Cardio-metabolic risk in children prenatally exposed to maternal psychosocial stress
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Introduction
Cardiovascular diseases are the number one cause of death globally, and the WHO projects that diabetes deaths will double between 2005 and 2030. The necessity of their prevention is growing rapidly, especially with the increasing prevalence of obesity in younger populations. Recent evidence, both animal and human, suggests that modifiable factors during fetal and infant development predispose for cardiovascular and metabolic disease in adult life and that they may become possible future targets for prevention.

**Developmental Origins of Health and Disease (DoHaD)**

Epidemiological and experimental animal studies convincingly show that adverse birth outcomes like shortened gestational duration and small-for-gestational-age birth are associated with a substantially higher risk of cardiovascular and metabolic disease in adult life, independent from genetic make-up and conventional risk factors like obesity and physical inactivity. This notion of ‘Developmental Origins of Health and Disease’ started in 1989, when epidemiologist David Barker and his colleagues published a paper on the observation that adult men with the lowest weights at birth had the highest death rates from ischemic heart disease. Many studies followed, and showed that small-for-gestational-age birth is associated with a substantial part of the risk for adult cardiovascular disease and its biological forerunners hypertension, impaired glucose tolerance, dyslipidemia and obesity. Recent research demonstrated that shorter gestation is also associated with later life insulin resistance and hypertension, irrespective of size at birth.

It is very unlikely that small-for-gestational-age birth is the single early-life factor towards adult cardiovascular disease. A common factor is likely to influence fetal intrauterine growth and simultaneously change the set point of adult physiological systems. This presumed mechanism has been called ‘fetal programming’, a process whereby suboptimal intrauterine conditions at a critical point during early development results in permanent adaptation of the organism’s structure. This could predispose the individual to chronic disease at adult age. Previous research revealing prenatal conditions with the potential to program the fetus mainly pointed towards maternal malnutrition. One import study that moved this field forward is the Dutch Famine birth cohort study. By studying the long term consequences of a period of starvation during World War 2, they showed that men and women who were exposed to undernutrition in the womb had an increased risk of cardiovascular diseases in later life. To a large extent, the associations were independent of gestational duration and size at birth, which is an important finding for further research: Fetal programming by prepartum factors may affect birth outcomes, but potentially also affects offspring parameters directly.

Aside from maternal malnutrition, another prenatal factor predisposing the fetus for chronic disease at adult age could be exposure to psychosocial stress, because it may alter maternal-placental-fetal endocrine and immune processes, which could lead to structural and functional changes in the fetus. Moreover, it has been associated with adverse birth
outcomes. However, (human) evidence linking prenatal maternal psychosocial stress to outcomes beyond birth is scarce.

**Psychosocial stress during pregnancy**

Psychosocial stress is highly prevalent in what are otherwise normal pregnancies. Research has revealed that 25% of pregnant women experience what Yali et al. call ‘emotional distress’. The prevalence of depressive symptoms was estimated at 9.6% in women of childbearing age, whereas 12.7% of pregnant women experience a major depressive disorder. The peak age at onset for anxiety disorders in women occurs also during the childbearing years. In literature, reports on the prevalence of anxiety symptoms and anxiety disorder during pregnancy ranged from 0.2 to 15%.

A recent meta-analytic review concluded that different forms of psychosocial stress during pregnancy, like elevated levels of anxiety and depressive symptoms, might be partially accountable for pregnancy complications and adverse obstetric outcomes. Associations with later life outcomes are however scarcely studied in human research. To our knowledge, so far, psychosocial stress has only in a few studies been related to offspring cardio-metabolic outcomes. An altered balance of the autonomic nervous system (ANS) has been reported in relatively small study samples of fetuses or infants, and an association between maternal bereavement and higher BMI has also been reported. Another study reported increased central adiposity and smaller size in 3-year-old children from mothers who reported high depressive symptoms prepartum. An association with insulin resistance was observed in young adults whose mothers experienced major stressful life events during pregnancy.

Further human evidence stems from research on the long term effects of antenatal administration of glucocorticoids, the category of hormones that encompasses the so called ‘stress hormones’. Glucocorticoid administration has been linked to higher blood pressure in adolescence and insulin resistance in adult life. Those studies have, however, been complicated by high doses of glucocorticoids, which are not comparable to levels normally occurring during pregnancy. In addition, glucocorticoid treatment usually takes place when pre-term birth is expected, adding bias because of the complications of premature birth.

As existing research illustrates, stress can be assessed in numerous ways, ranging from self-reported psychosocial complaints, e.g. experienced life events, anxiety, depression or job strain (work stress), to measurement of physiological indicators, such as glucocorticoids. Experienced psychosocial stress is accompanied by increases in stress hormones that occur naturally, with the potential to program the fetus.
**HOW STRESS IN THE MOTHER COULD CAUSE CARDIOVASCULAR DISEASE IN THE OFFSPRING**

Stress during pregnancy may affect the risk of cardiovascular disease in the offspring through at least three different mechanisms:

- **Through the HPA-axis**: The fetal hypothalamus-pituitary-adrenal (HPA) axis is responsible for stress-regulation. It is particularly susceptible to programming or reprogramming during fetal or early postnatal life. Chronic stress conditions such as psychosocial stress in the mother during pregnancy may influence her HPA axis. This leads to hyper secretion of the glucocorticoid cortisol, which could influence the development of the fetal HPA axis and/or immune function as it partly crosses the placenta. Consequently, hyperactivity of the offspring’s HPA axis is associated with cardiovascular risk factors such as obesity, insulin resistance, glucose intolerance, hypertension and hyperlipidemia, in both animal models and humans.

A part of this pathway of fetal programming may rollout through lower birthweight for gestational age: Extensive evidence has linked maternal cortisol concentrations during pregnancy to lower birthweight and shortened gestational duration, which, as described in the previous sections, has in turn been associated with adverse health outcomes in the offspring.

- **Through the autonomic nervous system**: Psychosocial stress may also exert its effects on the fetus through programming of the ANS. Maternal stress could cause a shift towards increased activation of the sympathetic nervous system and a decrease in the parasympathetic nervous system of the mother, together with increased secretion of catecholamines, all leading to elevated blood pressure and heart rate in the mother. This could have detrimental effects on the development of the fetal nervous system, potentially causing long-term changes in, for example, the sympathetic-parasympathetic nervous system balance, which may lead to cardiovascular diseases at adult age. Increased sympathetic and decreased parasympathetic nervous system activity has been found in fetuses or infants of depressed or anxious pregnant women. Recent research has linked maternal cortisol concentrations with adverse health outcomes in the offspring.

- **Through maternal inflammation**: Maternal psychosocial factors can contribute to increased inflammation during pregnancy, which influences the development of adult cardiovascular disease, although this mechanism has not been extensively investigated.

Most research either studied associations of prenatal maternal stress with birth outcomes, or took birth outcomes as a starting point and studied associations with health outcomes in adulthood.
later (adult) life. Evidence directly linking prenatal maternal stress to cardiovascular status in the offspring is mainly available from animal studies: Adding evidence from studies in humans is the main motivation for this thesis.

**Boy-Girl Differences**
Prenatal stress exposure has been found to exert different effects on male or female human fetuses. After the 9/11 terrorist attacks in 2001, the United States population experienced heightened stress and anxiety, which appears to have resulted in increasing male fetal loss 68. Generally, male fetuses are found to be more sensitive to stress in utero 68-70. Results from the Dutch Famine birth cohort study also suggest sex-specific effects. For example, only women exposed to famine in early gestation had a higher overall adult cardiovascular mortality risk 71. On the other hand, only in men, in utero exposure to famine was associated with compensatory expansion of the placental surface and increased risk of hypertension 72. In a recent review, dr. Clifton 73, who has done important research on prenatal exposure to maternal asthma and inhaled glucocorticoids 74, emphasizes the sex differences in placenta functioning. She argues to take potential sex differences into account when testing fetal programming hypotheses. Therefore, in all associations studied in this thesis, boy-girl differences are considered.

**Aims & Hypotheses**
In sum, psychosocial stress has been associated with short-term offspring outcomes and may have the potential to program the fetus. Previous research in humans focusing on long-term outcomes studied the programming effects of prenatal corticosteroid administration 50,51 as opposed to psychosocial stress, adding bias because this treatment usually takes place when pre-term birth is expected. Furthermore, such increases in stress hormones are many times the size of increases that occur naturally in response to stress and thus incomparable.

Therefore, the present thesis aims to elucidate whether prenatal maternal psychosocial stress can affect the fetus with consequences for cardio-metabolic health in childhood, namely at five-six years of age. To address this goal, we formulated the following research questions:

1) Is early pregnancy psychosocial stress associated with adverse birth outcomes?

*We hypothesize that prenatal psychosocial stress is associated with shorter gestation and lower birthweight for gestational age.*
2) Is early pregnancy psychosocial stress associated with an adverse cardio-metabolic profile in the child?
   
   *We hypothesize that prenatal psychosocial stress is associated with increased adiposity, an adverse ANS balance, impaired blood glucose metabolism, increased blood pressure and adverse cardiovascular function.*

3) To what extent is the effect of psychosocial stress on cardio-metabolic profile mediated by gestational duration and/or birthweight for gestational age?
   
   *We hypothesize that gestational duration and birthweight for gestational age partly mediate the association between stress and cardio-metabolic profile.*

4) Is the effect of psychosocial stress on cardio-metabolic profile different between boys and girls?
   
   *We hypothesize that effect-modification by sex could be present, but based on previous research, the direction of this modification remains to be determined.*

We address these questions using data from a Dutch and a British birth cohort, following up the offspring of women enrolled during pregnancy. These will be introduced further in the following chapter.

**Outline**

In this chapter, the background of the research presented has been described. In chapter 2, the methods used answering the research questions will be described further. In section A, we report on the potential association of psychosocial stress in early pregnancy with adverse birth outcomes, i.e. shorter gestation and lower birthweight for gestational age (chapter 3 and 4). In section B, we report on the potential association of psychosocial stress with an adverse cardio-metabolic profile in childhood, i.e. increased adiposity (chapter 5 and 7), adverse autonomic nervous system balance (chapter 6), impaired blood glucose metabolism (chapter 7), increased blood pressure (chapter 8 and 9) and adverse vascular function (chapter 9). Table 1 summarizes the topics covered in each chapter.
### Table 1 Overview of the topics covered in each chapter

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Determinants</th>
<th>Outcomes</th>
<th>Study population</th>
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<tbody>
<tr>
<td>3</td>
<td>Psychosocial stress during pregnancy is related to birth outcomes</td>
<td>clusters based on: - depressive symptoms - state anxiety - job strain - pregnancy-related anxiety - parenting stress</td>
<td>- gestational duration - birth weight</td>
<td>Amsterdam Born Children and their Development (ABCD) study</td>
</tr>
<tr>
<td>4</td>
<td>Maternal depressive symptoms, serum folate status and pregnancy outcome</td>
<td>- depressive symptoms - serum folate status</td>
<td>- gestational duration - birth weight</td>
<td>ABCD study</td>
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<td>5</td>
<td>The relation of maternal job strain and cortisol levels during early pregnancy with body composition later in the 5-year-old child</td>
<td>- job strain - serum total cortisol</td>
<td>- body mass index - waist-to-height-ratio - fat mass index</td>
<td>ABCD study</td>
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<tr>
<td>6</td>
<td>Prenatal stress and balance of the child’s cardiac autonomic nervous system at age 5-6 years</td>
<td>- depressive symptoms - state anxiety - job strain - pregnancy-related anxiety - parenting stress and a cumulative score</td>
<td>- heart rate - pre-ejection period - respiratory sinus arrhythmia - cardiac autonomic balance</td>
<td>ABCD study</td>
</tr>
<tr>
<td>7</td>
<td>The influence of prenatal psychosocial stress on BMI and blood glucose metabolism in the child at age 5-6</td>
<td>“</td>
<td>- body mass index - fasting glucose - C-peptide - insulin resistance</td>
<td>ABCD study</td>
</tr>
<tr>
<td>8</td>
<td>The influence of prenatal psychosocial stress on blood pressure in the child at age 5-6 years</td>
<td>“</td>
<td>- blood pressure - hypertension</td>
<td>ABCD study</td>
</tr>
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REFERENCES


74) Clifton VL, Murphy VE. Maternal asthma as a model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. Placenta 2004; 25 Suppl A:S45-S52.
