Cardio-metabolic risk in children prenatally exposed to maternal psychosocial stress
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General discussion
Adverse birth outcomes like shortened gestational duration and low birth weight have been associated with a substantially higher risk of cardiovascular and metabolic disease in adult life, independent from conventional risk factors. Exposure to maternal psychosocial stress could be a common factor influencing fetal growth and changing the set point of adult physiological systems. Experiencing psychosocial stress is accompanied by increased endogenous stress hormones, and have the potential to program the fetus.

The research in this thesis aimed to elucidate whether prenatal exposure to maternal psychosocial stress can affect the fetus with consequences for cardio-metabolic health in later life. The mediating roles of gestational duration and birth weight for gestational age and sex-specific effects were also explored. In this chapter, we will first sum up the findings of the research presented and discuss some limitations of the research. Then, we will discuss the implications of those findings.

Is early pregnancy psychosocial stress associated with adverse birth outcomes?
Section A was focused on the association between psychosocial stress and adverse birth outcomes, namely shortened gestation and low birthweight. In chapter 3 we demonstrated that it is possible to combine validated questionnaires addressing psychosocial stress and derive distinct clusters of pregnant women using a latent class analysis. Mean offspring birth outcomes were different between the clusters: Babies from women in the ‘high depression & high anxiety, moderate job strain’ cluster (12%) had a lower birth weight, and those in the ‘high depression & high anxiety, not employed’ cluster (15%) had an increased risk of preterm birth. These findings led to the conclusion that babies from pregnant women reporting both high levels of anxiety and depressive symptoms are at highest risk for adverse birth outcomes.

And although the results in chapter 4 did not indicate an interactive effect between high depressive symptoms and low serum folate status, which are often co-prevalent, we demonstrated an association between high depressive symptoms and shorter gestational duration. The negative association between depressive symptoms and birthweight was explained by the shortened gestation.

The findings from both papers indicate small associations with birth outcomes.

Is psychosocial stress in early pregnancy associated with an adverse cardiometabolic profile in childhood?
Section B encompassed the papers on the association between psychosocial stress and cardiometabolic risk factors in the offspring in childhood.

Adiposity
The findings reported in chapter 5 showed a slight yet non-convincing association between the maternal psychosocial stressor job strain or maternal cortisol levels on the one hand and the child’s body mass index, central adiposity or body fat mass on the other. In chapter 7 we were able to include a slightly higher number of mother-child pairs. Also, in addition to job strain, we investigated the other psychosocial stressors and a cumulative stress score. The results showed that pregnancy-related anxiety, job strain and the cumulation of stress during pregnancy were associated with small increases in offspring BMI at 5-6 years of age.
**Balance of the cardiac autonomic nervous system**

Chapter 6 reports that none of the measures of prenatal psychosocial stress was associated with measures of the child’s ANS, i.e. heart rate, pre-ejection period, respiratory sinus arrhythmia and cardiac autonomic balance. The cumulation of psychosocial stressors was also not associated with these outcomes.

**Blood glucose metabolism**

The associations between prenatal psychosocial stress and measures of blood glucose metabolism in the 5-6 year old child are studied in chapter 7. The single psychosocial stress scales as well as the cumulative stress score were not associated with glucose, C-peptide or insulin resistance in the offspring.

**Blood pressure and vascular function**

In chapter 8 and 9, the single psychosocial stress scales were not associated with the child’s blood pressure or other vascular outcomes. The prenatal cumulation of stressors however was associated with increased blood pressure at age 5-6.

**Are gestational duration and birthweight for gestational age mediators?**

Mediation by gestational duration and birthweight was ruled out in many instances because of the absence of an association between maternal psychosocial stress and the offspring outcome. We additionally explored whether these birth outcomes were associated with cardiometabolic parameters in childhood (findings summarized in table 1).

Previous research has linked smaller birth size (low standardized birth weight for gestational age) to an unfavourable cardiometabolic risk profile, including increased abdominal fat deposition and obesity in adulthood. In our studies exploring standardized birthweight as a potential mediator, however, this pattern was not observed. Possibly, such an association does not emerge until later in adult life. However, in accordance with previous research, higher standardized birthweight was associated with higher childhood BMI.

Lower standardized birthweight was associated with increased heart rate and respiratory sinus arrhythmia in the offspring, which is in agreement with previous studies. Possibly, prenatal factors other than maternal psychosocial stress, related to intrauterine growth retardation, have the potential to affect the offspring’s ANS.

Previous research has reported on increased risk of type 2 diabetes in low and high birth weight infants. We did find a linear association between standardized birthweight and C-peptide, but we did not find an association with glucose or insulin resistance. This discrepancy may be attributed to our use of fasting glucose and C-peptide concentrations as opposed to a more rigorous oral glucose challenge, which may reveal subtle changes earlier.

Small size at birth has also been associated with an increased risk of high blood pressure in later life. In accordance with those studies, in our research, lower standardized birth weight was associated with higher offspring systolic and diastolic blood pressure at both 5-6 and 10-11 years of age (chapter 8 & 9) and a higher risk of hypertension at age 5-6 years (chapter 8).

We also studied gestational duration as a potential mediator, because it is often reported as an adverse pregnancy outcome following prenatal stress. Furthermore, in clinically premature populations, premature birth has been linked to adverse cardiometabolic health
in later life \(^18\). To our knowledge, however, there is no literature on a potential association between ‘normal’ gestational duration and later life cardiometabolic parameters. Our findings suggest that such an association is not overtly present (table 1).

**Table 1 Associations between birth outcomes and childhood cardiometabolic outcomes**

<table>
<thead>
<tr>
<th>Adiposity</th>
<th>Birthweight for gestational age</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>+</td>
<td>no association</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>no association</td>
<td>no association</td>
</tr>
<tr>
<td>Fat mass index</td>
<td>no association</td>
<td>no association</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac autonomic nervous system</th>
<th>Birthweight for gestational age</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>–</td>
<td>no association</td>
</tr>
<tr>
<td>Pre-ejection period</td>
<td>no association</td>
<td>no association</td>
</tr>
<tr>
<td>Respiratory sinus arrhythmia</td>
<td>–</td>
<td>no association</td>
</tr>
<tr>
<td>Cardiac autonomic balance</td>
<td>no association</td>
<td>no association</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose metabolism</th>
<th>Birthweight for gestational age</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>no association</td>
<td>no association</td>
</tr>
<tr>
<td>Fasting C-peptide</td>
<td>+</td>
<td>no association</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>no association</td>
<td>no association</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular status</th>
<th>Birthweight for gestational age</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>–</td>
<td>no association</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>ABCD: –</td>
<td>ABCD: +</td>
</tr>
<tr>
<td></td>
<td>ALSPAC: –</td>
<td></td>
</tr>
</tbody>
</table>

**IS SEX AN EFFECT MODIFIER?**

Effect-modification was ruled out in every hypothesized association of psychosocial stress with offspring outcome studied in this thesis, with one exception. There was one interaction with offspring sex, namely in the association between prenatal maternal cortisol concentration and fat mass index. Maternal cortisol was associated with marginally higher fat mass index in girls, but marginally lower fat mass index in boys.

The reason for the gender difference observed in the current study may be sought in the evolutionary theory underlying fetal programming \(^19\). Being exposed to elevated stress, the fetus retains more body fat in order to be more successful at reproduction in scarce times. This is based upon the knowledge that excess adiposity in girls is hypothesized to be a causal factor for early pubertal development in girls \(^20\).

So far, effect modification by sex in the prenatal stress-offspring cardiometabolic risk-association has not been studied before. Our one finding does not underline an important effect-modifying role of sex in the hypothesis of an association between maternal psychosocial stress and offspring cardiovascular risk factors.
Methodological Considerations

Selective loss to follow up

The ABCD cohort offered a large, population-wide sample of mother-child pairs in which we could test our hypothesis. As in almost every cohort, the ABCD study did encounter loss to follow up. The dropout was also not at random: conform expectations, the women lost to follow up were younger, lower educated and had a higher BMI. Also, the mean scores on the psychosocial stress scales were somewhat higher in the ABCD cohort as a whole than they were in the groups left in the current thesis’ analyses. As shown in table 2, the proportion of women in the higher stress categories would have been higher at the initial population level, although the drop in the prevalence of the cumulation of 3-4 stressors (3.2 to 2.7%) does not seem very severe.

Table 2 Drop-out analysis: Prevalences of stress cumulation scores

<table>
<thead>
<tr>
<th>No stressors</th>
<th>Population of live-born singletons with complete psychosocial stress-data</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=7,592</td>
<td>N=3,168</td>
<td></td>
</tr>
<tr>
<td>48.2%</td>
<td>54.0%</td>
<td></td>
</tr>
<tr>
<td>1 stressor</td>
<td>31.2%</td>
<td>31.3%</td>
</tr>
<tr>
<td>13.9%</td>
<td>12.0%</td>
<td></td>
</tr>
<tr>
<td>3-4 stressors</td>
<td>3.2%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

One could argue that this underrepresentation of maternal stress in the sample left for analysis at age 5 may have resulted in an underestimation of the actual associations. However, most associations in our studies are far from statistically significant: even in a population with higher stress levels, those associations are not very likely to become (statistically) significant, and if they would, the impact might be limited.
The assessment of stress
In chapter 3, the multiple psychosocial stress scales were captured in five latent classes, each encompassing women with distinct patterns of psychosocial stressors. Although the associations with birth outcomes were very informative from a public health perspective, the latent classes did not enable us to pinpoint those women with multiple high stress scores from various angles (e.g. work, parenting, intrinsic). In fact, it shows that different forms of psychosocial stress are generally not experienced by the same women. We therefore calculated a cumulative stress score, which was based on the 80th percentiles on each of the stress scales. Some reviewers considered this a limitation, as the 80th percentile point is a rather arbitrary cutoff. It however enabled us to consistently identify women scoring ‘high’ on each of the scales.

Maternal cortisol
The cortisol measurement in the pregnant mothers of the ABCD cohort (chapter 5) suffered from serious limitations. Therefore, the lack of an observed association with obesity and adiposity in the offspring may, in addition to such an association not existing, be due to methodological shortcomings.

First, for different participants, it was collected at different time points during gestation and at different times of the day. Although we did aim to standardize for gestational age and time of day at collection, it does add a certain amount of error to the resulting values. Also, a previous study among this cohort reported a possible moderation effect by time of day 21, which was supported by other studies in which only morning cortisol was associated with the outcomes 22,23. Such evidence from animal research suggests that the cortisol awakening response reflects a different HPA-axis functioning than the cortisol secretion throughout the rest of the day and it is hypothesized to be a fitter marker of psychosocial stress 24,25.

Second, we assessed total serum cortisol: some preliminary evidence suggests that free cortisol is a better marker of pathophysiological effects 26 and that exposure to stress alters the ratio of total vs. free cortisol through a decrease in corticotrophin-binding globulin (CBG) concentrations 27. Yet, even if total cortisol turns out to be an appropriate proxy for free cortisol, which would be more practical in a large cohort study, it might not be the major pathway for fetal programming. In the ABCD cohort, there is no correlation between maternal cortisol and the different psychosocial stress scales. Such a lack of correlation between self-reported and physiological stress is not uncommon in literature 28,29. Diego et al. did report correlations between maternal cortisol and psychological stress measures, but the highest correlation coefficient was 0.4 (cortisol and depressive symptoms). Thus, cortisol might not even be a relevant factor when studying fetal programming by maternal psychosocial stress.

Timing of prenatal stress
In the discussion-section of each research paper in this thesis, we discussed the timing of stress assessment in pregnancy, because it may be key to finding potential fetal programming effects. There are possibly critical periods of a fetus’ vulnerability to insults that remain unclear to date (e.g. 2,30).

The assessment of stress in the ABCD study took place in the first week of the second trimester, thus assessing experienced stress in the preceding first trimester-weeks. The first trimester is often considered the trimester with the highest fetal vulnerability because of the development of critical, basal organ systems 31. Unfortunately, we did not have multiple
measurements throughout pregnancy to test this hypothesis. In the ALSPAC study however, psychosocial stress was also assessed at a second time point later in gestation. Comparing the associations of the first and second assessment with the offspring outcomes did not indicate significant differences (chapter 9).

Our finding that the timing of stress assessment was not influencing the findings, fits with the knowledge that, although the prevalence of psychosocial stress symptoms slightly declines over the course of pregnancy, stress has the tendency to track over the perinatal period 32: A woman reporting high levels of stress early in pregnancy, will also experience high levels of stress in late pregnancy. The single gestational time point of stress assessment in the ABCD study is therefore unlikely responsible for the fact that we did not find convincing evidence of fetal programming by psychosocial stress.

**Reliability of offspring measurements**

Although all measurements in the five year old children were performed by trained staff following a strict protocol (chapter 2), the reliability of some of the measures can be called into question.

Measuring waist circumference is a challenging task, because of the localization of the measurement site most closely associated with metabolic risk in overweight boys and girls 33 – midpoint between the floating rib and iliac crest. Variability in measurement may increase with higher levels of body fat 34, but fortunately the proportion of overweight and obese children in the sample was modest: approximately 10% (based on definitions by Cole et al. 35). Moreover, in the research presented in chapter 5, waist circumference was standardized for height, a rather rigid measure.

The measurement of blood pressure proved to be a little more challenging in children as compared to adults. Many children were having difficulties relaxing their arm during the measurement. To ensure maximum reliability, in the ABCD study, one test measurement was taken before the actual recorded measurements. Also, the mean of two assessments was obtained, and the automatic oscillometric method may have eliminated potential inter-observer differences. Furthermore, the obtained values are fairly similar to those of, for instance, American and Italian children of the same age 36,37.

The bio-electrical impedance analysis allowed us to calculate body fat mass (chapter 5), but the applied equations 38,39 were not specifically intended for children of only five years old. In a recent paper, calculated reference values for four to seven year olds were reported, and those indicate that those original equations underestimate total body water in school age children, and thus overestimate fat mass 40. It is however still unclear whether ethnic-specific equations are warranted, which might be of importance in a multi-ethnic cohort like the ABCD study. In our analyses, we used the Fat Mass Index, which is the fat mass divided by height squared. We analyzed this variable continuously, so we would not have to use an external cutoff score that may not fit our population. After all, even if our assessment of Fat Mass Index led to a systematic over- or underestimation, studying this outcome continuously would lead to the same magnitude of associations. Therefore, we do not believe that our method of fat mass calculation has led to different conclusions.

One assessment at the age five consultation suffered dire limitations was the determination of plasma C-peptide concentrations. Almost half of the samples fell below the laboratory’s detection limit, which forced us to explore the associations with this outcome measure with survival analyses, possibly inducing error. Still, if an association with prenatal maternal...
stress had been present, we would have expected to see (at minimum) a subtle trend regarding either C-peptide or glucose concentrations (chapter 7). Therefore, we do not believe that this limitation influenced the conclusions drawn in this thesis.

**Offspring reactivity**
There is one aspect of the currently presented research that might leave a remaining possibility for an association between prenatal maternal psychosocial stress and offspring cardiometabolic risk factors: we assessed the children in a resting and fasting state. Some previous studies suggest that fetal programming might result in altered reactivity of glucose metabolism, through increased insulin resistance 41, and the autonomic nervous system, through increased sympathetic activity 8,10,42. A metabolic challenge, or induced stress paradigm, might be necessary to observe differences between prenatally exposed and non-exposed offspring.

**KEY ISSUES**

► A novel approach: Measuring cardiac autonomic nervous system activity
Using an ambulatory recording device to measure cardiac autonomic control allowed us to uniquely assess a relatively large cohort of over 3000 children – previous research was conducted in relatively small study populations. Yet we did not find an association between prenatal psychosocial stress and adverse cardiac autonomic control in the offspring, whereas previous studies did 43-49. The offspring age difference is one out of two main factors that might explain the discrepancy. Maybe the offspring of the stressed mothers is resilient: Previous physiological investigations of children suggest that the process of coping with moderate levels of stress early in life promotes the development of arousal regulation and resilience 50,51. This would mean that the differences in cardiac autonomic control have attenuated at age five. The second factor could be that we only assessed the offspring in a resting state. As mentioned above, fetal programming might result in altered reactivity.

► 'Regular' psychosocial stress not a likely cause of fetal programming of cardiometabolic risk
Regarding the cardiovascular risk factors assessed in the offspring in our population, the evidence presented here does not show a convincing pattern: There was no association of prenatal stress with measures of the cardiac autonomic nervous system or blood glucose metabolism. Some evidence did point towards increased adiposity and blood pressure in the children. In light of the null findings, however, such associations are interpreted here with caution. The small increases in offspring BMI in response to pregnancy-related anxiety, job strain, and the cumulation of stressors might be caused by residual confounding, since BMI can be affected by numerous developmental factors. Although we were able to adjust for many potential confounders, one important factor might still be present: Postnatal stress, which is correlated with both prenatal stress and parenting style. Furthermore, the evidence pointing towards a small blood pressure increase in the children was not confirmed in another cohort, and the limited size of this association combined with the absence of a trend (more stress – increasing blood pressure) also point toward residual confounding.

The few human studies that did report on associations between prenatal psychosocial stress and infant/childhood cardiometabolic outcomes were more often than not based on less common yet potentially more severe stressors, i.e. maternal bereavement 52, life stress from living in poverty 46, psychiatric symptoms 49 and major stressful life events 41. Hypothetically,
aside from the mostly null-findings presented in this thesis, severe stress is still suspect of fetal programming. But ‘regular’ prenatal psychosocial stress might just not provoke the fetus sufficiently to adapt, or provoke it in such manner that the effects are compensated in the first life years.

There is one option left that leaves the door slightly open for cardiometabolic programming by ‘regular’ psychosocial stress, which is the assessment of cardiometabolic responsiveness in the offspring: as mentioned before, in addition to the basal measures analyzed in this thesis, it would be informative to subject the offspring to a stress test when assessing ANS functioning, and a glucose challenge when assessing glucose metabolism. Until the outcomes of such research are available, we for now conclude that ‘regular’ psychosocial stress is not a likely cause of fetal programming of cardiometabolic risk.

► Prenatal psychosocial stress not to be disregarded, however

The stressors assessed in the ABCD cohort are present in the day-to-day life of many pregnant women. For instance, the prevalence of depressive symptoms was estimated at 9.6% in women of childbearing age. The peak age at onset for anxiety disorders in women occurs also during the childbearing years. Reports on the prevalence of anxiety symptoms and anxiety disorder during pregnancy range from 0.2 to 15%. But even among those not distressed before pregnancy, about 25% experience some form of psychosocial stress.

We observed small associations between stress during pregnancy and birth outcomes, in line with results from recent reviews. Shortened gestation and small size at birth are associated with adverse later health, and antenatal care should therefore always aim to improve these outcomes. However, first off, the associations are very small, so the benefits of primary prevention may be larger when aimed at other prenatal factors. Second, the stressors in the research presented in this thesis seem to be tightly woven into the pregnant woman’s normal life, and the majority of the population seems to score moderately on the levels of psychosocial symptoms. Therefore, these ‘regular’ psychosocial stressors might not form a very effective preventable factor.

It might be valuable to focus on other prenatal risk factors, correlated with psychosocial stress. As the descriptive characteristics in all of the research papers in this thesis already indicate, lower educated women (lower socioeconomic status) and women of non-Dutch origin have higher scores on the stress scales, and it is exactly this group that is already at increased risk of adverse birth outcomes. Also, previous research in the ABCD cohort revealed that psychosocial stressors are associated with continued smoking during pregnancy, which in itself is an important risk factor for adverse birth outcomes.

Also, prenatal ‘regular’ psychosocial stress has been associated with other outcomes, potentially the result of fetal programming. For instance, in the ABCD study, prenatal maternal anxiety has been associated with problem behavior as well as altered cognitive control in the five year old child. From other research, associations with poorer attention, hyperactivity, behavioral and emotional problems in (pre-school) children have been reported, as well as impulsive behavior and lower intelligence in adolescence (for reviews, see). Furthermore, prenatal stress is highly correlated with postnatal stress, which has been associated alterations of cognitive, behavioral, and psychological development of the offspring, observed from infancy through adolescence.
**FUTURE DIRECTIONS**

**For practice**
The results in this thesis do not directly call for action: primary prevention of psychosocial stress during pregnancy is not (yet) warranted in order to reduce cardiovascular risk in the offspring. However, identifying pregnant women experiencing high levels of psychosocial stress can alert the health care provider to associated (lifestyle) risk factors, as well as postpartum psychosocial complications, which do require intervening. Decreasing high antenatal stress in itself might therefore improve maternal and offspring well-being.

**For research**
As mentioned before, an important recommendation for future research in the field of fetal programming by maternal psychosocial stress would be to assess reactivity of the autonomic nervous system and glucose metabolism in response to challenges in the offspring (e.g. oral glucose tolerance test, ANS reactivity to a stress protocol).

Also, studying severe maternal stress, like major life events, clinical depression and clinical anxiety may result in observing (cardiometabolic) fetal programming effects. Such research should include ways to determine the pathways by which stress exerts its effects, considering increased maternal cortisol secretion, diurnal cortisol variation and the HPA-axis, as well as balance of the sympathetic and parasympathetic branches of the autonomic nervous system and immunological markers. Adding evidence in humans on the potential pathways will strengthen future reports on findings on the association between prenatal circumstances and offspring outcomes.

An up and coming branch of the Developmental Origins of Health and Disease research field is epigenetic research. Fetal circumstances, thus non-genetic factors, may change the expression potential of certain genes (through DNA methylation and histone modification), and these changes may remain throughout the cell’s life and may also last for multiple generations. Therefore, studying epigenetic gene regulation provides a novel approach in attempting to unravel the pathways of fetal programming. Research would have to identify candidate genes, associated with cardiometabolic risk/disease, and study gene expressions in a population of children/adults prenatally exposed to maternal psychosocial stress, with non-exposed matched controls.

The match-mismatch theory may also provide an interesting approach: Possibly, those prenatally exposed to stress will fare best in a high-stress postnatal (adult) environment (prenatal-postnatal match), and those not prenatally exposed fare best in a low-stress postnatal environment (again a match). Concordantly, this theory then suggests that those with a prenatal-postnatal mismatch are worst off: even those with no exposure to prenatal stress. This life-course approach would require, in addition to the assessment of maternal stress, the assessment of psychosocial stress in the offspring, preferably with a long follow-up time until adulthood.
**IN CONCLUSION**
The studies described in this thesis have led to the following main conclusions:

I. A large proportion of pregnant women experience both high levels of anxiety and depressive symptoms (nearly 30%). Such ‘regular’ maternal psychosocial stress is associated with shorter gestation and lower birthweight, but the associations are small.

I. We did not find evidence to support the hypothesis that ‘regular’ psychosocial stress has a role in fetal programming of cardiometabolic risk, measured in childhood during basal (resting) conditions. This finding also ruled out the potentially mediating roles of low birthweight for gestational age and shortened gestation. We did not find an effect-modifying role of offspring sex.

III. In future research, more severe forms of stress, like major life events, clinical depression and clinical anxiety, might still reveal fetal programming effects. Also in future studies, challenges and/or reactivity of the autonomic nervous system and glucose metabolism in the offspring might uncover effects of exposure to maternal stress.
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