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Prenatal maternal psychopathology and stress and offspring HPA axis function at 6 years

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ABSTRACT

Objective: Intrauterine exposures such as maternal psychopathology and stress are known to influence the physical and mental health of the offspring. One of the proposed pathways underlying these associations is dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity in the offspring. This study examined the relation of perinatal maternal symptoms of psychopathology and stress with offspring HPA axis activity at 6 years as measured by hair cortisol and cortisone concentrations.

Methods: The study was part of the population-based Generation R Study, a prospective population-based cohort from fetal life onwards. 2546 children and their mothers formed the study population. Perinatal maternal psychopathology and stress were assessed by questionnaires in the second and third trimester. Principal components for both psychopathology and stress were created to reduce the number of explanatory variables. Child hair samples for cortisol and cortisone measurements were collected at the age of 6. Linear regression analysis, adjusted for covariates, was used to examine associations between maternal psychopathology and stress and child hair cortisol and cortisone levels.

Results: The maternal psychopathology principal component was associated with higher child hair cortisone (adjusted B = 0.24, 95%CI 0.08;0.40, p-value < 0.01). Effect estimates of the individual dimensions ranged from 0.97 (95%CI 0.21;1.73, p-value = 0.01) for interpersonal sensitivity to 1.67 (95%CI 0.86;2.47, p-value < 0.01) for paranoid ideation. In addition, children exposed to intrauterine stress, as measured by the principal component, had higher hair cortisone levels (adjusted B = 0.54, 95%CI 0.21;0.88, p-value < 0.01). Exposure to maternal psychopathology and stress was not associated with offspring hair cortisol. Stratification by child sex resulted in associations between maternal symptoms of psychopathology during pregnancy and child hair cortisone levels in boys and associations between maternal symptoms of stress during pregnancy and child hair cortisone levels in girls.

Conclusion: Our results suggest that maternal psychopathology and stress during pregnancy are associated with long-term HPA axis activity of the offspring. The association of maternal psychopathology and stress during pregnancy with offspring hair cortisone levels is a novel finding. Future studies should examine whether these psychophysiological differences between exposed and non-exposed children underlie offspring morbidity associated with maternal psychopathology and stress during pregnancy.

1. Introduction

Many intrauterine exposures are known to influence the physical and mental health of the offspring (Barker, 2004; Van den Bergh, 2011). Maternal psychopathology and stress during pregnancy are among the most common intrauterine exposures associated with a

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negative impact on the offspring's health (Ding et al., 2014; Woody et al., 2017). Exposure to maternal psychopathology or stress during pregnancy is associated with preterm birth and low birth weight (Grote et al., 2010). In the long-term, maternal psychopathology or stress during pregnancy is related to behavioral, emotional, cognitive and motor problems in childhood (Field, 2011; Goodman et al., 2011) and psychiatric disorders in adolescence (Pearson et al., 2013; Van den Bergh et al., 2008). Inter-generational transfer of psychopathology and stress is believed to be caused by a combination of intrauterine environment, genetics and postnatal environmental factors (Braithwaite et al., 2014; Marceau et al., 2013; Pluess and Belsky, 2011). Previous research has shown associations between intrauterine maternal psychopathology and stress and child outcomes to be independent of genetics and postnatal factors (O'Connor et al., 2003; Pearson et al., 2013). This has led scientists to propose models adapted to the 'developmental programming hypothesis' (Barker, 1998, 1999, 2004). The original hypothesis was proposed to explain associations between low birth weight and later cardiovascular diseases and diabetes. According to this programming hypothesis, the fetus or infant adapts as a response to the health and physical state of the mother, thereby altering important physiological and metabolic processes that can endure into adulthood (Barker, 1998, 1999, 2004). This model has been adapted to explain associations between exposure to maternal psychopathology or stress and later behavioral, emotional and cognitive difficulties in offspring as well. Although a number of intrauterine mediation pathways have been proposed, the most widely accepted and most investigated candidate system that could be altered by adverse intrauterine exposures, is the hypothalamic-pituitary-adrenal (HPA) axis, especially since plasticity is high during early fetal development (Braithwaite et al., 2014; Talge et al., 2007). The HPA axis plays a key role in many homeostatic systems in the body and in the body's response to stress. In numerous studies, alterations in HPA axis activity have been associated with psychosomatic and psychiatric disorders, as well as with cardiovascular, infectious and inflammatory diseases (Gifford and Reynolds, 2017; Kudielka and Kirschbaum, 2005).

Cortisol, the end product of the HPA system, is often used to investigate HPA axis reactivity, especially in studies on psychological stress. There are several conventional methods to measure cortisol, such as saliva, blood or urine samples. These measures reflect cortisol levels at the time of sampling and are all highly influenced by daily fluctuations due to circadian rhythms and fluctuations based on homeostatic regulation (McEwen, 2000), potentially creating methodological problems associated with collection. Conventional measures therefore reflect a 'snapshot' of HPA axis activity and may not be the most informative measure in the evaluation of long-term HPA axis activity. An increasingly used non-invasive method for detecting differences in individual's long-term stress levels is hair cortisol analysis (Liu et al., 2016; Staufenbiel et al., 2013; Vanaelst et al., 2013). Cortisol extracted from hair samples reflects accumulated concentrations and can therefore give a more stable and long-term indication of HPA axis activity than saliva, blood or urine collection. Hair grows with approximately 1 cm per month (Pragst and Balikova, 2006), enabling assessment of mean cortisol concentrations of the last couple of months (Stalder et al., 2012). Previous research showed that hair cortisol is most strongly associated with the prior 30-day integrated cortisol production measure (Short et al., 2016), or three-day average of single-day salivary level (Zhang et al., 2018), both supporting the notion that hair cortisol reflects long-term cortisol levels. Low to moderate correlations with short-term levels as single-point saliva cortisol levels were observed (Zhang et al., 2018).

With the introduction of liquid chromatography tandem-mass spectrometry (LC–MS/MS) (Noppe et al., 2015), the additional quantification of cortisone in scalp hair has become possible, which is metabolized from cortisol in the peripheral tissues by the 11ß-hydroxysteroid-dehydrogenase enzyme type 2 (11ß-HSD-2), where it might act as reserve capacity for cortisol. Adding cortisone in parallel to cortisol may give even more insight into the cumulative amount of active and inactive corticosteroids in the body. Previous research showed elevated hair cortisone concentrations in young children under psychosocial stress (Vanaelst et al., 2013). Another study even suggests salivary cortisone can provide a better reflection of systemic cortisol levels than salivary cortisol (Perogamvros et al., 2010).

A limited number of studies have related maternal psychopathology and stress during pregnancy to changes in HPA axis functioning in the offspring, mostly in the first year of life. One prospective longitudinal study assessed maternal feelings of stress and anxiety in the last trimester of pregnancy and infant cortisol reactivity, measured through saliva, at 5 and 8 weeks and at 5 and 12 months of age (Tollenaar et al., 2011); higher infant cortisol reactivity was observed at 5 and 8 weeks and at 12 months in children exposed to intrauterine anxiety. In another prospective study the association of antenatal depression with infant cortisol reactivity at 2 months of age was examined and a U-shaped relationship between antenatal depression and cortisol reactivity was observed, suggesting that infants exposed to both low and high levels of maternal depression showed greater cortisol reactivity than infants exposed to moderate levels of antenatal depression (Fernandes et al., 2015). In contrast, another prospective study among 88 mother-child dyads did not observe an association of prenatal maternal depressive symptoms with infant cortisol reactivity at 2 months (Braithwaite et al., 2016). Yet, whether symptoms of psychopathology and stress during pregnancy affect long-term HPA axis activity in the offspring is largely unknown.

The objective of the current study was therefore to investigate whether maternal psychopathology and stress during pregnancy are associated with offspring HPA axis activity at 6 years of age. We examined several dimensions of psychopathology, including depression and anxiety, as well as different forms of experienced stress during pregnancy such as stressful life events and pregnancy-related anxiety. For long-term HPA axis activity we measured both hair cortisol and the novel biomarker hair cortisone when children were 6 years of age. We hypothesized, in line with previous short-term findings, that maternal symptoms of psychopathology and stress during pregnancy are related to heightened cortisol and cortisone levels in the offspring. As previous research suggests effects on child outcomes to be sex dependent (Braithwaite et al., 2018, 2017a; Braithwaite et al., 2017b; Gifford and Reynolds, 2017; Sandman et al., 2013), we additionally examined results by child sex.

2. Methods

2.1. Setting and population

The present study was embedded in an on-going population-based cohort, the Generation R Study, designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health from fetal life, childhood and young adulthood (Kooijman et al., 2016). In total, n = 8880 mothers were enrolled during pregnancy with deliveries from April 2002 to January 2006. The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, approved the study. Written informed consent was obtained from all participants.

For the present explorative analysis, only children who participated in the pre- and postnatal follow-up (n = 7510) were considered (Fig. 1). Of these, 1457 children were excluded, as they did not visit the research center in childhood, when hair samples are collected. Information on maternal psychopathology and stress parameters was missing in 338 children. Hair collection did not start immediately at onset of this data collection wave and 3161 children were not approached. The response rate for children that were approached for hair collection was 85% (Noppe et al., 2016). Cortisol concentration could be quantified in 2523 children and cortisone in 2485 children. Extreme outliers, defined as cortisol or cortisone levels > 4SD (standard deviation), indicating

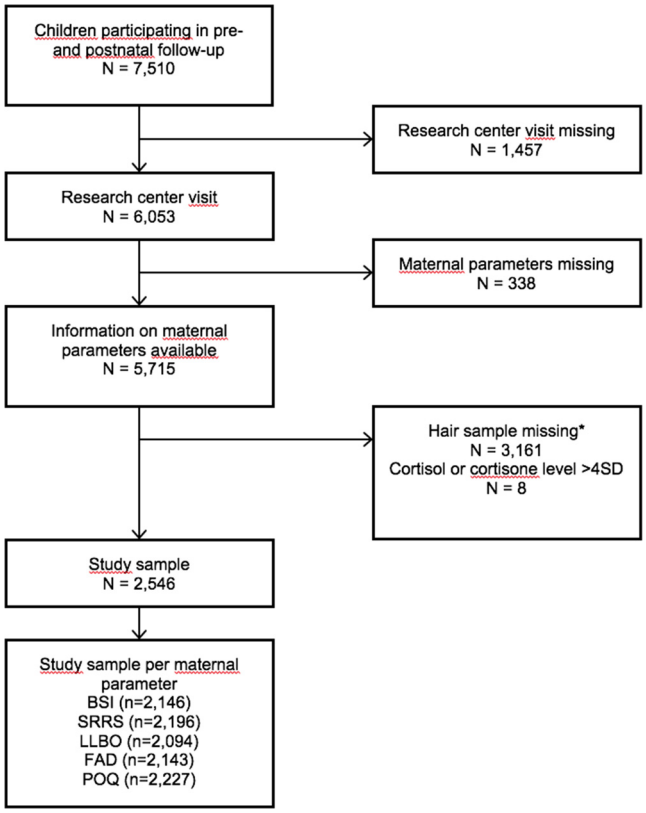

Fig. 1. Flowchart of study sample.
* Hair collection did not start immediately at onset of this research wave. The response rate for children asked for hair collection was 85%.

contamination, were excluded. Thus, n = 2546 formed the final study population for analysis.

2.2. Maternal psychopathology

In the second trimester (at 20–25 weeks of gestation), the Brief Symptom Inventory (BSI) was administered. The BSI is a validated 53-item (5-point scale) self-report symptom inventory outlined to ascertain the psychological state of individuals in the preceding 7 days (Beurs and Zitman, 2018; Derogatis and Melisaratos, 1983). The BSI has nine dimensions designed to assess individual symptom groups. For this study, we used the Global Severity Index (GSI), the overall mean designed to help quantify a patient's severity-of-illness. In addition, we used the specific dimensions of the BSI: somatization, obsessive-compulsivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The scores for the GSI and each dimension separately are calculated by dividing the sum of all items by the number of items. Sum scores per subscale therefore range from zero to four, with a higher score indicating more symptoms on that specific subscale.

2.3. Maternal stress

Multiple questionnaires were administered in the second and third trimester to measure different dimensions of stress, including stressful life events, long lasting difficulties, family functioning and pregnancy related stress. The Dutch-adapted version of the Social Readjusting Rating Scale (SRRS) was administered to assess the occurrence of repeated stressful life events in the preceding 12 months (Holmes and Rahe, 1967). The SRRS consists of 10 yes/no questions and items each have a certain amount of life change units (LCU). The sum score is the total of LCU's. The Long Lasting Difficulties Questionnaire (LLDQ) was administered for measurement of financial, health or social problems in the preceding 12 months (Hendriks and van de Willige, 1990). We used an adjusted version of the Dutch LLDQ consisting of 12 items that are scored on a 5-point scale. Maximum score per item is 3, leading to a sum score between 0 and 36. The Family Assessment Device (FAD) was administered to evaluate dimensions of family function (Epstein et al., 1983). In this study, we applied the General Family functioning subscale, which consists of 12 items rated on a 4-point scale. This subscale assesses the overall health and pathology of the family. The sum score is the mean of the items scores and therefore has a value between 1 and 4. A score above 2.17 is seen as pathological. To measure stress/anxiety concerning the pregnancy and the baby, a Dutch adapted version of the Pregnancy Outcome Questionnaire (POQ) was administered consisting of 13 items, rated on a 4-point scale, with a maximum score of 3 per item (Theut et al., 1988). The sum score is the mean of the item scores and is therefore a value between 0 and 3.

2.4. Hair cortisol/cortisone

For extraction of hair cortisol and cortisone, hair samples of approximately 100 strands were cut from the posterior vertex using small surgical scissors, as close to the scalp as possible. Hair locks were then taped to a piece of paper with the scalp end marked, and stored in an envelope at room temperature until further analysis. Briefly, the proximal 3 cm of hair samples were weighed using an electrical scale and minced. Hair samples were then washed in LC-grade isopropanol for 2 min at room temperature, and left to dry for at least 2 days. Deuterium labeled cortisol and cortisone were added prior to extraction. Extraction was performed using LC-grade methanol for 18 h at 25 °Celsius, in a gently shaking water basin. The extract was then transferred to a glass tube, centrifuged at 4300*g* (gravity), and evaporated to dryness at 37 °Celsius under a constant flow of N_2. After reconstitution in 1 ml 2% LC-grade methanol, the extract was loaded on an offline solid phase extraction plate (HLB Oasis 96-well SPE plate, Waters Chromatography), washed with 1 ml 30% LC-grade methanol, and eluted twice in 300 µl 100% LC-grade methanol. The extract was then evaporated to dryness at 50 °Celsius under a constant flow of N_2 and stored at 4 °Celsius until further analysis. Prior to analysis, the samples were reconstituted in 100 µl eluent (running fluid), mixed using a vortex mixer, and analyzed using LC–MS/MS (Xevo TQS, Waters Chromatography) (Rippe et al., 2016).

2.5. Covariates

Potential covariates were selected based on prior research (Fernandes et al., 2015; Rippe et al., 2016; Tollenaar et al., 2011). Age, marital status, parity, gender child, ethnicity, hair color of child, education, family income, number of persons in a household and alcohol and smoking behavior were based on self-report. Marital status was dichotomized into 'married, registered partnership or living together' versus 'no partner'. Maternal ethnicity was categorized according to the classification of Statistics Netherlands (Netherlands, 2004a, b). Educational level was categorized in three levels: primary, secondary and higher education (Netherlands, 2004b). Family income was defined as the total net monthly income of the household, categorized as less than €1200 (US $1551) (below social security level), €1200 to €2000 (US $1551-US $2586), and more than €2000 (US $2586) (more than modal income). Information about maternal prenatal alcohol use and smoking was based on questionnaires in each trimester. Both alcohol use and smoking were categorized in: never drank/smoked in pregnancy, drank/smoked in early pregnancy or drank/smoked throughout pregnancy.

2.6. Statistical analyses

First, descriptive statistics of the study population were provided.

Data was explored using histograms and calculating correlations between the different psychopathology and stress measures. The correlation of the subscales of the BSI were moderately to strongly correlated ($0.45 < r < 0.78$), while the stress parameters (SRRS, LLDQ, FAD and POQ) during pregnancy only showed weak to moderate correlations ($0.15 < r < 0.37$). Hair cortisol and cortisone measurements showed a strong correlation ($r = 0.66$).

To reduce the number of explanatory variables tested, we performed principal component analysis (PCA) in two groups: psychopathology (BSI subscales) and stress (SRRS, LLDQ, FAD and POQ). PCA is a statistical technique to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components. To check if we can factorize the original variables efficiently we used the Bartlett's sphericity test and the Kaiser-Mayer-Olkin index. Both indicated our data was suitable for PCA. Subsequently, we performed principal component regression with the retrieved principal components with an eigenvalue above one. For the psychopathology group, one principal component was retrieved with component loadings of the items between 0.74 and 0.90. For the stress parameters, one principal component with item loadings between 0.64 and 0.80 was retrieved. Only when an association between the principal component and outcome variable was observed (as defined by a p-value < 0.05), linear regression analysis was used to examine the relations of the individual psychopathology and stress measures with the outcome variable as to further examine the contribution of each individual measure. We performed the same analysis stratified by child sex.

Based on the 5% change-in-estimate (Rothman et al., 2008), we corrected for the following confounders: marital status, parity, ethnicity, education, family income, number of people in a household and alcohol behavior. The other covariates, namely age, gender child, hair color of child and smoking behavior, did not reach a 5% change-in-estimate. On average, 4.5% of data across the covariates was missing. To avoid complete case analysis bias, we accounted for missing information on the confounders (determinants and outcomes were not imputed) by using multiple imputation methods. As recommended, imputations were based on the relations between all variables in the study (Greenland and Finkle, 1995). We report only the pooled estimates of the analysis of the 10 imputed datasets. Analysis with non-imputed data gave similar results compared to the imputed dataset. Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis.

3. Results

3.1. Descriptive statistics

Prenatal and postnatal characteristics of the study population are shown in Table 1. Mean age of women at study inclusion was 30.5 years and the majority of women were primigravida. Due to the urban character of the study, a variety of ethnicities were present, with a little over half of the participants being Dutch. About half of the population had a higher education (48.5%). Median symptoms of psychopathology and stress during pregnancy were low, as to be expected in a population-based study.

3.2. Prenatal exposure to psychopathology and stress and child hair cortisol

The analysis of the maternal psychopathology principal component initially showed an association with child hair cortisol levels (B = 0.17, 95%CI 0.05;0.29, p-value < 0.01). However, this association was largely explained by confounding factors (adjusted B = 0.11, 95%CI -0.02;0.24, p-value = 0.10). The same was observed for the maternal stress principal component: the unadjusted association of the maternal stress principal component with child hair cortisol (B = 0.33, 95%CI 0.09;0.56, p-value < 0.01) attenuated after adjustment for confounders (adjusted B = 0.23, 95%CI -0.05;0.51, p-value = 0.11). No sex-specific associations of prenatal stress or psychopathology with child hair cortisol levels were observed.

Table 1
Descriptive characteristics of the study population.

Characteristic	n = 2546
Age, mean (SD)	30.5 (5.0)
Parity, median (range)	0 (0 – 6)
Marital status (%)	
No partner	282 (11.6)
Married, registered or living together	2157 (88.4)
Ethnicity (%)	
Dutch	1353 (53.6)
Turkish	241 (9.5)
Moroccan	161 (6.4)
Cape Verdean	82 (3.2)
Dutch Antillean	46 (1.8)
Surinamese	196 (7.8)
Other Western	223 (8.8)
Other Non-Western	223 (8.8)
Educational level mother (%)	
Primary education / none	232 (9.5)
Secondary education	1027 (42.0)
Higher education	1189 (48.6)
Drinking habits (%)	
Never drank in pregnancy	1064 (44.6)
Drank in early pregnancy	344 (14.4)
Drank throughout pregnancy	975 (40.9)
Smoking habits (%)	
Never smoked in pregnancy	1755 (75.1)
Smoked in early pregnancy	217 (9.3)
Smoked throughout pregnancy	366 (15.7)
Household income (%)	
< €1200	165 (7.5)
€1200-2000	320 (14.5)
> €2000-2400	1724 (78.0)
Number of people in household, mean (SD)	2.2 (0.8)
Maternal psychopathology during pregnancy, median (range)	
Somatisation	0.3 (0 – 4)
Obsessive-compulsivity	0.4 (0 – 3.8)
Interpersonal sensitivity	0 (0 – 3.8)
Depression	0 (0 – 3.8)
Anxiety	0.2 (0 – 4)
Hostility	0.2 (0 – 4)
Phobic anxiety	0 (0 – 3.8)
Paranoid ideation	0 (0 – 3.8)
Psychoticism	0 (0 – 3.4)
Global Severity Index	0.2 (0 – 3)
Maternal stress during pregnancy, median (range)	
Social Readjusting Rating Scale	0 (0 – 474)
Long Lasting Difficulties Questionnaire	1.0 (0 – 27)
Family Assessment Device	1.4 (1 – 3.7)
Pregnancy Outcome Questionnaire	0.8 (0 – 2.4)
Child hair measurements, median (range)	
Cortisol in pg/mg	1.6 (0.1 – 70.1)
Cortisone in pg/mg	7.6 (0.1 – 44.0)

3.3. Prenatal exposure to psychopathology and stress and child hair cortisone

Table 2 demonstrates the results of the linear regression models of maternal psychopathology and stress during pregnancy and child hair cortisone levels. There was an association of overall maternal psychopathology during pregnancy with child hair cortisone (B = 0.22, 95%CI 0.10;0.34, p-value < 0.01), which remained present after adjustment for confounders (adjusted B = 0.18, 95%CI 0.05;0.31, p-value < 0.01). Additionally, Table 2 shows that effect estimates of the different maternal psychopathology scales during pregnancy and child hair cortisone ranged from 0.54 (95%CI -0.02;1.10, p-value = 0.06) for

Table 2
Linear regression analysis of psychopathology and stress on cortisone.

Maternal predictors	Unadjusted, β (95% CI)	p-value	Partially adjusted[1], β (95% CI)	p-value	Fully adjusted[2], β (95% CI)	p-value
Principal component – psychopathology	0.22 (0.10;0.34)	< 0.01	0.18 (0.06;0.31)	< 0.01	0.18 (0.05;0.31)	< 0.01
Psychopathology (BSI)						
Overall psychopathology	1.77 (1.00;2.54)	< 0.01	1.49 (0.67;2.31)	< 0.01	1.48 (0.64;2.32)	< 0.01
Somatisation	1.37 (0.76;1.99)	< 0.01	1.08 (0.41;1.75)	< 0.01	1.05 (0.37;1.73)	< 0.01
Obsessive-compulsive	0.64 (0.09;1.18)	0.02	0.55 (-0.01;1.10)	0.05	0.54 (-0.02;1.10)	0.06
Interpersonal Sensitivity	0.95 (0.36;1.53)	< 0.01	0.76 (0.16;1.36)	0.01	0.73 (0.13;1.34)	0.02
Depression	0.99 (0.38;1.60)	< 0.01	0.79 (0.16;1.43)	0.01	0.78 (0.13;1.43)	0.02
Anxiety	1.25 (0.64;1.86)	< 0.01	1.00 (0.35;1.64)	< 0.01	0.98 (0.32;1.63)	< 0.01
Hostility	1.15 (0.47;1.83)	< 0.01	0.87 (0.16;1.58)	0.02	0.87 (0.15;1.59)	0.02
Phobic Anxiety	1.47 (0.64;2.31)	< 0.01	1.16 (0.28;2.03)	< 0.01	1.07 (0.19;1.95)	0.02
Paranoid Ideation	1.36 (0.75;1.97)	< 0.01	1.14 (0.51;1.78)	< 0.01	1.15 (0.50;1.80)	< 0.01
Psychoticism	1.60 (0.76;2.43)	< 0.01	1.32 (0.45;2.20)	< 0.01	1.28 (0.39;2.16)	< 0.01
Principal component – stress	0.50 (0.26;0.73)	< 0.01	0.48 (0.21;0.74)	< 0.01	0.51 (0.23;0.79)	< 0.01
Stress						
Social stress (SRRS)	0.01 (0.00;0.01)	0.01	0.00 (-0.00;0.01)	0.05	0.00 (0.00;0.01)	0.08
Long-lasting stress (LLBO)	0.18 (0.09;0.26)	< 0.01	0.17 (0.08;0.26)	< 0.01	0.18 (0.09;0.28)	< 0.01
Family functioning (FAD)	0.45 (-0.16;1.05)	0.15	0.10 (-0.54;0.75)	0.76	0.04 (-0.62;0.70)	0.90
Pregnancy specific anxiety (POQ)	1.12 (0.34;1.89)	< 0.01	0.85 (0.01;1.69)	0.05	0.77 (-0.08;1.63)	0.08

BSI = Brief Symptom Inventory.
GSI = Global Severity Index.
SRRS = Social Readjustment Rating Scale.
LLBO = Long Lasting Difficulties Questionnaire.
FAD = Family Assessment Device.
POQ = Pregnancy Outcome Questionnaire.
1. Adjusted for: ethnicity, education level, parity, alcohol use.
2. Adjusted for: ethnicity, education level, parity, alcohol use, marital status, family income, number of people in household.

obsessive-compulsive symptoms and child hair cortisone to 1.28 (95%CI 0.39;2.16, p-value < 0.01) for psychoticism and child hair cortisone.

The stress principal component was also associated with child hair cortisone, both before (B = 0.50, 95%CI 0.26;0.73, p-value < 0.01) and after adjustment for confounding factors (adjusted B = 0.51, 95%CI 0.23;0.79, p-value < 0.01). Subsequent analysis of all individual stress measures in relation to child hair cortisone pointed out that the association was largely driven by long-lasting difficulties (adjusted B = 0.18, 95%CI 0.09;0.28, p-value < 0.01).

Analyses were stratified by sex (Table 3). In boys, maternal psychopathology during pregnancy was associated with child hair cortisone levels (adjusted B = 0.20, 95%CI 0.02;0.38, p-value 0.03), while in girls maternal stress during pregnancy was associated with child hair cortisone levels (adjusted B = 0.64, 95%CI 0.26;1.02, p-value < 0.01).

4. Discussion

In this population-based study, we found that maternal symptoms of psychopathology during pregnancy were associated with hair cortisone levels in children 6 years of age. Higher levels of symptoms on different psychopathology subscales prenatally were associated with increased levels of child hair cortisone. Additionally, we found an association of maternal symptoms of stress during pregnancy, in particular long-lasting difficulties, with child hair cortisone. In contrast, the exposure to maternal symptoms of psychopathology and stress during pregnancy was not related to child hair cortisol levels. However, the direction of the effect on cortisol, while not significant, was similar to that of cortisone. Stratification by child sex resulted in associations between maternal symptoms of psychopathology during pregnancy and child hair cortisone levels in boys and associations between maternal symptoms of stress during pregnancy and child hair cortisone levels in girls.

Previous studies examining exposure to prenatal psychopathology and stress and child HPA axis functioning mostly use salivary cortisol, which is more susceptible to daily fluctuations than the hair cortisol measurement used in the present study. These prior studies have shown higher cortisol levels in children exposed to both low and high levels of intrauterine psychopathology (Fernandes et al., 2015; Gutteling et al., 2005). For example, a prospective study performed among 133 infants in India showed infants exposed to the lowest and highest levels of maternal depressive symptoms during intrauterine life had elevated salivary cortisol responses to immunization at 2 months of age (Fernandes et al., 2015). Another study among 29 mother-child pairs showed children whose mothers had pregnancy specific anxiety showed higher levels of salivary cortisol on school days at 5 years of age (Gutteling et al., 2005). Contrary to our expectations that were based on prior literature, we found no associations of prenatal maternal psychopathology and stress with hair cortisol levels in children 6 years of age. The discrepancy could originate from the difference in measurement method of cortisol. Salivary cortisol reflects the level at the time of sampling. In both prior studies (Fernandes et al., 2015; Gutteling et al., 2005), cortisol was measured after induction of a stressor to measure the stress response reaction. Cortisol assessed from hair samples is a more stable long-term stress indicator, not dependent on stressors during sampling (Staufenbiel et al., 2013). Possibly, intrauterine exposure to maternal psychopathology and stress influences the immediate stress response but not long-term (basal) cortisol levels.

As expected, higher levels of hair cortisone in children exposed to intrauterine psychopathology and stress were observed in the present study. Especially long-lasting difficulties were associated with child hair cortisone levels, indicating that chronicity of stress might have a greater influence than other forms of stress such as single stressful events. Interest in the use of hair cortisone as an additional biomarker to cortisol for psychopathology and stress has recently increased. Cortisone, conversed from cortisol by the 11ß-hydroxysteroid-dehydrogenase enzyme type 2, has been shown to be higher than cortisol in hair of children (Raul et al., 2004), just as in our study, and might therefore be a more sensitive measure of HPA axis activity than cortisol. For example, one previous prospective cohort study has examined the influence of stress in children on hair cortisone levels (Vanaelst et al., 2013). Hair cortisone levels of 168 elementary school girls (5 to 10 years old) were measured and child-reported stress was obtained through questionnaires. Associations of increased hair cortisone and concurrent stressful events were observed. Another recent study among

Table 3
Linear regression analysis of psychopathology and stress principal component on cortisone per gender child.

Maternal predictors	Unadjusted, β (95% CI)	*p*-value	Partially adjusted[1], β (95% CI)	*p*-value	Fully adjusted[2], β (95% CI)	*p*-value
Gender: boy (n = 1163)						
Principal component – psychopathology	0.19 (0.03;0.35)	0.02	0.21 (0.03;0.38)	0.02	0.20 (0.02;0.38)	0.03
Overall psychopathology	1.22 (0.15;2.29)	0.03	1.39 (0.24;2.54)	0.02	1.32 (0.15;2.49)	0.03
Somatisation	0.83 (-0.03;1.69)	0.06	0.87 (-0.07;1.82)	0.07	0.78 (-0.17;1.74)	0.11
Obsessive-compulsive	0.56 (-0.21;1.33)	0.15	0.69 (-0.11;1.48)	0.09	0.66 (-0.15;1.46)	0.11
Interpersonal Sensitivity	0.75 (-0.07;1.58)	0.07	0.75 (-0.10;1.61)	0.08	0.70 (-0.17;1.56)	0.11
Depression	0.54 (-0.32;1.40)	0.22	0.65 (-0.26;1.13)	0.16	0.62 (-0.31;1.54)	0.19
Anxiety	0.90 (0.07;1.72)	0.03	0.94 (0.07;1.82)	0.04	0.85 (-0.04;1.74)	0.06
Hostility	0.80 (-0.18;1.78)	0.11	0.89 (-0.14;1.90)	0.09	0.89 (-0.15;1.92)	0.10
Phobic Anxiety	1.46 (0.30;2.62)	0.01	1.51 (0.30;2.72)	0.01	1.37 (0.16;2.59)	0.03
Paranoid Ideation	1.01 (0.18;1.85)	0.02	1.10 (0.21;1.98)	0.02	1.09 (0.19;1.99)	0.02
Psychoticism	0.68 (-0.42;1.78)	0.22	0.73 (-0.43;1.89)	0.22	0.66 (-0.51;1.83)	0.27
Principal component – stress	0.29 (-0.05;0.63)	0.10	0.38 (0.00;0.77)	0.05	0.36 (-0.06;0.77)	0.09
Gender: girl (n = 1294)						
Principal component – psychopathology	0.24 (0.07;0.41)	< 0.01	0.14 (-0.03;0.32)	0.11	0.15 (-0.03;0.33)	0.11
Principal component – stress	0.70 (0.38;1.02)	< 0.01	0.55 (0.19;0.91)	< 0.01	0.64 (0.26;1.02)	< 0.01
Social stress (SRRS)	0.01 (0.00;0.02)	< 0.01	0.01 (0.00;0.01)	0.04	0.01 (0.00;0.01)	0.02
Long-lasting stress (LLBO)	0.23 (0.11;0.35)	< 0.01	0.18 (0.05;0.31)	< 0.01	0.21 (0.08;0.34)	< 0.01
Family functioning (FAD)	1.20 (0.40;2.00)	< 0.01	0.64 (-0.21;1.50)	0.14	0.67 (-0.20;1.55)	0.13
Pregnancy specific anxiety (POQ)	0.73 (-0.28;1.74)	0.16	0.10 (-1.00;1.20)	0.85	0.14 (-0.98;1.25)	0.81

BSI = Brief Symptom Inventory.
GSI = Global Severity Index.
SRRS = Social Readjustment Rating Scale.
LLBO = Long Lasting Difficulties Questionnaire.
FAD = Family Assessment Device.
POQ = Pregnancy Outcome Questionnaire.
1. Adjusted for: ethnicity, education level, parity, alcohol use.
2. Adjusted for: ethnicity, education level, parity, alcohol use, marital status, family income, number of people in household.

62 pregnant women evaluated the association between maternal symptoms of depression, somatization and stress and maternal hair cortisol and cortisone levels and observed stronger associations with hair cortisone than with hair cortisol (Scharlau et al., 2018). To our knowledge, there are no studies that examined intrauterine exposure to maternal psychopathology and stress and influence on child hair cortisone levels. An explanation for our findings – increased cortisone levels but an absence of increased cortisol levels – is therefore not readily available. Further research has to examine influence of 11ß-HSD-2 activity and corticoid binding globulin (CBG) levels or affinity resulting in different concentrations of free corticosteroids and thus influencing incorporation of cortisol and cortisone into hair from the bloodstream.

Sex-specific analyses resulted in slightly different associations than overall analyses. Where in boys only maternal symptoms of psychopathology during pregnancy were associated with child hair cortisone, in girls only an association between maternal symptoms of stress during pregnancy and child hair cortisone was observed. A recent systematic review examined available studies on sex-differences in early-life programming of the HPA axis in humans and concluded, based on 23 studies, increased vulnerability of the female HPA axis compared to males (Carpenter et al., 2017). Our finding, an association between maternal prenatal stress and increased cortisone levels in girls only, is in accordance with previous studies (Braithwaite et al., 2017a, b; Yong Ping et al., 2015). For example, an included prospective study investigating the association between objective and subjective prenatal maternal stress due to a natural disaster (Iowa floods) and stress reactivity in the offspring at 2,5 years of age in 94 mother-baby dyads, observed a positive association between subjective maternal stress and increased reactivity in females only, with little effect in males (Yong Ping et al., 2015). However, sex-differences after intrauterine exposure to symptoms of psychopathology are less clear (Carpenter et al., 2017). For example, a prospective study examining 444 women and their children found prenatal maternal symptoms of anxiety and depression to be associated with child outcomes in both boys and girls, but in different ways based on timing of maternal complaints (de Bruijn et al., 2009).

4.1. Mechanisms of HPA axis alteration

The expanded fetal programming hypothesis suggest that the fetus responds to intrauterine exposure, in this case psychopathology and stress or associated high levels of maternal cortisol, with altered physiological and metabolic processes, in this case alteration of the HPA axis, as preparation for the anticipated postnatal environment (Seckl and Holmes, 2007). It is hypothesized that higher levels of glucocorticoids crossing the placenta alter fetal HPA axis development (Cottrell and Seckl, 2009). High levels of maternal cortisol reaching the fetus could either be the result of extreme maternal stress, overruling the capacity of placental 11ß-HSD-2 to convert cortisol into the inactive metabolite cortisone and thereby accumulating cortisol, or the result from altered expression of 11ß-HSD-2 in the placenta, as maternal psychopathology and stress during pregnancy have been associated with down regulation of 11ß-HSD-2, leading to active transfer of maternal cortisol into fetal circulation (Jensen Pena et al., 2012; O'Donnell et al., 2012). It is hypothesized that observed sex-differences could originate in part from differences in placental glucocorticoid handling, as previous research has observed changes in the expression of 11ß-HSD-2 in female placenta's (Mericq et al., 2009; Mina et al., 2015).

A promising biological mechanism for the fetus' response to high maternal cortisol is epigenetic programming of the HPA axis (Pluess and Belsky, 2011; Stonawski et al., 2018). Focus has been on genes encoding HPA axis relevant receptors such as the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), or genes coding for proteins influencing HPA axis function. One of these candidate genes is NR3C1, the gene encoding the GR. Higher DNA methylation of NR3C1 has been associated with prenatal depression and stress (Braithwaite et al., 2015). Methylation of this gene results in decreased GR expression and thus to an overactive stress response in the offspring (Oberlander et al., 2008). This effect seems to be sex-specific, with research showing increased methylation for female infants (Braithwaite et al., 2015; Ostlund et al., 2016; Stonawski et al., 2018) compared to males, potentially explaining differences found in sex-specific infant outcomes (Braithwaite et al., 2017a, b).

Although epigenetic factors appear to play an important role in HPA axis alteration, not all variation can be attributed to these epigenetic findings.

4.2. Strengths and limitations

Primary strengths of the study are the large population-based sample, the prospective nature of the study and the ability to take many confounders into account. Another strength of the current study is the used method of the hair corticosteroid measurements, as performed with the state-of-the-art LC–MS/MS based method. A known limitation of hair corticosteroid measurement is that over time hormone levels may decrease in parts of the hair samples that are most distal from the scalp. However, we used the proximal three cm and there is agreement that the wash-out decline occurs only after a time span of 3 to 6 months (Kirschbaum et al., 2009). Despite the strengths of our study, there are some limitations that need to be discussed. We only used self-reported information of maternal psychopathology symptoms and stress during pregnancy. It was not feasible to perform diagnostic interviews in such a large cohort. In addition, not all dimensions of stress, e.g. work-related stress, were measured in the current study, even though we used multiple questionnaires to assess stress. Next, women with symptoms of psychopathology and stress during pregnancy potentially experienced symptoms of psychopathology and stress over a longer period of time after pregnancy, influencing stress levels of the offspring. The current study did not correct for postnatal psychopathology and stress and future studies should focus on the influence of chronicity of stress. Additionally, no assessment of experienced stressful events in the children in the three months before collection of the hair sample was available, which could have caused increased stress and thus cortisol levels in the children. Finally, selection bias and residual confounding cannot be ruled out, and thus results must be interpreted carefully.

4.3. Conclusion and future recommendations

In the current study an association was observed between maternal psychopathology and stress during pregnancy and hair cortisone levels in children 6 years of age, suggesting alterations in long-term HPA axis activity in children exposed to maternal psychopathology and stress during pregnancy. Altered HPA axis functioning may increase susceptibility for physical disease and mental health problems in later life (Harris and Seckl, 2011; Van den Bergh et al., 2017). Nevertheless, we must be careful when interpreting these results and infer causality. The use of hair cortisone as a valid biomarker should be further established and future studies should examine whether these psychoendocrinological differences between exposed and non-exposed children underlie offspring morbidity associated with maternal psychopathology and stress during pregnancy.

Conflict of interest

None.

Contributors

Nina M. Molenaar – conception and design of the study, analysis and interpretation of data, drafting the manuscript, critical revision and final approval of the version to be published.

Henning Tiemeier – conception and design of the study, data acquisition, interpretation of the data, critical revision and final approval of the version to be published.

Elisabeth F.C. van Rossum – conception and design of hair cortisol and cortisone measurements, interpretation of the data, critical revision and final approval of the version to be published.

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