

**Maternal hypertensive disorders during pregnancy and the mental health and cognitive functioning of the adult offspring:
the Helsinki Birth Cohort Study**

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ABSTRACT

Hypertensive pregnancy disorders complicate approximately 10% of all pregnancies. They may compromise placental functioning and, thus, affect the fetal developmental milieu. It is therefore highly plausible that they have consequences for the developmental outcomes of the offspring. However, their role in the developmental plasticity phenomenon dubbed ‘programming’ remains relatively unexplored.

This thesis examines whether adult offspring born to mothers with hypertensive pregnancy disorders differ from their counterparts born to normotensive mothers in mental health and cognitive functioning, and whether the potential group differences vary according to sex, length of gestation, parity, and childhood socio-economic status.

This thesis capitalizes on the Helsinki Birth Cohort Study. The study cohort comprises 13 345 individuals born in Helsinki between 1934 and 1944. Maternal hypertension status was defined based upon blood pressure and urinary protein measurements during pregnancy and was available for 6410 individuals. Data on mental disorders come from validated national registers extending over four decades (n = 5970 eligible for this study; Study II). Depressive symptoms were measured with a standardized questionnaire (BDI) in conjunction with a clinical follow-up study at a mean age of 62 years (n = 788; Study I) and in conjunction with a further follow-up including a more detailed psychological survey at a mean age of 64 years (n = 661; Study I). Cognitive test scores were obtained from the Finnish defence forces basic ability test taken during military service at a mean age of 20 years (n = 1196; Study III) and in a re-test at a mean age of 69 years (n = 398; Study IV). Cognitive impairment was measured with psychological questionnaires (DFQ and DEX) in conjunction with a further follow-up at a mean age of 69 years (n = 876; Study V).

In comparison to the offspring born to normotensive mothers, offspring born to pre-eclamptic mothers showed higher self-reported cognitive impairment (Study V). Offspring born to mothers with hypertension without proteinuria showed a higher risk of mental disorders (Study II), although they did not differ in the severity of self-reported depressive symptoms. Maternal hypertensive pregnancy disorders as a diagnostic entity were associated with lower cognitive functioning (Study III and IV) and higher cognitive decline (Study IV). Sex, parity and childhood socio-economic

status modified some of associations. Maternal pre-eclampsia was associated with higher self-reported depressive symptom scores in primiparous, but not in multiparous, offspring (Study I), and with a lower risk of mental disorders in male, but not female, offspring (Study II). Maternal hypertension without proteinuria was associated with self-reported cognitive impairment in female, but not male, offspring (Study V). Finally, the associations between maternal hypertensive pregnancy disorders as a diagnostic entity and lower cognitive functioning (verbal reasoning) in young adulthood were most evident in primiparous offspring and in offspring with a high childhood socio-economic status (Study III).

These study findings showed that maternal hypertensive pregnancy disorders were associated with all studied mental health and cognitive functioning outcomes. Overall, maternal hypertensive disorders during pregnancy carried an increased risk of a wide spectrum of problems in mental well-being and cognitive functioning among the offspring several decades later. However, protective effects were also observed, and, in future studies, it will be important to unravel the developmental pathways and underlying biological mechanisms. Being the longest follow-up on the transgenerational consequences of maternal hypertensive disorders reported thus far, the findings highlight the role of the prenatal environment in developmental programming.

TIIVISTELMÄ

Hypertensiivisiin raskaushäiriöihin (eli raskaudenaikaisen verenpaineen nousuun) sairastuu 10% kaikista raskaana olevista. Ne voivat vaikuttaa istukan toimintaan ja siten merkittävästi sikiön kasvuympäristöön. Onkin hyvin todennäköistä, että äidin hypertensiiviset raskaushäiriöt ovat syy-yhteydessä lapsen myöhempään kehitykseen. Kuitenkin niiden merkitystä lapsen myöhemmän kehityksen kannalta on tutkittu suhteellisen vähän. Sikiön kasvuymäristön tutkiminen tarjoaa mielenkiintoisen mahdollisuuden tutkimukselle, jossa korostetaan elinten rakenteen ja toiminnan muotoutuvuutta, ja joka on nimetty sikiöaikaisen ohjelmoitumisen tutkimussuunnaksi.

Tässä väitöskirjassa tutkitaan, eroavatko aikuiset lapset, joiden äideillä on ollut raskauteen liittyvä kohonnut verenpaine, mielenterveyden ja kognitiivisten taitojen osalta ikätovereistaan, joiden äideillä ei ole on ollut raskauteen liittyvää kohonnutta verenpainetta. Lisäksi tutkitaan, vaikuttavatko sukupuoli, raskauden kesto, synnyttäneisyys tai lapsuuden sosioekonominen asema mahdollisiin eroihin ryhmien välillä.

Tämä väitöskirja pohjautuu Helsingin syntymäkohortti -tutkimukseen (engl. Helsinki Birth Cohort Study). Tutkimuskohorttiin kuuluu 13345 miestä ja naista, jotka syntyivät Helsingissä vuosien 1934–1944 aikana. Äitien verenpaine- ja virtsan valkuaispitoisuustiedot saatiin raskausaikana kirjattujen mittausten perusteella. Ne olivat saatavilla 6410 äidiltä. Tiedot mielenterveyshäiriödiagnoseista saatiin kansallisista rekistereistä, ja ne kattoivat yli neljä vuosikymmentä (n = 5970 kelpoista tähän tutkimukseen; Osajulkaisu II). Masennusoireita mitattiin psykologisella kyselylomakkeella (BDI) seurannan yhteydessä, joka toteutettiin 62 vuoden keski-iässä (n = 788; Osajulkaisu I) ja lisäksi seurannan yhteydessä, joka toteutettiin 64 vuoden keski-iässä (n = 661; Osajulkaisu I). Kognitiiviset testitulokset saatiin puolustusvoimien kognitiivisia kykyjä mittaavasta testistä, joka toteutettiin varusmiespalveluksen aikana 20 vuoden keski-iässä (n = 1196; Osajulkaisu III) ja uusintatestissä 69 vuoden keski-iässä (n = 398; Osajulkaisu IV). Kognitiivista heikkenemistä mitattiin lisäksi psykologisilla kyselylomakkeilla (CFQ ja DEX) psykologisen seurannan yhteydessä, joka toteutettiin 69 vuoden keski-iässä (n = 876; Osajulkaisu V).

Äidin pre-eklampsia (raskausmyrkytys) oli yhteydessä korkeampaan itseraportoituun kognitiiviseen heikkenemiseen (Osajulkaisu V). Äidin raskauteen liittyvä kohonnut verenpaine ilman valkuaisvirtaisuutta oli yhteydessä kohonneeseen riskiin sairastua mielenterveyshäiriöihin (Osajulkaisu II), mutta ei itseraportoituihin masennusoireisiin. Äidin hypertensiiviset raskaushäiriöt yhtenä diagnostisena kokonaisuutena olivat yhteydessä heikompaan kognitiiviseen suoriutumiseen (Osajulkaisut III ja IV) ja suurempaan kognitiivisten taitojen heikentymiseen (Osajulkaisu IV). Sukupuoli, pariteetti ja lapsuuden sosioekonominen asema vaikuttivat osiin yhteyksistä. Äidin pre-eklampsia oli yhteydessä yleisimpiin ja vakavimpiin masennusoireisiin esikoislapsilla, muttei toisilla tai sitä seuraavilla lapsilla (Osajulkaisu I), ja pienentyneeseen mielenterveyshäiriöiden riskiin miehillä, muttei naisilla (Osajulkaisu II). Äidin raskauteen liittyvä kohonnut verenpaine ilman valkuaisvirtaisuutta oli yhteydessä suurempaan kognitiivisten taitojen heikentymiseen naisilla, muttei miehillä (Osajulkaisu V). Lisäksi äidin hypertensiivisten raskaushäiriöiden ja heikomman kognitiivisen suoriutumisen yhteydet varhaisessa aikuisuudessa tulivat selkeimmin esiin esikoislapsilla ja heillä, joiden lapsuuden sosioekonominen asema oli korkea (Osajulkaisu III).

Tässä väitöstutkimuksessa äidin hypertensiiviset raskaushäiriöt olivat yhteydessä kaikkiin tutkittuihin mielenterveyden ja kognitiivisten taitojen osa-alueisiin. Sikiöaikainen altistuminen äidin hypertensiivisille raskaushäiriöille ennusti yleisesti ottaen heikompaa mielenterveyttä ja kognitiivista suoriutumista vuosikymmeniä myöhemmin. Kuitenkin myös suojaavia vaikutuksia löydettiin, ja näiden myönteisten kehityspolkujen tunnistaminen onkin jatkossa tärkeää. Tämä tutkimus on pisin seuranta äidin raskauteen liittyvän kohonneen verenpaineen ja lapsen myöhemmän psykologisen kehityksen yhteyksistä. Löydökset tukevat sikiöaikaisen ohjelmoitumisen näkökulmaa ja varhaisen ympäristön merkitystä myöhemmän kehityksen kannalta.

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- V Tuovinen, S., Eriksson, J. G., Kajantie, E., Lahti, J., Pesonen, A.-K., Heinonen, K., Osmond, C., Barker, D. J., & Räikkönen K. (2013). Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. *American Journal of Obstetrics and Gynecology*, *208*, 200.e1–9.

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ABBREVIATIONS

11 β -HSD2 11 β -hydroxysteroid dehydrogenase type 2 enzyme

AOR Adjusted odds ratio

BDI Beck Depression Inventory

BMI Body mass index

CDR Causes of Death Register

CFQ Cognitive Failures Questionnaire

CI Confidence interval

DEX Dysexecutive Questionnaire

DOHaD Developmental Origins of Health and Disease

DSM Diagnostic and Statistical Manual of Mental Disorders

HBCS Helsinki Birth Cohort Study

HDR Hospital Discharge Register

HPAA Hypothalamic-pituitary-adrenal axis

ICD International Statistical Classification of Diseases and Related Health Problems

IUGR Intrauterine growth restriction

M Mean

MDI Mental developmental index

OR Odds ratio

SD Standard deviation

WHO World Health Organization

1 INTRODUCTION

Children and adults born preterm or with a small body size are at a higher risk for any mental disorders (Abel et al., 2010), as well as specific mental disorders including schizophrenia (Abel et al., 2010; Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Cannon, Jones, & Murray, 2002; Nilsson et al., 2005; St Clair et al., 2005; Wahlbeck, Forsén, Osmond, Barker, & Eriksson, 2001), personality disorder (Hoek et al., 1996; M. Lahti et al., 2010; Neugebauer, Hoek, & Susser, 1999), mood disorder (Abel et al., 2010; Costello, Worthman, Erkanli, & Angold, 2007; Patton, Coffey, Carlin, Olsson, & Morley, 2004; Räikkönen et al., 2008) and substance use disorder (Abel et al., 2010), and show higher depressive symptoms (Alati et al., 2007; Cheung, Khoo, Karlberg, & Machin, 2002; Gale & Martyn, 2004; Mallen, Mottram, & Thomas, 2008; Nomura et al., 2007; Paile-Hyvärinen et al., 2007; Räikkönen et al., 2007; Thompson, Syddall, Rodin, Osmond, & Barker, 2001) than their peers born at term or with a normal birth weight. Children and adults born preterm or with a small body size have also poorer cognitive and executive functioning than their peer born at term or with a normal birth weight (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Erickson, Kritz-Silverstein, Wingard, & Barrett-Connor, 2010; Martyn, Gale, Sayer, & Fall, 1996; Matte, Bresnahan, Begg, & Susser, 2001; Pyhälä et al., 2011; Räikkönen, Forsén et al., 2009; Richards, Hardy, Kuh, & Wadsworth, 2002; Shenkin et al., 2001; Shenkin, Starr, & Deary, 2004; Sommerfelt, Markestad, & Ellertsen, 1998; H. T. Sørensen et al., 1997; Strang-Karlsson et al., 2010). Recent evidence suggests that those born small also show a greater cognitive decline up to old age (Räikkönen et al., 2013). Although contradictory findings also exist, the existing evidence is in favour of negative rather than no associations.

While prematurity and small body size at birth have been extensively studied as proxies of prenatal environmental adversities, they do not inform what the underlying specific adversities are. A key factor that may underlie prematurity and restricted fetal growth is maternal hypertensive pregnancy disorders (J. M. Roberts, Pearson, Cutler, Lindheimer, & NHLBI Working Group on Research on Hypertension During Pregnancy, 2003; Villar et al., 2006). These disorders include chronic hypertension, gestational hypertension and (pre-)eclampsia. Together they complicate approximately 10% of all pregnancies (C. L. Roberts et al., 2011). Pre-eclampsia, which is a severe

form of these disorders, comprises up to 4% of maternal hypertensive pregnancy disorders. These disorders are characterised by elevated blood pressure where proteinuria is an additional characteristic of pre-eclampsia. While these disorders may not always result in prematurity or a small body size at birth, they may have a major impact on later development.

Although maternal hypertensive pregnancy disorders are very likely to compromise the fetal developmental milieu, they have attracted relatively little research interest in relation to the psychological outcomes of the offspring. This is surprising, since they are strong candidates for causing permanent developmental programming effects manifesting in mental health and cognitive functioning even decades later. Therefore, the overarching aim of this thesis is to test whether maternal hypertensive disorders during pregnancy are associated with the mental health and cognitive functioning of the offspring by capitalising on the large epidemiological Helsinki Birth Cohort Study (HBCS).

1.1 Developmental origins of health and disease

It is widely accepted that development during prenatal life may have long-lasting effects. This relationship reflects the plastic responses made by a developing organism whereby it changes its phenotype in response to changes in the environment (e.g. Price, Qvarnstrom, & Irwin, 2003). The Development Origins of Health and Disease (DOHaD) hypothesis emphasises the importance of developmental plasticity in phenotypic variability, but this idea is also rooted in other theories.

Kermack, McKendrick and McKinlay (1934) published a noteworthy paper in *Lancet* in 1934 which initiated the discussion of birth cohort influences on adult disease risk. They showed that death rates in Europe from 1751 to 1930 fell with each successive year-of-birth cohort. They proposed that the health of an individual during his/her entire life is affected by their environment in the period between 0 to 15 years of age rather than by later living conditions. Thus, infant death rates were considered a marker of early living conditions. Similarly, in 1977, Forsdahl discovered considerable variations in rates of heart disease mortality in 1964–1967 between Norwegian counties. The variations were not explained by present-day differences in standards of living, but by differences in the past as shown by infant mortality rates 70 years earlier.

A series of independent observations made in the UK and Sweden a decade later by Wadsworth, Cripps, Midwinter and Colley (1985), Gennser, Rymark and Isberg (1988) and Barker, Winter, Osmond, Margetts and Simmonds (1989) have also given impetus to the idea that developmental factors might influence susceptibility to disease later in life. Each showed a relationship between birth size and cardiovascular and/or metabolic health later in life. Studies by Barker and coworkers have been the most influential in the field. Originally, they showed that differences in neonatal mortality in 1921–1925 in the UK predicted death rates from stroke and heart disease in 1968–1978 (Barker & Osmond, 1986). The normal cause of death in newborn babies at that time was low birth weight. Subsequently, they presented direct evidence of the associations between low birth weight (and weight at 1 year) and an increased risk of death from cardiovascular disease in a study of men born in Hertfordshire where birth records have been kept since 1911 (Barker et al., 1989). Based on these findings, Barker put forward a theory suggesting that cardiovascular disease is associated with specific patterns of disproportionate fetal growth that result from fetal under-nutrition (Barker, 1994; Barker, 1995).

These original findings have since been replicated in several epidemiological studies around the world (Barker, Osmond, Forsén, Kajantie, & Eriksson, 2005; Eriksson, Forsén, Tuomilehto, Osmond, & Barker, 2000; Frankel, Elwood, Sweetnam, Yarnell, & Smith, 1996; Hyppönen, Leon, Kenward, & Lithell, 2001; Lawlor, Ronalds, Clark, Smith, & Leon, 2005; Leon et al., 1998; Martyn, Barker, & Osmond, 1996; Stein et al., 1996). Low birth weight has also been associated with an increased risk of a wide spectrum of other health outcomes in later life, including type 2 diabetes (Barker et al., 1993), chronic lung disease (Edwards, Osman, Godden, Campbell, & Douglas, 2003) and osteoporosis (Cooper et al., 2002). Further studies have led to a new branch of scientific knowledge and the hypothesis has further developed into the DOHaD hypothesis. According to this hypothesis, a suboptimal prenatal environment (and early postnatal life) may permanently alter organ structure and function, and render an individual susceptible to diseases (Barker, 2004). In line with this hypothesis, a wide range of behavioural and cognitive problems has also been associated with early life adversities. Indeed, as stated previously, prematurity and a small body size at birth are associated with any mental disorder (Abel et al., 2010) as well as specific mental

disorders, including schizophrenia (Abel et al., 2010; Byrne et al., 2007; Cannon et al., 2002; Nilsson et al., 2005; St Clair et al., 2005; Wahlbeck et al., 2001), personality disorder (Hoek et al., 1996; M. Lahti et al., 2010; Neugebauer et al., 1999), mood disorder (Abel et al., 2010; Costello et al., 2007; Patton et al., 2004; Räikkönen et al., 2008) and substance use disorder (Abel et al., 2010) in adulthood and with depressive symptoms in populations of various ages (Alati et al., 2007; Cheung et al., 2002; Gale & Martyn, 2004; Mallen et al., 2008; Nomura et al., 2007; Paile-Hyvärinen et al., 2007; Räikkönen et al., 2007; Thompson et al., 2001). Furthermore, prematurity and a small body size at birth are associated with lower cognitive and executive functioning in childhood, adolescence and adulthood (Bhutta et al., 2002; Erickson et al., 2010; Martyn, Gale et al., 1996; Matte et al., 2001; Pyhälä et al., 2011; Räikkönen et al., 2009; Richards et al., 2002; Shenkin et al., 2001; Shenkin et al., 2004; Sommerfelt et al., 1998; H. T. Sørensen et al., 1997; Strang-Karlsson et al., 2010), and a small body size at birth is also associated with a greater cognitive decline up to old age (Räikkönen et al., 2013).

While it was fortuitous that a relationship between birth size and later disease risk was found, the existing evidence strongly suggests that size itself is not part of the causal pathway leading to disease. Birth weight acts as a crude proxy for the fetal environment. Disease risk can be elevated even in those with an apparently normal birth weight. Barker and co-workers suggested that the phenomenon being observed reflects the operation of the developmentally plastic responses rather than being pathological. They later showed that the relationship between birth size and disease outcome was not restricted to those with the lowest birth weight, but that death rates from cardiovascular disease fell progressively between those with the lowest and highest birth weights (Barker et al., 1989; Osmond, Barker, Winter, Fall, & Simmonds, 1993). Indeed, the theory is not based on a causal role of birth size, but on the consequences of fetal responses to its environment. That is, while birth weight as a crude proxy of an adverse fetal environment is most studied, other factors may also be involved. These may include maternal hypertensive pregnancy disorders despite not gaining much research attention. Such disorders are common causes of a low birth weight; and, while they may not always result in a small body size at birth, they may have a major effect on later development.

The validity of the DOHaD hypothesis is largely based upon epidemiological associations, but the model is also supported by extensive clinical and experimental data and has both a conceptual and mechanistic basis (of these, the mechanistic basis, which is related to epigenetic evidence, is discussed in detail in section 1.4.4). Experimental data allow for the examination of causal effects of early life adversity on the outcomes of offspring later in life while keeping covariate effects constant. Animal models have indeed shown that early life adversities—exposures such as nutritional manipulation, maternal stress and exogenously administered glucocorticoids—have long-term effects on an offspring's physiology (for reviews, see Bertram & Hanson, 2001; McMillen & Robinson, 2005; Nuyt & Alexander, 2009) and behavioural and cognitive performance (Vallee et al., 1999; Wang et al., 2012; Weaver, Meaney, & Szyf, 2006). In humans, the cause and effect associations of prenatal adversity are generally impossible to study for ethical reasons. However, the circumstances of the Dutch famine of 1944–1945 provided a natural experiment allowing for the examination of how maternal undernutrition during gestation may affect the subsequent life course of offspring who experienced the famine in utero. The findings have consistently shown associations between prenatal famine and adult body size, diabetes and schizophrenia (Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011).

Two conceptual models are suggested as the basis of such associations. The thrifty phenotype hypothesis (Hales & Barker, 1992) states that a fetus adapts in utero to survive maternal undernutrition or other environmental stressors, one possible consequence being a reduction in fetal growth of either the whole body or some organs. Later, Gluckman and Hanson (2004) modified the model and termed it the predictive adaptive response model. This model proposes that many of the adaptive responses made by the fetus are not made for immediate advantage, but rather in expectation of the future postnatal environment. Successful adaptation to the predicted environment improves biological fitness. However, this normative human developmental experience may be associated with adverse health outcomes when there is a mismatch between the predicted environment and the actual environment into which the fetus is born.

The window of developmental plasticity extends from the preconception or prenatal period to life afterwards. A life cycle model has been developed to explain why different disorders emerge in individuals exposed to a stress and/or adversities at

different times in their lives (Lupien, McEwen, Gunnar, & Heim, 2009). This model proposes a link between the different phases of brain development in humans and the impact of a stress and/or adversities at key timepoints (Lupien et al., 2009). Different regions of the brain that are sensitive to stress hormones develop at different times in an individual's life. The effects of a stress and/or adversity at different stages in life depend on the brain areas that are developing or declining at the time of the exposure. The data obtained in animals and humans suggest that chronic or repeated exposure to a stress has enduring effects on the brain through the activation of the hypothalamic–pituitary–adrenal axis (HPAA) and the release of glucocorticoids (reviewed in more detail in section 1.4.3).

In humans, maximal brain growth and most of the neuroendocrine maturation occurs in utero (Dobbing & Sands, 1979; Lupien et al., 2009). HPAA is highly responsive at birth, but the brain continues to develop. Lupien et al. (2009) summarise the development of the brain regions that are involved in regulating HPAA (the hippocampus, the frontal cortex and the amygdala). The volume of the hippocampal formation increases sharply until the age of 2 years, whereas amygdala volume continues to increase slowly until the late 20s. By contrast, the development of the frontal cortex in humans takes place mostly between the ages of 8 and 14 years. Thus, from the prenatal period onwards, all areas of the brain that are still developing are sensitive to the effects of stress hormones, while exposure to a stress during a particular period should have major effects on areas that undergo rapid growth during that period. In a similar vein, although significant decreases in brain volume have been reported in aged animals and humans, different brain regions are differently affected by aging and the impact of a stress exposure is highest on those structures that are undergoing the most rapid age-related changes during a particular period. Accordingly, depending on the timing (and duration) of exposure to a stress and/or adversity, varying effects on behaviour and cognition may be observed.

Finally, it seems that individuals differ in terms of developmental plasticity. Some individuals are more vulnerable to the adverse effects of negative experiences because of their biological, temperamental and/or behavioural characteristics, whereas others are relatively resilient to them. The idea that individuals vary in their responsivity to qualities of the environment is framed in diathesis-stress (Monroe & Simons, 1991;

Zuckerman, 1999) or dual-risk terms (Sameroff, 1983). An alternative view is Belsky's differential susceptibility hypothesis, which suggests that individuals vary not only in the degree to which they are vulnerable to the negative effects of an adverse experience, but also with respect to their susceptibility to the beneficial effects of supportive and enriching environments (Belsky & Pluess, 2009). Boyce and Ellis (2005) provided a related notion known as biological sensitivity to context. Several susceptibility factors, including a negative emotion or difficult temperament and endophenotypic and genetic markers, have been identified (Belsky & Pluess, 2009). Interestingly, fetal programming (e.g. maternal prenatal distress) appears to influence several of these factors (Pluess & Belsky, 2011). These findings have led to the proposition that postnatal plasticity (vs. later development) may be programmed by the prenatal environment (Pluess & Belsky, 2011).

All of these theories suggest that early life effects within even a normative range of developmental exposures have lifelong consequences on human health.

1.2 Hypertensive disorders during pregnancy: Definitions and epidemiology

Pre-eclampsia: A sudden flash or development (derived from the Greek eklampsis)

Globally, hypertensive pregnancy disorders complicate approximately 6–16% of all pregnancies, with pre-eclampsia accounting for 3–7% (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; C. L. Roberts, Algert, Morris, Ford, & Henderson-Smart, 2005). In high-income countries, the rates are around 10%, with pre-eclampsia accounting for ~4% (C. L. Roberts et al., 2011). These disorders are the leading causes of maternal, fetal and neonatal morbidity and mortality. Overall, 10–15% of maternal deaths from pregnancy-related causes are associated with pre-eclampsia and eclampsia (Duley, 2009). While most of these deaths occur in low- and middle-income countries, the proportion associated with pre-eclampsia and eclampsia is similar between countries (Duley, 2009). Pre-eclampsia and eclampsia also drastically increase the risk of maternal morbidity (Carty, Delles, & Dominiczak, 2010) as well as the risks to the infant. Immediate risks to the infant include perinatal death, poor growth and prematurity (reviewed in section 1.2.6). Less

information is available on the long-term implications of these disorders. As well as pre-eclampsia, gestational hypertension may increase the risk of adverse perinatal and long-term outcomes (Villar et al., 2006).

1.2.1 Classification

Hypertensive pregnancy disorders are characterised by elevated blood pressure where proteinuria is an additional characteristic in pre-eclampsia. Table 1 describes the diagnostic criteria according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000) and the American College of Obstetricians and Gynecologists and Task Force on Hypertension in Pregnancy (American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013).

Table 1. Classification of hypertensive pregnancy disorders

Category	Definition
Chronic hypertension	HT \geq 140/90 mmHg present before pregnancy or diagnosed before 20 th week of gestation or does not resolve post-partum
Gestational hypertension	HT \geq 140/90 mmHg on \geq 2 occasions at least 4 h apart in a women who was normotensive before 20 th week of gestation and whose blood pressure returns to normal post-partum
Pre-eclampsia-eclampsia	HT \geq 140/90 mmHg on \geq 2 occasions at least 4 h apart in a women who was normotensive before 20 th week of gestation with proteinuria \geq 300 mg/ 24 h
Pre-eclampsia superimposed on chronic hypertension	HT \geq 140/90 mmHg present before pregnancy or diagnosed before 20 th week of gestation with (new-onset) proteinuria \geq 300 mg/ 24 h

(American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000)

HT, hypertension

According to the criteria, it is recommended that gestational blood pressure elevation is defined on the basis of at least two measurements. Certainty regarding pre-eclampsia diagnoses is indicated when blood pressure is \geq 160/110 mmHg with proteinuria. However, differentiating between mild and severe disease is the subject of debate

(Steeegers, von Dadelszen, Duvekot, & Pijnenborg, 2010). Diagnosing proteinuria is suggested on the basis of a 24-hour urine sample, but the excretion of ≥ 300 mg/24 h usually correlates with ≥ 30 mg/dL ($\geq 1+$ reading on the dipstick). Furthermore, disease is highly suspect when an increased blood pressure accompanies headache, blurred vision and abdominal pain, or by abnormal laboratory test results, specifically low platelet counts and abnormal liver enzyme values. Eclampsia is defined as the occurrence of seizures that cannot be attributed to other causes in a woman with pre-eclampsia. In past decades, the rates of eclampsia declined largely in relation to improved medical care (Ness & Roberts, 2009). Accordingly, epidemiological research has focused on pre-eclampsia and hypertension without proteinuria.

1.2.2 History of hypertensive pregnancy disorders

Hypertensive pregnancy disorders have a history of divergent diagnostic criteria. During the 20th and 21st centuries, disease classifications have undergone various changes (Bell, 2010). In 1966, new criteria for the diagnosis of pre-eclampsia included the presence of hypertension, edema or proteinuria after the 24th week of gestation. Women had to meet only one of the three criteria to be diagnosed with pre-eclampsia. Ten years later, the classification of pre-eclampsia included the development of hypertension with proteinuria, edema or both commencing after 20 weeks of gestation. In 1988, mild and moderate pre-eclampsia were classified as the presence of hypertension and edema, while severe pre-eclampsia was classified as the presence of hypertension and proteinuria with or without other symptoms such as edema. According to current clinical criteria (Table 1), edema as a criterion for diagnosing pre-eclampsia is not recommended (American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). In addition, while blood pressure increases of 30 mmHg systolic or 15 mmHg diastolic with a blood pressure $< 140/90$ mmHg were considered diagnostic markers in the past, they are not included in the current clinical criteria (American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000).

Only a few of the studies reviewed for this thesis have used the modern diagnostic criteria. In the remaining, the criteria have varied or have not been reported. Some of these studies have been able to define maternal hypertension status based on a true maternal blood pressure and urinary protein measurements. Some studies have relied on discharge diagnoses of pregnancy hypertension using different versions of the International Statistical Classification of Diseases and Related Health Problems (ICD) coding depending on the time, with the criteria differing even within a specific coding version. Importantly, a validation study of medical records at New York Hospital showed that 25% of ICD-9 codes incorrectly diagnosed pre-eclampsia and that 53% of true cases were missed by ICD-9 coding (Ales & Charlson, 1991). Thus, studies that did not report the exact criteria are not discussed in detail in this thesis. The divergent diagnostic criteria may complicate interpretation of the data from follow-up studies.

1.2.3 Pharmacologic treatment

In addition to diagnostic criteria, the treatment of pre-eclampsia and hypertension has evolved (Bell, 2010). In terms of the pharmacologic management of pre-eclampsia and eclampsia (convulsions), magnesium sulfate was popularized during the 1920s (Chesley, 1984). However, the first treatments were given e.g. in Helsinki in 1943 (Tarkiainen, 1946). For mothers at risk of preterm birth, glucocorticoids came into widespread use after 1972 in order to regulate fetal lung maturation (Liggins & Howie, 1972). Currently, magnesium sulfate is recommended for the prevention of or to deter convulsions in women with pre-eclampsia or eclampsia, glucocorticoids are administered to accelerate fetal pulmonary maturity and antihypertensive therapy is used to treat acute hypertensive episodes (Bell, 2010; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). Pharmacologic management may decrease the risk or severity of pre-eclampsia and hypertension and promote fetal lung maturity, but it will also affect—either favourably or adversely—fetal brain development (for studies on the use of methyldopa, labetalol and glucocorticoid treatment during pregnancy and the effects on offspring neurologic or behavioural outcomes, see Davis, Sandman, Buss, Wing, & Head, 2013; Koren, 2013; Peltoniemi, Kari, & Hallman, 2011; Trautman, Meyer-Bahlburg, Postelnek, & New, 1995).

1.2.4 Pathophysiology

The underlying causes of pre-eclampsia and gestational hypertension remain unknown. Inadequate placentation due to deficient trophoblastic invasion of the uterine spiral arteries is one probable underlying cause. This may result in the release of a variety of factors into the circulatory system that alter endothelial function (Taylor, Davidge, & Roberts, 2009). While the factors may differ between individuals, they may include angiogenic factors, metabolic factors and inflammatory mediators. It is possible that these give rise to oxidative stress and endothelial dysfunction, culminating in pre-eclampsia (Taylor et al., 2009). Clinical manifestations result from systemic endothelial dysfunction, in which the target organ may be the brain, the liver and/or the kidney. It is of note that at least some forms of gestational hypertension may share certain pathophysiologic and pathogenic mechanisms with pre-eclampsia (Levine et al., 2006; Strevens et al., 2003).

1.2.5 Risk factors

The risk factors for hypertensive pregnancy disorders have been well documented (Table 2), and the factors associated with a decreased risk for pre-eclampsia and hypertension in pregnancy are also recognised (Table 3). These can be divided into factors associated with a maternal predisposition to cardiovascular disease and factors that represent the placental or pregnancy-related component of pre-eclampsia and hypertension without proteinuria. In addition, it is possible that psychological risk factors such as job stress, depression and anxiety have a positive association (Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000; Paarlberg, Vingerhoets, Passchier, Dekker, & Van Geijn, 1995; Qiu, Williams, Calderon-Margalit, Cripe, & Sorensen, 2009).

While poor placentation is commonly associated with disease, this is not always the case. Maternal constitutional susceptibility may be a determining factor. This assumption is consistent with the shared risk factors associated with both pre-eclampsia and gestational hypertension and cardiovascular disease. In addition, although pre-eclampsia is associated with intrauterine growth restriction (IUGR), most infants born to pre-eclamptic women have a normal birth weight for gestational age (reviewed in section 1.2.6). This may be explained by factors such as diabetes and obesity, which are

risk factors for pre-eclampsia and gestational hypertension, yet are often associated with larger babies (King, 2006).

Table 2. Risk factors for pre-eclampsia and hypertension in pregnancy

Risk factors for pre-eclampsia	Risk factors for hypertension in pregnancy*
Higher maternal age	Higher maternal age
Primiparity	Elevated body mass index
Previous pre-eclampsia	African ethnicity
Family history of pre-eclampsia (mum)	Previous preeclampsia
Multifetal gestation	Family history of pre-eclampsia (mum)
Pre-existing medical conditions	Primiparity
Type 1 diabetes	Multifetal gestation
Pre-existing hypertension	
Renal disease	
Chronic autoimmune disease	
Longer time between pregnancies	
Changing paternity	
Raised body mass index	
African ethnicity	
Use of ovulation induction	

(Duckitt & Harrington, 2005; Poon, Kametas, Chelemen, Leal, & Nicolaides, 2010)

*Note that all risk factors for pre-eclampsia may also apply to gestational hypertension despite lack of published data

Table 3. Associates with decreased risk for pre-eclampsia and hypertension in pregnancy

Placenta praevia
Smoking
Summer births
Low-dose aspirin and calcium supplementation
Treatment of gestational diabetes
Use of antihypertensive medication
Early elective delivery

(Conde-Agudelo, Althabe, Belizan, & Kafury-Goeta, 1999; C. L. Roberts et al., 2011)

1.2.6 Geographic and temporal variations

Trends for hypertensive pregnancy disorders in part reflect the effects of changes in risk and protective factors. Geographic variations may be due to different diagnostic criteria as discussed above and methods of data collection, but may also reflect true variations. All of these factors pose challenges for the comparison of epidemiological studies. Temporal variations are easier to interpret, at least when methods of reporting rates do not change. Based on an international comparative study of population-based trends in pregnancy hypertension from 1997 to 2007, surprisingly rates are decreasing in northern Europe and Australia, but are increasing in Massachusetts (C. L. Roberts et al., 2011). A rise in rates of pre-eclampsia in the USA as a whole is also supported by an individual study showing a 25% increase in rates from 1987 to 2004 when the indicated rate was 3.2 (Wallis, Saftlas, Hsia, & Atrash, 2008). In Finland, according to a large national study conducted between 2000 and 2001, the incidence of pre-eclampsia was 5%, while that of elevated blood pressure was almost 19% among pregnant women (Kaaja & Luoto, 2004). Some evidence shows that women in northern Finland may be at a higher risk of both pre-eclampsia and gestational hypertension compared to women in southern Finland (Kaaja, Kinnunen, & Luoto, 2005).

Since the etiology of hypertensive pregnancy disorders remains unclear and the prevention and prediction of them are still not possible (Steegers et al., 2010), it is important not only to recognise mothers at risk for adverse outcomes, but to also understand the risks for the offspring.

1.2.7 Perinatal outcomes: Prematurity, low birth weight, still birth and infant death

Past studies have attempted to quantify the effect of hypertensive pregnancy disorders on adverse perinatal outcomes. Pregnancies complicated by hypertension with or without proteinuria are characterised by an increased rate of preterm delivery (Ananth, Savitz, Luther, & Bowes, 1997; Bakker, Steegers, Hofman, & Jaddoe, 2011; Ferrazzani et al., 2011; C. L. Roberts et al., 2005; Villar et al., 2006), but the rates vary considerably across studies. The higher rate is at least partly due to delivery being the only curative treatment for pre-eclampsia. Indeed, due to medically indicated preterm

births, pre-eclampsia is implicated in 10–15% of all preterm births (Ananth & Vintzileos, 2006; J. M. Roberts et al., 2003).

Compared to children born after normotensive pregnancies, children born after hypertensive pregnancy disorders often also have lower birth weights (Bakker et al., 2011; Himmelmann, Himmelmann, Niklasson, & Svensson, 1996; Villar et al., 2006; Zhang, Klebanoff, & Roberts, 2001) and a higher risk of being born with a birth weight of less than 2500 g (Bakker et al., 2011; Zhang et al., 2001). Naturally, this may in part be explained by their increased risk of preterm birth or a shorter length of gestation. In addition, it is intuitive that if placental blood flow is reduced with pre-eclampsia and hypertension, it should result in decreased fetal growth. This should not only increase the risk of low birth weight, but also intrauterine growth restriction. Poor fetal growth is, indeed, often considered a characteristic of pregnancies complicated by hypertension and supported by many studies (Allen, Joseph, Murphy, Magee, & Ohlsson, 2004; Bakker et al., 2011; Ferrazzani et al., 2011; C. L. Roberts et al., 2005; Villar et al., 2006; Zhang et al., 2001). The reported rates of IUGR reach up to 50% in hypertensive pregnancy disorders. It has been suggested that approximately 10% of all cases of IUGR are secondary to pre-eclampsia or gestational hypertension (Villar et al., 2006). A few studies have reported an association between pre-eclampsia and/or gestational hypertension and with large-for-gestational age births (Eskild, Romundstad, & Vatten, 2009; Xiong, Demianczuk, Buekens, & Saunders, 2000). This may reflect the involvement of multiple pathophysiologic processes. Birth outcomes may also depend on gestational age at the time of onset of the disease (Xiong, Demianczuk, Saunders, Wang, & Fraser, 2002) and the severity of the disease (Buchbinder et al., 2002). In general, outcomes are usually more favorable when hypertension is mild or develops beyond 36 weeks of gestation (Sibai, Dekker, & Kupferminc, 2005).

Hypertensive pregnancy disorders are also important contributors to stillbirth worldwide and one of the most important factors in high-income countries. A recent meta-analytic review revealed that pre-eclampsia was associated with a 60% increase in the odds of a stillbirth in high-income countries over the past two decades (Flenady et al., 2011). Gestational hypertension was associated with a 30% increase in the odds. The risk associated with pre-existing hypertension was even higher than that for pre-eclampsia or gestational hypertension. According to a Norwegian study, the rates of

survival from pre-eclamptic pregnancies have improved from 1967 to 2003: the risk was 4.2 times higher with pre-eclampsia in earlier years and 1.3 times higher during more recent years in the follow-up (Basso et al., 2006). However, the risk of neonatal death is still twofold with pre-eclampsia and has changed little over time (Basso et al., 2006). In Finland, in 1936 and 1937 when infant death rates during the first year of life were up to 7%, eclampsia accounted for 0.3–0.5% (Central Statistical Office of Finland, 1939). This is indicative of high infant mortality among eclamptic mothers. During 1990–1994, eclampsia led to fetal death in 5% of cases and neonatal death in 3.3% of cases (Salmi, Ekholm, Polo, & Erkkola, 1999). Selection related to variations in survival across (location and) time may introduce a bias and challenge comparisons between different studies.

This thesis is based upon men and women who were born in Helsinki between 1934 and 1944. During that time, the pre-eclamptic state was recognised, but pre-eclampsia-eclampsia was not restricted to an obstetric definition. Nephrogestosis was clinically classified as (1) albuminuria, a small amount of sediment in the urine (Esback: >1%); (2) nephropathy, a large amount of sediment in the urine and ambie edema, which usually flares up during the third trimester of pregnancy; (3) eclapcism, imminent eclampsia; or (4) eclampsia, a convulsion (Teräsvoori, 1933). Eclampsia rates were 0.6% of all pregnancies in Helsinki and up to 1.7% in Viipuri in Eastern Finland (Parviainen, 1946). Blood pressure and proteinuria were not included in the diagnostic criteria for the prenatal nephrogestosis disorder, although they were recognised as a part of the disorder and were recorded (Figure 1). Based on archival data, studying the consequences of maternal hypertensive pregnancy disorders over many decades is possible.

Vlim. kuuk.: 22. tammik. 34	tavalliset tav. nukkemat	Ens. sikiönl. <i>Cygnuslappuella 34.</i>	
Lask. aika: (k.k.) 29. huhtik. 35 (s. l.) huhtik. pöytäkirja	Vointi raskauden aikana (pahavoiminta, oksentelu, turvotusta muita häiriöitä, milloin)	<i>Rauhallinen</i>	
<i>Alussa raskauden päivät pahain pöytäkirja ja Oksentelu. Muutamat päivät liian vähe, tällöin vähe turvotusta iltaisin.</i>	8. II. 35	Laäkärin tutki, milloin, miksi <i>uuvasta-arex.</i>	
Yleistutkimus:	terve. Ruumiinrakenne	tavallinen. Pituus 160 sm. <i>vähän</i>	
Keuhkot <i>ei erikseen.</i>	Paino 73 kg.	Sydän <i>ei erikseen.</i>	
Virtsat <i>Kirkas, keeli.</i>	Syvä munanvalk. Esbach — %	Suoni 80 /min.	
Valkovuotoa	Verenvuotoa —	Ruumiinl. 37,2 °C (r)	
	Hgb — %	Verenpaine 90 mm/Hg.	
		Synn. vaihe <i>I: uen</i>	
Ulkoisutkimus 12/II klo 11,30	Vatsan seinämä	Raskauserä	Vatsan ympärys 96,0 sm.
Emänpohja 3 sorm. lev.	Emänsseinämä	Sikiön selkä	Pienet osat <i>oik. emin yläosassa.</i>
Tarj. osa <i>pieni</i> liikku <i>maahan</i>	lantion	isompi osa	Sydänäänet <i>vas. navan alapuol. säänn.</i> 140 /min.
Epäsuhtaa			
Yleisluoto <i>tavall.</i>	Häpyliitoksen korkeus <i>tavall.</i>	kaltevuus <i>tavall.</i>	takapinta <i>hileä</i>
Lantio säännöll.	Häpyliitteen kutsua	Ristikukkua	Istuinkärjet
D. sp. 23,0 sm. A. 23,0 sm.	kaarvevuus	Ristiluun etupinta	
D. cr. 27,0 sm. C. ext. 21,0 sm.	Lantion luusto	takapinta	
D. tr. 31,5 sm. C. diag. (tutkimatta)		Peräluulitos	
Conj. vera			
Sisätutkimus 12/II klo 12,10	Ulkosynnytykset <i>terveet</i>	Emätin	
Emänkaulakanava	Emänsuu 8 sm; sen reunat <i>tav.</i>		
Rakko	Kalvot <i>ehät</i>	Tarj. osa <i>pieni</i> liikku <i>maahan</i>	lantion

Figure 1. Birth record from year 1935

1.3 Mental health and cognitive functioning

As stated above, prematurity and a small body size at birth have been associated with a wide range of behavioural and cognitive problems later in life. Accordingly, it makes sense to study whether exposure to maternal hypertensive disorders in utero is associated with later mental health and cognitive functioning. Increasingly higher proportions of the global burden of disease can be attributed to disorders of the brain including mental, neurological and substance use disorders (Collins et al., 2011). Disorders of the brain are the largest contributor to all causes of morbidity as measured by disability adjusted life years in the European Union (Wittchen et al., 2011). Below, I briefly describe the prevalence of mental disorders and cognitive impairment.

1.3.1 Prevalence of mental health problems

According to the World Health Organization (WHO; WHO International Consortium in Psychiatric Epidemiology, 2000), over one-third of all people in most countries report problems at some time in their life which meet the diagnostic criteria for one or more of the most common types of mental disorders. These disorders are burdensome because of their high prevalence, chronicity, early age of onset and because they often result in serious impairment (Demyttenaere et al., 2004; Whiteford et al., 2013; WHO International Consortium in Psychiatric Epidemiology, 2000). The prevalence rates vary widely across studies. According to a recent meta-analytic review of the global prevalence of common mental disorders, the period prevalence of mood disorders is 5.4% (with an inter-quartile range of 3.4–8.4%), 6.7% (4.3–10.9%) for anxiety disorder and 3.8% (2.1–6.4%) for substance use disorder (Steel et al., 2014). The corresponding prevalence estimate for any personality disorder is 6.1% (Huang et al., 2009). Compared to the estimated period prevalences, lifetime prevalences are higher. According to the meta-analytic review, lifetime prevalences for mood, anxiety and substance use disorders are 9.6% (6.1–17.8%), 12.9% (9.6–19.3%) and 3.4% (5.5–18.8%), respectively (Steel et al., 2014). According to two population-based studies, any psychotic disorders have a lifetime prevalence of approximately 3% (Bogren, Mattisson, Isberg, & Nettelbladt, 2009; Perälä et al., 2007).

It has been suggested that depression is associated with higher mortality, morbidity and financial costs than any other mental disorder (Murray & Lopez, 1996). In particular, depression later in life is perhaps the most frequent cause of emotional suffering that significantly decreases one's quality of life (Blazer, 2003).

In this thesis, severe mental disorders over four decades and depressive symptoms in late adulthood are studied.

1.3.2 Cognitive functioning and the prevalence of cognitive impairment

Cognitive impairment, including dementia and mild cognitive impairment, has a major impact on cognitive ability and the capacity for independent living. The global prevalence of dementia for those aged ≥ 60 years varies between 5% and 7% (Prince et al., 2013). For mild cognitive impairment, which often leads to dementia, rates vary from 0.5% to 42% (Ward, Arrighi, Michels, & Cedarbaum, 2012).

In this thesis, cognitive ability in both young and late adulthood, and age-related cognitive decline as well as self-reported cognitive impairment are studied. Importantly, lower cognitive skills in childhood and young adulthood are associated with an increased risk of late-onset dementia (McGurn, Deary, & Starr, 2008; Riley, Snowdon, Desrosiers, & Markesbery, 2005; Whalley et al., 2000). Furthermore, low cognitive test scores in late adulthood have been shown to predict the onset of cognitive decline and dementia up to 4 years (Schmand, Smit, Geerlings, & Lindeboom, 1997) and a decade (Cervilla, Prince, Joels, Lovestone, & Mann, 2004) later. Finally, self-reported cognitive impairment in old age may be one of the earliest behavioural markers of dementia (Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007).

Cognitive functioning not only predicts or is a marker for dementia, but it also affects quality of life in other dimensions. Cognitive test scores are highly predictive of educational performance (Deary, Strand, Smith, & Fernandes, 2007) and job performance (Hunter & Schmidt, 1996), as well as health (Hart et al., 2004) and survival (Whalley & Deary, 2001).

1.4 Mechanisms: Potential pathways linking maternal hypertensive pregnancy disorders and the mental health and cognitive functioning of the offspring

The long-term consequences of intrauterine exposure to maternal hypertensive disorders may originate from several different underlying factors. These may be related to physiological mechanisms in terms of placental implantation (and, hence, less placental perfusion), inflammatory mechanisms, hormonal processes such as glucocorticoid metabolism and genetic and epigenetic mechanisms. While not comprehensive, glucocorticoids have drawn much research attention as a potential underlying factor. In addition, while not reviewed in detail here, it is obvious that psychosocial mechanisms relating to parenting and attachment development may also be involved.

Pre-eclampsia and hypertension without proteinuria may share certain pathophysiologic and pathogenic mechanisms (Levine et al., 2006; Strevens et al., 2003). In some cases of gestational hypertension, the risk of adverse outcomes may be

similar to that for pre-eclampsia (Buchbinder et al., 2002). Furthermore, it is possible that pre-eclampsia and hypertension without proteinuria exert effects on the developing fetus through shared mechanisms, although this still needs confirmation. Pre-eclampsia is the most studied condition and allows us to discuss the possible mechanisms linking maternal hypertensive pregnancy disorders to the developmental sequelae for offspring. The mechanisms discussed below may also apply to other hypertensive pregnancy disorders despite the lack of published data. Figure 2 (page 37) shows the potential factors and mechanisms that may affect and underlie the long-term psychological consequences among offspring exposed intrauterine to maternal hypertensive disorders.

1.4.1 Placental functioning

The most obvious possible pathways linking maternal hypertensive pregnancy disorders with adverse fetal development—brain development in particular—involve fetal growth restriction and prematurity. Deficient trophoblastic invasion of the uterine spiral arteries is probable in pre-eclampsia. This, in turn, leads to uteroplacental hypoperfusion, which may result in inadequate fetal nutrition, hypoxic damage and adverse fetal development and brain development in particular (J. P. Newnham, Moss, Nitsos, Sloboda, & Challis, 2002).

Both gestational hypertension and pre-eclampsia, if severe, may necessitate preterm delivery of the fetus (e.g. Villar et al., 2006). In this pathway, the association between maternal hypertensive disorders and adverse psychological outcomes in the offspring may be mediated by prematurity.

1.4.2 Inflammatory mechanisms

An inflammatory state may be involved in several potential causal mechanisms that connect gestational hypertensive disorders with the offspring's brain development. Pre-eclampsia involves a range of key immune responses at different stages of the syndrome (Redman & Sargent, 2010). The final, symptomatic stage is characterised by a maternal systemic inflammatory response without known infectious agents. It can be hypothesised that the possible associations between maternal pre-eclampsia and offspring developmental outcome may reflect the prenatal induction of systemic inflammation. However, the exact factors remain unknown.

1.4.3 Hormonal processes: Glucocorticoid metabolism

One major underlying hypothesis for early life programming is fetal glucocorticoid exposure. Placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) protects the fetus from high maternal glucocorticoid levels, and there is evidence that 11 β -HSD2 is down-regulated in pre-eclampsia.

The areas of the brain involved in regulating stress are particularly affected by early life adversities (cp. the DOHaD hypothesis and the life cycle model of stress). These include HPAA and its key limbic regulator, the hippocampus, as well as the amygdala and frontal lobes. The activation of HPAA culminates in the production of glucocorticoids. Furthermore, the secretion of glucocorticoids from the adrenal cortex is controlled by HPAA in an endocrine negative feedback loop (Lupien et al., 2009)—corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are released from the hypothalamus. This triggers the subsequent secretion of the adrenocorticotrophic hormone (ACTH) from the pituitary gland, leading to the production of glucocorticoids by the adrenal cortex. The responsiveness of HPAA to stress is, in part, determined by the ability of the glucocorticoids to regulate ACTH and the release of CRH by binding to two corticosteroid receptors, the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). These receptors can act as transcription factors and, thus, regulate gene expression (Lupien et al., 2009). Glucocorticoids can have long-lasting effects on the functioning of the regions of the brain that regulate their release. Anatomical connections between the hippocampus, amygdala, frontal lobes and hypothalamus regulate the activation of HPAA through their own glucocorticoid and mineralocorticoid receptors. Although glucocorticoids are essential for brain development, elevated levels are detrimental and affect neuronal division, maturation, migration, interactions and apoptosis (Harris & Seckl, 2011).

A suboptimal prenatal environment caused by overexposure to glucocorticoids can influence HPAA development. Intrauterine exposure to excess glucocorticoids and maternal stress have been associated with an increase in HPAA activity in animal models (Harris & Seckl, 2011; Lupien et al., 2009) and changes in activity in humans (Harris & Seckl, 2011; Kajantie & Räikkönen, 2010; Lupien et al., 2009). Recent evidence in humans suggests that high maternal cortisol levels during pregnancy predict higher pre-stress cortisol values and a blunted response to stress exposure in offspring in

infancy (O'Connor, Bergman, Sarkar, & Glover, 2013). Furthermore, stress and increased glucocorticoid concentrations can alter the hippocampal structure in young and aged animals (Khulan & Drake, 2012; Wyrwoll & Holmes, 2012). In addition, a low birth weight combined with lower levels of maternal care is associated with a reduced hippocampal volume in adulthood in humans (Buss et al., 2007). Effects on other brain regions have also been found (for a review see Lupien et al., 2009). As a consequence, over-exposure to glucocorticoids during prenatal life has been linked with developmental and behavioural outcomes in both animal models and humans (for reviews, see Lupien et al., 2009; Wyrwoll & Holmes, 2012).

One of the proposed mediators of glucocorticoid programming is 11 β -HSD2. This enzyme plays an important role in protecting the developing fetus from the mother's relatively high glucocorticoid levels by catalysing the conversion of cortisol to inactive cortisone (Benediktsson, Calder, Edwards, & Seckl, 1997), thus preventing the activation of glucocorticoid receptors. There is evidence that pre-eclampsia may down-regulate placental 11 β -HSD2 activity leading to greater fetal exposure to maternal prenatal glucocorticoids (Aufdenblatten et al., 2009; Kajantie et al., 2003; McCalla, Nacharaju, Muneyyirci-Delale, Glasgow, & Feldman, 1998; Schoof et al., 2001).

In animal models, placental 11 β -HSD2 deficiency has been associated with defective brain functioning later in life (Benediktsson et al., 1997; Holmes et al., 2006; Holmes & Seckl, 2006; Langley-Evans et al., 1996; Leao et al., 2007; Welberg, Seckl, & Holmes, 2000). Recent evidence in humans suggests that the potential inhibition of placental 11 β -HSD2 activity by glycyrrhizin in liquorice confectionery (Benediktsson et al., 1997) is associated with poorer verbal and visuospatial abilities and narrative memory in the offspring at 8 years (Räikkönen, Pesonen et al., 2009). These findings suggest that the transcriptional activity of the 11 β -HSD2 enzyme may be predicted by maternal adversity or pre-eclampsia and predictive of high-risk long-term outcomes (see section 1.4.4 below).

In addition to the reduced activity of 11 β -HSD2, a hypothesised mechanism linking maternal pre-eclampsia to fetal over-exposure to glucocorticoids may be related to maternal distress conditions. Psychological distress conditions may lead to the development of pre-eclampsia (Kurki et al., 2000; Paarlberg et al., 1995; Qiu et al., 2009) by enhancing cortisol levels (Vianna, Bauer, Dornfeld, & Chies, 2011), and pre-

eclampsia may, in turn, induce further psychological changes (Vianna et al., 2011). In the presence of high maternal glucocorticoid levels, fetal exposure is also substantially high. A positive correlation between maternal and amniotic fluid cortisol levels has been reported (Sarkar, Bergman, Fisk, O'Connor, & Glover, 2007) notwithstanding the role of 11 β -HSD2.

Finally, other factors may also be involved. A tentative mechanism underlying the associations between maternal hypertensive disorders and offspring development could be associated with the renin–angiotensin–aldosterone system (RAAS), an important regulator of blood pressure and blood volume in the body. Alterations in components of RAAS are seen in pre-eclampsia (Conti et al., 2013; Verdonk, Visser, Van Den Meiracker, & Danser, 2014); however, alterations in components of RAAS may also be associated with decreased 11 β -HSD2 activity (Lanz et al., 2003) and restricted fetal growth (Mistry, Kurlak, & Broughton Pipkin, 2013).

All of these influences have the potential to cause life-long changes in the body's organ structure and functioning, as well as epigenetic changes affecting gene expression, which persist into the adult life of the offspring and may increase the risk of adverse outcomes.

1.4.4 Epigenetic mechanisms

The hypothesised effects reflect a specific biological mechanism possibly associated with the effects on the epigenome. The epigenome can be conceived of as a series of switches that cause various parts of the genome to be expressed or not. This alteration of gene expression takes place without affecting the DNA sequence. The factors that contribute to the epigenetic regulation of transcriptional activity (epigenetic marks) are numerous, but DNA methylation and histone modifications are the most studied. These are increasingly explored within the context of environmentally induced changes resulting in later disease risk (Waterland & Michels, 2007).

Studies on the associations between early experiences and its epigenetic effects were given impetus from the studies by Meaney and colleagues. They showed that, in rats, low levels of maternal care were linked to an increased methylation of the promoter region of the glucocorticoid receptor (GR) gene, as well as to changes in behaviour and HPA axis functioning (Weaver et al., 2004). In addition, in humans, early life adversity has

been linked to methylation changes in genes regulating the stress system (Mueller & Bale, 2008; Oberlander et al., 2008; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). Epigenetic dysregulation of various genes have also been associated with mental disorders, depression (Lester, Conradt, & Marsit, 2013; Sabunciyan et al., 2012) and schizophrenia (e.g. Aberg et al., 2014).

The period while the fetus is in utero may be particularly important for altering gene expression (Heijmans et al., 2008). The effects may be mediated by the placenta. Thus, the epigenetic status of the placenta predicts corresponding changes in the fetal brain (Jensen Pena, Monk, & Champagne, 2012). In pre-eclampsia, placental stress pathways may be altered. Hogg, Blair, von Dadelszen and Robinson (2013) found DNA methylation plasticity of many genes involved in cortisol signaling, cortisol bioavailability and placental hormonal signaling associated with early onset pre-eclampsia. While null findings in relation to the methylation of the HSD11B2 gene encoding the 11 β -HSD2 were reported in Hogg and colleagues' study, other studies have shown that maternal prenatal stress alters the methylation of this gene (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013; Jensen Pena et al., 2012). It seems that maternal adversity during gestation can induce epigenetic changes in the placenta and fetal tissues related to stress regulation. The evidence shows that maternal adversity during gestation accounts not only for the heightened HPA reactivity among offspring (Oberlander et al., 2008), but also for poorer neurodevelopmental outcomes (Conradt et al., 2013; Marsit, Maccani, Padbury, & Lester, 2012). It is also possible that other epigenetic influences related to pre-eclampsia and/or gestational hypertension cause life-long changes in the offspring at the level of the epigenome and transcriptome and the body's organ structure and functioning (e.g. see Sundrani et al., 2013 on methylation changes in the vascular endothelial growth factor (VEGF) promoter region related to pre-eclampsia).

1.4.5 Common underlying factors

It is also possible that a common genetic background for hypertensive pregnancy disorders and later adversities in mental health and cognitive functioning exist. These conditions are probably genetically heterogeneous, yet their genetic architecture remains poorly known. Supporting the role of genes, formerly pre-eclamptic women scored

lower on cognitive tests (Brusse, Duvekot, Jongerling, Steegers, & De Koning, 2008). However, this impairment is probably attributable to the presence of lesions on the brain of pre-eclamptic women due to cerebral ischemia and edema in the clinical phase of the disease rather than a genetic susceptibility. Furthermore, psychological distress conditions may predispose a mother to pre-eclampsia and hypertension and it seems plausible that these women also carry a higher risk of postpartum depression (Duley, 2009). Finally, the offspring of pre-eclamptic mothers are themselves at a higher risk of stroke (Kajantie, Eriksson, Osmond, Thornburg, & Barker, 2009). However, the role of genes versus environmental factors remains unknown. Genetic variants probably play a role, but their relative roles in the modulation of adaptive responses to environmental factors and adverse consequences in adulthood are yet to be determined. Common environmental factors such as lifestyle factors may also explain the associations.

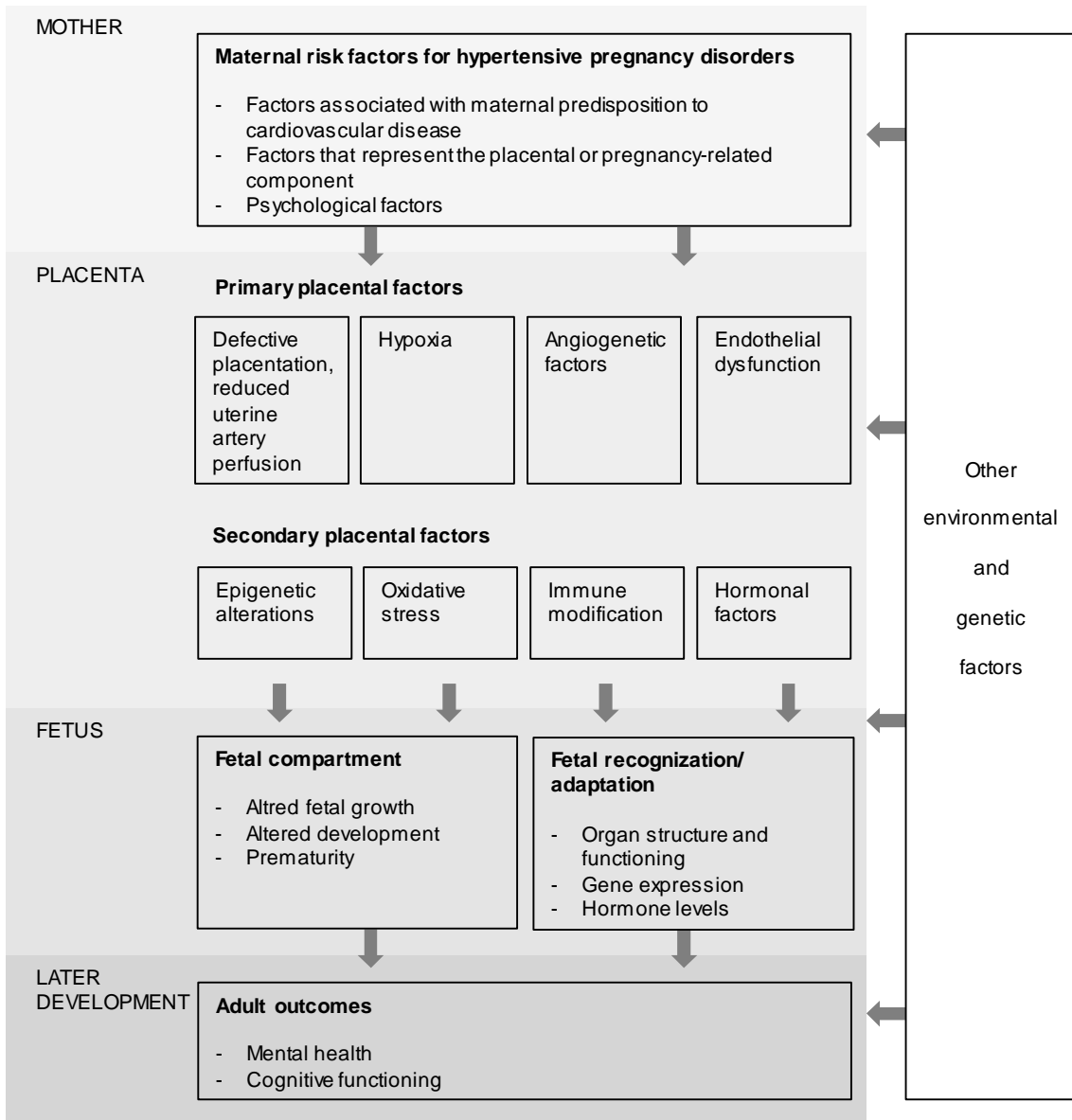


Figure 2. Potential factors and mechanisms that may affect and underlie the long-term psychological consequences among offspring exposed intrauterine to maternal hypertensive disorders

1.5 Maternal hypertensive disorders during pregnancy and developmental sequelae for the offspring: A review of previous findings

In order to gain a deeper understanding of the previous findings, this thesis summarises the available evidence from human studies that have tested the effects of maternal hypertensive disorders during pregnancy on the mental health and cognitive ability of the offspring later in life. The literature search strategy and study selection are described in detail in the Appendix.

1.5.1 Maternal hypertensive disorders during pregnancy and the mental health of the offspring

Schizophrenia is the most studied adult mental disorder as an outcome of prenatal exposure to maternal hypertensive pregnancy disorders. Geddes et al. (1999) performed a meta-analysis of individual data based on studies published up to May 1996 which reported associations between obstetric complications and schizophrenia. They found no statistically significant associations between maternal pre-eclampsia and schizophrenia (likelihood ratio statistics = 13.88, $df = 8$, $p = 0.09$). However, in a more recent meta-analytic review based on five studies (Byrne et al., 2007; Dalman et al., 2001; Jones, Rantakallio, Hartikainen, Isohanni, & Sipilä, 1998; Kendell, McInnery, Juszczak, & Bain, 2000), Cannon et al. (2002) highlighted the importance of the associations between obstetric complications and schizophrenia. Their meta-analytic synthesis revealed three groups of complications that were significantly associated with schizophrenia, one of which was complications in pregnancy; pre-eclampsia was more common in the mothers of children with schizophrenia compared to the mothers of healthy control children (odds ratio (OR) = 1.36, 95% confidence interval (CI): 0.99–1.85, $p = 0.05$). Maternal hypertensive pregnancy disorders may also play a role in the etiology of other mental health outcomes.

Sixteen studies have been published where associations between maternal hypertensive pregnancy disorders and mental disorders and symptoms of the offspring later in life have been studied. The findings from these studies have varied. Some of the studies found that maternal hypertensive pregnancy disorders are associated with a

higher risk of mental disorders or more severe symptoms of these disorders later in life, while some of the studies reported null associations or positive effects. Tables 4a and 4b summarise the findings from these studies. Table 4a summarises register-based longitudinal studies that measure lifetime risk for severe mental disorders, and Table 4b summarises studies that have assessed sub-clinical symptoms and mental disorders at single time points by parental or self-ratings or psychiatric interviews. Both tables are organised according to the year of birth of the offspring, reflecting changes in disease classification between past and present. In addition, Table 4b is organised within two broad categories—namely, whether the offspring was followed-up a) to childhood or b) to adulthood. Tables 4a and 4b show that, in these studies, the criteria used to define maternal hypertensive pregnancy disorders varied from that presented in Table 1 or were not reported. Tables 4a and 4b also provide the details of these studies including sample sizes. With the exception of three studies (Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999; Eide et al., 2013; H. J. Sørensen, Mortensen, Reinisch, & Mednick, 2003), the register-based longitudinal studies are retrospective case-control studies where cases and controls differ in the outcomes, but not in terms of exposure. Naturally, compared to prospective cohort studies, these offer a greater power to detect differences (if they exist). All of the studies that have assessed sub-clinical symptoms and mental disorders are cohort follow-up analyses conducted in general populations. Below, the findings from these studies are reviewed.

First, I review the findings from studies that focused on pre-eclampsia. I then describe the findings from studies that focused on gestational hypertension without proteinuria. Finally, I review the findings from studies that did not differentiate between the specific diagnoses, but which treated maternal hypertensive disorders as a single diagnostic entity.

Table 4a. Severe mental disorders of the offspring born after pregnancies complicated by hypertensive pregnancy disorders

First author, publishing year/ Reference	Country and birth year	Study design	Sample size	Definition of hypertensive spectrum disorders (obtained from)	Offspring characteristics	Offspring age at follow-up	Mental health outcome	Diagnostic criteria (obtained from)	Main findings on maternal hypertensive disorders and mental health outcome (95% CI)
PRE-ECLAMPSIA									
Suvisaari et al., 2013	Finland 1941–77	Case-control	63 cases, 208 controls; 8 PE	Hypertension: BP \geq 150/95 mm Hg at least once with proteinuria	Mothers with psychotic disorder	<60	Schizophrenia, other mental disorders	DSM-IV (Hospital Discharge Register)	No associations*
Sørensen et al., 2003	Denmark 1959–61	Follow-up of the Copenhagen Perinatal Cohort	313 PE, total 7866; 84 schizophrenic, 7782 no schizophrenic	BP \geq 140/90 mm Hg on \geq 2 occasion with edema and proteinuria after 20th week of gestation irrespective of previous BP		<35	Schizophrenia, psychosis	ICD-8 (Psychiatric Central Register)	No associations; 4% vs. 1.2% affected with schizophrenia
Jones et al., 1998	Finland 1966	Case-control	70 cases, 1074 controls; 33 PE 1111 non-PE	Diastolic BP >105 mm Hg and albuminuria		<28	Schizophrenia	DSM-III-R criteria	No associations; AOR for pre-eclampsia 0.5 (0.1 to 4.0)
Eide et al., 2013	Norway 1967–82	Cohort follow-up	15 622 PE, 857990 non-PE	BP \geq 140/90 mm Hg after 20th week of gestation or rise in BP \geq 30/15 mm Hg from the level measured before 20 th week, combined with proteinuria \geq 300 mg/d		Adulthood	Schizophrenia	ICD-9/ ICD-10 (National Insurance Scheme)	OR for schizophrenia 1.3 (1.0, 1.8)
Kendell et al., 2000	Scotland 1971–74	Case-control	296 case-control pairs	ICD-8 (Scottish Morbidity Record)		<26	Schizophrenia	ICD-9/ ICD-10 (Morbidity Record)	No associations; OR for pre-eclampsia 1.12 (0.65, 1.92)
Kendell et al., 2000	Scotland 1975–78	Case-control	156 case-control pairs	ICD-8 (Scottish Morbidity Record)		<22	Schizophrenia	ICD-9/ ICD-10 (Morbidity Record)	No associations; OR for pre-eclampsia 0.85 (0.45, 1.62)

Dalman et al., 1999	Sweden 1973–77	Cohort follow-up	238 schizophrenic, 507278 no schizophrenic	ICD-8		<22	Schizophrenia	ICD-8	RR for schizophrenia 2.5 (1.4, 4.5)
Dalman et al., 2001	Sweden 1960–	Case-control	524 cases, 1043 controls; 25 PE, 1542 non-PE	BP \geq 140/90 mm Hg and proteinuria		<34 y	Schizophrenia	ICD-8/ ICD-9	No associations; OR for schizophrenia 1.6 (0.7, 3.5)
Byrne et al., 2007	Denmark 1978–83	Case-control	227 cases, 5416 controls 5643	ICD-8 (Medical Birth Register)		15-20	Schizophrenia	ICD-8/ ICD-10 (Psychiatric Central Register)	AIRR for pre-eclampsia 2.72 (1.0, 7.3)
Fazel et al. 2012	Sweden 1973–86	Case-control	150 cases, 97 offender controls, 1498 general population controls; 127 PE-E	ICD-8 (code 637; Medical Birth Register)	Offenders	15-27	Personality disorders	Forensic psychiatric evaluation: ICD-9/ DSM-IV	AOR for pre-eclampsia 1.7 (1.0, 3.0) when compared with general populations controls; No other associations
O'Dwyer et al., 1997	UK N/A	Case-control	50 cases, 50 controls	N/A (interview or obstetric case notes)	Intellectual disability	N/A	Schizophrenia	DSM-IV (interview or case notes)	PE associated with an increased risk of schizophrenia
HYPERTENSION WITHOUT PROTEINURIA									
Suvisaari et al., 2013	Finland 1941–77	Case-control	63 cases, 208 controls; 18 HT	BP \geq 150/ 95 mm Hg at least once	Mothers with psychotic disorder	<60	Schizophrenia, other mental disorders	DSM-IV (Hospital Discharge Register)	HRR for schizophrenia 4.10 (1.15, 14.59) No other associations*
Sørensen et al., 2003	Denmark 1959–61	Follow-up of the Copenhagen Perinatal Cohort	1457 HT, total 7866; 84 schizophrenic, 7782 no schizophrenic	BP \geq 140/90 mm Hg on \geq 2 occasion		<35	Schizophrenia, psychosis	ICD-8 (Psychiatric Central Register)	AOR for schizophrenia 1.69 (1.02, 2.80)/hypertension No other associations*

*No association refers to $p > 0.05$

BP, blood pressure; HT, hypertension; PE, pre-eclampsia; PE-E, pre-eclampsia/eclampsia

AIRR, adjusted incidence rate ratio; AOR, adjusted odds ratio; HRR, hazard rate ratio; OR, odds ratio; RR, relative risk

DSM, Diagnostic and Statistical Manual for Mental Disorder; ICD, International Statistical Classification of Diseases and Related Health Problems

Table 4b. Subclinical symptoms and mental disorders of the offspring born after pregnancies complicated by hypertensive pregnancy disorders

First author, publishing year/ Reference	Country and birth year	Study design	Sample size	Definition of hypertensive spectrum disorders (obtained from)	Offspring characteristics	Offspring age at follow-up	Mental health outcome	Outcome measure	Main findings on maternal hypertensive disorders and cognitive outcome (95% CI)
PRE-ECLAMPSIA									
FOLLOW-UP TO CHILDHOOD									
Robinson et al., 2009	Australia 1989–92	Follow-up of the Western Australian Pregnancy Cohort Study	80 PE, 2804 NT	BP \geq 140/90 mm Hg after 24th week of pregnancy with proteinuria \geq 300 mg/24h		2,5,8,10 and 14 y	Total behaviour score, internalizing behaviour, externalizing behaviour	ASEBA - CBCL (parent report)	Pre-eclampsia reduced internalizing morbidity at ages 5 and 8 years No other associations*
Zammit et al., 2009	UK 1991–92	Follow-up of the Avon Longitudinal Study of Parents and Children Cohort	33 PE, 1536 non-PE	BP \geq 140/90 mm Hg with proteinuria + on at least 2 occasions	Term born only	12 y	Non-clinical psychotic symptoms	PLIKSi (interview)	No associations; OR for suspected or definite PLIKS 1.07 (0.52 to 2.20)
FOLLOW-UP TO ADULTHOOD									
Tuovinen et al., 2014	Finland 1934–44	Follow-up of the Helsinki Birth Cohort Study	24 PE, 494 NT	BP \geq 140/ 90 mm with proteinuria +		69.3 y	Adaptive functioning and psychiatric and psychological problems	ASEBA - OASR	AOR for total problems 4.00 (1.64 to 9.77), AOR for critical items 5.28 (1.87 to 14.96)
Wiles et al., 2005	UK 1950–56	Follow-up of the Aberdeen Children of the 1950s Cohort Study	57 severe PE, 121 moderate PE, 4557 NT	N/A (Aberdeen Maternal and Neonatal Databank)		45–51 y	Psychological distress	GHQ: 4 items (self-report)	No associations; fully adjusted OR 1.17 (0.74, 1.85)/ moderate PE, 1.59 (0.86,

2.97)/ severe PE

Berle et al., 2006	Norway 1967–74	Follow-up of the Nord-Trøndelag Health Study	155 PE, 1029 non-PE	N/A (Medical Birth Register)	20–30 y	Anxiety disorder, depression	HADS (self-report)	No associations; fully adjusted OR 1.45 (0.97, 2.16)
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HYPERTENSION WITHOUT PROTEINURIA**FOLLOW-UP TO CHILDHOOD**

Robinson et al., 2009	Australia 1989–92	Follow-up of the Western Australian Pregnancy Cohort Study	605 HT, 2804 NT	BP \geq 140/90 mm Hg after 24th week of pregnancy, in pre-eclampsia additionally proteinuria \geq 300 mg/24h	2,5,8,10 and 14 y	Total behaviour score, internalizing behaviour, externalizing behaviour	ASEBA-CBCL (parent report)	Gestational hypertension associated with externalizing behaviour from age 8 to 14 years and for internalizing behaviour at age 14 years No other associations*
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FOLLOW-UP TO ADULTHOOD

Tuovinen et al., 2014	Finland 1934–44	Follow-up of the Helsinki Birth Cohort Study	260 HT, 494 NT	BP \geq 140/ 90 mm	mean 69.3 y	Adaptive functioning and psychiatric and psychological problems	ASEBA - OASR	No associations*
Wiles et al., 2005	UK 1950–56	Follow-up of the Aberdeen Children of the 1950s Cohort Study	837 HT, 4557 NT	N/A (Aberdeen Maternal and Neonatal Databank)	45–51 y	Psychological distress	GHQ: 4 items (self-report)	No associations: fully adjusted OR 1.09 (0.90, 1.32)

HYPERTENSIVE PREGNANCY DISORDERS AS A SINGLE DIAGNOSTIC ENTITY**FOLLOW-UP TO CHILDHOOD**

Hirsfeld-Becker et al., 2004	USA N/A	Follow-up	138 parental PD and MD, 26 parental PD, 47 parental MD,	N/A (interview)	At risk for anxiety disorder because of	mean 6.8 y (range 5–25 y)	Anxiety disorders	KSADS-E (interview with or without	OR for multiple anxiety disorders 3.9 (1.8, 8.5)
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95 neither
parental PD nor
MD

having at least
one parent with
panic disorder

mothers)

*No association refers to $p > 0.05$

BP, blood pressure; HT, hypertension; NT, normotension; PE, pre-eclampsia

AOR, adjusted odds ratio; OR, odds ratio

MD, major depression; PD, panic disorder

ASEBA - CBCL, Achenbach System of Empirically Based Assessment - Child Behavior Checklist; ASEBA - OASR, Achenbach System of Empirically Based Assessment - Older Adult Self-Report; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Rating Scale; KSADS-E, Schedule for Affective Disorders and Schizophrenia -

Epidemiologic version; PLIKSi, Psychosis-like symptoms semistructured interview

Register-based longitudinal studies: Lifetime risk for mental disorders

Pre-eclampsia

Ten studies examined whether maternal pre-eclampsia was associated with a risk of any or a specific mental disorder in the offspring (Table 4a). Of these studies, five reported that maternal pre-eclampsia was associated with a higher risk of mental disorders in the offspring (Byrne et al., 2007; Dalman et al., 1999; Eide et al., 2013; Fazel et al., 2012; O'Dwyer, 1997), while five found no associations (Dalman et al., 2001; Jones et al., 1998; Kendell et al., 2000; H. J. Sørensen et al., 2003; Suvisaari et al., 2013).

In four of the studies reporting negative associations (Byrne et al., 2007; Dalman et al., 1999; Fazel et al., 2012; O'Dwyer, 1997) and in one of the studies reporting no associations (Kendell et al., 2000), detailed methodological information—namely, the exact diagnostic criteria for pre-eclampsia and/or the number of exposed offspring—were not reported. The findings from these studies are, thus, not discussed in any further detail.

The study that reported associations with a higher risk for mental disorders was a cohort follow-up. The findings from this study suggest that, compared to the offspring born to non-pre-eclamptic mothers, offspring born to pre-eclamptic mothers have a higher risk for schizophrenia (adjusted odds ratio (AOR) = 1.3, 95% CI: 1.0–1.8) (Eide et al., 2013). Adjustments were made for maternal age and education, parity, marital status, sex and birth year of the child. The results also showed that the effect of pre-eclampsia on schizophrenia was stronger among preterm (OR = 2.0, 95% CI: 1.0–4.0) rather than full-term (OR = 1.3, 95% CI: 1.0–1.7) offspring.

One of the studies reporting null associations was a cohort follow-up (H. J. Sørensen et al., 2003), while the remainder were case-control studies (Dalman et al., 2001; Jones et al., 1998; Suvisaari et al., 2013).

The covariates and confounders accounted for between the study where maternal pre-eclampsia was associated with a higher risk of mental disorders in the offspring and studies reporting no associations vary. Table 15 in the Appendix presents a detailed list of the covariates and confounders taken into account in these studies. It is also worth nothing that all of these studies used the offspring of non-pre-eclamptic mothers as a

comparison group to the offspring of pre-eclamptic mothers, i.e., the comparison group may include offspring born to mothers with gestational or chronic hypertension.

Gestational hypertension without proteinuria

Two studies tested whether maternal hypertension during pregnancy without proteinuria was associated with a risk of mental disorders in the offspring (Table 4a). Both report associations with a higher risk for any or more specific mental disorders (H. J. Sørensen et al., 2003; Suvisaari et al., 2013). The findings from these studies were reported in conjunction with the findings on maternal pre-eclampsia and the risk of mental disorders in the offspring reviewed above.

Suvisaari et al. (2013) reported that schizophrenic offspring are more often born to hypertensive mothers (17.2%) compared to the healthy comparison offspring (5.4%, $p = 0.04$). The study found no differences in the risk for other mental disorders, however. Sørensen et al. (2003) found that, compared to the offspring of normotensive mothers, the offspring of hypertensive mothers had an odds ratio of 1.69 (95% CI: 1.02–2.80) for having schizophrenia. However, when the authors further studied whether diuretic treatment explains the associations, they found that the combination of both maternal hypertension and diuretic treatment in the third trimester was a significant predictor of schizophrenia in the offspring (AOR = 4.10, 95% CI: 1.41–11.40).

Sub-clinical symptoms and mental disorders measured by parental or self-ratings or psychiatric interviews

Pre-eclampsia

Follow-up studies to childhood

Two studies tested whether maternal pre-eclampsia is associated with sub-clinical mental health symptoms among the offspring in childhood. One study found no significant associations between maternal pre-eclampsia and psychotic symptoms (Zammit et al., 2009), while the other study reported that maternal pre-eclampsia was associated with lower internalising symptoms (Robinson et al., 2009).

In the study that reported positive effects, pre-eclampsia was associated with lower internalising behaviour scores (AOR for clinically significant scores at age 5 years: 0.22,

95% CI: 0.05–0.97; and 8 years: 0.33, 95% CI: 0.11–0.98) (Robinson et al., 2009). However, maternal pre-eclampsia was not associated with externalising symptoms in the offspring ($p > 0.41$). The covariates and confounders accounted for included sex, gestational age and proportion of optimal birth weight, maternal age, education, smoking and experiencing stressful events during pregnancy, total family income, the presence of the biological father and the family functioning score.

Follow-up studies to adulthood

Three studies tested whether maternal pre-eclampsia was associated with sub-clinical symptoms or mental disorders in the offspring in adulthood. One of these studies reported that maternal pre-eclampsia was associated with more severe psychiatric or psychological symptoms in the offspring (Tuovinen et al., 2014), while two found no significant associations (Berle, Mykletun, Daltveit, Rasmussen, & Dahl, 2006; Wiles, Peters, Leon, & Lewis, 2005).

In the two studies reporting a lack of associations, the exact diagnostic criteria were not reported (Berle et al., 2006; Wiles et al., 2005). The findings from these studies are, therefore, not discussed in any further detail.

In the study that reported negative associations, maternal pre-eclampsia was associated with an increased odds of reporting total problems (AOR = 4.00, 95% CI: 1.64–9.77) and problems of particular concern to clinicians (critical items) (AOR = 5.28, 95% CI: 1.87–14.96) at a mean age of 69 years (Tuovinen et al., 2014). These scales tap problems across all scales measuring problems. Maternal pre-eclampsia was also associated with anxious/depressed, functional impairment, memory, thought and irritable/disinhibited problems on syndrome scales; and depressive, somatic and psychotic problems on Diagnostic and Statistical Manual of Mental Disorders (DSM) - oriented scales; and adjustment problems with regards to relationship satisfaction with one's spouse or partner. The covariates and confounders accounted for in the analysis included sex, year of birth (1934–38 versus 1939–44), gestational age, weight for gestational age and head circumference at birth, placental weight, father's occupational status during the subject's childhood, parity, mother's age and body mass index (BMI) at delivery and breastfeeding, maximum level of education in adulthood and age at completion of the questionnaire.

Gestational hypertension without proteinuria

Findings from studies focusing on maternal hypertension without proteinuria were reported in conjunction with the findings on maternal pre-eclampsia and sub-clinical mental health symptoms or disorders in the offspring reviewed above. Table 4b provides further details of these comparisons.

Follow-up studies to childhood

One study tested whether maternal hypertension without proteinuria was associated with mental health symptoms in the offspring in childhood (Table 4b). The findings from that study showed that maternal gestational hypertension was associated with higher externalising behaviour scores in the offspring from the age of 8 to 14 years and for higher internalising behaviour scores at the age of 14 years (Robinson et al., 2009). In addition, maternal hypertension was predictive of clinically significant Child Behavior Checklist scores from ages 8 to 14 years, with the largest risk seen at 14 years (AOR = 1.83, 95% CI: 1.21–2.77).

Follow-up studies to adulthood

Two studies tested whether maternal hypertension without proteinuria was associated with mental health symptoms in the offspring in adulthood (Table 4b). Neither of these studies found significant associations (Tuovinen et al., 2014; Wiles et al., 2005). Wiles et al. (2005) did not report the exact diagnostic criteria, and the findings from their study are, therefore, not discussed in any further detail.

Hypertensive pregnancy disorders

Follow-up studies to childhood

Finally, one study on sub-clinical symptoms and mental disorders in the offspring focused on hypertensive pregnancy disorders as a single diagnostic entity. The study reported significant associations with a higher risk of anxiety disorders at the mean age of 7 years (Hirshfeld-Becker et al., 2004). In that study, the exact diagnostic criteria were not reported, and the findings are, therefore, not discussed in any further detail.

1.5.2 Maternal hypertensive disorders during pregnancy and the cognitive functioning of the offspring

The oldest study examining the associations between maternal hypertensive disorders and the cognitive functioning of the offspring was that of Barker and Edwards (1967) (Table 5). In this population-based study, 3321 children born after toxemic and 46 735 children born after non-toxemic pregnancies were followed to 11 years of age. The verbal reasoning test scores of those children born after toxemic pregnancies were above the population mean. This was consistent across birth ranks when compared to the mean for all children in the same birth rank. However, in further analyses using the same dataset, the authors compared siblings born to the same mother after a pregnancy that was complicated by toxemia and after a pregnancy that was not. The affected siblings scored lower on verbal reasoning when compared with their unaffected siblings. This difference was most obvious among those born at term. The authors did not report the diagnostic criteria for toxemia. However, in cohorts born before the late 1990s, the diagnostic criteria for pre-eclampsia and hypertension did not follow the current diagnostic criteria.

After the study by Barker and Edwards, 22 studies were published where associations between maternal hypertension spectrum disorders and the cognitive functioning of the offspring later in life were studied. The findings vary. Some of these studies found that maternal hypertensive pregnancy disorders were associated with poorer cognitive functioning among the offspring later in life, while some of the studies reported null or positive effects. Table 5 summarises the findings from these studies. The data are organised according to the year of birth of the sample reflecting changes in disease classification between past and present and within two major categories, namely whether the offspring were followed-up to a) childhood or b) adulthood, and whether the childhood and adulthood follow-up studies were conducted in a) a general population or b) in samples born preterm or with a small body size at birth. Table 5 shows that, of these studies, only three used the current diagnostic criteria described in Table 1 (Leveresen et al., 2011; Schlapbach et al., 2010; Silveira, Procianny, Koch, Benjamin, & Schlindwein, 2007), while the criteria used in the remaining studies varied or were not reported at all. Table 5 also provides the details of these studies including the sample sizes. Below, these findings are reviewed in more detail.

First, I review studies that focused on pre-eclampsia. I then describe studies that focused on gestational hypertension without proteinuria. Finally, I review studies that did not differentiate between the specific diagnoses, but which treated maternal hypertensive pregnancy disorders as a single diagnostic entity.

Table 5. Cognitive functioning of the offspring born after pregnancies complicated by hypertensive pregnancy disorders

First author, publishing year/ Reference	Country and birth year	Study design	Sample size	Definition of hypertensive spectrum disorders (obtained from)	Offspring characteristics at birth	Offspring age at follow-up	Cognitive outcome	Outcome measure	Main findings on maternal hypertensive disorders and cognitive outcome (95% CI/ SD)
PRE-ECLAMPSIA									
FOLLOW-UP TO CHILDHOOD									
Population-based cohort studies									
Barker & Edwards, 1967	UK 1950–1954	Population based study	3321 PE, 50046 non-PE	N/A (Birth records)		11 y	Verbal reasoning	N/A (Eleven-plus)	Toxemia/PE associated with lower verbal reasoning within sibpairs
Seidman et al., 1991	Israel 1964–1971	Follow-up of the Jerusalem Perinatal Study	428 PE 33117 non-PE	BP \geq 140/ 90mm Hg or rise in BP \geq 30/ 15 mm Hg (two readings, \geq 6 hour apart) or significant proteinuria or edema or any combination of two or more after 24th week gestation		17 y	IQ (mean 100, SD 15)	Verbal Otis test, matrices test	No associations; Mean 109.3 (1.2) vs. 110.9 (0.1)/ females, 101.9 (1.0) vs. 103.1 (0.1)/ males
Heikura et al., 2012	Finland, 1985–1986	Follow-up of the Northern Finland Birth Cohort	258 PE, 6761 NT	BP \geq 140/ 90 mm Hg after 20 th weeks of gestation twice after a 5 min rest plus proteinuria \geq 300 mg/L		11.5 y	Mild cognitive limitations (IQ 50–85)	Psychological tests (WISC-R for 78%) in routine clinical care, individual data reviewed by study authors	No associations; Crude OR 1.7 (0.9, 3.4), OR adjusted for parental characteristics 1.2 (0.5, 2.8)
Whitehouse et al., 2012	Australia 1989–1992	Follow-up of the Western Australian Pregnancy	34 PE, 1076 NT	BP \geq 140/ 90mm Hg after 24 th weeks of gestation in women whose BP had previously been normal		10 y	Verbal (mean 100, SD 15) and non-verbal (range 0-60) ability	PPVT-R, RCPM	No associations; MD for verbal ability -3.53 (-8.41, 1.35), for non-verbal ability -1.82 (-12.59, 8.95)

			Cohort Study	plus proteinuria ≥ 300 mg/d					
Studies in clinical populations									
Szymonowicz & Yu, 1987	Australia 1982–1984	Case-control	35 PE, 35 non-PE	BP $\geq 140/90$ mm Hg, persistent proteinuria with urinary tract infection and generalised edema before 32 weeks of gestation	VLBW	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID	PE associated with lower mean mental developmental index; Mean 94 (25) vs. 106 (21)
Spinillo et al., 1994	Italy 1986–1990	Case-control	68 PE, 184 non-PIH	Diastolic BP ≥ 110 mmHg or in 2 consecutive measures ≥ 90 mmHg plus proteinuria ≥ 300 mg/d	GL 24–35 weeks	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID	ORs for minor neurodevelopmental impairment 4.0 (1.61, 10.2)
Spinillo et al., 2009	Italy 1990–2004	Cohort follow-up	185 PE, 569 NT	Diastolic BP ≥ 110 mm Hg or in 2 consecutive measures ≥ 90 mm Hg at any time during pregnancy plus proteinuria ≥ 300 mg/d	GL 24–35 weeks	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID-II	OR for neurodevelopmental impairment 0.52 (0.32, 0.85)
Many et al., 2003	Israel 1992–1993	Cohort follow-up	11 PE, 64 non-PE	Persistent BP $\geq 140/90$ mm Hg with proteinuria of either 100 mg/dL or >500 mg/d	Severe FGR (birth weight $<5^{\text{th}}$ percentile)	3 y	IQ (normative mean 100, SD 15)	Stanford-Binner IQ test	PE associated with lower IQ; Mean 85.5 vs. 96.9
Leitner et al., 2012	Israel 1992–1993	Cohort follow-up	17 PE, 78 NT	BP $\geq 140/90$ mmHg after 20 th weeks of gestation in women whose BP had previously been normal plus proteinuria ≥ 300 mg/d or +2	IUGR (birth weight $<10^{\text{th}}$ percentile)	9 to 10 y	IQ, school achievement	WISC-R95, K-ABC	No associations; Mean IQ 101.2 (18.4) vs. 101.7 (13.4), mean school achievement score 612.9 (98.9) vs. 602.9 (80.4)
Cheng et al., 2004	Taiwan 1997–1999	Follow-up	28 PE, 61 NT	Diastolic BP ≥ 110 mm Hg or in two consecutive measures ≥ 90 mm Hg at any time during pregnancy plus proteinuria ≥ 300 mg/d	GL <32 weeks	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID-II	PE associated with lower MDI score; AOR for mildly delayed MDI 10.9 (1.4–84.9)

Morsing & Maršál, 2014	Sweden, 1998–2004	Case-control	11 PE-IUGR, 23 non-PE-IUGR, 34 non-PE AGA	Diastolic BP \geq 90 mmHg in \geq two measures plus proteinuria \geq 300 ml/L	GA <30 weeks	5–8 y	IQ (normative mean 100, SD 15)	WPPSI-III, WISC-III	PE associated with lower IQ; Mean 70.1 (19) vs. 83.3 (14)/ 90.1 (14)
Leveresen et al., 2011	Norway 1999–2000	Cohort follow-up	73 PE, 233 non-PE	Current clinical criteria/ Medical Birth Register	GL 22–27 weeks	5 y 10 m	Full-scale IQ (normative mean 100, SD 15)	WPPSI-R	MD -7.7 (-12.7, -2.7) in IQ
Schlapbach et al., 2010	Switzerland 2002–2005	Case-control	33 PE, 33 non-PE (no chorioamnionitis)	Current clinical criteria	GL 25–32 weeks	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID-II	PE associated with a lower MDI in an unadjusted model, after adjustment for multiple factors no significant association; Median 86 vs. 96 in the unadjusted model
Silveira et al., 2007	Brazil 2003–2005	Cohort follow-up	40 PE, 46 non-PE	Current clinical criteria	VLBW (<1500 g)	12 and 18 m CA	Mental developmental index (normative mean 100, SD 15)	BSID-II	No associations; Mean 79.6 (0.4) vs. 79 (0.5)/ 6 m, 82.9 (0.5) vs. 81.1 (0.7)/ 12 m

FOLLOW-UP TO ADULTHOOD

Population-based cohort studies

Ehrenstein et al., 2009	Denmark 1978–1983	Follow-up	604 PE, 16 555 NT	BP \geq 140/ 90 mmHg after 20 weeks of pregnancy with proteinuria >300 mg/d or edema; severe pre-eclampsia BP \geq 180/ 110 mmHg and/or proteinuria >5000 mg/d + subjective symptoms/ Medical Birth Register		19 y	IQ (mean 100, SD 15); low cognitive functioning (IQ < 85)	BPP	ORs for scoring below 1 SD 1.22 (1.02 to 1.44); No evidence of a severity associated dose-response pattern of association.
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HYPERTENSION WITHOUT PROTEINURIA

FOLLOW-UP TO CHILDHOOD

Population-based cohort studies

Heikura et al., 2012	Finland, 1985–1986	Follow-up of the Northern Finland Birth Cohort	423 HT, 6761 NT	BP \geq 140/ 90 mmHg after 20 th weeks of gestation twice after a 5 min rest with no proteinuria		11.5 y	Mild cognitive limitations (IQ 50–85)	Psychological tests	AOR 2.4 (1.4, 3.9)
Whitehouse et al., 2012	Australia 1989–1992	Follow-up of the Western Australian Pregnancy Cohort Study	279 HT, 1076 NT	BP \geq 140/ 90mmHg after 24 th weeks of gestation with no proteinuria		10 y	Verbal (mean 100, SD 15) and non-verbal (range 0-60) ability	PPVT-R, RCPM	MD for verbal ability -1.71 (-3.39, -0.03) No other associations; MD for non-verbal ability 0.15 (-3.60, 3.90)

Studies in clinical populations

Spinillo et al., 1994	Italy 1986–1990	Case-control	52 severe HT, 184 non-PIH	Diastolic BP \geq 110 mmHg or in two consecutive measures \geq 90 mm Hg at any time during pregnancy with no proteinuria	GL 24–35 weeks	2 y CA	Mental developmental index (normative mean 100, SD 15)	BSID	AORs for minor neurodevelopmental impairment 4.0 (1.34, 12.1)
Leitner et al., 2012	Israel 1992–1993	Cohort follow-up	25 HT, 78 NT	BP \geq 140/ 90mmHg after 20 th weeks of gestation on at least once occasion with no proteinuria	IUGR (birth weight $<$ 10 th percentile)	9 to 10 y	IQ (normative mean 100, SD 15), school achievement	WISC-R95, K-ABC	No associations; Mean IQ 99.6 (9.7) vs. 101.7 (13.4), mean school achievement score 598.2 (79.1) vs. 602.9 (80.4)

FOLLOW-UP TO ADULTHOOD

Population-based cohort studies

Ehrenstein et al., 2009	Denmark 1978–1983	Follow-up	287 HT, 16 555 NT	BP \geq 140/ 90 mmHg after 20 weeks of pregnancy on at least once occasion with no		19 y	IQ (mean 100, SD 15); low cognitive functioning (IQ $<$ 85)	BPP	ORs for scoring below 1 SD 1.28, (1.01 to 1.62)
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proteinuria/
Medical Birth Register

HYPERTENSIVE PREGNANCY DISORDERS AS A SINGLE DIAGNOSTIC ENTITY

FOLLOW-UP TO CHILDHOOD

Population-based cohort studies

Lawlor et al., 2005	Scotland 1950–1956	Follow-up of the Aberdeen Children of the 1950s cohort study	1979 PIH, 9702 non-PIH	N/A (Aberdeen Maternal and Neonatal Databank)		7,9,11 y	IQ (normative mean 100, SD 15)	The Moray house intelligence test/ the Schonell and Adams essential intelligence test	Mean difference 2.35 IQ points (1.56, 3.14), attenuated to null when adjusted for parental characteristics
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Studies in clinical populations

Mutch et al., 1977	England 1970–1973	Case-control	100 treated HT, 101 untreated HT, 151 NT	BP \geq 140/ 90 mmHg in two consecutive measures 24 h apart and before 28 weeks of gestation	Comparison group: offspring born AGA to normotensive mothers	6 and 12 m	Language development, social skills	DDST	No associations*
Ounsted et al., 1980	England 1970–1973	Cohort follow-up	86 treated HT, 82 untreated HT, 107 NT	BP \geq 140/ 90 mmHg in two consecutive measures 24 h apart and before 28 weeks of gestation	Comparison group: offspring born AGA to normotensive mothers	4 y	Language development	DDST	No associations*
Ounsted et al., 1986	England 1970–74	Cohort follow-up	N/A; 118 SGA, 137 AGA, 181 LGA	BP \geq 140/ 90 mmHg on at least one occasion	Comparison group: offspring born AGA to normotensive mothers	7 y	Verbal ability, practical reasoning	DDST	Hypertension associated with lower verbal ability and practical reasoning scores in the SGA group No other associations*
Winer et al., 1982	USA 1973–1976	Follow-up	20 HT, 35 NT	As recommended by the American College of Obstetricians and	SGA	4 to 7 y	Verbal, performance and full scale IQ	WPPSI-R/ WISC-R, RCPM,	Hypertensive disorders associated with better verbal IQ; Mean for

				Gynecologist			(normative mean 100, SD 15), arithmetic skills, reading	WRAT-Arith, WRAT-Read	verbal IQ 105.8 (13.5) vs. 93.7 (12.8) No other associations; Mean for non-verbal IQ 99.4 (14.4) vs. 93.9 (15.2)
Many et al., 2005	Israel 1992–1993	Cohort follow-up	22 HT, 70 NT	N/A (Many et al., 2003)	Severe FGR (birth weight <5th percentile)	6 y	IQ (normative mean 100, SD 15)	WPPSI-R	No associations; Mean 106 (11) vs. 101 (14)
Gray et al., 1998	Australia 1992–1993	Cohort follow-up	96 PE+HT, 101 NT	BP \geq 140/ 90 mmHg at any time during pregnancy (two readings, \geq 6 hour apart) or rise in BP \geq 25/ 15 mm Hg	Very preterm (24-32 weeks of gestation)	2 y CA	General quotient (developmental delay) (normative mean 100, SD 15)	NSMDA, Griffiths' Infant Ability Scale	No associations; Mean 96.9 (11.5) vs. 96.5 (11.1)
McCowan et al., 2002	New Zealand 1993–1997	Cohort follow-up	88 PE+HT, 131 NT	BP \geq 140/ 90 mmHg or rise in diastolic BP \geq 15 mm Hg (two readings, \geq 4 hour apart) after 20th week of pregnancy	SGA (birth weight <10 th percentile)	18 m CA	Mental developmental index (normative mean 100, SD 15)	BSID-II	PIH associated with lower risk to have abnormal MDI scores; Mean 98.6 (12.9) vs. 93.7 (15.1)

*No association refers to $p > 0.05$

BP, blood pressure; HT, hypertension; NT, normotension; PE, pre-eclampsia; PIH, pregnancy induced hypertension including pre-eclampsia and gestational hypertension

GL, gestational length; AGA, appropriate for gestational age; FGR, fetal growth restriction; IUGR, intrauterine growth restriction; SGA, small for gestational age; VLBW, very low birth weight; CA, corrected age

95% CI, 95% confidence interval; AOR, adjusted odds ratio; MD, mean difference; OR, odds ratio; SD, standard deviation

MDI, mental developmental index; IQ, intelligence quotient

BPP, Boerge Prien group intelligence test; BSID, Bayley Scales of Infant Development; DDST, Denver Developmental Screening Test; K-ABC, Kaufman Assessment Battery for Children; NSMDA, Neurosensory motor developmental assessment; PPVT, Peabody Picture Vocabulary Test; RCPM, Ravens Colored Progressive Matrices; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WRAT-Arith, Wide-range achievement tests in arithmetic; WRAT-Read, Wide-range achievement tests in reading

Pre-eclampsia

Follow-up studies to childhood

Thirteen studies examined whether pre-eclampsia was associated with poorer cognitive functioning or the mental development of the offspring in childhood. Of these studies, six reported an association between maternal pre-eclampsia and poorer cognitive functioning in the offspring (Cheng, Chou, Tsou, Fang, & Tsao, 2004; Leversen et al., 2011; Many et al., 2003; Morsing & Maršál, 2014; Spinillo et al., 1994; Szymonowicz & Yu, 1987), six found no association or the association was rendered non-significant when adjustments were made for important covariates and confounders (Heikura et al., 2013; Leitner et al., 2012; Schlapbach et al., 2010; Seidman et al., 1991; Silveira et al., 2007; Whitehouse, Robinson, Newnham, & Pennell, 2012) and one reported that maternal pre-eclampsia was associated with better cognitive functioning or a lower likelihood of impairment in mental development (Spinillo et al., 2009).

Those studies that reported an association between maternal pre-eclampsia and poorer cognitive functioning in the offspring were conducted among clinical populations. Szymonowicz and Yu (1987) reported that children born to pre-eclamptic mothers had a significantly lower mental developmental index (MDI) (mean (m) = 94, standard deviation (SD) = 25) compared to children born to non-pre-eclamptic mothers (m = 106, SD = 21) at the age of 2 years even when the infants in the two groups were appropriately matched for gestational length, male-to-female ratio and 2-year survival. Spinillo et al. (1994) reported that, compared to children born to normotensive mothers, children born to pre-eclamptic mothers had a higher risk for minor neurodevelopmental impairment at the age of 2 years even after adjustments were made for the social class of the family and maternal education (OR = 4.0, 95% CI: 1.61–0.2). Many et al. (2003) reported that children born to pre-eclamptic mothers relative to those born to non-pre-eclamptic mothers scored lower on an intelligence test at the age of 3 years (m = 85.5, SD = 16 vs. m = 96.9, SD = 18). Covariates and confounders included gestational age, birth weight and number of neonatal complications (such as respiratory problems, convulsions, hyperbilirubinemia, abnormal temperature, late feeding, infection and metabolic and blood disturbances). Cheng et al. (2004) reported that children born to pre-eclamptic mothers had lower MDI index scores compared to children born to non-

pre-eclamptic mothers at the age of 2 years. After adjusting for the use of antenatal steroids, infant sex, gestation length, birth weight and parental education, AOR for mildly delayed MDI was 10.9 (95% CI: 1.4–84.9). Morsing and Maršál (2014) reported that full-scale intelligence (IQ) and verbal IQ scores were lower in IUGR children born to pre-eclamptic mothers (70.1 ± 19) compared to IUGR children born to non-pre-eclamptic mothers (83.3 ± 14 ; $p = 0.03$) and the non-IUGR control children (90.1 ± 14 ; $p = 0.001$) at 5–8 years of age. The children of pre-eclamptic mothers also had lower performance IQ scores compared to the control children. The groups were matched for gestational age, sex of the infant and age at testing. The authors showed that the associations remained the same after adjustment for gestation length and weight deviations at birth and infant sex. Finally, Leversen et al. (2011) reported that children born to pre-eclamptic mothers had lower intelligence test scores compared to the children born to non-pre-eclamptic mothers at the mean age of 5 years ($B = -7.7$, 95% CI: -12.7 to -2.7). The associations were adjusted for gestation length, small for gestational age status, the use of antenatal steroids, retinopathy of prematurity, infant sex and maternal education.

The six studies that reported null associations between maternal pre-eclampsia and cognitive functioning were conducted in both general and clinical study populations. Three of the studies were conducted in general populations (Heikura et al., 2013; Seidman et al., 1991; Whitehouse et al., 2012) and three in clinical populations (Leitner et al., 2012; Schlapbach et al., 2010; Silveira et al., 2007).

Similar to the studies where maternal pre-eclampsia was associated with poorer cognitive functioning in the offspring, the studies reporting a lack of association vary greatly in covariates and confounders accounted for in the analyses. Table 16 in the Appendix presents a detailed list regarding which covariates and confounder the studies took into account. It is also important to note that the studies that used the offspring of mothers without pre-eclampsia as a comparison group may include offspring born to mothers with gestational or chronic hypertension.

The only study that reported an association between maternal pre-eclampsia and a lower risk of poor cognitive functioning in the offspring was conducted in a clinical population (Spinillo et al., 2009). Maternal pre-eclampsia was associated with a lower risk of moderate-to-severe and overall neurodevelopmental impairment in the offspring

at the age of 2 years (OR for overall impairment = 0.52, 95% CI: 0.32–0.85). Adjustments were made for multiple births, infant sex, maternal lifestyle behaviours during pregnancy and other parental characteristics. However, as the authors discussed, the findings should be interpreted with caution because the group of normotensive mothers included a large number of women who delivered preterm as a consequence of premature rupture of the membranes or spontaneous preterm labour. Hence, it remains possible that these factors may be associated with adverse cognitive outcomes in the offspring rather than pre-eclampsia having any beneficial effects.

Follow-up studies to adulthood

One study which was conducted in a general population extended the follow-up of the offspring born to mothers with pre-eclampsia into adulthood. Ehrenstein, Rothman, Pedersen, Hatch and Sørensen (2009) showed that the crude mean difference in the intelligence test scores associated with maternal pre-eclampsia at the mean age of 19 years was -2.7 (95% CI: -3.7 to -1.2). The prevalence rate for low cognitive functioning associated with maternal pre-eclampsia was 1.22 (95% CI: 1.02–1.44). The estimates changed little after restricting the analysis to those not born small for gestational age or when adjusting for maternal age at delivery, parity, marital status, history of diabetes, conscripts' year of birth, county of birth, birth weight and being born large for gestational age.

Gestational hypertension without proteinuria

Follow-up studies to childhood

Four studies—two carried out among the general population and two among clinical study populations—tested whether maternal hypertension without proteinuria was associated with cognitive outcomes among offspring in childhood (Table 5). Three of these reported associations with a poorer cognitive functioning among the offspring (Heikura et al., 2013; Spinillo et al., 1994; Whitehouse et al., 2012) and one reported no association (Leitner et al., 2012). The findings from these studies were reported in conjunction with the findings on maternal pre-eclampsia and the cognitive functioning of the offspring reviewed above.

The findings from studies reporting associations with a poorer cognitive functioning suggest that, compared to the offspring born after normotensive pregnancies, offspring born after pregnancies complicated by maternal hypertension without proteinuria carry an increased risk of minor neurodevelopmental impairment at the age of 2 years (AOR = 4.0, 95% CI: 1.34–12.1) (Spinillo et al., 1994), score lower on a verbal ability test at the age of 10 years ($B = -1.71$, 95% CI: -3.39 to -0.03) (Whitehouse et al., 2012) and have an increased risk of mild cognitive limitations at the age of 11 years (AOR = 2.4, 95% CI: 1.4–3.9) (Heikura et al., 2013).

The only study reporting null associations was conducted in a clinical sample (Leitner et al., 2012).

Follow-up studies to adulthood

One study conducted in a general population tested whether maternal hypertension without proteinuria is associated with cognitive functioning among offspring in adulthood and reported the effects on poorer cognitive functioning (Table 5) (Ehrenstein et al., 2009). The findings from that study showed that those offspring born after hypertensive pregnancies tended to score lower on an intelligence test at the age of 19 years (mean difference in intelligence test score = -1.6, 95% CI: -3.5 to 0.2; odds for scoring 'low' on cognitive functioning = 1.28, 95% CI: 1.01 to 1.62). This study was also reported in conjunction with the findings on maternal pre-eclampsia and the cognitive functioning of the offspring reviewed above.

Maternal hypertensive pregnancy disorders as a single diagnostic entity

Follow-up studies to childhood

Eight studies did not discriminate between maternal pre-eclampsia and gestational hypertension, but focused on maternal hypertensive disorders as a single diagnostic entity. One of these studies reported an association between maternal hypertensive pregnancy disorders and poorer cognitive functioning among the offspring (Ounsted, Moar, & Scott, 1986), five found no significant associations (Gray, O'Callaghan, Mohay, Burns, & King, 1998; Lawlor et al., 2005; Many, Fattal-Valevski, & Leitner, 2005; Mutch, Moar, Ounsted, & Redman, 1977; Ounsted, Moar, Good, & Redman, 1980) and two reported an association between maternal hypertensive pregnancy disorders and

better cognitive performance or a lower likelihood of impairment in mental development (McCowan, Pryor, & Harding, 2002; Winer, Tejani, Atluru, DiGiuseppe, & Borofsky, 1982).

In the only study reporting an effect on poorer cognitive functioning, the authors did not provide data on the number of exposed offspring (Ounsted et al., 1986). Two of the studies reporting no association turned out to be hypertensive medication treatment trials mainly comparing offspring born to hypertensive mothers who did and who did not receive hypertensive medication during pregnancy (Mutch et al., 1977; Ounsted et al., 1980). In two of the studies reporting no association (Lawlor et al., 2005; Many et al., 2005) and in one of the studies reporting beneficial effects (Winer et al., 1982), the exact diagnostic criteria for maternal hypertensive pregnancy disorders were not reported. The findings from these studies are, therefore, not discussed in any further detail.

The study reporting no association was conducted among a clinical sample (Gray et al., 1998).

The study that reported beneficial effects restricted the sample to those born small for gestational age (SGA) (McCowan et al., 2002). The offspring born to mothers with hypertensive disorders were less likely to have abnormal (<85 or <-1 SD) MDI scores at the mean age of 18 months. The authors discussed the possibility that maternal hypertension had a protective effect on neurodevelopment, but also acknowledged that the many other causes of SGA may be associated with adverse neurodevelopmental outcomes.

1.5.3 Summary

In summary, maternal hypertensive pregnancy disorders have gained relatively little research attention in relation to the mental health and cognitive outcomes of the offspring, although they may compromise placental functioning and, thus, affect the fetal developmental milieu. Previous studies do not provide a consistent picture on the associations. There is insufficient evidence to draw firm conclusion on the associations, due in part to the varied criteria used across different studies to define maternal hypertensive pregnancy disorders, the various definitions of the control groups and the limited controls for significant covariates and confounders. Furthermore, no previous

studies have taken into account that some subgroups of offspring may be particularly vulnerable to the effects of maternal hypertensive disorders; yet, hypertensive pregnancy disorders may differ in terms of frequency, severity and/or etiology based on the length of gestation (Luo et al., 2007; Skjærven et al., 2005), parity (Allen et al., 2004; Luo et al., 2007) and socio-economic status (Gudmundsson, Björgvinsdóttir, Molin, Gunnarsson, & Maršál, 1997; Silva et al., 2008). The occurrence of mental disorders and cognitive decline may also vary by sex (Bijl, Ravelli, & van Zessen, 1998; Kessler et al., 1994; Leray et al., 2011; Perrig-Chiello & Hutchison, 2010). Finally, previous studies have been conducted among offspring that are much younger in age than our follow-up extends. Thus, there is a need for future longitudinal studies in order to clarify the associations.

2 AIMS OF THE STUDY

The primary aim of this thesis was to evaluate the psychological developmental sequelae for the adult offspring born to mothers with hypertensive disorders during pregnancy and to compare these with the offspring of normotensive mothers by capitalising on a well-defined birth cohort. The secondary aim was to test whether any potential associations between hypertensive disorders during pregnancy and the outcomes of the offspring differ according to sex, length of gestation, parity and childhood socio-economic status.

The focus was on the mental health and cognitive functioning of the offspring. Five separate studies were conducted to evaluate the following outcomes:

Study I: The severity of depressive symptoms in late adulthood.

Study II: The risk of mental disorders in adulthood.

Study III: Cognitive ability in early adulthood.

Study IV: Cognitive functioning in late adulthood and any change in cognitive functioning from early up to late adulthood.

Study V: Cognitive impairment including cognitive failures and dysexecutive functioning in late adulthood.

3 METHODS

3.1 Helsinki Birth Cohort Study 1934–1944

HBCS comprises 13 345 individuals (men, $n = 6975$; women, $n = 6370$) who were born as singletons in one of the two maternity hospitals (the University Central Hospital and the City Maternity Hospital), in Helsinki between 1934 and 1944. These men and women attended child welfare clinics during childhood, and were living in Finland at that time when a unique personal identification number was assigned to each resident of the country. HBCS has been approved by the Ethics Committee of the National Public Health Institute.

3.1.1 Follow-ups of HBCS utilized in this thesis

Since 1969 nationwide data on all inpatient episodes and deaths of residents in Finland at an individual level have entered to the Finnish Hospital Discharge Register (HDR) and the Finnish Causes of Death Register (CDR). Regarding to mental disorders, the participants were followed up from year 1969 to their death, migration, onset of mental disorders or December, 31, 2004. In other words, follow-up data from these registers were available for the participants from between 24 and 35 years to between 60 and 70 years of age.

In 2001–2004, all 7078 people belonging to the original cohort (of 8760 born at Helsinki University Central Hospital) who were still alive and resident in Finland in year 2000 were sent a questionnaire. A total of 4515 individuals responded. In order to achieve a sample size over 2000 people for a clinical study, random number tables were used to select 2902 subjects. Of these, 2003 participated at a mean age of 61.5 years ($SD = 2.8$, Range 56.7–69.8) (Ylihärsilä et al., 2007), referred as time 1. In conjunction with the clinical examination, depressive symptoms were measured. In 2004, a more detailed psychological survey, again including measures of depressive symptoms, was sent to the randomly selected population, with 1735 returning the questionnaire at a mean age of 63.4 years ($SD = 2.9$, Range = 59.7–70.7), referred as time 2.

Between 1952 and 1972, a subsample ($n = 2786$) of the HBCS male participants served in the defense forces and completed the test on cognitive ability at an average

age of 20.1 years (SD = 1.4; Range 17.0–28.1). In 2009, a subsample of them (n = 931) were re-tested at an average age of 67.9 years (SD = 2.5; Range = 64.5–75.7). The mean time interval between the two cognitive tests was 47.7 years (SD = 2.9, Range = 38.9–54.7).

Between 2009 and 2010, a psychological questionnaire that included questions on cognitive failures and executive function was administered to (1) a randomly selected subsample of women and men who had between 2001 and 2004 participated in a detailed clinical examination (n = 2003) and (2) a subsample of men only (n = 2786; 642 of whom belonged also to the randomly selected clinical subsample) who participated in a testing of cognitive ability during their compulsory military service between 1952 and 1972. At a mean age of 69.3 years (SD = 3.1, Range = 64.7–76.6), 1893 returned the questionnaire.

The antenatal clinics were introduced in Helsinki from 1928 onwards (Pelkonen, 1940), and all pregnant women were encouraged to attend these clinics. Of the 13 345 participants in the cohort, these maternal data were available for 6410 (48.0%).

In view of the above described selection related to different follow-ups, the participant numbers vary between the individual studies of this thesis. The final numbers and exclusion criteria used are described in detail in Figure 3. The participation rates can be calculated on the basis of these numbers. The attrition analyses, including representativeness of the subpopulation with data available on maternal hypertension and proteinuria in relation to the entire Helsinki Birth Cohort study cohort and subsets of each individual study participants, are described in the individual articles. The descriptive statistics according to the individual studies are presented in Table 6. The descriptive statistics according to maternal hypertension status during pregnancy for all participants with maternal antenatal data available are presented in Table 7.

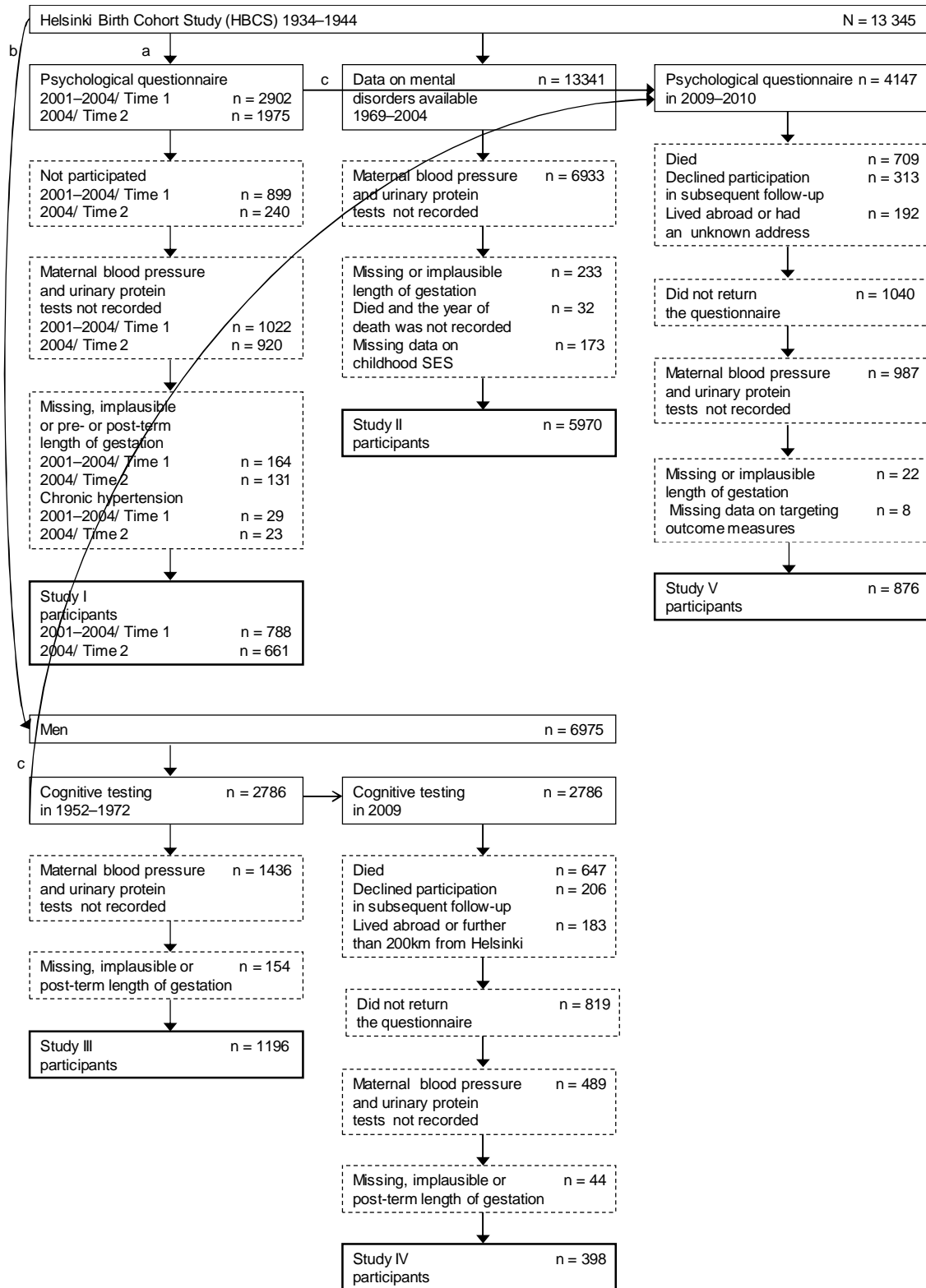


Figure 3. Selection of the participants in the Helsinki Birth Cohort Study and the final participant numbers included in the original studies of this thesis

Footnotes are on page 67.

Footnotes for Figure 3.

a Described in text

b Between 1952 and 1972 only men served in the compulsory military service

c In 2009–2010, a psychological questionnaire administered to those participated in a detailed clinical examination (n = 2003) in 2001–2004 and to those participated in cognitive testing in 1952–1972

Table 6. Characteristics of the participants according to the individual studies of this thesis

	Study I		Study II	Study III	Study IV	Study V
n	Time 1: 788	Time 2: 661	5970	1196	398	876
PE/HT	36 (4.6)	27 (4.1)	274 (4.6)	449 (37.5)	146 (36.7)	31 (3.5)
	PE/ 239 (30.3)	PE/ 194 (29.3)	PE/ 1733 (29.0)	Any HT	Any HT	PE/ 292 (33.3)
	HT	HT	HT			HT
Age at testing (y), mean (SD)	62.2 (3.1)	64.1 (3.1)	24-70	20.1 (1.4)	68.5 (2.9)	69.3 (3.1)
Primiparous, n (%)	390 (49.4)	327 (49.5)	3031 (50.8)	602 (50.3)	197 (49.5)	431 (49.2)
Men, n (%)	371 (47.1)	290 (43.9)	3131 (52.4)	1196 (100)	398 (100)	499 (57.0)
Preterm birth (<37 weeks), n (%)	-	-	347 (5.8)	74 (6.2)	27 (6.8)	54 (6.2)
Birth weight <2500 g, n (%)	19 (2.4)	16 (2.4)	200 (3.4)	38 (3.2)	14 (3.5)	25 (2.9)
Manual working father, n (%)	546 (70.2) ^a	454 (69.5) ^b	3826 (64.1)	794 (66.4)	247 (62.1)	593 (67.7) ^c

^aBased on the latest available data on father's occupation, n = 500 (63.5 %) for the highest achieved occupation

^bBased on the latest available data on father's occupation, n = 415 (68.8 %) for the highest achieved occupation

^cBased on the latest available data on father's occupation, n = 542 (61.9 %) for the highest achieved occupation

Table 7. Characteristics of the participants according to mothers' hypertension status during pregnancy

	Normotension	Hypertension without proteinuria	Pre-eclampsia
n ^a	4271 (66.6%)	1855 (28.9%)	284 (4.4%)
Characteristic	Mean (SD)/ n (%)	Mean (SD)/ n (%)	Mean (SD)/ n (%)
Maternal			
Mother's age at delivery (years)	27.8 (5.2)	28.9 (5.7)***	28.5 (5.6)*
Mother's Body Mass Index at delivery (kg/m ²)	26.0 (2.8)	26.8 (3.2)***	26.9 (3.1)***
Parity			
<i>Primipara</i>	2076 (48.6)	991 (53.5)***	198 (70.0)***
<i>Multipara</i>	2195 (51.4)	863 (46.5)	85 (30.0)
Offspring			
At birth or in childhood			
Sex			
<i>Men</i>	2247 (52.6)	959 (51.7)	151 (53.2)
<i>Women</i>	2024 (47.4)	896 (48.3)	133 (46.8)
Birth year			
1934-38	1084 (25.4)	444 (23.9)	97 (34.2)**
1939-44	3187 (74.6)	1411 (76.1)	187 (65.8)
Length of gestation (days)	279.2 (12.8)	279.2 (12.7)	275.1 (16.0)***
Preterm birth (<37 weeks)	238 (5.8)	97 (5.4)	30 (10.7)**
Birth weight (g)	3435.2 (468.4)	3395.8 (496.3)**	3030.0 (588.2)***
Birth weight <2500 g	102 (2.4)	66 (3.6)*	50 (17.6)***
Head circumference (cm)	35.0 (1.5)	35.1 (1.5)**	34.4 (1.7)***
Father's highest occupation in subject's childhood			
<i>Manual worker</i>	2672 (64.4)	1193 (66.1)	163 (58.2)

<i>Junior clerical</i>	990 (23.8)	410 (22.7)	72 (25.7)
<i>Senior Clerical</i>	489 (11.8)	203 (11.2)	45 (16.1)
In adulthood			
Own maximum level of education in adulthood			
<i>Basic or less</i>	1746 (44.3)	803 (46.5)	107 (42.5)
<i>Upper secondary</i>	1007 (25.6)	434 (25.1)	59 (23.4)
<i>Lower tertiary (polytechnic, vocational, bachelors)</i>	843 (21.4)	352 (20.4)	56 (22.2)
<i>Upper tertiary (masters or higher)</i>	344 (8.7)	137 (7.9)	30 (11.9)
Blood pressure medication	795 (18.6)	412 (22.2)**	68 (23.9)*
Hospitalization for coronary heart disease	327 (7.7)	151 (8.1)	28 (9.9)
Hospitalization for stroke	219 (5.1)	129 (7.0)**	20 (7.0)

*p < 0.05; **p < 0.01; ***p < 0.001 against the normotension group

^aMaximum number of participants reported. Across the characteristic variables, the number of participants varies slightly because of missing information.

3.2 Hypertensive disorders during pregnancy - Antenatal records (All studies)

For identifying pregnancy hypertensive disorders we used mothers' blood pressure and urinary protein measurements recorded at antenatal clinics or at birth hospital. For the mothers with antenatal data available, there were on average 2.0 blood pressure and 2.5 urinary protein measurements recorded in each pregnancy. Based on this information we defined four groups of mothers: 1) mothers with hypertension, i.e. the highest systolic blood pressure ≥ 140 mmHg or the highest diastolic blood pressure ≥ 90 mmHg with proteinuria + reading on dipstick in a random urine sample; 2) mothers with

gestational hypertension, with hypertension as in 1) after 20 weeks of pregnancy but no proteinuria; 3) mothers with any systolic blood pressure ≥ 140 mmHg or any diastolic blood pressure ≥ 90 mmHg before 20 weeks of pregnancy, considered to have chronic hypertension; 4) normotensive mothers with neither a systolic pressure attaining 140 mmHg nor a diastolic pressure 90 mmHg during pregnancy. For the purpose of the Studies III and IV, the three groups of mothers with any hypertensive disorder during pregnancy were combined; for the purpose of the Study II and V the groups of mothers with either gestational hypertension or chronic hypertension were combined.

These definitions are consistent with the current clinical criteria (American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000) with two exceptions: first, we considered one high blood pressure measurement to be sufficient for diagnosis because our data did not allow us to require two separate measurements, as the current clinical criteria do; second, our data included only a qualitative measurement of protein; proteinuria + approximates to 1 mg/mL of albumin (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; Pelkonen, 1940)

3.3 Depressive symptoms -questionnaire (Study I)

The Beck Depression Inventory (BDI) was used to evaluate the severity of depressive symptoms (Beck, Steer, & Carbin, 1988). BDI consists of 21 items assessing symptoms of depression during the previous 2 weeks. Each item contains four statements reflecting varying degree of symptom severity. Respondents are instructed to circle the number that corresponds with the statement that best describes them, ranging from zero to three, indicating increasing severity. Ratings are summed to calculate a total BDI score which can range from 0 to 63. Although BDI is designed to screen but not diagnose depression, there exist commonly used and well indicative cut-off points: none or minimal depression is < 10 ; mild to moderate depression is 10–18; moderate to severe depression is 19–29; and severe depression is 30–63 points (Beck et al., 1988). In this thesis, BDI score ≥ 10 for mild depressive symptoms were used as the cut-off. The internal reliability coefficients (Cronbach's alpha) of the BDI scores ranged from 0.84 to 0.87.

3.4 Diagnoses of mental disorders - HDR and CDR (Study II)

Diagnoses on mental disorders severe enough to warrant or contribute to hospital treatment were identified from HDR, and severe enough to be the underlying, intermediate, or contributing cause of death from CDR. The diagnoses were entered using International Statistical Classification of Diseases (ICD) coding system. Table 8 presents the diagnostic codes. Cases with serious mental disorders were defined as having a primary or subsidiary diagnosis for mental disorders in HDR or an underlying, intermediate and contributing mental disorder as cause of death in CDR. The psychiatric diagnostic classification used in Finland was ICD-8 until 1986; from 1987 to 1995, the classification was ICD-9 based on DSM-III-R criteria, and from 1996, it was ICD-10. For this study, we converted ICD-8 and ICD-9 diagnoses to current ICD-10 codes.

The principal outcome was first-ever diagnosis of a serious mental disorder, defined as a HDR or CDR diagnosis convertible to an ICD-10 code for a mental or behavioural disorder (ICD-10 codes F10–F69; for ICD-8 and ICD-9-codes, see Table 8). Our definition of mental disorders excluded organic disorders (ICD-10: F0) and learning disabilities (ICD-10: F7). Due to the age range of participants, disorders of development and disorders typically occurring in childhood and adolescence (ICD-10: F8–F9) were also not recorded. Sub-analyses were per protocol carried out for the following diagnostic groups: mental and behavioural disorders due to psychoactive substance use (ICD-codes F10–19), schizophrenia and other non-affective psychotic disorders (ICD-codes F20–F29), mood disorders (ICD-codes F30–F39), anxiety disorders (ICD-codes F40–F48), and personality disorders (F60–F61). However, in the case of acute intoxication due to substance abuse (F1x.0 in ICD-10 and 305 in ICD-9), only the primary diagnosis was used from both registers because alcohol intoxication is a frequent subsidiary diagnosis in Finnish medical practice and does not necessarily indicate a substance use disorder.

HDR (Keskimäki & Aro, 1991) and CDR (R. A. Lahti & Penttilä, 2001) have been found to be valid and reliable tools for epidemiological research. HDR has been validated with regard to the diagnoses of bipolar disorder (Kieseppä, Partonen, Kaprio, & Lönnqvist, 2000), any psychotic disorder (Perälä et al., 2007), and schizophrenia (Mäkikyrö et al., 1998; Pihlajamaa et al., 2008). All these diagnoses show high levels of

specificity in the register against medical records (Kieseppä et al., 2000; Mäkikyrö et al., 1998; Perälä et al., 2007). The validity of the alcohol psychosis- and alcoholism - diagnoses in HDR during the usage of ICD-8 has also found support in one earlier study (Poikolainen, 1983). We are not aware of studies where the validity of the other substance use disorder, or depressive, anxiety, and personality disorder diagnoses in HDR would have been formally examined against medical records.

Table 8. Mental disorders according to International Statistical Classification of Diseases (ICD) codes used in the Finnish Hospital Discharge Register and the Finnish Causes of Death Register

Mental disorders:	International Classification of Diseases 10th (ICD-10; in use 1996–present), 9th (ICD-9; in use between 1987–1995), and 8th (ICD-8; in use between 1969–1986) diagnostic codes:
Any^a	ICD-10: F1–F6 ICD-9: 291–292, 295–298, 300–304, 305, 3071A, 3074, 3075A–3075B, 3078A, 3079X, 3090A, 3092C–3099X, 312 ICD-8: 291, 295, 296-305, 306.4–306.5, 306.8, 306.98, 307
Substance Use (ICD-10: Mental and behavioural disorders due to psychoactive substance use)	ICD-10: F10–F19 ICD-9: 291–292, 303–305 ICD-8: 291, 303–304
Psychotic (ICD-10: Schizophrenia, schizotypal, and delusional disorders)	ICD-10: F20–F29 ICD-9: 295, 297–298 ICD-8: 295, 297, 298.10–299.99
Mood (ICD-10: Mood (affective))	ICD-10: F30–F39 ICD-9: 296, 3004A, 3011D ICD-8: 296, 298.00, 300.40, 300.41, 301.10
Anxiety (ICD-10: Neurotic, stress-related and somatoform disorders)	ICD-10: F40–F48 ICD-9: 3000A–3003A, 3006A–3009X, 3078A, 309 ICD-8: 300.00–300.30, 300.50–300.99, 305, 306.80, 307.99
Personality (ICD-10: Specific and mixed personality disorders)	ICD-10: F60–F61 ICD-9: 3010A, 3012A–3015A, 3016A–3018X ICD-8: 301.00, 301.20–301.99

^aA variety of behavioural syndromes (corresponding to codes F50–F59 or F62–F69 in ICD-10) were included in the Any mental disorder –category, but due to heterogeneity and small sample size, we were not able to treat it as a separate category.

3.5 Cognitive ability test (Study III and IV)

The cognitive ability test scores were obtained from the Finnish Defence Forces Basic Ability Test, which was developed at the Finnish Defence Forces Education Development Centre (described in Tiihonen et al., 2005). The compulsory test is given to all new recruits during the first two weeks of their military service and the results are used when a proportion of the conscripts are selected for leadership training later during their military service. The test battery is designed to measure general ability and logical thinking, and is composed of verbal, arithmetic, and visuospatial reasoning subtests. Each subtest is timed and consists of 40 multiple-choice questions in a series proceeding from the easiest to the most complicated. Correct answers are summed to yield a test score. The verbal and arithmetic subtests comprise 4 types of questions. In the verbal reasoning test the subject has to choose synonyms or antonyms of a given word, select a word belonging to the same category as a given word pair, identify which word of a word list does not belong to the group, and discern similar relations between 2 word pairs. In the arithmetic reasoning test, the subject has to complete a series of numbers that have been arranged to follow a certain rule, to solve verbally expressed short problems, to complete simple arithmetic operations, and to choose similar relations between 2 pairs of numbers. The visuospatial reasoning subtest comprises a set of matrices containing a pattern problem with 1 part removed: it is analogous to Raven's Progressive Matrices (Raven, Raven, & Court, 2000). The subject is asked to decide which of the given single figures completes the matrix, and the test requires the subject to conceptualize spatial relations ranging from the very obvious to the very abstract. The total cognitive ability score, analysed as the mean of the three individual subtests, was also used in this thesis. Tiihonen et al. (2005) have previously reported the test-retest reliabilities of the subtests varying from 0.76 to 0.88.

3.6 Cognitive impairment -questionnaires (Study V)

Self-reported cognitive failures and executive function were measured with the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) and with the Dysexecutive Questionnaire (DEX) (Burgess, Alderman, Evans, Emslie, & Wilson, 1998). CFQ is composed of 25 questions that inquire about basic cognitive problems that people may have had in everyday activities in the past 6 months.

The CFQ items are self-rated on a scale that ranges from 0 (never) to 4 (very often). Sample items include “Do you fail to notice signposts on the road?” and “Do you find you forget whether you've turned off a light or a fire or locked the door?” The scale yields a total score and three subscale scores that measure forgetfulness, distractibility, and false triggering (Rast, Zimprich, Van Boxtel, & Jolles, 2009). Higher scores reflect more frequent complaints. The reliabilities (Cronbach's alpha) of the CFQ total score and subscale scores were 0.92, 0.84, 0.79, and 0.79 for total score of forgetfulness, distractibility, and false triggering, respectively.

DEX, which was derived from the Behavioral Assessment of Dysexecutive Syndrome (Wilson, Alderman, Burgess, Emslie, & Evans, 1996), is a 20-item scale that was designed to screen for changes in observable everyday manifestations of executive function, such as abstract thinking, impulsivity, confabulation, and planning problems. The DEX items are self-rated on a scale that ranges from 0 (never) to 4 (very often). Sample items include “I have problems in understanding what other people mean unless they keep things simple and straightforward,” “I have difficulties in planning for the future,” and “I talk in one way but act in another.” The scale yields a total score and three subscale scores that measure behavioural-emotional self-regulation, metacognition, and executive cognition (Simblett & Bateman, 2011). Higher scores reflect more frequent complaints. The reliabilities (Cronbach's alpha) of the DEX total score and subscale scores were 0.90, 0.78, 0.72, and 0.73 for total score, behavioural-emotional self-regulation, metacognition, and executive cognition, respectively.

3.7 Covariates and moderating variables

Offspring's date of birth (year) and weight (g) and head circumference (cm) at birth, mother's age, weight (kg) and height (cm) at delivery, parity and date of last menstruation were obtained from hospital birth records. Length of gestation was based upon the date of mother's last menstrual period. Mother's BMI was calculated as weight divided by height² (kg/m²). Childhood socio-economic status, based on father's occupation (manual workers, junior clericals, senior clericals) was extracted from birth, child welfare clinic, and school health care records. While in the studies I and V, latest available data on father's occupation was used as a variable (most data from school records), in the studies II, III and IV, the variable was based on the father's highest

achieved occupation. The analyses of studies I and V were now re-run with the father's highest occupation as a covariate.

Adult socio-economic status was indicated by the level of educational attainment determined in conjunction with the clinical examination in 2001-2004 (elementary school, vocational school, senior high school, college/university degree; Study I) or by the highest level of education achieved (basic or less/ upper secondary/ lower tertiary/ upper tertiary) from census data at 5-year intervals since 1970, obtained from Statistics Finland (Study IV and V). Adult height (cm) was attained at military service (Study III) and at a retest of cognitive ability (Study IV). Diagnoses of stroke (international classification of disease codes 430–434 and 436–437 from ICD-8 and 9, 438 from ICD-9, and I60–I69 from ICD-10) and coronary heart disease (codes 410–414 from ICD-8 and ICD-9 and I21–I25 from ICD-10) since 1969 were obtained from the Finnish Hospital Discharge Register (until 2008) (Study IV). Blood pressure medication was obtained from the national register of people receiving reimbursement from the state for the costs of their medication (Study IV).

3.8 Statistical analyses

We used the Statistical Package for the Social Sciences (SPSS) version 17, Predictive Analytics SoftWare (PASW) versions 17 to 18, and IBM SPSS Statistics (IBM SPSS) 19–22 to analyse the data.

We used linear and logistic regression analyses to test the differences between the offspring of normotensive and hypertensive mothers in the severity of depressive symptoms and cognitive functioning. We used Cox proportional hazard models to examine the differences in the odds of mental disorders. The two-sided p-values were obtained from the regression and hazard models and were based on comparison of the coefficient and its standard error.

The associations were adjusted for the neonatal, maternal, and adult factors known to be associated with an increased risk of hypertensive pregnancy disorders and/or offspring psychological outcomes as follows: Maternal age and BMI at delivery, parity, sex (Studies I, II, and V), year of birth (Studies II and III) and/or age at testing (Studies I, III, IV and V), length of gestation, birth weight for gestational age, and father's

occupational status were treated as covariates in all the analyses; Sex and year of birth were adjusted for in regression analyses and stratified for in hazard models.

In addition, analyses of all outcomes measured in late adulthood were adjusted for own attained level of education (Studies I, IV and V). Analyses related to cognitive ability were adjusted for head circumference at birth and adult height (Studies III and IV) and also diagnoses of stroke and coronary heart disease and blood pressure medication (Study IV). The covariates were included into the regression equation simultaneous to hypertensive disorders.

To test whether sex, prematurity, parity or childhood socio-economic status moderate any potential associations 'sex, prematurity, parity, father's occupation status (grouped into manual workers and junior/senior clericals) x hypertensive disorder during pregnancy' -interactions were included in the regression equation or hazard models followed by their main effects.

Due to skewness of distributions of some outcome variables, data transformations were made. The BDI scores were log transformed to attain normality, with regression coefficients reverse transformed and expressed as the percentage change in the dependent variable for each unit change in the independent variable. The DEX and CFQ scores were transformed into normalized z-scores with a mean of 0 and SD of 1. The cognitive ability test scores were converted into z-scores with a mean of 0 and SD of 1 in Study III and with a mean of 100 and SD of 15 in Study IV. A z -score represents the difference from the mean value for the whole cohort and is expressed in standard deviations (SD). Change in cognitive ability was modelled in analyses by cognitive ability at age 68 years used as the outcome and cognitive ability at age 20 years as the predictor (Twisk, 2003).

4 RESULTS

4.1 Maternal hypertensive disorders during pregnancy and the mental health of the offspring (Studies I and II)

4.1.1 Depressive symptoms (Study I)

When we compared participants born after primiparous pregnancies complicated by pre-eclampsia to the participants born after primiparous normotensive pregnancies with adjustments for mother's age and BMI at delivery, father's occupational status in childhood, participant's sex, age at testing and level of education attained, the depressive symptom scores were more than 30% higher at time 1 and time 2 among offspring born after pre-eclamptic pregnancies (Table 9, Model A). Adding birth weight adjusted for gestation to the model had little effect on the results (Table 9, Model B). When length of gestation was added to the model the results were slightly attenuated (time 1, $p = 0.06$; time 2, $p = 0.04$; average of time 1 and time 2, $p = 0.08$).

Table 9. Comparison of depression symptom scores in the offspring born at term to mothers with pre-eclamptic versus normotensive (referent) pregnancies

Data presented as percent difference (95 % CI)

	n	Model A	Model B
Primiparous			
BDI at time 1	28 vs. 237	36.9 (2.0 to 71.8)*	36.5 (1.1 to 71.9)*
BDI at time 2	22 vs. 203	52.2 (7.8 to 96.6)*	49.1 (3.8 to 94.4)*
Average BDI	21 vs. 201	39.7 (1.6 to 77.7)*	38.4 (-0.4 to 77.1)
Multiparous			
BDI at time 1	8 vs. 276	-15.8 (-71.5 to 40.0)	-13.4 (-69.3 to 42.5)
BDI at time 2	5 vs. 237	-58.9 (-142.2 to 24.4)	-54.8 (-138.7 to 29.0)
Average BDI	5 vs. 236	-41.7 (-109.2 to 25.8)	-38.8 (-106.9 to 29.2)

* $p < 0.05$ against the normotension group

Both models are adjusted for gender, father's occupational status in subject's childhood, mother's age at delivery, mother's BMI and age at clinical questionnaires and own attained level of education, and Model B additionally for birth weight for gestational age.

When we applied the mild cut-off criterion for the BDI scores (≥ 10 versus < 10), as compared with those born after primiparous normotensive pregnancies, the participants

born after primiparous pregnancies complicated by pre-eclampsia had an odds ratio of 3.7 for having depressive symptom scores above the cut-off (Table 10, Model A). Further adjustment taking birth weight for gestation into account had little effect on the results (Table 10, Model B). When length of gestation was added to the model the results were slightly attenuated ($p = 0.05$). Pre-eclampsia was not associated with depressive symptom scores in multiparous pregnancies (Tables 9 and 10).

Table 10. Comparison of the risk for having depressive symptoms scores above at least mild severity in the offspring born at term to mothers with pre-eclamptic versus normotensive (referent) pregnancies
Data presented as odds ratio (95% CI)

	Model A	Model B
Primiparous		
Average BDI < vs. ≥ 10	3.7 (1.2 to 11.3)*	3.8 (1.2 to 11.9)*
Multiparous		
Average BDI < vs. ≥ 10	0.9 (0.1 to 8.6)	0.8 (0.1 to 8.3)

* $p < 0.05$ against the normotension group

BDI scores ≥ 10 indicate at least mild severity and are compared to scores < 10 indicative of no to low severity.

Both models are adjusted for gender, father's occupational status, mother's age at delivery, mother's BMI and age at clinical questionnaires and own attained level of education, and Model B additionally for birth weight for gestational age.

Gestational hypertension did not have any significant effects on depressive symptoms ($p_s > 0.34$; data not shown). Analyses testing whether sex, birth weight, or father's occupational status in subject's childhood modulated any associations between pre-eclampsia/ gestational hypertension and depressive symptoms revealed no significant results ($p_s > 0.19$). The adjustment for father's highest occupation (vs. latest available data on father's occupation) did not change any of the reported results.

4.1.2 Severe mental disorders (Study II)

Table 11 shows the associations between maternal hypertensive disorders during pregnancy and the risk for severe mental disorders in the offspring after stratifications for sex and year of birth and adjustments for gestational age, weight at birth, father's occupational status in childhood, parity, mother's age and BMI at delivery. Because the unadjusted and adjusted associations were virtually identical, the adjusted associations

are only presented. When compared to the offspring born after normotensive pregnancies, the offspring born after pregnancies complicated by hypertension without proteinuria were at an increased risk of any mental disorder and mood disorder. They were also at an increased risk of anxiety disorder, which approached the level of significance. Maternal hypertension without proteinuria was not associated with other mental disorders. Maternal pre-eclampsia was not associated with any or the more specific mental disorders.

Table 11. Risk of severe mental disorder among the offspring born after hypertensive without proteinuria (n = 1733)/ pre-eclamptic (n = 274) versus normotensive (n = 3963, referent) pregnancies

Data presented as hazard ratios (95% CI)

Disorders	n	Normotension % ^a	Hypertension % ^a	Pre-eclampsia % ^a	Hypertension vs. normotension ^b	Pre-eclampsia vs. normotension ^b
No disorders vs.	5264					
Any	706 ^c	11.4	13.2	8.8	1.19 (1.01, 1.41)*	0.75 (0.48, 1.17)
Substance use	379	6.6	7.4	4.7	1.11 (0.88, 1.40)	0.61 (0.32, 1.17)
Psychotic	142	2.4	3.2	2.5	1.38 (0.96, 1.99)	1.15 (0.49, 2.69)
Mood	266	4.4	5.9	4.1	1.44 (1.11, 1.88)**	0.96 (0.48, 1.91)
Anxiety	166	2.8	3.8	2.2	1.39 (0.99, 1.93)	0.86 (0.35, 2.16)
Personality	94	1.7	1.8	1.7	1.09 (0.68, 1.73)	1.12 (0.39, 3.17)

*p < 0.05; **p < 0.01 against the normotension group

^a% refers to the cumulative incidence (calculated by the number of new cases during a period divided by the number of subjects at risk in the population at the beginning of the study) of severe mental disorders according to mothers' hypertensive disorder during pregnancy derived from models adjusting for sex, year of birth and father's occupational status in childhood.

^bCox regression models are stratified for sex and year of birth and adjusted for gestational age, weight at birth, father's occupational status in childhood, parity, mother's age and BMI at delivery.

^cParticipants whose mental disorder diagnose changed over time or with co-morbid disorders were included in each specific mental disorder category and in any mental disorder category. Thus, participants with specific mental disorders do not sum up to participants having any mental disorder.

Modifying effects of sex, preterm/term length of gestation, parity and childhood socio-economic status

Men born after pregnancies complicated by maternal pre-eclampsia ($n = 145$), compared to men born after normotensive pregnancies ($n = 2089$) had a lower, a 0.45-fold (95% CI: 0.23 to 0.88, $p = 0.01$) risk of any mental disorder and also had a lower, 0.44-fold (95% CI: 0.19 to 0.99, $p = 0.04$) risk of substance use disorder. In women, maternal pre-eclampsia was not associated with mental disorders ($p > 0.24$). The interaction ‘pre-eclampsia vs. normotension x sex’ was significant for any mental disorder ($p = 0.04$) (Figure 4, Panel A) and approached significance in the analyses of substance use disorder ($p = 0.06$) (Figure 4, Panel B). Other interactions ‘hypertension without proteinuria/ pre-eclampsia vs. normotension x sex/ preterm vs. term length of gestation/ parity/ father’s occupational status in subject’s childhood/’ were not significant in tests of mental disorders ($ps > 0.07$).

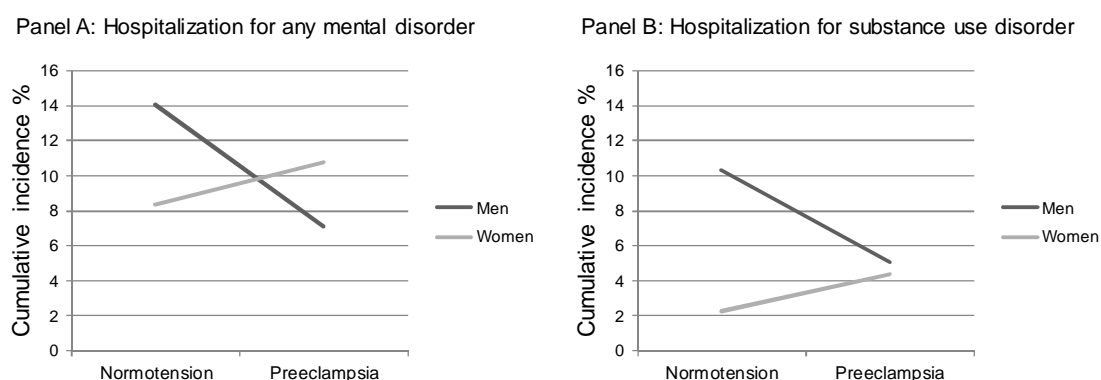


Figure 4. Panel A: The interaction ‘pre-eclampsia vs. normotension x sex’ for any mental disorder ($p = 0.04$)

Panel B: The interaction ‘pre-eclampsia vs. normotension x sex’ for substance use disorder ($p = 0.06$)

Note. Analyses were stratified for sex and year of birth and adjusted for gestational age, weight at birth, father’s occupational status in childhood, parity, mother’s age and BMI at delivery.

% refers to the cumulative incidence of any mental disorder and substance use disorder according to mothers’ hypertensive disorder (pre-eclampsia vs. normotension) during pregnancy derived from models adjusting for year of birth and father’s occupational status in childhood.

(Tuovinen et al., 2012. Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. *The Journal of Psychiatric Research*, 46, 303-310, reprinted with permission.)

4.2 Maternal hypertensive disorders during pregnancy and the cognitive functioning of the offspring (Studies III, IV and V)

4.2.1 Cognitive ability in young adulthood (Study III)

In comparison to the offspring born after normotensive pregnancies, offspring born after pregnancies complicated by any maternal hypertensive disorder scored 0.13 (95% CI: -0.25 to -0.01, $p = 0.03$) SD units lower on the verbal reasoning test and had 0.12 (95% CI: -0.24 to -0.00, $p = 0.04$) SD units lower total cognitive test score at a mean age of 20.1 years. The MDs in visuospatial and arithmetic reasoning tests were -0.09 (95% CI: -0.21 to 0.04, $p = 0.17$) and -0.10 (95% CI: -0.22 to 0.03, $p = 0.13$), respectively, not reaching the formal statistical significance. The associations were adjusted for gestational age, weight, and head circumference at birth, year of birth, childhood socio-economic status, and parity, mother's age, and BMI at delivery, and age, and height at military service.

Modifying effects of preterm/term length of gestation, LBW/NBW, parity and childhood socio-economic status

The following interactions were significant (Figure 5, Panel A and B). In comparison to the offspring born after primiparous and normotensive pregnancies ($n = 366$), offspring born after primiparous pregnancies complicated by any maternal hypertensive disorder ($n = 236$), scored 0.24 (95% CI: -0.41 to -0.08, $p = 0.004$) SD units lower on verbal reasoning test ($p = 0.89$ for multiparous offspring) ($p = 0.04$ for any hypertensive disorder vs. normotension x parity -interaction). In comparison to the offspring of junior/senior clerical fathers born after normotensive pregnancies ($n = 260$), offspring of junior/senior clerical fathers born after pregnancies complicated by any maternal hypertensive disorder ($n = 142$) scored 0.32 (95% CI: -0.53 to -0.10, $p = 0.004$) SD units lower on verbal reasoning test ($p = 0.58$ for offspring of manual working fathers; offspring of manual working fathers scored the lowest on cognitive tests regardless of hypertensive disorders) ($p = 0.04$ for any hypertensive disorder vs. normotension x father's occupational status subject's childhood -interaction). Prematurity, low birth weight, parity, father's occupational status in subject's childhood did not modulate any other associations ($ps > 0.09$ for interactions).

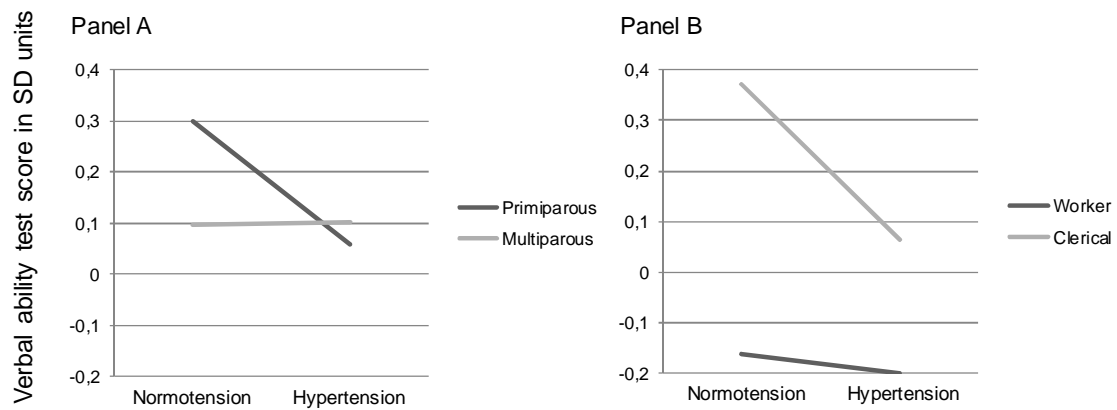


Figure 5. Panel A: The interaction ‘any hypertensive disorder vs. normotension x parity’ for verbal reasoning ($p = 0.04$)

Panel B: The interaction ‘any hypertensive disorder vs. normotension x childhood socio-economic status’ for verbal reasoning ($p = 0.04$)

Note. Derived from models including the corresponding interaction term and adjusted for gestational age, weight, and head circumference at birth, year of birth, childhood socio-economic status (Panel A), and parity (Panel B), mother’s age and BMI at delivery, and age and height at military service.

(Tuovinen et al., 2012. Hypertensive disorders in pregnancy and intellectual abilities in the offspring in young adulthood: the Helsinki Birth Cohort Study. *Annals of Medicine*, 44, 394-403, reproduced with permission.)

4.2.2 Cognitive change up to late adulthood (Study IV)

Table 12 shows that men born after pregnancies complicated by any maternal hypertensive disorder, compared with men born after normotensive pregnancies, scored lower on arithmetic and total cognitive ability at the mean age of 68.5 years (p s in unadjusted and adjusted models < 0.05). They also displayed a greater decline in arithmetic and total cognitive ability after age 20.1 years (Table 12). Prematurity, parity, or father’s occupational status in subject’s childhood did not modulate the associations (p s > 0.10 for interactions).

Table 12. Cognitive ability at the ages of 20.1 and 68.5 years in the offspring who were born after pregnancies complicated by hypertensive disorders (n = 146) and normotensive pregnancies (n = 252, referent)

	Normotension		Hypertensive disorders		Hypertensive disorders vs. normotension	
	M ^a at 20.1 years (95% CI)	M ^a at 68.5 years (95% CI)	M ^a at 20.1 years (95% CI)	M ^a at 68.5 years (95% CI)	MD ^b at 68.5 years (95 % CI)	MD ^{b,c} of change (95 % CI)
Unadjusted model						
Verbal	28.45 (27.47 to 29.44)	31.36 (30.56 to 32.16)	27.64 (26.35 to 28.94)	30.26 (29.21 to 31.31)	-2.67 (-5.67 to 0.33)	-1.54 (-3.85 to 0.77)
Visuospatial	25.64 (24.94 to 26.34)	23.43 (22.81 to 24.05)	25.70 (24.78 to 26.62)	22.52 (21.70 to 23.34)	-2.62 (-5.60 to 0.35)	-2.70 (-5.17 to -0.23)*
Arithmetic	28.61 (27.50 to 29.71)	27.76 (26.59 to 28.94)	27.00 (25.55 to 28.45)	25.31 (23.76 to 26.86)	-4.27 (-7.28 to -1.25)**	-2.30 (-4.43 to -0.18)*
Total	27.57 (26.76 to 28.38)	27.52 (26.79 to 28.25)	26.78 (25.72 to 27.85)	26.03 (25.07 to 26.99)	-3.71 (-6.67 to -0.74)*	-2.23 (-4.24 to -0.22)*
Adjusted model^{d,e}						
Verbal	29.48 (28.15 to 30.81)	32.03 (30.96 to 33.09)	28.87 (27.24 to 30.50)	30.68 (29.38 to 31.98)	-3.35 (-6.54 to -0.17)* ^e	-2.32 (-4.79 to 0.16)
Visuospatial	26.36 (25.41 to 27.30)	23.51 (22.63 to 24.39)	26.47 (25.31 to 27.63)	22.53 (21.45 to 23.60)	-2.83 (-6.15 to 0.49)	-2.64 (-5.37 to 0.10)
Arithmetic	29.30 (27.85 to 30.75)	28.20 (26.60 to 29.80)	27.97 (26.19 to 29.74)	25.14 (23.18 to 27.10)	-4.91 (-8.17 to -1.65)**	-3.14 (-5.51 to -0.77)**
Total	28.38 (27.31 to 29.45)	27.91 (26.92 to 28.91)	27.77 (26.46 to 29.08)	26.11 (24.90 to 27.33)	-4.36 (-7.55 to -1.17)**	-2.88 (-5.06 to -0.70)*

Footnotes are on page 86.

Footnotes for Table 12.

* $p < 0.05$; ** $p < 0.01$ against the normotension group

^aMean level of cognitive ability in raw test scores (0-40 points).

^bMean difference in standardized (mean = 100, SD = 15) cognitive ability test scores.

^cChange is modeled in a linear regression analysis where cognitive ability at age 68 years is predicted by cognitive ability at age 20 years.

^dThe adjusted model refers to adjustments made for length of gestation, weight and head circumference at birth, father's occupational status in childhood, parity, mother's age and BMI at delivery, age at testing cognitive ability at 20 years, time interval between tests of cognitive ability from 20 to 68 years, height at testing of cognitive ability in late adulthood and blood pressure medication.

^eFurther model adjusted as in footnote d, above, plus highest own achieved level of education and diagnoses of stroke and coronary heart disease. The marked associations were rendered nonsignificant. Unmarked associations remained as in the adjusted model in footnote d.

4.2.3 Self-reported cognitive impairment (Study V)

In comparison to the participants who were born after normotensive pregnancies, participants who were born after pregnancies that were complicated by pre-eclampsia reported more frequent complaints of cognitive failures, distractibility, and false triggering. These associations remained significant in the unadjusted and adjusted models (Table 13). In comparison to the participants who were born after normotensive pregnancies, participants who were born after pregnancies that were complicated by pre-eclampsia reported also more frequent complaints of dysexecutive functioning and executive cognition. These associations were significant in the unadjusted model, but were rendered nonsignificant in the adjusted models (Table 13). Participants who were born after hypertensive pregnancies without proteinuria and normotensive pregnancies did not differ from each other in cognitive failures or dysexecutive functioning (Table 13).

Table 13. Comparison of the CFQ and DEX scores in the offspring born after pregnancies complicated by hypertension without proteinuria (n = 292) or pre-eclampsia (n = 31) versus normotensive pregnancies (n = 553, referent)

Data presented as mean difference in SD units (95% CI)

	Hypertension vs. normotension		Pre-eclampsia vs. normotension	
	Unadjusted model	Adjusted model ^a	Unadjusted model	Adjusted model ^a
CFQ				
Total score	0.09 (-0.05, 0.23)	0.12 (-0.04, 0.27)	0.48 (0.12, 0.84)*	0.45 (0.02, 0.87)*
Forgetfulness	0.08 (-0.06, 0.22)	0.13 (-0.02, 0.28)	0.32 (-0.04, 0.68)	0.18 (-0.25, 0.60)
Distractibility	0.07 (-0.07, 0.21)	0.09 (-0.06, 0.24)	0.46 (0.11, 0.82)*	0.51 (0.08, 0.93)*
False triggering	0.12 (-0.02, 0.26)	0.13 (-0.02, 0.29)	0.42 (0.06, 0.78)*	0.48 (0.06, 0.90)*
DEX				
Total score	0.09 (-0.05, 0.23)	0.07 (-0.08, 0.22)	0.36 (0.004, 0.71)*	0.31 (-0.11, 0.73)
Behavioural-emotional self-regulation	0.08 (-0.05, 0.21)	0.06 (-0.08, 0.20)	0.28 (-0.05, 0.61)	0.31 (-0.08, 0.70)
Metacognition	0.05 (-0.08, 0.18)	0.04 (-0.10, 0.19)	0.34 (-0.002, 0.67)	0.23 (-0.17, 0.63)
Executive cognition	0.07 (-0.06, 0.20)	0.06 (-0.08, 0.20)	0.35 (0.01, 0.68)*	0.37 (-0.02, 0.76)

*p < 0.05 against the normotension group

^aThe adjusted model refers to adjustments made for sex, length of gestation, weight and head circumference at birth, father's occupational status in childhood, parity, mother's age and BMI at delivery, and age at completing the questionnaires

Modifying effects of sex, preterm/term length of gestation, parity and childhood socio-economic status

Sex, prematurity, parity or father's occupational status in subject's childhood did not modulate the associations between pre-eclampsia and complaints of cognitive failures/dysexecutive functioning (p for interactions > 0.10). Analyses that tested modulation by sex revealed, however, that, in comparison with women who were born after normotensive pregnancies ($n = 238$), women who were born after pregnancies that were complicated by hypertension without proteinuria ($n = 125$) reported more frequent complaints of cognitive failures, forgetfulness, and false triggering (Figure 6). There were no differences between men born after normotensive ($n = 315$) and hypertensive pregnancies without proteinuria ($n = 167$) in complaints of cognitive failures (Figure 6). Sex did not modulate the associations between hypertensive pregnancy disorders without proteinuria and dysexecutive functioning, and there were no significant interactions with prematurity, parity or father's occupational status in subject's childhood (p s for interactions > 0.15). Further adjustment for highest attained level of education in adulthood had little effect on any of the reported results. The adjustment for father's highest occupation (vs. latest available data on father's occupation) did not change any of the reported results.

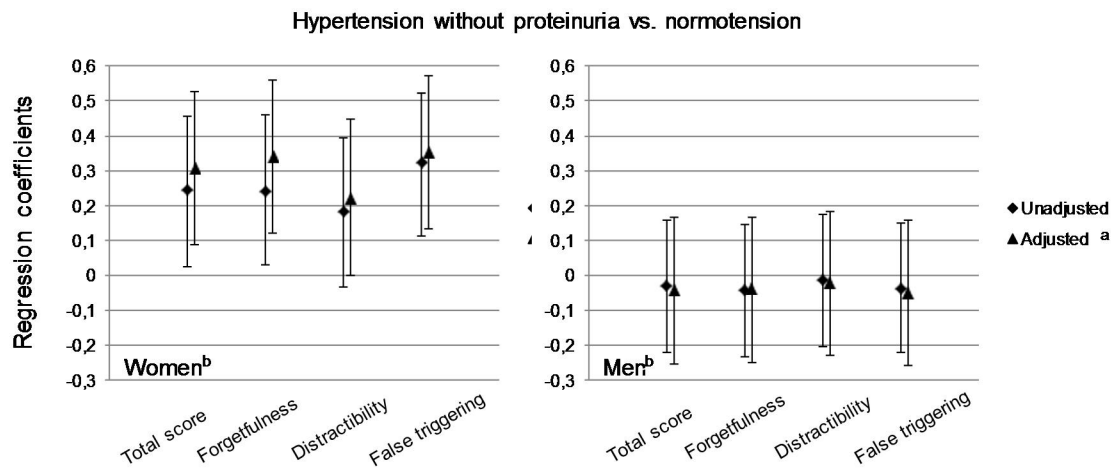


Figure 6. Comparison of the CFQ scores among men and women who were born after pregnancies that were complicated by hypertension without proteinuria versus normotensive pregnancies (referent; zero line)

The horizontal lines represent unstandardized regression coefficients (i.e., difference in standard deviations), and the vertical lines represent the upper and lower bounds of the 95% confidence intervals.

^aThe adjusted model refers to adjustments made for length of gestation, weight, and head circumference at birth, father’s occupational status in childhood, parity, mother’s age and body mass index at delivery, and age at completion of the questionnaires.

^bA significant interaction (sex and maternal hypertension without proteinuria) was found for total score ($p = 0.01$), forgetfulness ($p = 0.03$), and false triggering ($p = 0.01$).

(Tuovinen et al. 2013. Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. American Journal of Obstetrics and Gynecology, 208, 200.e1-9, reprinted with permission.)

5 DISCUSSION

The primary aim of this thesis was to test whether maternal hypertensive disorders during pregnancy were associated with the mental health and cognitive functioning in the offspring from early to late adulthood. The study capitalised on the large and well-characterised HBCS from 1934–44. The main results confirmed that maternal pre-eclampsia and/or hypertension without proteinuria during pregnancy have a negative effect on a wide spectrum of psychological outcomes in the offspring. A secondary aim was to test whether any potential associations differ according to sex (Studies I, II and V), length of gestation, parity and childhood socio-economic status. Overall, some evidence was found that primiparity, female sex and a high socio-economic status may increase the risk of adverse outcomes, while male sex seemed to decrease the risk of severe mental disorders.

5.1 Theoretical and mechanistic considerations

Hypothesising why intrauterine exposure to maternal hypertensive disorders should affect the development of the offspring is of interest. In general, the current findings proposed that vulnerability to poorer mental health and cognitive functioning was programmed by prenatal exposure to maternal hypertensive disorders during pregnancy. These findings can be conceptualised within the framework of DOHaD and the life cycle model of stress, respectively. According to these theories, early life adversities may permanently alter organ structure and functioning, and affect developmental outcomes later in life. In humans, maximal brain growth and most of the neuroendocrine maturation occurs in utero (Lupien et al., 2009; Dobbing & Sands, 1979). This may explain the importance of prenatal life in developmental programming.

Although the current findings may point to mechanisms by which prenatal adversity is associated with these problems later in life, the exact mechanisms linking maternal hypertensive pregnancy disorders with poorer cognitive functioning and mental health later in life are not yet determined. The pathophysiological changes associated with hypertensive disorders could reasonably have an adverse effect on offspring development. As reviewed above, maternal hypertensive pregnancy disorders may compromise the fetal developmental milieu by resulting in inadequate fetal nutrition and

hypoxic damage (J. P. Newnham et al., 2002), inducing systemic inflammation (Redman & Sargent, 2010) or leading to overexposure to maternal glucocorticoids (Aufdenblatten et al., 2009; Kajantie et al., 2003; McCalla et al., 1998; Schoof et al., 2001). All of these influences may potentially cause lifelong changes in the offspring at the epigenomic and transcriptomic levels, and in the organ structure and functioning of the body and physiological feedback systems.

Contrary to our expectation, the current findings showed that maternal pre-eclampsia was associated with a lower risk of severe mental disorders in male offspring. The possibility that this result was due to chance cannot be excluded. However, the brain continues to develop after birth. Given that prenatal programming may be moderated by the early postnatal environment (Buss et al., 2007; Vickers et al., 2005) and that epigenetic changes are reversible, it is also possible that postnatal factors have overridden the effects of an adverse prenatal environment. Indeed, not all effects need to be adverse—it is plausible that the seriousness of pre-eclampsia is associated with more effective and sensitive parenting (J. P. Newnham et al., 2004) and more extensive concentration on motherhood in life (Leeners et al., 2009), which explains the counterintuitive associations of pre-eclampsia (moderation by sex is discussed in section 5.6). It may be that such a parenting style serves as a buffer from any ill effects of pre-eclampsia-associated early environmental adversity. This assumption remains, however, untested in this thesis. Yet, it is of further importance to note that the prenatal environment may alter individual susceptibility not only to the negative effects of an adverse environment, but also to the beneficial effects of an enriching environment (Belsky & Pluess, 2009).

In addition to the theoretical alignment, previous findings agree with our results. The current findings here are discussed in more detail and compared to previous findings in the following two sections.

5.2 Maternal hypertensive disorders during pregnancy and the mental health of the offspring

Pre-eclampsia

Pre-eclampsia occurring in term primiparous pregnancies was associated with higher depressive symptom scores in the offspring several decades later. These offspring born to pre-eclamptic mothers had higher depressive symptom scores and a higher risk of having depressive symptom scores above the cut-off indicating mild severity compared to their counterparts born after normotensive pregnancies. Pre-eclampsia did not predict depressive symptoms among participants born at term after multiparous pregnancies. Testing associations separately in the offspring born after primiparous and multiparous pregnancies was deemed necessary since the preliminary findings showed no significant associations among the entire group of offspring and since pre-eclampsia may be qualitatively different in primiparous and multiparous pregnancies (Allen et al., 2004; Luo et al., 2007).

Offspring born preterm were excluded from the analyses. This differed from the analyses carried out for the other original publications included as a part of this thesis. However, the overall pattern of the results remained unchanged even after including the offspring born preterm into the analyses.

In support of our findings, a further study in HBCS showed that maternal pre-eclampsia carries an increased risk of problems in the adaptive functioning and mental well-being of the offspring seven decades later (Tuovinen et al., 2014). However, one previous study reported null associations between maternal pre-eclampsia and psychotic symptoms in the offspring in childhood (Zammit et al., 2009), while one study reported maternal pre-eclampsia reducing internalising behaviours, including withdrawal and anxiety or depressed behaviours and somatic complaints, in the offspring in childhood (Robinson et al., 2009). The current findings are, thus, not in line with these findings among children.

Contrary to our expectations, the current findings revealed that maternal pre-eclampsia was associated with a lower risk of any mental disorder and substance use disorder among male offspring. These findings are, thus, not in line with our findings

regarding the severity of depressive symptoms. However, it is of note that, in this latter study, serious mental disorders identified from HDR and CDR over four decades were examined, while in the former study self-ratings assessed at a single time point as tools to measure sub-clinical symptoms were used. Hence, the former study also addresses symptoms that do not require hospital treatment or contribute to death.

These findings regarding the risk of mental disorders also disagree with the previous findings of studies that have focused on severe mental disorders. Among them, one reported an association between maternal pre-eclampsia and schizophrenia in the offspring (Eide et al., 2013), and four found no associations with schizophrenia (Dalman et al., 2001; Jones et al., 1998; H. J. Sørensen et al., 2003; Suvisaari et al., 2013) or other mental disorders (Suvisaari et al., 2013). However, the previous studies did not examine sex-specific associations. When interpreting the correspondence between the current and previous findings, it should also be emphasised that we identified disorders over four decades from early to late adulthood. The previous studies examined disorders in samples that were much younger in age than our sample.

Hypertension without proteinuria

Maternal gestational hypertension did not have any significant effect on depressive symptoms in the offspring. Contrary to the other original publications forming this thesis, offspring born to mothers with chronic hypertension were excluded from the analyses. The exclusion of those offspring born to mothers with chronic hypertension may be arbitrary since not all women with antenatal data available had blood pressure records taken before their 20th week of gestation. It may well be that some mothers diagnosed as having gestational hypertension had elevated blood pressure prior to the pregnancy or prior to the 20th week of gestation. Therefore, the analyses were re-run with the inclusion of offspring born to mothers with any hypertension without proteinuria, and as discussed above, with the offspring born preterm, but the results remained unchanged.

Two previous studies tested whether maternal hypertension without proteinuria was associated with sub-clinical symptoms and mental disorders in the offspring. In keeping with the current findings, a follow-up study of HBCS, where the offspring were tested in late adulthood, showed that maternal hypertension without proteinuria was not

consistently associated with adaptive functioning and psychiatric and psychological problems in the offspring (Tuovinen et al., 2014). However, contrary to the current findings, a previous study that followed the offspring up to childhood showed that maternal gestational hypertension was associated with higher externalising behaviour and internalising behaviour scores in the offspring (Robinson et al., 2009).

Maternal hypertension without proteinuria was associated with a higher risk for any mental disorder and for a mood disorder, and also showed an association with a higher risk for anxiety disorder in the offspring. These disorders were serious and were identified from the Finnish nationwide registers of hospitalisations and deaths from early to late adulthood. The differences in the mental health outcomes from this thesis are discussed above and, hence, are not repeated here.

Two previous studies have tested the associations between maternal hypertension without proteinuria during pregnancy and the risk of mental disorders in the offspring (H. J. Sørensen et al., 2003; Suvisaari et al., 2013). Both studies reported associations with a higher risk of schizophrenia. Overall, these are in line with the current findings.

5.3 Maternal hypertensive disorders during pregnancy and the cognitive functioning of the offspring

Pre-eclampsia

Compared with the offspring who were born after normotensive pregnancies, offspring born after pre-eclamptic pregnancies more frequently reported complaints related to cognitive failures, distractibility and false triggering in late adulthood. No previous studies have tested the long-term consequences of maternal pre-eclampsia on the cognitive functioning of the offspring in late adulthood from a life-course perspective.

In general and in agreement with the findings, the only other study that has tested the associations in adults reported that maternal pre-eclampsia was associated with poorer cognitive functioning in the offspring in young adulthood (Ehrenstein et al., 2009). Thirteen studies tested the associations between maternal pre-eclampsia and the cognitive functioning of the offspring and followed the offspring up to childhood. In agreement with our findings, six of these studies reported that maternal pre-eclampsia was associated with poorer cognitive functioning in the offspring (Cheng et al., 2004;

Leveresen et al., 2011; Many et al., 2003; Morsing & Maršál, 2014; Spinillo et al., 1994; Szymonowicz & Yu, 1987). However, in disagreement with the current findings, six of the previous studies reported null associations or that the associations were rendered non-significant after adjusting for covariates and confounders (Leitner et al., 2012; Schlapbach et al., 2010; Seidman et al., 1991; Silveira et al., 2007; Whitehouse et al., 2012), while one reported a potential beneficial effect of maternal pre-eclampsia on the cognitive functioning of the offspring in childhood (Spinillo et al., 2009). When interpreting the findings, it should be emphasised that, with the exception of two analyses (Heikura et al., 2013; Whitehouse et al., 2012), these studies among children were conducted in samples born preterm or with a small body size. This kind of sample selection may affect the generalisability of the findings.

Pre-eclampsia was also associated with more frequent complaints of dysexecutive functioning, behavioural–emotional self-regulation and executive cognition, but the associations were attenuated or rendered non-significant when controlling for factors that may increase the risk of pregnancy hypertensive disorders and/or cognitive aging. It is of note that, whereas CFQ measures lapses in cognition in everyday life, DEX is designed to measure behavioural executive dysfunctions. Executive functions generally refer to ‘higher-level’ cognitive functions that are involved in the control and regulation of ‘lower-level’ cognitive processes and goal-directed, future-oriented behaviour (Alvarez & Emory, 2006). Our study sample possibly included the healthiest men and women who were able to take part in the study and complete the self-reported questionnaire. Our study did not reach those men and women who may have experienced more frequent and more severe problems related to cognitive functioning. This was also reflected in the relatively small number of study participants experiencing stroke and with diagnoses of coronary heart disease.

Hypertension without proteinuria

Among women, maternal hypertension without proteinuria was associated with cognitive failures, forgetfulness and false triggering. These associations were not seen in men. Maternal hypertension without proteinuria was not significantly associated with complaints of dysexecutive functioning.

In general and in agreement with our findings, the only other study conducted among adults reported that maternal hypertension without proteinuria was associated with poorer cognitive functioning among offspring in young adulthood (Ehrenstein et al., 2009). Four studies testing the associations followed the offspring up to childhood. In agreement with our findings, three of them reported that maternal hypertension without proteinuria was associated with poorer cognitive functioning among the offspring (Heikura et al., 2013; Spinillo et al., 1994; Whitehouse et al., 2012), while one reported null findings (Leitner et al., 2012).

Maternal hypertensive pregnancy disorders as a single diagnostic entity

In two of the original publications from this thesis, in order to attain more statistical power, we used maternal hypertensive disorders as a single diagnostic entity as a predictor variable. Compared with men born after normotensive pregnancies, men who were born to mothers with any hypertensive disorders fared somewhat poorer on tests measuring verbal and total cognitive ability in a follow-up conducted on average 20 years later. The offspring who were born to primiparous mothers or with a higher childhood socio-economic status were particularly vulnerable to the adverse consequences of maternal hypertensive disorders during pregnancy since their performances were poorer on the verbal reasoning test than their counterparts born after normotensive pregnancies.

Furthermore, compared with men born after normotensive pregnancies, men who were born to mothers with any hypertensive disorders scored lower on tests measuring arithmetic and total cognitive ability in late adulthood. They also displayed a greater decline in arithmetic reasoning and total cognitive ability from young up to late adulthood.

No previous study tested whether maternal hypertensive disorders during pregnancy were associated with the cognitive ability of the offspring in old age, let alone a decline in cognitive ability after young adulthood. Three previous studies tested whether maternal hypertensive pregnancy disorders as a single diagnostic entity were associated with the cognitive functioning of the offspring, but all followed the offspring up to childhood. Furthermore, previous studies have been conducted among offspring born very preterm or growth restricted. The findings from these studies disagree with the

current findings, given that one reported null findings (Gray et al., 1998) and two found that maternal hypertension was associated with better cognitive functioning in the offspring (McCowan et al., 2002; Winer et al., 1982).

5.4 Moderation by sex, prematurity, parity and childhood socio-economic status

Some of the associations reported in this thesis were modified by sex, parity or childhood socio-economic status. No previous studies tested whether some subgroups were particularly vulnerable to the effects of maternal hypertensive disorders during pregnancy. Thus, our findings also extend the previous findings in this way. First, men—but not women—who were born to pre-eclamptic mothers had a lower risk of mental disorders than their counterparts born to normotensive mothers. As discussed above, one possibility is that the seriousness of pre-eclampsia is associated with more effective parenting. It is of note that authoritative parenting (compared with uninvolved) is more strongly associated with men's psychological well-being than with women's (Rothrauff, Cooney, & An, 2009).

On the other hand, women—but not men—who were born to mothers with hypertension without proteinuria reported more frequent complaints of cognitive failures in late adulthood. This is contrary to the proposition that men might be more vulnerable than women to the consequences of early environmental adversities (Barker, 1998). Although similar studies do not exist, previous research has consistently demonstrated that women tend to have a higher incidence of dementia than men, particularly Alzheimer's disease (Gao, Hendrie, Hall, & Hui, 1998; Katz et al., 2012; Launer et al., 1999). However, studies that have tested the cognitive functioning of patients with Alzheimer's disease have produced conflicting results; some studies report that women have a higher incidence of cognitive impairment than men (Henderson & Buckwalter, 1994) and some studies report no differences in cognition between the sexes (Hebert et al., 2000). Moreover, studies that have tested cognitive aging in healthy participants have produced conflicting results. Some studies report men showing greater age-related cognitive decline (Maylor et al., 2007), while others report a faster decline in women (Castro-Costa et al., 2011; Karlamangla et al., 2009). In this study sample, men and women did not differ in the mean frequency of complaints related to cognitive

failures nor to dysexecutive functioning. This does not rule out developmental pathways related to brain diseases nor that plausible early behavioural markers may differ based on sex. It is of interest, however, that, in pregnancies complicated by asthma, a fetal sex-specific effect on the maternal immune system in those carrying a female, but not a male, fetus was found with adverse effects on placental functioning including reduced placental 11 β -HSD2 activity and female fetal growth (Murphy et al., 2003).

Second, primiparous offspring appeared to be particularly vulnerable to the adverse consequences of maternal hypertensive disorders during pregnancy. Primiparous offspring—but not multiparous offspring—who were born to mothers with pre-eclampsia had higher depressive symptom scores compared to the offspring of normotensive mothers. Indeed, there is evidence that pre-eclampsia may be qualitatively different in primiparous and multiparous pregnancies (Allen et al., 2004; Luo et al., 2007). However, it is also important to note that we found that pre-eclampsia was more common among primi- (11%, $n = 29$) than multiparous pregnancies (3%, $n = 8$). Thus, we clearly have more statistical power for detecting differences among primi- than among multipara. However, the results also showed that primiparous offspring—but not multiparous offspring—born to mothers with any hypertensive pregnancy disorders scored lower on verbal reasoning in young adulthood compared to the offspring of normotensive mothers. These latter analyses were limited to men.

Finally, men born to hypertensive mothers and coming from families with a high childhood socio-economic status had lower verbal reasoning scores than their counterparts who were born to normotensive mothers also with a higher childhood socio-economic background. These associations were not seen among men coming from families with a lower childhood socio-economic status. This may seem contradictory to our expectations, but it suggests that a higher socio-economic status may not be sufficient in buffering offspring from the adversities of the prenatal developmental milieu. One should also keep in mind that men with a low childhood socio-economic position fared the poorest in cognitive tests regardless of their mother's hypertensive disorders. Thus, hypertensive disorders may not have additive 'accumulating adversity' effects on cognitive functioning above and beyond the effects of a lower social class. However, because of the small sample sizes, all of these group-specific effects should be interpreted with caution.

5.5 Methodological considerations

This study represents the longest follow-up analysis of the consequences of maternal hypertensive pregnancy disorders reported thus far. The strength of our study is the large and well-characterised birth cohort. Yet, data on maternal hypertension and proteinuria were only available for a subpopulation of this cohort. Therefore, sample attrition may limit the generalisability of our findings if the associations between maternal hypertensive disorders and the mental health and cognitive functioning of the offspring were different between those for whom data were available and those for whom data were missing. This seems unlikely, but cannot be discounted. In addition, it is inevitable that individuals will be lost to follow-up across decades. This may introduce a bias, since some of the findings (Study I, IV and V) may apply only to the healthiest men and women who have survived to late adulthood. Furthermore, some findings (Study III and IV) are limited to men. Moreover, not all men in HBCS underwent the cognitive ability test. It is possible that men born to mothers with hypertensive disorders during pregnancy were more likely exempt from military service because of a chronic condition associated with perinatal events, such as mental retardation or cerebral palsy. These aspects would, however, simply attenuate the associations we observed.

Our data did not allow us to require two elevated blood pressure measurements to establish diagnoses (American College of Obstetricians and Gynecologists & Task Force on Hypertension in Pregnancy, 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). It is of note that there were, on average, 2.0 blood pressure measurements recorded in each pregnancy. However, as a possible consequence of this, the prevalence of hypertensive disorders of 33.3% was higher than that reported in the literature. Only qualitative measurements of proteinuria were available for the diagnosis of pre-eclampsia. All the same, the 4.4% prevalence for maternal pre-eclampsia in our sample is in line with the rates found in other studies (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; C. L. Roberts et al., 2005). We had no data on eclampsia itself, which, when our study subjects were born, was common, with rates of 0.6% at the Helsinki University Central Hospital (Parviainen, 1946), and could be associated with more severe consequences for the offspring. One of the most obvious

methodological differences between existing studies is related to the criteria used in the definition of maternal hypertensive pregnancy disorders. This methodological variation mainly reflects the difference in birth year of the samples studied, since, as mentioned, during the 20th and 21st centuries, disease classifications have undergone various revisions (Bell, 2010). Only three of the studies reviewed in this thesis reported using current clinical criteria to define pre-eclampsia (Table 1, page 20) (Leveresen et al., 2011; Schlapbach et al., 2010; Silveira et al., 2007).

We were able to compare the offspring born to mothers with pre-eclampsia or hypertension without proteinuria to the offspring born to normotensive mothers. Of the studies reviewed focusing on cognitive functioning, seven reported using offspring born to non-pre-eclamptic mothers as the comparison group (Leveresen et al., 2011; Many et al., 2003; Morsing & Maršál, 2014; Schlapbach et al., 2010; Seidman et al., 1991; Silveira et al., 2007; Szymonowicz & Yu, 1987). Of those studies focusing on mental disorders and symptoms, six used offspring born to non-pre-eclamptic mothers as the comparison group (Dalman et al., 2001; Eide et al., 2013; Jones et al., 1998; H. J. Sørensen et al., 2003; Suvisaari et al., 2013; Zammit et al., 2009). In these studies, the comparison group may have included offspring born to mothers with gestational or chronic hypertension.

We had no data on medication use for individual mothers; however, at that time, the care given was mainly expectant management. Glucocorticoid treatment was not known; chloral hydrate was administered to patients at risk for convulsions. A small number, if any, of the mothers may have received magnesium sulphate, given that the first treatment was administered in Helsinki in 1943 (Tarkiainen, 1946). We do not have data on the treatment that the mothers or their babies received. Limited neonatal care, in addition to the limited availability of medications at that time, may restrict the generalisability of our findings to babies born in high-resource settings more recently. The reviewed studies did not systematically report on either the medications or the care the mothers and the offspring may have received, and, thus, do not allow for a discussion of the possible effects of these factors.

We examined a wide variety of psychological functions with well-validated methods. However, the results derived from questionnaires (depressive symptoms, Study I; cognitive impairment, Study V) reflect the subjective views of the respondents. Thus,

they may not reflect the absolute levels of symptoms and everyday competence, but only the relative success of individuals' adaptations to idiosyncratic environments. Yet, subjective self-ratings may allow us to gain insight into any changes and individual differences in psychological well-being and functional efficiency in everyday life. Mental disorders (Study II) were identified from the Finnish nationwide registers of hospitalisations and deaths. While HDR and CDR are valid and reliable tools for epidemiological research, this may not pertain to all of the mental disorder diagnoses. The magnitude of some of the differences in cognitive functioning and mental health between the offspring who were born to normotensive and hypertensive mothers may be relatively modest, despite being statistically significant. However, they may translate into highly significant and meaningful differences over the course of one's life.

Focusing on different domains of mental health and cognition and variations in the methods for measuring mental health and cognition may explain the contradictions between current and previous findings. Among the studies that tested mental disorders and symptoms, five studies focused on serious mental disorders identified from registers (Dalman et al., 2001; Eide et al., 2013; Jones et al., 1998; H. J. Sørensen et al., 2003; Suvisaari et al., 2013), while three studies focused on maternal (Robinson et al., 2009) and self-ratings (Tuovinen et al., 2014) and psychiatric interviews (Zammit et al., 2009) as tools to measure sub-clinical symptoms and mental disorders, and, hence, also address symptoms and disorders that do not require hospital treatment or contribute to death. The majority of studies—six, in fact—focused mainly on schizophrenia (Dalman et al., 2001; Eide et al., 2013; Jones et al., 1998; H. J. Sørensen et al., 2003; Suvisaari et al., 2013) or psychotic symptoms in the offspring (Zammit et al., 2009), while one study tested a variety of psychiatric and psychological problems and adaptive functioning (Tuovinen et al., 2014) and one study focused on internalising and externalising behaviour among the offspring (Robinson et al., 2009). The current studies were the first to our knowledge to examine cognitive decline and impairment after prenatal exposure to maternal hypertensive pregnancy disorders. Among previous studies that tested cognitive functioning, nine studies focused on full-scale or specific domains of intelligence (Ehrenstein et al., 2009; Gray et al., 1998; Heikura et al., 2013; Leitner et al., 2012; Leversen et al., 2011; Many et al., 2003; Morsing & Maršál, 2014; Seidman et al., 1991; Whitehouse et al., 2012), while seven studies focused on the level of mental

development in the offspring (Cheng et al., 2004; McCowan et al., 2002; Schlapbach et al., 2010; Silveira et al., 2007; Spinillo et al., 1994; Spinillo et al., 2009; Szymonowicz & Yu, 1987). Naturally, methods for measuring cognition are also partially age-specific, making it impossible to utilise the same methods for individuals at different ages. This complicates comparisons between studies.

The possible mechanisms involved are discussed above. In addition, environmental factors may contribute to associations between maternal hypertensive pregnancy disorders and the psychological functioning of the offspring. The risk and protective factors for pre-eclampsia and hypertension without proteinuria are stated in section 1.2.5. Among these factors, maternal obesity (Van Lieshout et al., 2011), smoking (Braun, Daniels, Kalkbrenner, Zimmerman, & Nicholas, 2009; Heinonen et al., 2011) and prenatal stress and anxiety (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005; Van den Bergh, Van Calster, Smits, Huffel, & Lagae, 2008; Watson, Mednick, Huttunen, & Wang, 1999) are, in turn, associated with less optimal developmental outcomes in the offspring. Maternal age has been associated with both poorer (Chapman, Scott, & Mason, 2002) and better developmental outcomes (Fergusson & Lynskey, 1993). Moreover, both low (Silva et al., 2008) and high (Gudmundsson et al., 1997) socio-economic statuses are associated with a higher risk of pre-eclampsia. Low childhood socio-economic status is a significant predictor of poorer cognitive and mental health outcomes among offspring (Hackman & Farah, 2009; McLaughlin et al., 2011). Furthermore, hypertensive pregnancy disorders often require preterm delivery and result in a lower birth weight of the babies, and as reviewed, preterm birth and low birth weight are known risk factors for poorer cognitive functioning and mental health. Our data allowed us to adjust for a number of covariates and confounding factors including offspring characteristics at birth and maternal constitutional factors. With the exception of associations between maternal hypertension without proteinuria and dysexecutive functioning of the offspring, the significant findings were virtually identical between the unadjusted and adjusted models. Thus, in general, the associations were not explained by these factors.

However, we did not have data available on maternal stress and anxiety and smoking during pregnancy. While we also do not have exact figures, data on the incidence of

lung cancer in women suggest that smoking during pregnancy between the years of 1934–44 was uncommon in Finland (Finnish Cancer Registry - Institute for Statistical and Epidemiological Cancer Research, 2009). Furthermore, complications around the time of birth may increase the risk of postpartum depression (Duley, 2009). Postpartum depression may compromise maternal sensitivity to the infant's needs, influence the developing mother–child attachment relationship and, thereby, increase the risk of adverse outcomes in the offspring. We did not have data on maternal postpartum psychopathology nor on paternal psychopathology. Thus, it is possible that, to some extent, these factors explain the findings.

Most studies reviewed have failed to take into account significant covariates and confounders. However, some studies have accounted for maternal and/or family characteristics, while others have accounted for offspring characteristics at birth or at assessment (see Tables 15–16 in the Appendix). Given that the covariates and confounders taken into account in studies vary, it is difficult to interpret the effects of individual covariates and confounders.

Finally, interpreting our findings in relation to previous findings may present a challenge related to statistical power and publication bias. Statistical power refers to the probability that a test will find a statistically significant difference when such a difference actually exists. Many of the studies reviewed were conducted in relatively small samples. Null findings may, therefore, reflect a lack of statistical power rather than a true lack of association. In addition, in our studies, the numbers of exposed offspring were relatively small, particularly for subgroup-specific analyses. Publication bias is also a possibility and should be taken into account when interpreting the findings between our studies and the studies reviewed. This refers to the bias in what is published among what is available to publish. This is usually manifest in a bias towards reporting significant results.

5.6 Implications of the study

The findings reported here conducted in a general population showed that maternal hypertensive pregnancy disorders carry an increased risk of a wide spectrum of problems related to the mental well-being and cognitive functioning of offspring several

decades later. These problems are burdensome because of their chronicity and because they often result in serious impairment or impact one's quality of life in multiple ways.

The current findings highlight the importance of preventing hypertensive pregnancy disorders. The risk factors for pre-eclampsia and other hypertensive pregnancy diseases are well documented (Duckitt & Harrington, 2005; Poon et al., 2010). However, the etiology remains unknown. Despite several randomised trials reporting the use of various methods to reduce the rate or severity (or both) of these conditions, there is no specific method for preventing these maternal conditions (Abalos, Duley, Steyn, & Henderson-Smart, 2001; Sibai et al., 2005). That said, a few modifiable risk factors exist. One of these is maternal BMI; a higher BMI is associated with an increased risk of both pre-eclampsia and hypertension in pregnancy. According to one overview of increasing BMI and the risk of pre-eclampsia, consideration should be given to the potential benefits of pre-pregnancy weight-reduction programmes (O'Brien, Ray, & Chan, 2003). In addition, psychological risk factors such as stress, depression and anxiety seem to be positively associated with hypertensive pregnancy disorders (Kurki et al., 2000; Paarlberg et al., 1995; Qiu et al., 2009). Preventing these risk factors should be considered. Thus far, adequate and proper prenatal care is the most important factor in the management of pre-eclampsia and hypertension (Sibai et al., 2005) and mitigating the consequences for both the mother and the child.

Most of the current findings cannot be directly translated into clinical recommendations. However, they highlight the role of prenatal events as factors that may help to identify high-risk children and families who could benefit from targeted interventions early in life. The postnatal environmental effect can override any prenatal adversities since the brain continues to develop after birth and 'the windows of opportunity' remain open (Buss et al., 2007; Lupien et al., 2009). Such potential postnatal environmental effects may include sensitive parenting (C. A. Newnham, Milgrom, & Skouteris, 2009; Nordhov et al., 2010).

A few protective effects related to maternal hypertensive disorders on the offspring's psychological development were found. It should be noted that not all of the effects are necessarily adverse, and it is important to unravel these developmental pathways.

The causes of adverse mental health and cognitive outcomes are generally complex and vary between disorders and individuals. Maternal hypertensive disorders may add to the known risk factors for these psychological conditions and point to mechanisms by which prenatal adversity is associated with these problems in subsequent life. This may be crucial for clinicians in both understanding these conditions and in planning care.

5.7 Future directions

Given that maternal hypertensive pregnancy disorders may be associated with poorer mental health and cognitive ability among offspring, future studies should focus on finding a way to prevent these maternal conditions and addressing the impact of preventive interventions in the treatment of mental health problems and poor cognitive functioning.

In addition, due to the concerns addressed in this thesis, further studies are needed that will test the associations between maternal hypertensive pregnancy disorders and psychological outcomes among offspring in larger samples using the current clinical criteria of pre-eclampsia and gestational hypertension. Further studies are also needed to test whether the findings translate into significant improvements among cohorts born recently, vis-à-vis the treatment of pre-eclampsia and hypertension as well as neonatal care, accomplished in recent decades. Future studies should assess whether the associations reflect the true causal effects of hypertensive pregnancy disorders, either attributed to the complications of hypertensive disorders or across a range of severities of hypertensive disorders. One challenge for future studies lies in unraveling the maternal, placental and fetal mechanisms through which maternal hypertensive pregnancy disorders affect the offspring.

5.8 Conclusions

The findings from this thesis show that the adult offspring born to mothers with pre-eclampsia or hypertension without proteinuria during pregnancy differ from their peers born after normotensive pregnancies in several areas of mental health and cognitive functioning. In comparison to the offspring born to normotensive mothers, offspring born to pre-eclamptic mothers showed higher cognitive impairment, and offspring born to mothers with hypertension without proteinuria showed a higher risk of mental

disorders, although they did not differ in the severity of depressive symptoms. Maternal hypertensive pregnancy disorders as a diagnostic entity were associated with a lower cognitive functioning and a higher cognitive decline in the offspring. Sex, parity and childhood socio-economic status modified some of the associations. Maternal pre-eclampsia was associated with higher depressive symptom scores in primiparous—but not in multiparous—offspring and with a lower risk of mental disorders in male—but not female—offspring. Maternal hypertension without proteinuria was associated with cognitive impairment in female—but not male—offspring. Finally, the associations between maternal hypertensive pregnancy disorders as a diagnostic entity and lower cognitive functioning in young adulthood were most evident in primiparous offspring and in offspring with a high childhood socio-economic status. The associations were not explained by factors associated with the risk of maternal hypertensive pregnancy disorders and/or psychological functioning, such as the mother's age and obesity, and socio-economic status in childhood. The associations were identified even after accounting for birth weight for gestational age and gestational age, suggesting that the associations are not likely solely explained by these complications related to hypertensive pregnancy disorders.

These studies contribute significantly to the existing literature given that they represent the longest follow-up analysis of transgenerational consequences of maternal hypertensive disorders reported thus far in the literature. The findings highlight the role of the prenatal environment in developmental programming. Interpretation of the current findings in relation to previous findings may suggest a causal chain linking intrauterine exposure to maternal hypertensive pregnancy disorders with a vulnerability to childhood and adolescent risk factors and, thus, to poorer mental health and cognitive functioning in adulthood. Alternatively, it is possible that the associations arise during the course of one's lifetime.

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APPENDIX

Data collection for the systematic review

Search strategy

I searched the database MEDLINE in February 2013 and February 2014 and evaluated the results systematically. I looked for articles whose main focus was maternal hypertensive disorders but also mentioned cognition (or any of its synonyms) or cognitive tests (or any of its synonyms) or mental health (or any of its synonyms) or whose main focus was on cognition (or any of its synonyms) or cognitive tests (or any of its synonyms) or mental health (or any of its synonyms) but also mentioned maternal hypertensive disorders. For specific search items see Table 14. This search strategy had high sensitivity but low specificity. I read through a large number of article titles of which a large proportion turned out to be irrelevant. This was necessary owing to the lack of a specific search term to identify relevant studies. Also, I used Web of Knowledge - Citation information to find any additional studies citing primary articles. Further, I checked that I included relevant studies cited by primary articles.

Study selection

The database searches produced 2805 article titles (Figure 7). Several publications were rejected at the first stage after reading the title. After retrieving 82 of these articles I ended up with 36 articles that met our selection criteria. Thirty-four articles were rejected, five because the articles was a review or summary, 22 because the outcomes variables fell out the scope of this review, five because the independent variable lacked clear specificity, 11 because a control group was lacking or its characteristics remained unclear, one because it was published in other languages than English, and one because a replication of the study was published in authors' later study. Three additional studies were identified from an extended search and were included in the final review. I double-checked the performance of the search strategy; I ensured that the strategy results in a collection of the most important articles that I was aware of beforehand.

Table 14. Search items

Maternal hypertensive disorders

preeclampsia
pre-eclampsia
eclampsia
gestosis
toxemia
maternal pregnancy hypertension
maternal chronic hypertension
gestational hypertension
hypertensive pregnancy disorders

Cognition

cogniti*
intell*
neurodevelopment*
mental development*
cognitive test
intelligence test
neuropsychological test
child development

Mental health

mental health
mental processes
mental disease
mental disorder
mental illness
psychological disease
psychological disorder
psychological illness
psychological development
psychopathology
depression
anxiety
schizophrenia
mood
neurotic
personality
psychotic
substance use

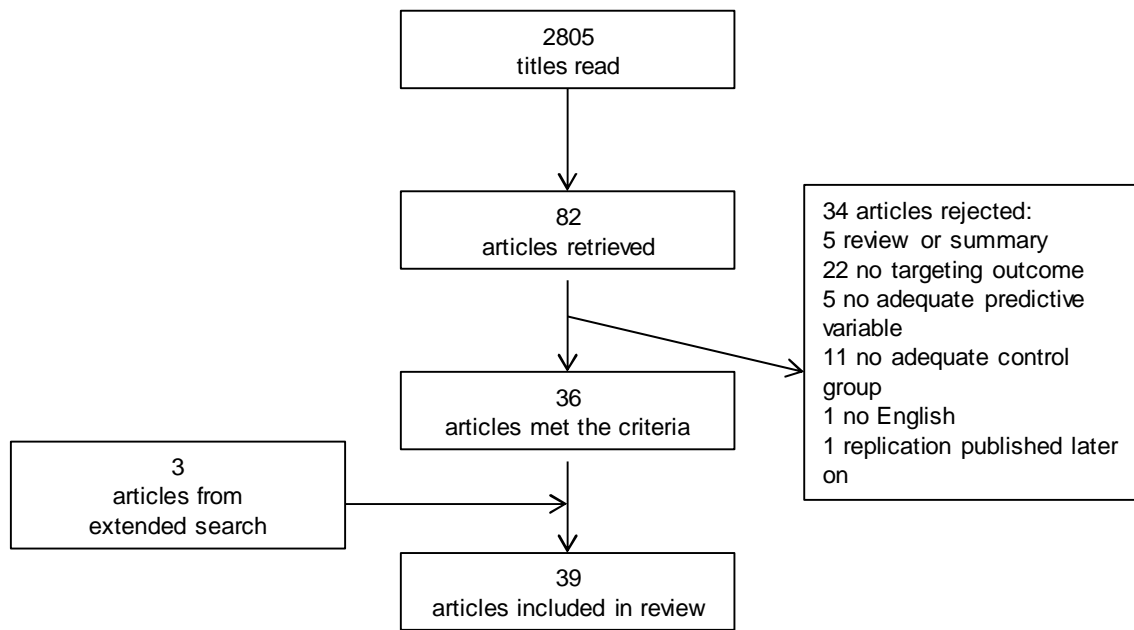


Figure 7. Selection of studies focusing on maternal hypertensive pregnancy disorders and the mental health and cognitive functioning of the offspring

Table 15. Covariates and confounders available in the reviewed studies focusing on the mental health of the offspring

First author, publishing year/ Reference	GA	BWT	SGA status	Neonatal health factors	Sex	Parity	Maternal BMI	Maternal age	Childhood socio-economic status	Maternal education	Maternal life-style behaviours	Maternal psychological functioning
Dalman et al., 2001						x		x	x			x
Eide et al., 2013					x	x		x		x		
Jones et al., 1998					x				x		x	x
Robinson et al., 2009	x	x			x			x	x	x	x	x
Suvisaari et al., 2013		x			x							
Sørensen et al., 2003					x			x				x
Tuovinen et al., 2014	x	x			x	x	x	x	x			
Zammit et al., 2009					x			x			x	x

BWT, birth weight; GA, gestational age; SGA, small for gestational age; BMI, body mass index

Table 16. Covariates and confounders available in the reviewed studies focusing on the cognitive functioning of the offspring

First author, publishing year/ Reference	GA	BWT	SGA status	Neonatal health factors	Sex	Parity	Maternal BMI	Maternal age	Childhood socio-economic status	Maternal education	Maternal life-style behaviours	Maternal psychological functioning
Cheng et al., 2004	x	x		x	x					x		
Ehrenstein et al., 2009		x	x			x		x				
Gray et al., 1998	x				x							
Heikura et al., 2012			x		x	x	x	x	x			
Leitner et al., 2012												
Lerversen et al., 2011	x		x	x	x					x		
Many et al., 2003	x	x		x								
McCowan et al., 2002												
Morsing & Maršál, 2014	x	x			x							
Schlapbach et al., 2010	x	x		x								
Seidman et al., 1991 ^a		x				x			x			
Silveira et al., 2007												
Spinillo et al., 1994	x								x	x		
Spinillo et al., 2009	x	x			x							
Szymonowicz & Yu, 1987	x				x							
Whitehouse et al., 2012	x	x		x		x		x	x	x	x	

^aAdjusted associations were not reported as the associations were not significant in the unadjusted model

BWT, birth weight; GA, gestational age; SGA, small for gestational age; BMI, body mass index