Cardio-metabolic risk in children prenatally exposed to maternal psychosocial stress

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The research in this thesis aimed to elucidate whether prenatal exposure to maternal psycho-social stress could be a common, underlying factor influencing fetal growth and cardio-metabolic health in the offspring in childhood. To address this goal, we formulated the following research questions:

1) Is early pregnancy psychosocial stress associated with adverse birth outcomes? (Section A)
2) Is early pregnancy psychosocial stress associated with an adverse cardio-metabolic profile in the child? (Section B)
3) To what extent is the effect of psychosocial stress on cardio-metabolic profile mediated by adverse birth outcomes: shortened gestational duration and/or lower birthweight for gestational age? (Section B)
4) Is the effect of psychosocial stress on cardio-metabolic profile different between boys and girls? (Section B)

These questions were addressed using data from a Dutch (ABCD) and a British prospective birth cohort (ALSPAC), following up the offspring of women enrolled during pregnancy. In the ABCD study, the women filled out a questionnaire at around gestational week 16 (the beginning of the second trimester), that included validated instruments for state anxiety, depressive symptoms, pregnancy-related anxiety, parenting daily hassles and job strain. A cumulative stress score was also calculated (based on 80th percentiles). The children underwent a physical assessment at age five, six or seven (mean age 5.7 years) which included measures of body composition, autonomic nervous system activity, blood glucose metabolism and blood pressure. In the ALSPAC cohort, self-reported anxiety and depressive symptoms were assessed at two time points, in the first and third trimester. Among many other offspring assessments and outcome measures, blood pressure and further vascular parameters were measured at age ten or eleven (mean age 10.7).

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. These findings led to the conclusion that babies from pregnant women reporting both high levels of anxiety and depressive symptoms are at risk for adverse birth outcomes.

In chapter 4, we studied a potential interactive effect between high depressive symptoms and low serum folate status, which are often co-prevalent. This interactive effect was not observed, but we did demonstrate an association between high depressive symptoms and slightly shorter gestational duration. Depressive symptoms was also associated with lower birthweight, however, this was explained by the shortened gestation.

Chapter 5 focused on the question whether high maternal job strain during early pregnancy, as well as high maternal cortisol levels, were associated with increased body mass index (BMI), central adiposity or body fat mass in the offspring at age five. Additionally, we explored whether these associations were modified by gender or mediated by gestational duration and fetal growth restriction. Results showed no associations between prenatal job strain and offspring BMI, central adiposity or body fat mass. Higher maternal cortisol was independently associated with marginally higher body fat mass in girls, but marginally lower body fat mass in boys. This association was not mediated by gestational duration or fetal growth restriction. We concluded that prenatal maternal job strain and cortisol may not program
obesity and adiposity in the next generation in humans at childhood age.

The focus of chapter 6 was on balance of the cardiac autonomic nervous system (ANS) of the child, because a misbalance is a potential causal factor in the development of cardiovascular disease, and it may be programmed during pregnancy due to various maternal factors. We aimed to study maternal prenatal psychosocial stress as a potential disruptor of cardiac ANS balance in the child. The indicators of cardiac ANS were pre-ejection period, heart rate, respiratory sinus arrhythmia and cardiac autonomic balance, measured with electrocardiography and impedance cardiography in a resting state. None of the multiple stress scales (state anxiety, depressive symptoms, pregnancy-related anxiety, parenting daily hassles and job strain) was associated with the ANS measures, and neither was the cumulation of said stress scales. We concluded that these results do not support the hypothesis that prenatal maternal psychosocial stress deregulates cardiac ANS balance in the offspring, at least in rest, and at the age of five years. We recommended further research on offspring cardiac ANS functioning in response to stress.

In chapter 7, like in chapter 5, we focused on BMI (and were able to include more mother-child pairs), but also on blood glucose profile in the children. Furthermore, we studied potential associations with multiple prenatal stressors, as well as the cumulation of psychosocial stressors. The single stress scales and the cumulative stress score were not associated with glucose, C-peptide or insulin resistance. Pregnancy-related anxiety and high job strain were associated with slightly higher offspring BMI. BMI was also slightly higher in the highest cumulative stress category (3%), as compared to the children of women in the no stress-category (54%). We concluded that prenatal psychosocial stress was associated with small increases in offspring BMI at age five, but not with fasting glucose metabolism. We recommended further research on offspring glucose metabolism in response to a metabolic challenge.

Chapter 8 focused on a potential association between prenatal maternal psychosocial stress and blood pressure in the child at age five. The single stress scales were not associated with blood pressure or hypertension. The cumulation of stressors was associated with slightly higher systolic and diastolic blood pressure, but it did not significantly increase the risk for hypertension. Associations did not differ between sexes. We concluded that the presence of multiple psychosocial stressors during pregnancy may be associated with higher blood pressure in the child.

The focus of chapter 9 is also on blood pressure in the child, but using data from a different birth cohort (UK-based ALSPAC) allowed us to also study other vascular parameters, namely endothelial function, arterial stiffness, brachial artery distensibility and brachial artery diameter. These outcomes were assessed in the offspring at age 10. We investigated whether 1) maternal psychosocial stress (depression and anxiety) during pregnancy was associated with offspring vascular function 2) any association differed depending on whether maternal stress was assessed during the first or third trimester, and whether there was evidence that any associations were likely to be due to intrauterine mechanisms by 3) comparing associations with paternal depression and anxiety and 4) examining whether prenatal associations were explained by maternal postnatal stress. With the exception of diastolic blood pressure and brachial artery diameter, there were no associations of maternal depressive symptoms with any of the vascular outcomes. Maternal anxiety symptoms were associated with lower offspring diastolic blood pressure. Paternal symptoms were not associated with offspring outcomes. Maternal postnatal depressive symptoms were associated with higher offspring
systolic blood pressure. We concluded that our results do not support the hypothesis that maternal stress during pregnancy adversely affects offspring vascular function, detectable at age 10, via intrauterine mechanisms.

In chapter 10, we discussed the main findings in light of the current literature, we considered some methodological issues, and made recommendations for future research. Overall, the evidence presented in this thesis showed no association of prenatal stress with measures of the cardiac autonomic nervous system or blood glucose metabolism in the child. Some evidence pointed towards increased adiposity and blood pressure, but these associations need to be interpreted with caution due to potential residual confounding. Mediation by gestational duration and birthweight was ruled out in many instances because of the absence of the main association, but independently they were associated with some of the offspring cardio-metabolic outcomes, with generally more convincing results for reduced birthweight for gestational age than shorter gestation. There was no persuasive evidence of effect-modification by offspring sex.

In future research, it would be recommendable to study more severe forms of stress, like major life events, clinical depression and clinical anxiety. This in order to assess potential fetal programming effects in more challenged conditions. Another recommendation is to assess reactivity of the autonomic nervous system and glucose metabolism in the offspring, because the exposure to maternal stress may not have affected basal values yet, but it may have affected the sensibility of these systems.

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.

II. We did not find evidence to support the hypothesis that ‘regular’ psychosocial stress has a role in fetal programming of cardio-metabolic 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.