blood pressure $\geq 140/90$ mmHg present pre-pregnancy or diagnosed before 20th week of gestation.

Gestational hypertension is defined as blood pressure $\geq 140/90$ mmHg on ≥ 2 occasions at least 4 h apart in a women who was normotensive before 20th week of gestation.

Pre-eclampsia is a pregnancy-specific disorder defined as blood pressure $\geq 140/90$ mmHg on ≥ 2 occasions at least 4 h apart in a woman who was normotensive before 20th week of gestation with proteinuria ≥ 300 mg/24 h.

Chronic hypertension accounts for about 3% of pregnancies, pre-eclampsia accounts for about 3-7% of all pregnancies, and gestational hypertension occurs in about 2-6% of pregnancies (Wagner, Barac et al. 2007, Yoder, Thornburg et al. 2009, Hutcheon, Lisonkova et al. 2011). Women with gestational hypertension progress to pre-eclampsia in 15% to 45% of cases, and women with chronic hypertension progress to pre-eclampsia in up to 25% of pregnancies (Yoder, Thornburg et al. 2009).

As stated above, overweight and obesity are among the most essential maternal risk factors for developing hypertensive pregnancy disorders (Baeten, Bukusi et al. 2001, Sebire, Jolly et al. 2001, Poon, Kametas et al. 2010). Previous studies have demonstrated that maternal obesity is associated with 2.4-7-fold increased risk of chronic and gestational hypertension (Robinson, O'Connell et al. 2005, Vernini, Moreli et al. 2016). Systematic review including thirteen cohort studies comprising nearly 1.4 million women reported that the risk of pre-eclampsia doubled with each 5-7 kg/m² increase in pre-pregnancy BMI (O'Brien, Ray et al. 2003). Morbid obesity was found to be associated with almost 5-fold increase of the risk of developing pre-eclampsia (Cedergren 2004). Rates of hypertensive pregnancy disorders are growing in parallel with the growing rates of obesity among women of reproductive age (Wagner, Barac et al. 2007, Yoder, Thornburg et al. 2009, Hutcheon, Lisonkova et al. 2011). In addition, women with gestational hypertension and pre-eclampsia are at increased risk of developing gestational diabetes and vice versa (Carpenter 2007).

1.2.1.2. Diabetic disorders in pregnancy

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycemia due to an absolute or relative deficit in insulin production or action (Alam, Asghar et al. 2014). Majority of cases of diabetes fall into the two broad etiopathogenetic categories of type 1 diabetes mellitus (T1DM) caused by

autoimmune pancreatic β -cell destruction and characterized by absolute insulin deficiency, and type 2 diabetes mellitus (T2DM) characterized by insulin resistance and relative insulin deficiency. T2DM results from the interaction between a genetic predisposition and behavioral and environmental risk factors, one of these important risk factors being obesity (Tuomilehto, Lindstrom et al. 2001). T2DM accounts for around 90-95% cases of diabetes mellitus (Alam, Asghar et al. 2014), and its onset is strongly correlated with age (Hu, Manson et al. 2001); however, in the current global epidemic of T2DM, the age of onset has decreased significantly, with an increasing proportion of women of reproductive age being affected (Ma, Tutino et al. 2015). For example, in Asia, as much as 18% of patients with T2DM had age of onset below 40 years (Yeung, Zhang et al. 2014). T1DM and T2DM are often referred to as pre-pregnancy diabetes and despite the rise in their prevalence (Simmons 2011), together account for less than 1% of the pregnancies (Oyen, Diaz et al. 2016).

Gestational diabetes mellitus (GDM) is a specific form of diabetes that occurs in pregnancy. GDM is considered a separate entity from T2DM. As pregnancy progresses, the increasing insulin resistance creates a demand for more insulin. In the great majority of pregnancies, the demand is readily met, and the balance between insulin resistance and insulin supply is maintained. However, if resistance becomes dominant, the pregnant woman becomes hyperglycemic (Alam, Asghar et al. 2014). This usually occurs in the second half of pregnancy, with insulin resistance increasing progressively until delivery, when, in most cases, it rapidly disappears (Ben-Haroush, Yogev et al. 2004). Risk of developing GDM is strongly associated with maternal obesity (Weiss, Malone et al. 2004, Chu, Callaghan et al. 2007). In fact, number of pregnancies complicated by GDM is increasing in parallel with the increase in prevalence of maternal obesity (Ferrara 2007, Ma and Chan 2009): GDM prevalence doubled between 1994 and 2002 (Dabelea, Snell-Bergeon et al. 2005). Currently, prevalence of GDM in the Western countries is 5–16% depending on the population, screening, and diagnostic criteria used (Buckley, Harreiter et al. 2012, Ellenberg, Sarvilinna et al. 2016, Karcaaltincaba, Calis et al. 2017). Furthermore, GDM, hypertension and pre-eclampsia are highly co-morbid (Bryson, Ioannou et al. 2003, Carpenter 2007, Tieu, McPhee et al. 2017).

1.2.2. Quality of life in pregnancy

Multidimensional term “health-related quality of life” refers to physical, mental, psychological, and social aspects of health (Ware 1995, Naughton and McBee 1997). Concept of health-related quality of life is broader than direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life. Health-related quality of life also encompasses well-being, which refers to the positive aspects of one’s life, such as positive emotions and life satisfaction (People 2010). Obesity in pregnant women is one of the important factors affecting their quality of life both during pregnancy and postpartum (Kushner and Foster 2000).

1.2.2.1. Depression

Evidence suggests that maternal obesity is associated not only with more medical complications, but also with poorer mental health. For example, pre-pregnancy obesity was linked with higher prevalence of depression during pregnancy and postpartum (Molyneaux, Poston et al. 2014, Kumpulainen, Girchenko et al. 2018).

Estimates of the prevalence of depression among women of reproductive age range from 10% to 50%, depending on the instrument used and the characteristics of the study sample (Setse, Grogan et al. 2009). Depression is associated with excessive pregnancy weight gain, gestational diabetes, hypertensive pregnancy disorders, caesarian section delivery, and shows high continuity to the postpartum stage (Palmsten, Setoguchi et al. 2012, Kumpulainen, Girchenko et al. 2018). Pregnant women with high depressive symptoms experience more bodily pain, more fatigue, more problems with daily activities because of physical health, more problems with daily activities because of emotional difficulties, and more limitations in social activities because of physical or emotional complications as compared to pregnant women with low depressive symptoms (Nicholson, Setse et al. 2006). Hence, depression negatively affects multiple dimensions of health-related quality of life during pregnancy.

Association between depression and obesity is bidirectional. Depression dysregulates functioning of Hypothalamic-Pituitary-Adrenal (HPA) axis (Varghese

and Brown 2001) and is associated with unhealthy lifestyle choices such as binge eating and decreased levels of physical activity (Bonnet, Irving et al. 2005), which leads to the development of obesity, while obesity, for example through its detrimental impact on self-esteem or somatic consequences, often results in the development of depression (Luppino, de Wit et al. 2010).

1.2.2.2. Lifestyle

Obesity is bidirectionally associated with lifestyle choices diminishing quality of life, including consumption of processed, energy rich foods, reducing energy expenditure and creating environments that encourage less physical activity and promote a more sedentary lifestyle (Lean, Gruer et al. 2006). There are multiple lifestyle factors contributing to the growing rates of obesity, social and economic status being one of the important determinants.

Lower social and economic status has been systematically linked to the higher rates of overweight and obesity (Garn, Bailey et al. 1977). Reviews on obesity highlight the importance of obesogenic environments promoting excessive food consumption and discouraging physical activity. From a physical activity perspective, obesogenic environments include those with poor access to recreational facilities and infrastructure that discourages incidental activity, walking, and cycling (Giles-Corti, Macintyre et al. 2003). Lower social and economic status groups have reduced access to facilities, which in turn results in disparities in physical activity and increased risk of overweight and obesity (Gordon-Larsen, Nelson et al. 2006).

Education is one of the main indicators of social and economic status and one of the important predictors of the risk of overweight and obesity (Krieger, Williams et al. 1997). Education strongly predicts the level of income and consequently lifestyles ensuring adequate access to non-obesogenic environments (Cohen, Rai et al. 2013). Further, education affects choices related to healthy lifestyles via health literacy and sense of control and empowerment (Fletcher and Frisvold 2009).

Another important factor influencing lifestyle of people affected by obesity is stigmatization and self-stigmatization (Myers and Rosen 1999). Unlike racial and ethnic discrimination, stigmatizing attitudes towards obese people are

expressed more freely based on the perception that weight is controllable (Crandall 1994). Obese people are often perceived to be unattractive, weak-willed and unlikable. Obese people tend to hold these prejudiced attitudes towards themselves (Crandall 1994). Stigmatization and self-stigmatization is associated with mental health problems, one of them being depression, which perpetuates the vicious cycle diminishing quality of life of women affected by overweight/obesity.

1.3. Pregnancy obesity and offspring health

Because obese women are at risk for multiple medical and obstetric problems during pregnancy, high prevalence of maternal obesity launches an intergenerational public health problem carrying short- and long-time consequences for the offspring. Developmental origins of health and disease (DOHaD) framework provides an insight into the pathways involved into intergenerational transmission of health related problems associated with pregnancy obesity.

1.3.1. Developmental origins of health and disease

Mounting evidence indicates that prenatal environment affects offspring's health, disease, and aging trajectories throughout the lifespan (Gillman 2005). According to the DOHaD concept, individuals start to diverge in their aging trajectories already during prenatal life (Barker 2004). According to the DOHaD hypothesis, altered long-term disease risk is induced through the adaptive responses made by the fetus to maternal environmental cues. The fetal responses may include alterations in structure and function of cells, tissues and organs leading to altered physiological set points and adverse outcomes (Barker 2004, Baird, Jacob et al. 2017). Adaptiveness of the fetus to its mother's condition before birth is known as "developmental plasticity" phenomenon (Bateson, Barker et al. 2004). Phenotypic changes inducing altered responses to the challenges later in life are referred to as "developmental programming" (Heindel, Balbus et al. 2015).

The DOHaD hypothesis originated from the findings of epidemiological studies of infant and adult disease and mortality. Variations in mortality from the cardiovascular disease in England and Wales were shown to correlate with past

differences in death rates among newborn babies (Barker and Osmond 1986, Barker, Winter et al. 1989, Barker, Gluckman et al. 1993). Since in the past neonatal mortality was mostly attributed to low birthweight, these findings stimulated interest in epidemiological studies of birthweight in relation to long-term health outcomes (Hales and Barker 1992, Bateson, Gluckman et al. 2014). Multiple studies linked size at birth and chronic disease in the adulthood, including ischemic heart disease (Koupilova, Leon et al. 1999), coronary disease (Barker, Osmond et al. 2005, Kajantie and Hovi 2014), stroke (Rich-Edwards, Stampfer et al. 1997), insulin resistance and type 2 diabetes (Newsome, Shiell et al. 2003, Rogers 2005), osteoporosis (Harvey and Cooper 2004), and asthma and atopic dermatitis (Steffensen, Sorensen et al. 2000).

Over the past decade, the body of evidence linking low birthweight to adult disease continued to expand: researchers' interests extended to study the effects of prematurity and weight at birth on mental health and disease (O'Donnell and Meaney 2017). Findings from numerous epidemiological studies suggest that preterm birth and low birthweight are associated with increased risk of mental disorders later in life (Schlotz and Phillips 2009, Raikkonen, Pesonen et al. 2012, O'Donnell and Meaney 2017), including attention deficit hyperactivity disorder (ADHD) (Breslau and Chilcoat 2000, Wiles, Peters et al. 2006, Banerjee, Middleton et al. 2007, Raikkonen, Pesonen et al. 2012), schizophrenia (Nilsson, Stalberg et al. 2005, Abel, Wicks et al. 2010), alcohol and drug use disorders, anxiety disorders, and somatoform disorders (Abel, Wicks et al. 2010).

The association between birthweight and the risk of disease later in life, however, is not linear, but U-shaped (Calkins and Devaskar 2011). Findings from multiple studies show that high birthweight and macrosomia are also associated with increased risk of the disease later in life, namely breast cancer (Michels, Trichopoulos et al. 1996, Michels and Xue 2006), childhood leukemia and testicle cancer (Hjalgrim, Westergaard et al. 2003), and cardiometabolic disease (Ornoy 2011, Lin, Wu et al. 2016). Macrosomia has been also linked with depression and anxiety (Colman, Ploubidis et al. 2007), schizophrenia (Van Lieshout and Boyle 2011), and behavioral problems (Buschgens, Swinkels et al. 2009).

To explain the factors underlying associations between birthweight and disease later in life, and given that determinants of birthweight lie in prenatal period, a "thrifty phenotype" conceptual model was proposed. "Thrifty phenotype" concept

states that a consequence of surviving undernutrition during prenatal development is a reduction of fetal growth (Hales and Barker 1992). One of the main controversies related to the “thrifty phenotype” concept was that adverse events during prenatal life may not result in a reduced birth size, but still affect a fetus and have long-term negative consequences for health. For example, women who on average consumed less than 800 calories per day in the first pregnancy trimester during the Dutch famine gave birth to normal-sized infants, who in their 50s developed obesity (Godfrey, Robinson et al. 1996, Ravelli, van Der Meulen et al. 1999). Furthermore, it was also found that the consequences of fetal adaptation to undernutrition exceeded a life course of the exposed individual: women who were exposed to Dutch famine during prenatal life had grandchildren who were born with reduced birth size (Lumey 1992). To overcome this controversy, “thrifty phenotype” concept evolved to predictive adaptive response model (Gluckman and Hanson 2004). Predictive adaptive response concept postulates that fetal response to the adverse environmental cues is not only to gain an immediate advantage, but also to adapt to anticipated postnatal environment, which, in case of maternal undernutrition, is expected to be lacking sufficient nutrition. Hence, the predictive adaptive response concept raises the possibility of the response to prenatal environment in expectation of a postnatal environment. In case postnatal environment would mismatch the expected conditions, these same adaptations would increase the risk of disease later in life (Gluckman and Hanson 2004).

Growing body of epidemiological evidence linking birthweight and disease later in life in parallel with generation of conceptual models explaining these findings catalyzed development of the hypothesis of prenatal origins of physical (Barker 2007) and mental (O'Donnell and Meaney 2017) health. The definition developed and used by the DOHaD Society is the following: “The Developmental Origins of Health and Disease is a multidisciplinary field that examines how environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with its environment in later life” (Heindel, Balbus et al. 2015).

Developmental plasticity is one of the mechanisms generating variation in phenotypes suitable for different environments (West-Eberhard 2005, Beldade, Mateus et al. 2011). Developmental plasticity is usually beneficial to the organism (Bateson, Gluckman et al. 2014), giving advantage in environments that change over

several generations (Gluckman, Hanson et al. 2009) and promoting Darwinian fitness by improvement of survival and reproductive success and developing the life-course strategy for maximum fitness, adapting to the present conditions and preparing for the future environment (West-Eberhard 2005, Bateson 2001). Developmental trajectories defined by the environment during the stage of early development affect the response of the individual to the exposures later in life, the phenomena known as “developmental programming” (Hanson, Godfrey et al. 2011). As discussed above, developmental plasticity may also induce changes contributing to the development of the disease later in life (Gluckman, Hanson et al. 2005) by producing non-adaptive outcomes, to which the fetus should adapt in order to survive (Bateson, Barker et al. 2004, Gluckman, Hanson et al. 2005). Thus, adversities during development can generate responses that may be of short-term benefit for the mother or the fetus but then have long-term consequences, such as increased risk of developing the disease (Gluckman, Hanson et al. 2005). Hence, developmental programming refers to phenotypic changes induced during the period of developmental plasticity, which can be either beneficial or adverse for health later in life (Heindel, Balbus et al. 2015).

DOHaD hypothesis triggered an interest in studying the processes and mechanisms underlying developmental programming in general and in relation to specific exposures during prenatal life (Wadhwa, Buss et al. 2009). Theory linking prenatal environment with health and disease trajectories stimulated interest in studying environmental exposures that may trigger fetal maladaptation in relation to short- and long-term human morbidity and mortality (Gluckman, Hanson et al. 2005, Kemp, Kallapur et al. 2012). The examples of such environmental exposures include maternal nutrition and nutritional deficiencies (Ramakrishnan 2004, Khan, Dekou et al. 2005), maternal stress (Entringer, Buss et al. 2012) and depression (Raikkonen, Pesonen et al. 2015), use of medication during pregnancy (Swanson, Entringer et al. 2009), tobacco smoking (Eskenazi and Castorina 1999, Toschke, Montgomery et al. 2003, Herrmann, King et al. 2008, Oken, Levitan et al. 2008, von Kries, Bolte et al. 2008), et cetera.

Current work is focused on examining neurodevelopmental consequences of prenatal exposure to maternal overweight, obesity and co-morbid conditions: chronic and gestational hypertension, pre-eclampsia, and GDM, all of these maternal conditions being among the well documented causes of prematurity

and low/high birthweight (Meis, Goldenberg et al. 1998, Roberts, Pearson et al. 2003, Valero De Bernabe, Soriano et al. 2004, Goldenberg, Culhane et al. 2008, Torloni, Betran et al. 2009, Papachatzi, Dimitriou et al. 2013) and therefore representing environmental exposures that may trigger fetal maladaptation.

1.3.2. Obesity and co-morbid disorders in pregnancy and offspring health

1.3.2.1. Obesity in pregnancy and offspring health

Apart from increasing long-term health risks for the mother, maternal obesity is among the key underlying causes of preterm birth and low birth weight (Meis, Goldenberg et al. 1998, Goldenberg, Culhane et al. 2008, Torloni, Betran et al. 2009, Kemp, Kallapur et al. 2012, Cnattingius, Villamor et al. 2013, Papachatzi, Dimitriou et al. 2013). Maternal obesity is also associated with macrosomia (Spellacy, Miller et al. 1985, Jolly, Sebire et al. 2003, Chiavaroli, Castorani et al. 2016, Kim, Zhu et al. 2016, Oster and Toth 2016) and being large for gestational age (Sebire, Jolly et al. 2001).

In agreement with the concept that birthweight is a crude proxy of exposure to environmental adversity in the prenatal period, prenatal exposure to maternal obesity has been found to increase the offspring's risk of developing the disease. Findings from multiple studies linked maternal obesity with a number of long-term adverse health outcomes in the offspring, including lifelong risk of obesity and metabolic dysregulation with increased insulin resistance, hypertension and dyslipidemia, and risk of asthma (Shankar, Harrell et al. 2008, Drake and Reynolds 2010, Poston 2012, O'Reilly and Reynolds 2013). Evidence also suggests that maternal pre-pregnancy / early pregnancy obesity is associated with long-term neurodevelopmental adversities in the offspring (Godfrey, Reynolds et al. 2016). These include disadvantages in motor function (Wylie, Sundaram et al. 2015), intelligence quotient (Basatemur, Gardiner et al. 2013, Casas, Chatzi et al. 2013, Bliddal, Olsen et al. 2014, Huang, Yu et al. 2014, Pugh, Richardson et al. 2015), verbal skills (Jo, Schieve et al. 2015), developmental delay (Krakowiak, Walker et al. 2012), increased risk for symptoms of ADHD (Rodriguez 2010, Van Lieshout, Schmidt et al. 2013, Jo, Schieve et al. 2015), and diagnoses of autism spectrum disorder (ASD) (Krakowiak, Walker et al. 2012, Jo, Schieve et al. 2015). Furthermore, existing

evidence suggests that prenatal exposure to maternal obesity can be manifested already at birth via altered umbilical cord blood and placental DNA methylation profiles (Lesseur, Armstrong et al. 2014, Nomura, Lambertini et al. 2014, Soubry, Murphy et al. 2015).

Yet, literature on the effect of maternal obesity on child's neurodevelopment is not entirely consistent: some studies have reported null associations between maternal obesity and cognitive and motor function (Polanska, Muszynski et al. 2015) and some even beneficial effects on cognitive and language development in the offspring (Torres-Espinola, Berglund et al. 2015).

Many of the previous studies reporting on neurodevelopmental consequences of prenatal exposure to maternal obesity are limited by relying on maternal self-reported, and not objectively measured weight and height, in some studies even months after delivery (Basatemur, Gardiner et al. 2013, Bliddal, Olsen et al. 2014, Jo, Schieve et al. 2015, Pugh, Richardson et al. 2015, Aubuchon-Endsley, Morales et al. 2016), or by using a measure that pools self-reported data with data from medical records (Krakowiak, Walker et al. 2012, Van Lieshout, Schmidt et al. 2013, Huang, Yu et al. 2014, Polanska, Muszynski et al. 2015, Torres-Espinola, Berglund et al. 2015, Wylie, Sundaram et al. 2015, Yeung, Sundaram et al. 2017). Self-reports of weight and height tend to be inaccurate, with reports of women and obese individuals showing higher bias (Brunner Huber 2007, Stommel and Schoenborn 2009). Potential misclassification of women into groups according to BMI may have biased the results of previous studies. Thus, it remains unknown whether some of the discrepancies in the previous literature arise from bias in anthropometric measurements.

Further, there are still gaps in the literature linking maternal obesity and child neurodevelopment: for example, it remains unclear what are the neurodevelopmental trajectories of the prenatal exposure to maternal obesity. Namely, it is not known whether maternal obesity is associated with early signs of neurobehavioral adversity manifested as regulatory problems in infancy, which are predictive of later neurodevelopmental problems (Wolke, Rizzo et al. 2002, Wolke, Schmid et al. 2009, Schmid, Schreier et al. 2010, Hemmi, Wolke et al. 2011, Bilgin and Wolke 2017). Hence, it needs to be clarified whether prenatal exposure to

maternal obesity can be manifested already in infancy by affecting regulatory behavior problems.

Additionally, it still remains to be verified whether neurodevelopmental disadvantages in the offspring are specific to maternal pre-pregnancy obesity, or are driven or amplified by the often co-morbid hypertensive and/or diabetic disorders.

Finally, although in adults obesity has been found to accelerate biomarker of aging (“epigenetic clock”) based on DNA methylation (DNAm) levels (Horvath, Erhart et al. 2014), it remains unclear whether prenatal exposure to maternal obesity affects DNA methylation-based biomarkers of aging at birth. Given the novelty of infant DNAm gestational age biomarkers, the latter gap in the literature is not surprising (Bohlin, Haberg et al. 2016, Javed, Chen et al. 2016, Knight, Craig et al. 2016). Hence, it is unclear whether prenatal exposure to maternal obesity causes changes in epigenetic clock in newborns the same way as obesity is associated with accelerated epigenetic clock in adults (Horvath, Erhart et al. 2014).

At last, although some studies suggest that not only children born to the obese mothers are at increased risk of neurodevelopmental adversity, but also children born to the overweight mothers (Casas, Chatzi et al. 2013, Jo, Schieve et al. 2015), the effect of maternal overweight on child neurodevelopment is studied to the much lower extent than the effect of obesity.

1.3.2.2. Hypertensive disorders in pregnancy and offspring health

There is a number of risks to the infant attributed to hypertensive pregnancy disorders including stillbirth and perinatal death (Roberts, Pearson et al. 2003, Flenady, Middleton et al. 2011). Furthermore, hypertensive pregnancy disorders are among the well documented risk factors for prematurity, low birth weight, and IUGR (Roberts, Pearson et al. 2003, Valero De Bernabe, Soriano et al. 2004, Lasker, Coyle et al. 2005, Yucesoy, Ozkan et al. 2005, Villar, Carroli et al. 2006, Bakker, Steegers et al. 2011). In line with the DOHaD framework, existing evidence suggests that prenatal exposure to hypertensive pregnancy disorders carry adverse effects on development of the offspring (Tuovinen, Raikkonen et al. 2012, Tuovinen, Eriksson et al. 2013, Grace, Bulsara et al. 2014, Morsing and Marsal 2014, Ghassabian, Sundaram et al. 2015, Tearne, Allen et al. 2015). For example, previous research

linked gestational hypertension with externalizing and internalizing behavior problems in children and adolescents (Robinson, Mattes et al. 2009, Tearne, Allen et al. 2015), and pre-eclampsia with impaired cognitive ability in children (Morsing and Marsal 2014). Many studies reported that pre-eclampsia and gestational hypertension had long-term consequences on the mental health of the adult offspring, including severe mental disorders: schizophrenia and personality disorders (Dalman, Allebeck et al. 1999, Byrne, Agerbo et al. 2007, Fazel, Bakiyeva et al. 2012, Eide, Moster et al. 2013, Suvisaari, Taxell-Lassas et al. 2013), adaptive functioning and mental wellbeing (Tuovinen, Aalto-Viljakainen et al. 2014), and anxiety disorders (Hirshfeld-Becker, Biederman et al. 2004). Furthermore, existing evidence suggests that detrimental effect of hypertensive pregnancy disorders on child development may be independent of maternal BMI (Tuovinen, Raikkonen et al. 2012, Tuovinen, Eriksson et al. 2013, Ghassabian, Sundaram et al. 2015, Tearne, Allen et al. 2015).

However, there are considerable gaps in the literature on long-term consequences of prenatal exposure to maternal hypertensive pregnancy disorders. First, there is still controversy regarding the effects of prenatal exposure to maternal hypertensive pregnancy disorders. Several studies reported null associations between pre-eclampsia and psychological distress in adults (Wiles, Peters et al. 2005), pre-eclampsia and anxiety disorder and depression in adults (Berle, Mykletun et al. 2006), pre-eclampsia and schizophrenia in adults (Jones, Rantakallio et al. 1998, Kendell, McInnery et al. 2000, Sorensen, Mortensen et al. 2003), hypertension and adaptive functioning and psychiatric and psychological problems in adults (Tuovinen, Aalto-Viljakainen et al. 2014), hypertension and psychological distress in adults (Wiles, Peters et al. 2005), and pre-eclampsia and internalizing and externalizing problems in children and adolescents (Robinson, Mattes et al. 2009).

Second, high rates of co-morbidities between hypertensive pregnancy disorders, diabetic disorders and overweight/obesity make it difficult to disentangle the unique effects of each of these conditions. The very few studies, which attempted to separate the effects of hypertensive disorders on the offspring neurodevelopment from the effects of obesity (Tuovinen, Raikkonen et al. 2012, Tuovinen, Eriksson et al. 2013, Grace, Bulsara et al. 2014, Morsing and Marsal 2014, Tearne, Allen et al. 2015), are limited by not accounting for highly co-morbid diabetic disorders. In addition, adjustment of statistical models predicting offspring outcomes based on

hypertensive pregnancy disorders for maternal BMI may bias the estimates because of high collinearity of the predictors.

Third, since for timely interventions it is crucial to identify individuals at risk of developing neurological health problems as early in life as possible, it is essential to determine the earliest age when the consequences of prenatal exposure to hypertensive pregnancy disorders start to manifest themselves. Existing evidence suggests that prenatal exposure to hypertensive pregnancy disorders, and more specifically to pre-eclampsia, may be detected already at birth, since pre-eclampsia affects DNA methylation of placental tissue (Kulkarni, Chavan-Gautam et al. 2011, Blair, Yuen et al. 2013, Anderson, Ralph et al. 2014) and umbilical cord blood (He, Zhang et al. 2013, Nomura, Lambertini et al. 2014). However, whether DNAm changes would impact DNAm biomarker of gestational age remains unknown. Thus, it remains to be determined whether neurodevelopmental consequences of prenatal exposure to maternal hypertensive disorders can be identified at birth by assessing DNAm based biomarker.

1.3.2.3. Diabetic pregnancy disorders and offspring health

Immediate perinatal risks of prenatal exposure to maternal diabetes include macrosomia and large for gestational age (Lawlor, Fraser et al. 2010), small for gestational age (Ornoy 2005), respiratory distress syndrome (RDS), shoulder dystocia, and hypoglycemia (Jensen, Sorensen et al. 2000, Esakoff, Cheng et al. 2009), and major congenital anomalies (Farrell, Neale et al. 2002). Prenatal exposure to maternal diabetes increases the risks of overweight and obesity (Gillman, Rifas-Shiman et al. 2003), T2DM (Clausen, Mathiesen et al. 2009), cardiovascular disease (Wright, Rifas-Shiman et al. 2009), and cancer (Wu, Nohr et al. 2012) later in life. Existing evidence also suggests that diabetes in pregnancy, both pre-existing and GDM, alters neurodevelopment of the offspring. More specifically, prenatal exposure to maternal diabetes has been linked with lower offspring cognition and educational attainment, impaired motor development, disorders of the attention span, and autism (Rizzo, Metzger et al. 1991, Silverman, Rizzo et al. 1991, Ornoy, Ratzon et al. 2001, Ornoy 2005, Dionne, Boivin et al. 2008, Gardener, Spiegelman et al. 2009, Fraser,

Nelson et al. 2012, Krakowiak, Walker et al. 2012, Nomura, Marks et al. 2012, Fraser, Almqvist et al. 2014, Ghassabian, Sundaram et al. 2015).

At the same time, the results of the studies on the long-term neurodevelopmental consequences of maternal diabetes are not entirely consistent. A few studies reported that maternal diabetes and neurodevelopment of the offspring were not associated (Rizzo, Ogata et al. 1994, Deb, Prasad et al. 1997, Hultman, Sparen et al. 2002). At the same time, not all of the studies examining neurodevelopmental consequences of diabetes in pregnancy did account for highly co-morbid obesity, and, to the best of our knowledge, no studies accounted for confounding effects of co-morbid hypertensive disorders.

As with the other exposures to suboptimal environment during prenatal life discussed earlier, the gaps in the literature on maternal diabetes and offspring neurodevelopment are similar. These include lack of agreement on the neurodevelopmental consequences of the exposure to maternal diabetes, difficulties to disentangle the effect of maternal diabetes from the effects of the co-morbid maternal conditions, absence of the biomarker allowing early identification of individuals exposed to maternal diabetes during prenatal life who will later develop neurological problems.

1.4. Epigenetic changes

Although the exact mechanisms linking maternal overweight/obesity and co-morbid hypertensive and diabetic disorders with neurodevelopment of the child are not yet determined, previously accumulated evidence suggests that these conditions are associated with epigenetic changes in fetal tissues (Lesseur, Armstrong et al. 2014, Nomura, Lambertini et al. 2014), changes in the maternal microbiota and subsequent changes in fetal microbiota (Borre, O'Keefe et al. 2014, Neri and Edlow 2015), altered placental function (Cuffe, Holland et al. 2017), and low-grade inflammation, which has been linked to acute central nervous system impairment (Hagberg, Gressens et al. 2012, O'Reilly and Reynolds 2013). Current work will focus on epigenetic changes as one of the possible mechanisms underlying associations between prenatal exposure to maternal overweight/obesity, hypertensive and diabetic disorders and neurodevelopmental adversity in a child.

Existing evidence suggests that adaptation to the signals from the environment during prenatal stage of development occurs, in part, through epigenetic mechanisms (Gluckman and Hanson 2004). Interactions between genotype and environment alter gene expression, which affects developmental trajectories (Khosla, Dean et al. 2001, Waterland and Michels 2007, Gluckman, Hanson et al. 2008, Bale, Baram et al. 2010). Epigenetic changes induce phenotypes with altered responses to the exposures later in life, and thus affect future health and disease (Daskalakis, Bagot et al. 2013). The major epigenetic processes are DNA methylation, histone modification and microRNAs (Heerwagen, Miller et al. 2010, Hanson, Godfrey et al. 2011).

To date, vast majority of the studies examining the effect of early life exposures on epigenetic regulation of genes focused on DNA methylation. DNA methylation (DNAm) is an epigenetic mechanism characterized by the addition of 1 methyl group primarily to cytosine-phosphate-guanine (CpG) sites on DNA. Patterns of DNA methylation are established early in development and methylation plays a key role in cell differentiation by silencing the expression of specific genes (Hanson, Godfrey et al. 2011). Numerous studies have linked adverse prenatal life events with alterations in DNA methylation in the offspring. Relevantly to the topic of this thesis, previous studies found that maternal and paternal obesity associated with altered DNA methylation patterns at imprinted genes in umbilical cord blood (Herrera, Keildson et al. 2011, Soubry, Murphy et al. 2015, Sharp, Salas et al. 2017), another study reported significant differences in DNA methylation in placental tissue associated with pre-eclampsia (Yeung, Chiu et al. 2016), yet another study showed that maternal gestational diabetes associated with genome-wide DNA methylation variation in placenta and cord blood of exposed offspring (Finer, Mathews et al. 2015).

Epigenetic profiles evolved during the stage of early development tend to persist into adulthood. At the same time, ageing is associated with changes in DNA methylation (Horvath, Zhang et al. 2012, Horvath 2013). Epigenetic biomarker of cellular aging based on DNA methylation, also known as epigenetic clock or epigenetic age, has been shown to accurately predict chronological age in adults (Horvath 2013), and the deviations of epigenetic age from chronological age in adults have been found to be associated with health outcomes: epigenetic age acceleration (AA), defined as a difference between epigenetic and chronological age, associated with smoking (Gao, Zhang et al. 2016), obesity (Horvath, Erhart et al. 2014), poor

physical and cognitive fitness (Marioni, Shah et al. 2015), stroke (Perna, Zhang et al. 2016), Parkinson disease (Horvath and Ritz 2015), cytomegalovirus infection (Kananen, Nevalainen et al. 2015), HIV-1 infection (Horvath and Levine 2015), Down syndrome (Horvath, Garagnani et al. 2015), and cancer (Horvath 2013). AA is also associated with all-cause mortality, cancer mortality, and mortality from cardiovascular diseases (Marioni, Harris et al. 2016, Perna, Zhang et al. 2016). Hence, methylation-based epigenetic age has a potential to become an accurate biomarker of cellular aging, since epigenetic age in relation to chronological age was shown to predict onset of age-related diseases.

If similarly to epigenetic clock for chronological age biomarker in adults, epigenetic clock for gestational age biomarker in newborns existed, it may have had a potential to predict future adversity and allow very early life interventions. Recently, Knight et al. (Knight, Craig et al. 2016) developed such a novel biomarker of epigenetic gestational age. This biomarker is based on methylation of 148 CpG sites in cord blood and it showed high correlation with ultrasound-based GA (Knight, Craig et al. 2016). No studies yet have examined whether prenatal and perinatal factors associate with this novel epigenetic GA biomarker and whether it can predict future adversities in the offspring.

1.5. Summary

In summary, although maternal obesity and co-morbid hypertensive and diabetic disorders have gained considerable research attention as predictors of neurodevelopmental adversity in the offspring, there are still many gaps in the existing literature. These gaps arise from self-reported data on maternal BMI and/or related co-morbid disorders, lack of control for their mutual effects and understanding their unique effects, and lack of understanding of the role of maternal overweight. In addition, trajectories of neurodevelopmental adversity from prenatal exposure to maternal obesity and/or co-morbid disorders from infancy to early childhood are still to be traced, mechanisms underlying the associations between maternal obesity and co-morbid conditions and child neurodevelopment are to be understood, and possibilities to identify individuals at risk for developing neurodevelopmental disorders already at birth are to be explored.

2. AIMS OF THE STUDY

The primary aim of this study was to examine the effects of maternal overweight/obesity and highly co-morbid hypertensive and diabetic disorders on the offspring neurodevelopment and to track the trajectory from these maternal conditions to early manifestations of neurodevelopmental adversity to developmental milestones/developmental delay in early childhood. The secondary aim of this study was to examine epigenetic changes as a potential mechanism underlying the associations between maternal overweight/obesity and co-morbid disorders and child neurodevelopment by assessing the associations between these maternal conditions and variations in the novel biomarker of DNAm GA.

Three separate studies were conducted to evaluate the following outcomes of prenatal exposure to maternal pre-pregnancy obesity and co-morbid pregnancy disorders:

- | | |
|-------------------|--|
| Study II: | Regulatory behavior problems in infancy |
| Study III: | Developmental delay in early childhood |
| Study IV: | Novel biomarker of cord blood-derived and gestational age-related epigenetic age (DNAm GA) |

3. METHODS

3.1. Participants

As described in the Study I (Girchenko, Lahti et al. 2017), the Prediction and Prevention of Pre-eclampsia (PREDO) study is a prospective, multicenter study of Finnish women who were pregnant between 2005 and 2010 and their singleton children. PREDO recruited women who visited antenatal clinics at any of the ten study hospitals for their first ultrasound screening at 12+0-13+6 weeks+days of gestation. The antenatal clinics included the Jorvi Hospital in Espoo, the Women's Hospital and the Kätilöopisto Maternity Hospital in Helsinki, the Hyvinkää Hospital in Hyvinkää, the Kanta-Häme Central Hospital in Hämeenlinna, the Iisalmi Hospital in Iisalmi, the North Karelia Central Hospital in Joensuu, the Kuopio University Hospital in Kuopio, the Päijät-Häme Central Hospital in Lahti, and the Tampere University Hospital in Tampere. The cohort comprises 4777 pregnant women and their singleton infants born alive between 2006 and 2010. To enrich the number of women with pre-eclampsia and intrauterine growth restriction in our sample, we recruited 1079 pregnant women with known risk-factor status for pre-eclampsia ("high risk subsample"). In the high risk subsample 969 women had at least one risk factor of pre-eclampsia, including pre-pregnancy obesity, pre-eclampsia in previous pregnancy, and chronic hypertension, and 110 had none of the known risk factors for pre-eclampsia and IUGR. Community-based subsample of the PREDO study comprised 3698 women pregnant women who volunteered to participate regardless of their risk factor status for preeclampsia and IUGR. Only women who volunteered to participate and signed an informed consent form were included into the PREDO study. The obstetric and perinatal characteristics of the PREDO study population are presented in Table 1.

Table 1. Characteristics of the PREDO study participants (N=4777)

	N (%)	Mean (SD)
Maternal characteristics		
Age at childbirth	31.5 (4.9)	
Data not available, n (%)	12 (0.3%)	
Education		
Primary	169 (3.5%)	
Secondary	1634 (34.2%)	
Tertiary	2591 (54.2%)	
Data not available, n (%)	383 (8.0%)	
Parity		
Nulliparous	1831 (38.3%)	
Multiparous	2904 (60.1%)	
Data not available, n (%)	42 (0.9%)	
BMI category		
Normal weight (<25 kg/m ²)	3146 (66.3%)	
Overweight (between 25 and 30 kg/m ²)	928 (19.4%)	
Obese (≥30 kg/m ²)	670 (14.0%)	
Data not available, n (%)	31 (0.6%)	
Hypertensive disorders during pregnancy		
Chronic hypertension	203 (4.2%)	
Gestational hypertension	196 (4.1%)	
Preeclampsia	188 (3.9%)	
Data not available, n (%)	0	
Diabetic disorders		
Gestational diabetes	512 (10.7%)	
Type 1 diabetes	25 (0.5%)	
Data not available, n (%)	32 (0.7%)	
Neonatal characteristics		
Delivery mode		
Vaginal delivery	3897 (81.6%)	
Caesarean section	832 (17.4%)	

Data not available n (%)	48 (1.0%)
Gestational age at delivery	39.9 (1.7)
Data not available n (%)	6 (0.1%)
Child sex	
Boy	2479 (51.9%)
Girl	2269 (47.5%)
Data not available n (%)	30 (0.6%)
Birth weight	3530.6 (527.5)
Data not available n (%)	37 (0.8%)

3.2. Follow-ups of the PREDO study relevant to this thesis

Study participants filled in a baseline study questionnaire at 12+0-13+6 weeks+days of gestation. In total, 3642 (76.2% of the initial study sample) women provided self-reported data on health, family history, lifestyle, and sociodemographics. Birth characteristics were extracted from Finnish Medical Birth Register (MBR) and are available for 4744 (99.3%) study participants. Fetal cord blood samples were collected at birth from the participants of the high risk subsample of the PREDO cohort. In total, fetal cord blood samples are available for 994 (20.8% of the initial study sample, 92.1% of the high risk subsample) of participating neonates. After conducting quality control procedures, 814 (81.9%) were included into analytic sample. Follow-up assessment of regulatory behaviors in infancy was conducted on average 2.4 weeks after the delivery. In total 3180 (66.6% of the initial study sample) women evaluated their infant's regulatory behaviors at the mean age of the infant of 17.7 days (range 1-348 days). Of them, 3117 (98%) were included in the analytic sample. Follow-up assessment of child's developmental milestones was conducted in 2011-2012. In total 2667 (58.2%) mother-child dyads participated. Developmental milestones were assessed at the child's mean age of 42.1 months (range 23.2-68.8 months), of them 2504 (93.9%) were included in the analytic sample.

3.3. Measurements

3.3.1. Maternal BMI and co-morbid hypertensive and diabetic disorders (all studies)

Data on maternal BMI and co-morbid disorders were extracted from the Finnish Medical Birth Registry (MBR). Each individual diagnosis was further verified by a clinical jury for the subsample recruited based on their increased risk of pre-eclampsia and IUGR.

Early pregnancy BMI was calculated from weight and height measured by a nurse at the first visit to the antenatal clinic (M=8+4 weeks+days, SD= 1+3 weeks+days of gestation). At the mean 8th gestational week, pregnancy weight gain is still minimal. Hence, this measurement is a close proxy of the pre-pregnancy BMI. Early pregnancy BMI was categorized to normal weight (24.99 kg/m² or less), overweight (25-29.99 kg/m²), and obese (30 kg/m²) groups according to the World Health Organization (WHO) criteria(2000); Less than 4% of women had a BMI below 18.5 kg/m² indicating underweight; the underweight and normal weight groups were pooled for the analyses (from here on referred to as ‘normal weight’) (Study II, III and IV). Overweight and obese groups were further pooled together to represent maternal weight 25 kg/m² and higher (Study III).

Gestational hypertension was defined as blood pressure $\geq 140/90$ mmHg on ≥ 2 occasions at least 4 h apart in a woman who was normotensive before 20th week of gestation.

Pre-eclampsia was defined as blood pressure $\geq 140/90$ mmHg on ≥ 2 occasions at least 4 h apart in a women who was normotensive before 20th week of gestation with proteinuria ≥ 300 mg/24 h.

Chronic hypertension was defined as blood pressure $\geq 140/90$ mmHg or medication before 20th week of gestation.

Gestational diabetes was defined as fasting, 1h or 2h plasma glucose during a 75g oral glucose tolerance test ≥ 5.1 , 10.0 or 8.5 mmol/L, respectively, that emerged or was first identified during pregnancy.

3.3.2. Maternal characteristics (all studies)

The following maternal characteristics were included as predictors (Study IV) or as covariates (Study II and III) in our analysis: maternal age at childbirth (years), parity (primiparous/multiparous), delivery mode (vaginal/caesarian), maternal smoking during pregnancy (did not smoke/quit during first trimester/smoked throughout pregnancy) with data extracted from patient case reports and/or the MBR, and maternal alcohol use during pregnancy (yes/no) and education level (basic/secondary vs. tertiary) as self-reported in a questionnaire given to the mothers at 12+0-13+6 weeks+days of gestation.

3.3.3. Neonatal characteristics (all studies)

Child's gestational age at delivery (weeks), sex (boy/girl), birth weight (kg), length (cm), head circumference (cm), and 1-minute Apgar score were extracted from medical records and/or MBR. Ponderal index (kg/m^3) at birth was calculated (Study IV). Fetal cord blood venous and arterial pH were measured at birth (Study IV). We further divided weight and length at birth into small ($\leq -2\text{SD}$) for GA by using Finnish national growth references (Pihkala, Hakala et al. 1989) (Study IV).

3.3.4. Infant regulatory behavior problems (Study II)

Infant's regulatory behavior problems were rated by the Neonatal Perception Inventory (NPI) (Broussard and Hartner 1970, Povedano 2011), which evaluates behaviors relating to crying, feeding, spitting, elimination (bowel movements), sleeping and predictability. In order to decrease the potential bias pertaining to subjective perceptions of infant behaviors, we first asked the mother to rate concerns related to regulatory behaviors she would expect an 'average' infant to display. Then we asked her to rate concerns regarding her own infant's regulatory behaviors. The ratings were made using a five-point scale ranging from no problems (1) to a great number of problems (5). A difference score between her own and the average

infant's regulatory behaviors (own infant – average infant) reflects more regulatory behavior problems in her own infant (Raikkonen, Pesonen et al. 2015). In addition to this difference score, we calculated an ordinal ‘accumulation’ variable which indicated the number of areas in which the infant had regulatory problems (own infant had more problems than an average infant on any of the six subscales; score 0-6).

3.3.5. Developmental milestones and developmental delay (Study II and III)

Developmental milestones were rated by the Ages and Stages Questionnaires (ASQ) Third edition (Squires, Bricker et al. 1997) (translated into Finnish and back-translated and approved by the publisher). ASQ is a reliable and valid tool with high sensitivity and specificity to screen children requiring further developmental assessment, monitoring or special education (Squires, Bricker et al. 1997, Kerstjens, Bos et al. 2009). It comprises 30 age-appropriate items (in our sample for Study III children aged 22.2-26.2, n=75, 24.5-29.5, n=67, 27.5-32.5, n=93, 30.5-35.5, n=199, 33.0-41.5, n=377, 37.0-47.0, n=463, 42.0-53.0, n=618, 55.0-59.0, n=205, and 54.0-69.0 months, n= 29, and for Study IV children aged 22.2-26.2, n=83, 24.5-29.5, n=83, 27.5-32.5, n=108, 30.5-35.5, n=241, 33.0-41.5, n=450, 37.0-47.0, n=564, 42.0-53.0, n=702, 55.0-59.0, n=239, and 54.0-69.0 months, n= 34) measuring communication, gross motor, fine motor, problem solving and personal/social skills.

Each domain comprises six questions with the responses ‘yes’ (scored 10) indicating the child can master the skill, ‘sometimes’ (scored 5) if the skill is emerging or occasional, and ‘not yet’ (scored 0) if the child is not able perform the skill; Scores range from 0 to 60 with the highest value indicating mastering of the skill. In study II, we used the total developmental milestones score calculated as a sum of the subscale scores (Charkaluk, Rousseau et al. 2017). In study III, according to the guidelines from Squires et al. (Squires, Bricker et al. 1997) we created categorical variables indicative of mild neurodevelopmental delay defined as scoring between 1SD and 2 SD below the age-specific mean and failure to achieve developmental milestone defined as 2 SD from the age-specific mean for each developmental domain. We also created a variable representing severity of

neurodevelopmental delay expressed as a total number of SD below the mean across the five ASQ domains.

3.3.6. DNA methylation and epigenetic GA at birth (Study IV)

As described in Study IV (Girchenko, Lahti et al. 2017), fetal cord blood samples were collected according to standard procedures. DNA was extracted at the National Institute for Health and Welfare, Helsinki, Finland and the Department of Medical and Clinical Genetics, University of Helsinki, Finland and methylation analyses were performed at the Max Planck Institute in Munich, Germany. DNA was bisulphite-converted using the EZ-96 DNA Methylation kit (Zymo Research). Genome-wide methylation status of over 485 000 CpG sites was measured using the Infinium Human Methylation 450 BeadChip (Illumina Inc., San Diego, USA) according to the standard protocol in 876 samples. The arrays were scanned using the iScan System (Illumina Inc., San Diego, USA). The quality control (QC) pipeline was set up using the R-package minfi. Samples were excluded if they were duplicates, outliers in the median intensities, and because of sex discrepancy. Furthermore, any probes on chromosome X or Y, cross-hybridizing probes as well as probes containing SNPs, and CpGs with a detection P-value > 0.01 in at least 50% of the samples, or maternal blood contamination were excluded. Maternal blood contamination was tested using DNAm data at 10 CpGs independently identified as differentially methylated between cord and adult blood and indicative of maternal blood contamination (paper under review). Eight samples with DNAm values above the previously-identified thresholds at five or more of these CpGs were considered contaminated and removed from future analysis. The final dataset contained 428 619 CpGs and 824 samples. Methylation beta-values were normalized using the funnorm function and incorporating the first ten principal components from the internal control probes. To check for batch effects, principal components were computed on these beta values. Two batches, i.e. slide and well, were significantly associated to the main principal components and were removed iteratively using the Combat package.

Cord blood cell counts were estimated for seven cell types (nucleated red blood cells, granulocytes, monocytes, natural killer cells, B cells, CD4(+)T cells,

and CD8(+)T cells) using the method of Bakulski (Bakulski, Feinberg et al. 2016) et al. which is also incorporated in the R-package minfi.

DNA methylation age was calculated using the method published by Knight et al. (Knight, Craig et al. 2016) and is based on the methylation profile of 148 selected CpGs.

We calculated a raw epigenetic age difference by subtracting from the predicted DNA methylation age the GA assessed at the first ultrasound screening conducted at 12+0-13+6 weeks+days of gestation. Epigenetic age residual was extracted from a linear regression of predicted DNA methylation age on ultrasound-based GA.

3.3. Statistical analyses

We used SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) to analyze the data. Mediation analysis (Study II) was performed using SPSS-IBM (Software, v.24.0 SPSS).

We tested the associations between maternal and neonatal characteristics with the raw epigenetic GA difference and epigenetic GA residual by applying linear regression. We controlled for cell-type composition and population stratification estimated with two multi-dimensional scaling components based on the genome-wide genotype data. Models testing associations with maternal characteristics were further adjusted for neonatal birth weight SD score, and models testing associations with neonatal anthropometrics were additionally adjusted for child's sex (Study IV).

We applied linear regression to examine the associations between maternal early pregnancy overweight/obesity and co-morbid disorders and infant regulatory behavior problems total difference score. To test the associations with the infant regulatory behavior problems on multiple behavioral domains we applied continuation-ratio ordinal logistic regression. Additionally, to exclude the effects of potential confounding or effect modification by co-morbid conditions, we conducted 'restricted' analyses excluding women with the co-morbid disorders from the analyses examining the unique effects of overweight/obesity, hypertensive and gestational diabetes. We tested whether any potential associations between maternal overweight/obesity and co-morbid disorders and child developmental milestones were mediated by infant regulatory behavior problems by using the PROCESS macro for

SPSS with 5000 bootstrapped samples (Hayes and Rockwood 2016). The models were adjusted for maternal age at childbirth and education level, parity, delivery mode, maternal smoking during pregnancy, maternal alcohol use during pregnancy, child's gestational age at delivery, birth weight, child sex, and child's age at follow-up reported in conjunction with filling in the child assessments (Study II).

We examined the associations between maternal overweight, obesity and co-morbid hypertensive and diabetic disorders and the odds of failing the ASQ domains using the 1SD/2SD cut-off points by applying multinomial logistic regression. We used continuation-ratio ordinal logistic regression to test if children born to overweight or obese vs. normal weight mothers, children born to mothers with gestational hypertension, pre-eclampsia and pre-pregnancy/chronic hypertension vs children of mothers without these disorders, and if children born to mothers with gestational diabetes and pre-pregnancy type 1 diabetes vs children of mothers without these disorders were more likely to display more severe neurodevelopmental delay. The models were adjusted for maternal age at childbirth and education level, parity, delivery mode, maternal smoking during pregnancy, maternal alcohol use during pregnancy, child's gestational age at delivery, birth weight, child sex, and child's age at follow-up. To test if any potential effects on neurodevelopmental delay were specific to maternal overweight, obesity, or to the other co-morbid hypertensive and diabetic disorders, we also made adjustments for their mutual effects. Additionally, we conducted 'restricted' analyses excluding women with the co-morbid disorders from the analyses of severity of neurodevelopmental delay (Study III).

4. RESULTS

4.1. Maternal overweight/obesity and co-morbid hypertensive disorders and gestational diabetes and infant regulatory behavior problems (Study II)

As shown in Table 2, infants of the overweight/obese mothers in comparison to infants of the normal weight mothers experienced more regulatory problems in infancy. Further, infants of overweight/obese mothers were more likely to display multiple regulatory behavior problems. These associations held when we excluded from the analyses women who had hypertensive and diabetic disorders. Pre-eclampsia was marginally associated with multiple infant regulatory behavior problems when the analytic sample was restricted to normal weight non-diabetic women, but not in the full sample. There were no associations between pre-eclampsia and infant regulatory behavior total difference score in any sample. There were no associations between GDM (women with type 1 diabetes were excluded from the analytic sample of Study II), gestational and chronic hypertension and infant regulatory behavior problems.

Table 2. Associations between maternal early pregnancy overweight/obesity and hypertensive and diabetic disorders and infant regulatory behavior problems

	Full sample		Restricted sample with other disorders excluded	
	β (95% CI)	P	β (95% CI)	P
Infant regulatory behavior problems total difference score (own infant-average infant), SD units				
Early pregnancy BMI				
Normal weight (BMI <25 kg/m ²)	Referent		Referent	
Overweight/obese (BMI \geq 25 kg/m ²)	0.08 (0.003, 0.16)	0.04	0.09 (0.001, 0.19)	0.05
Hypertensive disorders				
Normotension	Referent		Referent	
Gestational hypertension	-0.07 (-0.24, 0.11)	0.45	0.09 (-0.17, 0.34)	0.52
Pre-eclampsia	0.08 (-0.12, 0.27)	0.44	0.12 (-0.16, 0.41)	0.40
Chronic hypertension	0.13 (-0.05, 0.31)	0.15	0.26 (-0.06, 0.57)	0.11
Diabetic disorders				
No diabetes	Referent		Referent	
Gestational diabetes	0.04 (-0.08, 0.15)	0.51	0.06 (-0.15, 0.28)	0.57
Multiple infant regulatory behavior problems				
	OR (95% CI)	P	OR (95% CI)	P
Early pregnancy BMI				
Normal weight (BMI <25 kg/m ²)	Referent		Referent	
Overweight/obese (BMI \geq 25 kg/m ²)	1.23 (1.06, 1.43)	0.007	1.26 (1.05, 1.50)	0.01
Hypertensive disorders				
Normotension	Referent		Referent	
Gestational hypertension	0.91 (0.65, 1.29)	0.26	1.03 (0.62, 1.72)	0.90
Pre-eclampsia	1.31 (0.90, 1.89)	0.16	1.69 (1.0, 2.87)	0.05
Chronic hypertension	1.05 (0.74, 1.48)	0.77	1.09 (0.59, 2.02)	0.78
Diabetic disorders				
No diabetes	Referent		Referent	
Gestational diabetes	1.05 (0.84, 1.33)	0.66	0.89 (0.57, 1.40)	0.63

All analyses are adjusted for maternal age at delivery, mode of delivery, parity, maternal smoking and alcohol use during pregnancy, maternal education, child's gestational age, birthweight, sex and age at follow-up

4.2. Maternal overweight/obesity and co-morbid hypertensive and diabetic disorders and severity and pervasiveness of developmental delay in early childhood (Study III)

As shown in Table 3, children of overweight and obese mothers as compared to normal weight mothers were 32% and 58% respectively more likely to display more severe and pervasive developmental delay in early childhood, and these effects were independent of the co-morbid hypertensive and diabetic pregnancy disorders. We have also shown the independent effect of pre-eclampsia (OR 2.19) on severity of developmental delay in the early childhood. Further, we have shown that the effect of gestational diabetes on severity of developmental delay was partly driven by maternal overweight/obesity and/or pre-eclampsia. There were no associations between gestational and chronic hypertension and severity of developmental delay.

Table 3. Associations between maternal pregnancy and pre-pregnancy disorders and severity and pervasiveness of developmental delay in their children defined as total number of SD below the mean for the five ASQ subscales

Pregnancy and pre-pregnancy disorders	Severity of developmental delay					
	Model 1*		Model 2**		Model 3***	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Early pregnancy body mass index						
Normal weight	Reference		Reference		Reference	
Overweight	1.38 (1.11 to 1.72)	0.003	1.34 (1.09 to 1.66)	0.006	1.32 (1.04 to 1.68)	0.02
Obese	1.48 (1.14 to 1.92)	0.003	1.43 (1.10 to 1.86)	0.008	1.58 (1.13 to 2.20)	0.007
Hypertensive disorder						
Normotension	Reference		Reference		Reference	
Gestational	0.85 (0.53 to 1.34)	0.48	0.82 (0.53 to 1.29)	0.40	0.67 (0.34 to 1.32)	0.24
Hypertension						
Preeclampsia	1.55 (1.04 to 2.30)	0.03	1.52 (1.04 to 2.23)	0.03	2.19 (1.30 to 3.70)	0.003
Pre-pregnancy	1.04 (0.65 to 1.67)	0.86	0.89 (0.93 to 1.62)	0.63	1.0 (0.44 to 2.30)	1.0
Chronic						
Hypertension						
Diabetes						
No diabetes	Reference		Reference		Reference	
Gestational diabetes	1.31 (1.0 to 1.72)	0.05	1.23 (0.94 to 1.62)	0.13	1.20 (0.74 to 1.91)	0.46
Type 1 diabetes	1.77 (0.51 to 6.19)	0.37	1.51 (0.47 to 4.83)	0.49	****	

*Adjusted for maternal age at delivery, mode of delivery, parity, maternal smoking and alcohol use during pregnancy, maternal education, child's gestational age, birthweight, sex and age at follow-up.

** Adjusted for other pregnancy and pre-pregnancy disorders

***Women with other pregnancy disorders are excluded (i.e., analyses of pre-pregnancy body mass index excludes women with gestational hypertension, preeclampsia, pre-pregnancy/chronic hypertension, gestational diabetes and pre-pregnancy type 1 diabetes; analyses of hypertensive disorder excludes women with pre-pregnancy

4.3. Mediation of association between prenatal exposure to maternal overweight/obesity and developmental milestones in early childhood (Study II)

We limited mediation analyses to the prenatal exposure to maternal overweight/obesity, since we did not find associations between maternal hypertensive disorders and GDM (women with type 1 diabetes were excluded from the analytic sample of Study III) and infant regulatory behavior problems. Figure 1 shows that higher level of infant regulatory behavior problems total difference score associated with lower total developmental milestones score in childhood. Children of overweight/obese in comparison to normal weight mothers had lower total developmental milestones scores in childhood. Figure 3 shows that infant regulatory behavior problems partially mediated the effect of maternal overweight/obesity on lower childhood developmental milestones total difference score.

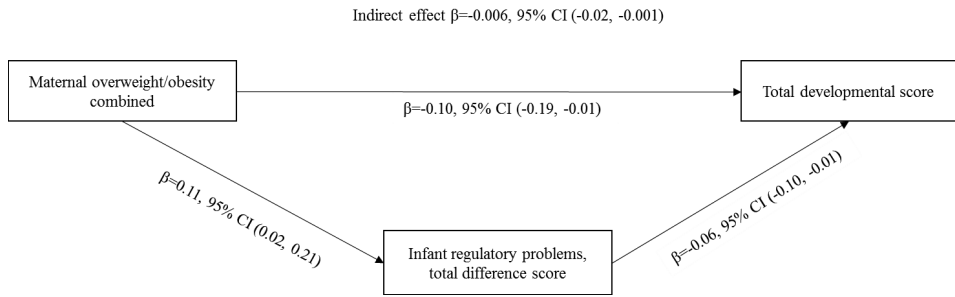


Fig 3. Mediation analyses results showing that maternal early pregnancy overweight/obesity partly acts via infant regulatory behavior problems total difference score to affect total developmental milestones score in early childhood. Numbers represent adjusted standardized coefficients and 95% confidence intervals.

4.4. Maternal overweight/obesity and co-morbid hypertensive and diabetic disorders and DNAm GA at birth (Study IV)

We did not find associations between maternal pre-pregnancy BMI neither as continuous, nor as categorical variable and the DNAm GA at birth expressed as raw DNAm GA difference (arithmetic difference between DNAm GA and GA) and the DNAm GA residual (the residual from a linear regression of DNAm GA on GA). Pre-eclampsia in previous pregnancy was associated with gestational age acceleration (GAA) in raw DNAm GA difference, but not in DNAm GA residual. Prenatal exposure to early pre-eclampsia and severe pre-eclampsia in index pregnancy increased DNAm GA expressed as a raw DNAm GA difference by almost 2 weeks, but was not associated with DNAm GA residual. Insulin treated gestational diabetes in previous pregnancy, but not in the index pregnancy, was associated with GAD using both measures of DNAm GA. We did not find associations between gestational and chronic hypertension and DNAm GA at birth (Table 4).

Table 4. Associations between maternal BMI, co-morbid hypertensive and diabetic disorders and offspring DNAm GA at birth based on cord blood methylation data.

	DNAm GA difference*			DNAm GA residual*		
	DNAm GAA /GAD in weeks	95% Confidence Interval	p-value	DNAm GAA /GAD in SD units	95% Confidence Interval	p-value
Maternal conditions						
Pre-pregnancy conditions						
Pre-eclampsia in a previous pregnancy	0.31	0.003, 0.61	0.05	0.07	-0.10, 0.23	0.44
Gestational diabetes in previous pregnancy	-0.21	-0.62, 0.20	0.32	-0.16	-0.39, 0.06	0.16
Diet treated	-0.05	-0.48, 0.38	0.83	-0.07	-0.31, 0.17	0.56
Insulin treated	-1.44	-2.63, -0.24	0.02	-0.84	-1.50, -0.19	0.01
Pre-pregnancy BMI, kg/m ²	-0.02	-0.04, 0.004	0.11	-0.007	-0.02, 0.004	0.19
Normal weight (<25 kg/m ²)	Ref			Ref		
Overweight (25 to 29.99 kg/m ²)	-0.13	-0.48, 0.22	0.45	-0.11	-0.30, 0.09	0.28
Obese (≥30 kg/m ²)	-0.18	-0.46, 0.10	0.21	-0.05	-0.20, 0.10	0.52
Pre-pregnancy chronic hypertension	0.003	-0.36, 0.37	0.99	-0.09	-0.29, 0.11	0.38
Pre-pregnancy type 1 diabetes	0.49	-0.56, 1.52	0.36	-0.29	-0.86, 0.28	0.32
Pregnancy disorders						
Gestational diabetes	0.06	-0.24, 0.36	0.68	0.01	-0.15, 0.18	0.87
Gestational diabetes treatment						
No gestational diabetes	Ref			Ref		
Diet treated	0.12	-0.20, 0.45	0.46	0.04	-0.14, 0.22	0.66
Insulin treated	-0.12	-0.73, 0.49	0.70	-0.18	-0.51, 0.16	0.30
Hypertension spectrum pregnancy disorders						
No hypertension spectrum pregnancy disorder	Ref			Ref		
Gestational hypertension	0.02	-0.40, 0.44	0.93	0.002	-0.23, 0.24	0.98
Pre-eclampsia	0.75	0.27, 1.22	0.002	0.06	-0.20, 0.33	0.64
Early	1.91	0.63, 3.20	0.004	-0.04	-0.74, 0.65	0.90
Late	0.58	0.07, 1.09	0.02	0.08	-0.20, 0.36	0.58
Non-severe	0.19	-0.37, 0.75	0.50	-0.08	-0.39, 0.24	0.63
Severe	1.99	1.17, 2.81	2*10 ⁻⁶	0.37	-0.09, 0.83	0.11
Chronic hypertension**	-0.03	-0.37, 0.32	0.88	-0.06	-0.25, 0.13	0.54

*All analyses were adjusted for cell-type composition and population stratification estimated with 2 multi-dimensional scaling components based on genome-wide data.

**This category includes 109 women with pre-pregnancy chronic hypertension and 25 women with hypertension detected before the 20th gestational week in the index pregnancy.

4.5. DNAm GA at birth and perinatal characteristics (Study IV)

As shown in the Table 5, GAA based on the raw DNAm GA difference was associated with lower birth weight, birth length, ponderal index at birth, birth head circumference, placental weight, being a lower birth weight for GA (continuous and being small-for-gestational-age, <-2 SD), a lower 1-minute Apgar score, and female sex. When based

on the DNAm GA residual, GAA was associated with a lower 1-minute Apgar score and female sex.

Table 5. Associations between perinatal characteristics and DNAm GA at birth based on cord blood methylation data.

Perinatal characteristics	DNAm GA difference*			DNAm GA residual*		
	DNAm GAA /GAD in weeks	95% Confidence Interval	p-value	DNAm GAA /GAD in SD units	95% Confidence Interval	p-value
Child sex (girls vs boys)	0.30	0.05, 0.55	0.02	0.16	0.02, 0.30	0.02
Birth weight, kg	-0.67	-0.90, -0.44	3*10 ⁻⁹	0.03	-0.10, 0.16	0.66
Small for gestational age**	1.08	0.33, 1.83	0.005	-0.04	-0.45, 0.37	0.84
Birth length, cm	-0.15	-0.21, -0.10	9*10 ⁻⁹	0.01	-0.02, 0.04	0.48
Head circumference, cm	-0.18	-0.26, -0.10	2*10 ⁻⁶	0.01	-0.03, 0.06	0.57
Ponderal index, kg/m ³	-0.05	-0.10, -0.01	0.01	-0.006	-0.03, 0.02	0.66
Placenta weight, g	-0.15	-0.25, -0.06	0.002	-0.0004	-0.05, 0.05	0.99
Apgar score						
9-10	Ref			Ref		
7-8	0.10	-0.23, 0.43	0.57	-0.01	-0.19, 0.17	0.89
≤ 6	0.72	0.19, 1.27	0.009	0.37	0.07, 0.67	0.01

*All analyses were adjusted for cell-type composition and population stratification estimated with 2 multi-dimensional scaling components based on genome-wide data; Anthropometric data were adjusted for sex.

**Small for gestational age indicates birth size for sex and gestational age SD ≤ -2 according to Finnish growth references (Pihkala, Hakala et al. 1989).

5. DISCUSSION

The primary aim of this study was to examine the effects of maternal overweight/obesity and highly co-morbid hypertensive and diabetic disorders on the offspring neurodevelopment and to track the trajectory from maternal overweight/obesity and co-morbid disorders to early manifestations of neurodevelopmental adversity to developmental milestones in early childhood. The study capitalized on the large PREDO pregnancy cohort combining biological data, biomarkers and epigenomic information with measures of medical, psychological, environmental and socio-demographic characteristics in pregnant women and their children. The main results demonstrate that maternal overweight and obesity were associated with both early signs of neurodevelopmental adversity and developmental delay in early childhood, and infant regulatory behavior problems partially mediated the association between maternal overweight/obesity and child developmental milestones. The effects of maternal overweight and obesity on the offspring neurodevelopment were independent of highly co-morbid hypertensive and diabetic disorders. We have also shown adverse effect of pre-eclampsia on severity and pervasiveness of developmental delay in early childhood and demonstrated that the effects of pre-eclampsia on regulatory behavior problems in infancy and on developmental delay in early childhood were stronger in normal weight non-diabetic women. There was no association between gestational diabetes and early signs of neurodevelopmental adversity; the effects of gestational diabetes on developmental delay in early childhood were partly driven by maternal overweight/obesity and/or pre-eclampsia. We did not find the associations between chronic and gestational maternal hypertension and neurodevelopmental adversity of the offspring neither in infancy nor in early childhood. The secondary aim of this study was to assess whether maternal overweight/obesity and co-morbid disorders associated with variations in the novel biomarker of epigenetic GA. Pre-eclampsia, both in index and previous pregnancy, as well as insulin treated gestational diabetes in previous pregnancy, were associated with offspring's DNAm GA, but in contrast to our expectations, maternal BMI was not.

5.1. Maternal overweight/obesity and child neurodevelopment (Studies II and III)

For the first time we have demonstrated that the infants of overweight/obese mothers as compared to the infants of normal weight mothers displayed more regulatory problems and were more likely to experience problems in multiple areas of self-regulation. We have also shown that the effects of maternal overweight/obesity on regulatory behavior problems in infancy were independent of the co-morbid hypertensive disorders and GDM (in the Study II we excluded women with T1DM from the analytic sample, since the number of cases was too small to study the effect of T1DM on infant regulatory behaviors). Further, we have shown separate effects of maternal overweight and obesity on the severity and pervasiveness of developmental delay in the childhood. These effects were also not confounded by the co-morbid hypertensive and diabetic disorders. Additionally, we showed that regulatory behavior problems in infancy partially mediated association between maternal overweight/obesity and developmental milestones in early childhood.

Our findings are in agreement with previous studies which have demonstrated negative impact of maternal obesity on child neurodevelopment (Rodriguez, Miettunen et al. 2008, Rodriguez 2010, Krakowiak, Walker et al. 2012, Basatemur, Gardiner et al. 2013, Casas, Chatzi et al. 2013, Papachatzi, Dimitriou et al. 2013, Van Lieshout, Schmidt et al. 2013, Bliddal, Olsen et al. 2014, Huang, Yu et al. 2014, Mehta, Kerver et al. 2014, Jo, Schieve et al. 2015, Pugh, Richardson et al. 2015, Wylie, Sundaram et al. 2015, Yeung, Sundaram et al. 2017). Our findings added to the previously existing evidence by confirming that early pregnancy obesity calculated from weight and height verified by a nurse at the first visit to the antenatal clinic had an independent adverse effect on the offspring neurodevelopment. The novelty of our study includes recognition of the adverse effect of maternal overweight on offspring's neurodevelopment, separation of the effects of maternal overweight/obesity from the effects of co-morbid hypertensive and diabetic disorders, and discovery of a partial mediation of the effects of maternal overweight/obesity on the offspring's poorer achievement on a measure of developmental milestones in early childhood by infant regulatory behavior problems. This last finding is noteworthy as existing evidence suggests that early life regulatory behavior problems predict

childhood neurobehavioral adversity, including externalizing behavior, ADHD, ASD and poorer cognition (Thunstrom 2002, Wolke, Rizzo et al. 2002, Becker, Holtmann et al. 2004, Wolke, Schmid et al. 2009, Liu, Bann et al. 2010, Schmid, Schreier et al. 2010, Hemmi, Wolke et al. 2011, Barnevik Olsson, Carlsson et al. 2013).

5.2. Hypertensive and diabetic disorders in pregnancy and child neurodevelopment (Study II and III)

We found that prenatal exposure to maternal pre-eclampsia was associated with multiple regulatory problems in the infants of normal weight non-diabetic mothers and more severe and pervasive developmental delay in early childhood. We have shown that the effect of pre-eclampsia on both regulatory problems in infancy and on severity of developmental delay in early childhood was stronger in the offspring of normal weight women without diabetic disorders. Our findings suggest that more pronounced effect of pre-eclampsia on neurodevelopment of the children of lean women without diabetes may be due to different etiology of pre-eclampsia, or associated with different risk factors as compared to overweight or obese women and/or women with diabetic disorders, which is in agreement with previous studies (Williams, Havel et al. 1999, Rudra and Williams 2005, Leavey, Bainbridge et al. 2015).

In contrast to our expectations, gestational diabetes was not associated with infant regulatory behavior problems, and its adverse effect on developmental delay was partly driven by maternal overweight/obesity and/or pre-eclampsia.

5.3. Maternal overweight/obesity and co-morbid hypertensive and diabetic disorders and DNAm GA at birth (Study IV)

The secondary aim of this study was to assess whether maternal overweight/obesity and co-morbid disorders associated with variations in the novel biomarker of epigenetic GA to provide more insight on epigenetic mechanisms underlying the associations between maternal conditions and child neurodevelopment (Study IV). In contrast to our expectations, in our sample maternal BMI was not associated with variations in the offspring's DNAm GA. However, the lack of association between maternal BMI and offspring's DNAm represents a conundrum,

since Suarez et al. (Suarez, Lahti et al. 2018) showed associations of the same biomarker of epigenetic GA with maternal antenatal depression. Moreover, this biomarker of epigenetic clock at birth partially mediated the association between maternal antenatal depression and psychiatric problems in 2 to 5 years old boys (Suarez, Lahti et al. 2018). Given that association between maternal obesity and antenatal depression has been well-established (Molyneaux, Poston et al. 2014, Molyneaux, Poston et al. 2016) and confirmed in the PREDO sample (Kumpulainen, Girchenko et al. 2018), and taking into account that both overweight and obesity were strongly associated with developmental delay in our study (Study III) the same way as DNAm biomarker was associated with psychiatric problems (at that, only in boys), the lack of association between maternal BMI and offspring's DNAm is surprising. However, since the analytic sample for Study IV mostly comprised women with pre-existing risk factors for pre-eclampsia and IUGR, the effects of maternal BMI may have been overshadowed by the effects of the concurrent adverse maternal factors during pregnancy.

In agreement with our initial hypothesis, we found that prenatal exposure to maternal pre-eclampsia was associated with variations in the offspring's DNAm GA at birth when it was used as a raw epigenetic age difference. These findings suggest that neurodevelopmental consequences of prenatal exposure to maternal pre-eclampsia have a potential to be detected at birth via acceleration of epigenetic clock for GA. The findings are in line with previous studies shown changes in DNA methylation associated with prenatal exposure to pre-eclampsia (He, Zhang et al. 2013, Nomura, Lambertini et al. 2014). However, to assess utility of the existing epigenetic clock for GA in predicting future neurodevelopmental adversity associated with prenatal exposure to maternal pre-eclampsia, future studies are warranted. Interestingly, although GDM in index pregnancy was not associated with variation in DNAm GA, insulin treated GDM in previous pregnancy associated with GAD.

Although our findings do not entirely support our initial hypothesis, they demonstrate that neonates exposed to prenatal environmental adversity related to maternal hypertensive and diabetic disorders show differences at birth in their DNAm GA. Furthermore, the finding that DNAm GAA based on both GA difference and GA residual was associated with the Apgar score 6 and lower may represent a very early manifestation of the exposure to maternal adversity. Both DNAm GAA and GAD

could represent indicators of risk. The increased risk of future adverse outcomes associated with DNAm GAA is consistent with the findings in children and adults showing that epigenetic age acceleration is associated with a number of adverse characteristics including higher BMI (Horvath, Erhart et al. 2014), lower physical and cognitive fitness (Marioni, Shah et al. 2015) and increased mortality (Chen, Marioni et al. 2016, Marioni, Harris et al. 2016, Perna, Zhang et al. 2016). Lower developmental maturity, as indicated by DNAm GAD, is consistent with the DOHaD hypothesis and findings from previous studies showing an increased risk of aging-related diseases in individuals exposed to prenatal environmental adversity associated with pre-term birth (Barker, Godfrey et al. 1991, Frankel, Elwood et al. 1996, Rich-Edwards, Stampfer et al. 1997, Osler, Lund et al. 2009, Visentin, Grumolato et al. 2014). Therefore, DNAm GAA or GAD may serve as summary indicators of epigenetic programming and indicate increased risk for adverse outcomes later in life. At the same time, future studies are warranted to clarify our findings and to assess utility of DNAm GA at birth in predicting future neurodevelopmental adversity.

5.4. Theoretical and mechanistic considerations

These study findings are in line the DOHaD theory suggesting that neurodevelopmental adversity may be programmed by intrauterine exposure to maternal overweight/obesity and/or pre-eclampsia. Given that most of the brain growth and neuroendocrine maturation occurs during prenatal period (Dobbing and Sands 1979), conceptualization of these findings within the DOHaD framework suggests that maternal overweight/obesity and pre-eclampsia permanently alter structure and functioning of the central nervous system. In addition to theoretical calibration, these study findings are in line with the existing evidence. Abundant experimental studies attempted to shed more light on the question why prenatal exposure to maternal overweight, obesity and co-morbid hypertensive and diabetic pregnancy disorders should affect neurodevelopment of the offspring (Neri and Edlow 2015). Current study attempted to provide insight on manifestation of only one of the possible mechanisms underlying the associations between intrauterine exposure to maternal overweight/obesity and neurodevelopmental adversity: changes in DNAm biomarker, based on the fact that changes in umbilical cord blood methylation patterns

caused by maternal overweight/obesity were established by previous studies (Nomura, Lambertini et al. 2014, Catalano and Shankar 2017). Lack of association between maternal BMI and changes in DNAm GA in our study may be conditioned by several factors: obscuring of the effects of maternal BMI by the other risk factors of pre-eclampsia and IUGR, insufficient sensitivity of this novel biomarker, or other mechanisms playing more significant role in pinpointing the associations between maternal overweight/obesity and neurodevelopmental adversity.

Another potential mechanism underlying associations between prenatal exposure to maternal overweight/obesity and child neurodevelopmental adversity may be related to the changes in the maternal microbiota caused by obesity. Maternal microbiota was found to affect the microbiota of the fetus via the bloodstream and placenta (Funkhouser and Bordenstein 2013, Borre, O'Keeffe et al. 2014, Neri and Edlow 2015). Gut microbiota plays a major role in the bidirectional communication between the gastrointestinal tract and the central nervous system (Borre, O'Keeffe et al. 2014). Formation of gut microbiota coincides with critical period of brain development, and thus affects neurodevelopment of the offspring (Dominguez-Bello, Costello et al. 2010).

Another potential mechanism linking maternal obesity and child neurodevelopment is an altered placental function (Cuffe, Holland et al. 2017, Godfrey, Reynolds et al. 2017). Animal studies identified a few potential factors crossing placenta and influencing fetal neuroendocrine and brain development, including high levels of nutrients, among others fatty acids and glucose, high levels of hormones like leptin and insulin, and inflammatory mediators, including interleukins and tumor necrosis factor (Jonakait 2007, Mehta, Kerver et al. 2014, Rivera, Christiansen et al. 2015). In addition, oxidative stress in the placenta in obese women alters cell membranes by increasing incorporation of cholesterol and oxidized free fatty acids and low-density lipoproteins (Jauniaux, Poston et al. 2006, Malti, Merzouk et al. 2014), inducing fetal epigenetic reprogramming (Marchlewicz, Dolinoy et al. 2016).

In agreement with the previous findings (He, Zhang et al. 2013, Nomura, Lambertini et al. 2014), current findings suggest that the mechanisms underlying the associations between prenatal exposure to maternal pre-eclampsia and child neurodevelopmental adversity may be related to epigenetic changes. Previous research

identified different etiological subtypes of pre-eclampsia, including pre-eclampsia driven by maternal cardiovascular risk factors, obesity being among those factors, pre-eclampsia arising from placental origin, and pre-eclampsia due to immunologic maternal–fetal incompatibility (Leavey, Benton et al. 2016). Pre-eclampsia of different etiology was found to manifest via different profiles of placental gene expression (Leavey, Benton et al. 2016). This may offer a potential explanation of the differences in the measure of neurodevelopmental adversity associated with the exposure to maternal pre-eclampsia between the offspring of the overweight/obese women and/or women with GDM and the offspring of the lean women without GDM found in this study. Future studies are warranted to clarify whether neurodevelopmental adversity associated with prenatal exposure to pre-eclampsia of different etiology may be recognized at birth using the same DNAm biomarker of gestational age.

5.5. Methodological considerations

The main strengths of the PREDO study include the large and homogeneous sample, prospective study design, data on maternal BMI derived from the Finnish MBR, and data on hypertensive and diabetic disorders and neonatal characteristics derived from the MBR and medical records. As described in Study I, PREDO follow-up rates varied between excellent and satisfactory. Moreover, availability of the personal identification numbers of the study participants allowed us to link almost 100% of individual records with Finnish MBR.

Around 20% of the study sample comprised women with pre-existing known risk factors for pre-eclampsia and IUGR, including obesity, chronic hypertension and GDM in previous pregnancy, which amplified the statistical power to study the unique effects of maternal overweight/obesity, hypertensive and diabetic disorders on child neurodevelopment by completely excluding potential confounding and/or effect moderation by the co-morbid conditions. On the other hand, oversampling of women with pre-existing risk factors for pre-eclampsia and IUGR is also a study limitation: generalizability of our findings pertaining to this high risk subsample may be precluded to the general population. As an illustration, majority of the women with DNAm GA data available belonged to the high risk subsample, which

may have muddled the associations between maternal risk factors and DNAm GA by the effects of the other risk factors.

At the same time, in an attempt to increase the external validity of the findings from the PREDO cohort, 80% of PREDO study participants were recruited regardless of their risk factor status. Hence, the study sample is comparable to the general population of pregnant women in Finland in many characteristics, such as prevalence of gestational diabetes, gestational age and birthweight of the child (Study I). At the same time, women in the PREDO sample were older at delivery, less often primiparous, and smoked less often during pregnancy as compared to the general population of Finnish pregnant women (Study I). As defined by the recruitment criteria, women in the PREDO study had slightly higher prevalence of pregnancy obesity and hypertensive disorders (Study I).

One of the other limitations of the study is the fact that some of the maternal characteristics, namely education and alcohol use during pregnancy, and child's neurodevelopmental outcomes in infancy and early childhood were mother-reported. To overcome any potential bias in reporting regulatory behaviors problems, the mothers were asked to rate regulatory behaviors they would expect an 'average' infant to display and then rate her own infant (Raikkonen, Pesonen et al. 2015). The majority of previous studies have also used mother- or parent-reports of infant regulatory behavioral challenges, as we did. Neurologists' assessments have been used in some studies, but these assessments usually concern oral motor functioning in relation to feeding problems (Schmid, Schreier et al. 2010). Hence, the use of mother-reports remains a limitation, as long as gold standards do not exist on how to measure regulatory behavioral challenges in infancy. The ASQ has been shown to be reliable instrument, it is well-validated, and demonstrates high sensitivity and specificity to screen children requiring further developmental assessment, monitoring or special education (Bricker, Squires et al. 1988, Squires, Bricker et al. 1997, Kerstjens, Bos et al. 2009).

Follow-up attrition, which was not independent from maternal characteristics, represent another study limitation. The mothers of children who participated in follow-ups were older and more often primiparous as compared to those who were eligible, but did not participate. This would be expected to cause a bias only if the associations between maternal overweight/obesity and co-morbid diabetic and

hypertensive disorders and child neurodevelopmental outcomes differ between participants and non-participants. In addition, although we were able to control for a number of potential covariates, we cannot entirely exclude the possibility of residual confounding.

5.6. Implications of the findings

These study findings showed that maternal overweight and obesity compromise already very early neurodevelopment of the offspring, and thus, the adverse effects of prenatal exposure to maternal overweight and obesity can be manifested already during infancy. Trajectory of neurodevelopmental adversity associated with prenatal exposure to maternal overweight/obesity may be traced from infancy to early childhood. Our findings contribute to previously existing evidence showing that maternal overweight and obesity carry increased risk of long-term neurological morbidity, show that these effects are independent from the co-morbid hypertensive and diabetic disorders, and suggest that epigenetic changes may play a role in explaining these associations. Future studies are warranted to unravel whether the neurodevelopmental risks associated with prenatal exposure to maternal overweight and obesity can be detected at birth by assessing variations in DNAm based biomarker.

Given the alarming rates of increase in global prevalence of overweight and obesity as well as of co-morbid hypertensive and diabetic disorders in pregnant women, our findings are of considerable public health importance. More than 20% of newborns globally are being born with perinatal complications largely attributed to overweight/obesity and co-morbid diabetic and hypertensive disorders in pregnancy: prevalence of preterm birth is about 11% (Blencowe, Cousens et al. 2013, Torchin, Ancel et al. 2015) and prevalence of macrosomia is about 12% (Ehrenberg, Mercer et al. 2004, Kc, Shakya et al. 2015). The rates of preterm birth and macrosomia are still growing. Taking into account the alarmingly high prevalence of immediate perinatal adversities associated with overweight/obesity and co-morbid disorders, the public health burden associated with long-term consequences of prenatal exposure to these maternal conditions imposed on the next generation is alarming.

These study findings highlight the importance of prevention and effective management of overweight and obesity among women of reproductive age.

Recognition of the adverse effect of not only maternal obesity, but already of maternal overweight, may have a potential implication for the design of prevention and intervention programs.

These study findings also suggest that among all of the pre-pregnancy and pregnancy disorders associated with maternal overweight/obesity, pre-eclampsia imposes the most detrimental effect on the offspring neurodevelopment. Our findings suggest that DNAm GA biomarker has a potential to identify individuals exposed to maternal pre-eclampsia already at birth, but future studies are warranted to identify the most accurate predictions of neurodevelopmental adversity associated with prenatal exposure to maternal pre-eclampsia. These study findings also suggest that gaining more knowledge on the etiology of pre-eclampsia occurring in lean normotensive women and taking early preventive measures should also benefit neurological health of the future generation.

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APPENDIX