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Stress-related genetic polymorphisms in association with peripartum depression symptoms and stress hormones: A longitudinal population-based study

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ABSTRACT

Individual differences in the response of the stress system to hormonal changes during pregnancy and the postpartum period render some women susceptible to developing depression. The present study sought to investigate peripartum depression and stress hormones in relation to stress-related genotypes. The Edinburgh Postnatal Depression Scale was used to assess peripartum depressive symptoms in a sample of 1629 women, followed from pregnancy week seventeen to six months postpartum. Genotypes of ninety-four haplotype-tag single nucleotide polymorphisms (SNPs) in sixteen genes of the hypothalamus-pituitary-adrenal axis pathway were analyzed and data on psychosocial and demographic factors was collected. In sub-studies, salivary cortisol awakening response in gestational week 35–39, salivary evening cortisol levels in gestational week 36 and postpartum week 6, and blood cortisol and cortisone levels in gestational week 35–39 were analyzed. SNP-set kernel association tests were performed at the gene-level, considering psychosocial and demographic factors, followed by post-hoc analyses of SNPs of significant genes. Statistically significant findings at the 0.05 *p*-level included SNPs in the hydroxysteroid 11-beta dehydrogenase 1 (*HSD11B1)* gene in relation to self-rated depression scores in postpartum week six among all participants, and serpin family A member 6 (*SERPINA6)* gene at the same time-point among women with *de novo* onset of postpartum depression. SNPs in these genes also associated with stress hormone levels during pregnancy. The present study adds knowledge to the neurobiological basis of peripartum depression by systematically assessing SNPs in stress-regulatory genes and stress-hormone levels in a population-based sample of women.

1. Introduction

Peripartum depression (PPD), as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), encompasses major depressive episodes with an onset during pregnancy and/or the postpartum period (American Psychiatric Association, 2013). Prevalence of PPD has been reported to range between 13% and 19% (O'Hara and McCabe, 2013), impacting not only the woman herself, but also her family, and the development of her child. Although rare, consequences include maternal mortality due to suicide (Cantwell et al., 2011; Esscher et al., 2016; Lindahl et al., 2005). More commonly, PPD has been associated with a broad spectrum of neurodevelopmental, cognitive, behavioral and mental health problems (Stein et al., 2014; Olivier et al., 2013, 2015), as well as grey and white matter structural differences in the offspring (Lebel et al., 2016). Although the epidemiological and psychosocial underpinnings of PPD have been extensively studied, the biology (Moses-Kolko et al., 2014; Skalkidou et al., 2012) as well as the psychobiology of PPD are largely unknown (Agrati and Lonstein, 2015; Yim et al., 2015). A moderate genetic basis of PPD has been suggested by family and twin studies (Murphy-Eberenz

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et al., 2006; Treloar et al., 1999), nevertheless, the specific genetic factors underlying risk for or resilience to PPD are largely unknown (Agrati and Lonstein, 2015; Skalkidou et al., 2012). To date, a small number of genetic association studies has provided sparse knowledge on genetics of PPD (Couto et al., 2015; Figueiredo et al., 2014), and only few considered psychosocial variables (e.g., (Comasco et al., 2011a, b)), as reviewed by (Yim et al., 2015).

Amongst the neurophysiological systems that contribute to regulate brain reactivity to endogenous and exogenous stressors, and in turn, contribute to the vulnerability to develop psychiatric symptoms, is the hypothalamic-pituitary-adrenal (HPA) axis. The response of the HPA-axis comprises the effect of the corticotrophin releasing hormone (CRH), to release adrenocorticotropic hormone (ACTH), which then stimulates the release of cortisol (Charmandari et al., 2005). In uncomplicated pregnancies, maternal baseline salivary cortisol levels rise, reaching a peak equivalent of at least two times higher than levels observed in healthy non-pregnant controls (Allolio et al., 1990; Harris et al., 1996). In most cases, salivary cortisol concentration normalizes within a few weeks after delivery. Altered HPA-axis correlates have been associated with PPD (Yim et al., 2015). Additionally, in this cohort, symptoms of postpartum depression have been associated with higher mid-pregnancy CRH levels as well as higher postpartum evening cortisol levels (Iliadis et al., 2015a, b; Iliadis et al., 2016). To further the understanding of the psychobiological background of PPD, the present study employed stress-related genetic and hormonal measures. Specifically, we sought to investigate: i) the association between peripartum depressive symptoms, assessed at four different time-points during pregnancy and the postpartum period, and haplotype-tagging single nucleotide polymorphisms (SNPs) in key HPA-axis genes, controlling for well-known psychosocial and demographic factors; and ii) the relation between HPA-axis hormones during the peripartum period and SNPs in key HPA-axis genes.

2. Materials and methods

2.1. Study population

2.1.1. Main population

The present study was undertaken as part of the BASIC project (Biology, Affect, Stress, Imaging, Cognition), a population-based, longitudinal study on psychological wellbeing during pregnancy and the postpartum period in Uppsala County, Sweden (Iliadis et al., 2015b). The study was conducted at the Department of Obstetrics and Gynecology, Uppsala University Hospital. All pregnant women over the age of 18 years in Uppsala County who attended their routine ultrasound in gestational week 16–18 were invited to participate in the study. Exclusion criteria for the BASIC study were: inability to adequately communicate in Swedish; confidential personal data; and pathologic pregnancy (e.g., major malformations or miscarriages) as diagnosed by routine ultrasound. After providing informed consent, the participants were asked to fill in web-based questionnaires including the Swedish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Rubertsson et al., 2011) in gestational week 17, gestational week 32, postpartum week six and, finally, at six months postpartum. Blood samples for genotyping were obtained at delivery.

Overall, 1662 women were genotyped. Of these, 33 women with non-Caucasian origin were excluded, leaving a study population of 1629 women.

Additionally, because of the high prevalence of prior mental health problems in the cohort, we did further analyses in a subset of women without previous mental health problems (n = 692). For the postpartum analyses on this subset, we further excluded women with elevated depressive symptoms (i.e. EPDS scores > 13) in gestational week 17 and 32. The postpartum analyses in this subset thus focus on women with *de novo* onset of postpartum depression (n = 635).

Some of the genotyped women had also participated in two sub-studies in the BASIC framework, in which various HPA-axis measures had been evaluated, Fig. 1. The differences between cases and controls in terms of HPA axis hormone levels have been reported previously (Iliadis et al., 2015a, b; Iliadis et al., 2016; Hellgren et al., 2013).

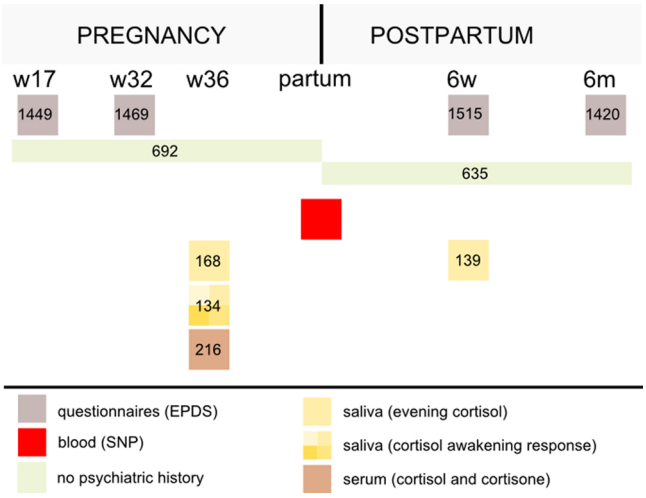

Fig. 1. Study design. A population-based sample of women (n = 1629) was followed during pregnancy and postpartum. These women donated a blood sample that was used for genetic analyses and self-reported their depressive symptoms on the EPDS questionnaire in gestational week 17 (n = 1449), in gestational week 32 (n = 1469), at six weeks postpartum (n = 1515), and at six months postpartum (n = 1420).
Additionally, from this sample, a subset of women without previous mental health problems was selected (n = 692). For the postpartum analyses on this subset, we further excluded women with elevated depressive symptoms in gestational week 17 and 32. The postpartum analyses in this subset thus represent women with *de novo* onset of postpartum depression (n = 635).
Moreover, some of the genotyped women had also participated in two independent sub-studies as part of the BASIC framework, in which various HPA-axis measures had been evaluated. Cases and controls were studied regarding salivary cortisol awakening response in gestational week 35–39 (n = 134), salivary evening cortisol levels in gestational week 36 (n = 168) and postpartum week 6 (n = 139), as well as blood cortisol and cortisone levels in gestational week 35–39 (n = 216).

2.1.2. Salivary cortisol awakening response (CAR) and serum cortisol and cortisone sub-study population

Between January 2010 and May 2013, pregnant and postpartum women in the BASIC study were invited to a sub-study on psychophysiology measures and HPA-axis hormone levels, including CAR. All women with EPDS at or above 12 in late pregnancy and postpartum were invited, as well as a corresponding number of controls with EPDS below 12 in the same time-period. Participation rates were about 60% and 234 women participated in total. Among these, 216 women donated serum samples. These samples were analyzed for a study on cortisol to cortisone ratio in relation to offspring birth weight (Hellgren et al., 2016). Women came in to the lab between 8 AM and 3 PM, with the majority scheduled either at 9 AM or at 1 PM, and blood samples were drawn after at least 90 min fasting. The majority of the samples were taken at either 10:30 AM or 2:30 PM, and the cortisone to cortisol ratio did not differ significantly between AM and PM samples (Hellgren et al., 2016). Blood samples were immediately centrifuged (1000 *g* for 10 min) and serum was stored in −70 °C, until assayed.

As part of this study, women did home-based saliva sampling for analyses of CAR. In total, 163 women returned morning salivary samples, and 134 had samples that could be used for analyses (Hellgren et al., 2013). All women received verbal and written instructions as how to perform the saliva sampling and were provided four labeled Salivette tubes (Sarstedt, Sweden). The first saliva sample was to be taken immediately after awakening and the remaining three samples at

15, 30, and 45 min post-awakening. Participants were instructed to refrain from any food intake, consumption of beverages, tobacco products or oral use of foreign bodies (i.e. chewing gum, toothpick or toothbrush) one hour before the saliva sampling (Hanrahan et al., 2006). Moreover, they were asked to report the presence of illness, oral lesions and whether they had received dental care a few days before sampling. After centrifugation at 1000 *g* for 10 min, samples were stored in −18 °C prior to further analysis. Detailed information on the sampling procedure and sample handling is provided elsewhere (Hellgren et al., 2013). For the purpose of the present study, awakening morning salivary cortisol levels (n = 134) and valid cortisol levels at all four time-points, allowing for calculation of the area under the curve with respect to the ground (AUCg) and increase (AUCi), nmol/l*min, were included to calculate the cortisol awakening response (n = 109).

2.1.3. Salivary evening cortisol sub-study population

Between December 2011 and March 2012 as well as between June and August 2012, a total of 365 pregnant women in gestational week 36 were asked to participate in this sub-study. Women were instructed to complete a self-administered structured questionnaire containing a Swedish validated version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at the 36th week of pregnancy as well as the sixth week postpartum. For the evening saliva samples, saliva kits were sent out to all participants, with 70% participation rate. Study subjects received written instructions to take a saliva sample between 8 and 10 PM, using Salimetrics-tubes (Electra-Box, Diagnostica AB, Sweden). Details on the sampling procedure were similar to the above CAR project and are also provided elsewhere (Clements and Parker, 1998; Iliadis et al., 2015b). Following exclusion of five outliers (> 3 standard deviations from the mean), 168 evening saliva cortisol samples obtained during pregnancy, and 139 evening saliva cortisol samples from the postpartum period were available for this study.

2.2. Genetic analyses

DNA was isolated from blood using the silica-based Kleargene™ XL nucleic acid extraction kit (®LGC, UK). Totally, sixteen candidate genes involved in the hypothalamic-pituitary-adrenal axis stress-response pathway were selected: *CRH, CRHBP, CRHR1, CRHR2, CYP17A1, CYP21A2, FKBP5, HSD11B1, HSD11B2, HSD3B1, HSD3B2, MC2R, NR3C2, NR3C1, POMC,* and *SERPINA6*.

Data on these genes was obtained from HapMap database for a region spanning ± 100 kb each gene, and haplotype-tag single nucleotide polymorphisms (SNPs) were selected using Haploview 4.2 (minimum minor allele frequency of 0.1; $r^2 \geq 0.8$, pairwise tagging only). Candidate markers from previous association studies were also considered. A detailed description of the selected polymorphisms as well as of allele and genotype frequencies is reported in Supplementary Table 1. Genotyping analyses were performed using the Kbioscience Allele-Specific Polymorphism assay (KASP) based on competitive allele-specific PCR and bi-allelic scoring of the SNP (KBioscience®, UK). No-template control samples were included to enable the detection of contamination or non-specific amplification. The genotyping call rate was ≥ 97% in the whole sample, except for rs10923819, which was discarded. The genotypes were in Hardy -Weinberg Equilibrium for all the markers, except for rs846914, rs2235543, rs10082248, rs12953076, and rs3744819, rs3785877 and rs1715747, which were excluded. Thus, ninety-four SNPs were included in the final analysis (Table S1).

2.3. Outcomes

2.3.1. The Edinburgh postnatal depression scale (EPDS)

Depressive symptoms were assessed by use of the Swedish version of the Edinburgh Postnatal Depression Scale, an internationally-used 10-item self-reported questionnaire, designed as a screening tool to identify depressive symptoms in the peripartum period (Cox et al., 1987). In the genetic analyses, the EPDS score was used as continuous variable.

To give an estimation of case-control status at the different time-points in the study, we also used cut-offs. A cut-off point of 13 for depression during pregnancy (Rubertsson et al., 2011) and 12 for postpartum depression (Wickberg and Hwang, 1996) were employed, as these are used for screening in clinical settings. A cut-off of 13 points for depression during pregnancy provides 77% sensitivity and 94% specificity (Rubertsson et al., 2011). For postpartum depression, study results vary, with sensitivity estimated between 72% (Statens beredning för medicinsk utvärdering (SBU), 2012) and 77% (Murray and Carothers, 1990) and specificity between 88% (Statens beredning för medicinsk utvärdering (SBU), 2012) and 92.5% (Murray and Carothers, 1990) for the cut-off of 12 points that was used to identify women with postpartum depressive symptoms.

2.3.2. Salivary cortisol

Salivary free cortisol concentrations were analyzed at the department of Laboratory Medicine at Uppsala University Hospital; but with two different methods, because of change of method used by the laboratory between the two sub-studies. Salivary free cortisol concentrations were measured using competitive ELISA (Salivary Cortisol Enzyme Immunoassay Kit, Salimetrics, Electra-Box, Diagnostica AB, Sweden) and used to compute the following variables: awakening saliva cortisol, CAR AUCg, CAR AUCi, CAR peak cortisol, and CAR Δ cortisol. The evening salivary cortisol analyses were performed on a Cobas8000 e602 instrument with the Cobas Elecsys cortisol reagent kit (Roche Diagnostics, Bromma, Sweden).

2.3.3. Serum cortisol and cortisone

Serum cortisol and cortisone were analyzed with Ultra-Performance Convergence Chromatography (UPC^2; Waters ACQUITY® UPC$^{2™}$, Milford, MA) coupled with tandem mass spectrometry (XEVO® TQ-S, Milford, MA) (Hellgren et al., 2016). The analysis was performed with an Acquity UPC^2 BEH column (150 mm 3.0 mm, 1.7 µm at 40 °C (Waters, Milford, MA, USA)). The sample preparation (100 µL of serum) involves liquid extraction together with derivatization into methoxyamine prior to the analysis (Hellgren et al., 2016). The quantification of steroid hormones was done with multiple reactions monitoring *(MRM)* coupled with stable isotope dilution mass spectrometry. All data collected in centroid mode were obtained using Masslynx NT4.1 software (Waters Corp., Milford, MA USA). Duplicate analyses of each sample were performed and the average values were reported (CV < 6%). The linearity of the method was evaluated over a range of concentrations (0.14–1379 nmol/l for cortisol); correlation coefficients (R^2) were 0.999 for cortisol and cortisone, and limit of quantifications were 0.14 nmol/l.

2.4. Psychosocial and demographic covariates

Covariates were chosen based on results of prior literature on differences between women with and without perinatal depressive symptoms. Most of these variables were also found to be significantly different between women reporting depressive symptoms and controls in this study, and in the whole of the BASIC cohort, including over 6.000 pregnancies. They included age (continuous, calculated form the woman's personal identification number and date of delivery), pre-pregnancy body mass index (BMI, continuous, self-reported and based on medical journals in case of non-realistic or missing values), parity (nulliparous, one, two, or more than two previous children, based on medical journals), educational level (university education or less, self-reported), and pre-pregnancy mental health problems (yes/no, self-reported). For the pre-pregnancy mental health problems, women were asked in the web-based questionnaire to indicate if they had ever seen a psychologist, a psychiatrist or suffered from depression. Women were

considered to have pre-pregnancy mental health problems if they acknowledged any of these three items. Additional covariates in the postpartum period included self-reports on breastfeeding (exclusive, partial, or not at all, self-reported), mean hours of night sleep during the past week (continuous, self-reported), and partner support (plenty, low, or none, self-reported). Information on psychosocial covariates was collected from the BASIC questionnaires. Low and high age are risk factors for PPD in the BASIC cohort as well as in previous studies (Silverman et al., 2017). For this reason, we modelled the influence of age based on quadratic dependence.

2.5. Statistical analyses

Differences between women with and without PPD in psychosocial and medical variables at pregnancy week 17 and 32 and post-partum week 6 and month 6 were investigated by independent t-tests or chi-square tests. Linear regression analyses were performed to test both genetic, psychosocial and medical factors as predictors. SNP-set (Sequence) Kernel Association Test (SKAT) (Ionita-Laza et al., 2013; Wu et al., 2010) was used to test the association between peripartum depressive symptoms and HPA-axis hormone levels with SNP-sets at the gene level, while adjusting for covariates. SNPs were weighted using beta weights 0.5, 0.5, instead of the default 1, 25 which down weights common variants (Ionita-Laza et al., 2013). The SNPs were coded numerically as 0, 1, or 2, where the number is the count of the minor allele. Additionally, as confirmatory analyses, the association between peripartum depressive symptoms and a SNP-set (gene), adjusted for covariates, was estimated using linear regression and likelihood ratio test. Both these analyses compare the full linear model with both SNPs and covariates as independent variables to the model based solely on the covariates.

Across all methods used, the genotype data was applied using the additive model (dd > Dd > DD). Further, all analyses were run with and without imputation of missing values, where missing covariate values were replaced by the median value. Post-hoc linear regression tests were performed to investigate the association between single SNPs and outcome variables if both the SKAT and likelihood ratio test indicated a significant association at the gene level. Regarding the HPA-axis hormone analyses; cortisol and cortisone levels in serum and saliva were log-transformed prior to analyses, whereas CARi and CARg followed normal distribution. No association with gestational age was noted for any of the HPA-axis hormones. Considering the literature, the present study can be considered explorative. Therefore, the significance threshold was set at 0.05 for the gene level associations, while in the post hoc analyses studying the single SNPs Bonferroni method for correction of multiple tests was applied. The R Foundation for Statistical Computing, R version 3.3.3 (2017-03-06), was used for data analysis.

3. Results

3.1. Study population

Descriptive statistics of the study population (n = 1629) and the subset without previous mental health problems (n = 692) are presented in Table 1. In the total sample, EPDS scores were available for 1449, 1469, 1515, and 1420 women in gestational week 17, gestational week 32, postpartum week six, and postpartum month six, respectively. The proportion of women with peripartum depressive symptoms varied between 9.5%- 11.5%, depending on time-point of assessment, Table 1. Psychosocial and demographic covariates in relation to peripartum depression at each time-point are displayed in Table S2.

Overall, 769 (52.6%) women reported previous mental health problems. In the subset of women with no previous mental health problems, the proportion of peripartum depressive symptoms was lower, between 4.5%–5.6% during pregnancy. The prevalence of *de novo* onset of postpartum depression was 4.7% (Table 1).

3.2. Association of peripartum depression with SNPs in HPA-axis genes

The results of SNP-set analyses at the gene level in the entire study population and in the subset without previous mental health problems are displayed in Tables S3 and S4, respectively. Statistically significant findings, noted both in the SKAT and likelihood ratio analyses, included *HSD11B1* in relation to self-rated depression scores in postpartum week six in the total study population (Table S3), and *SERPINA6* in relation to self-rated depression scores in postpartum week six in women with *de novo* onset PPD (Table S4). As analyses were adjusted for age, parity, education, previous psychiatric history, breastfeeding, partner support, and sleep pattern duration, these findings indicate independent genetic influences, beyond that of the regular psychosocial risk factors. Furthermore, these findings remained similar when imputed values for the covariates were used in the analyses (data not shown). None of the gene SNP-sets associations would be statistically significant after correction for multiple testing.

Post-hoc analyses on individual *HSD11B1* SNPs in relation to peripartum depression scores in the entire sample are displayed in Table 2. As illustrated in Fig. 2, a statistically significant (after Bonferroni correction), dose-dependent effect of the rs12565406 G allele was observed on depressive symptoms in gestational week 32 and postpartum week six; where carriers of the minor allele (T) reported the lowest EPDS scores, and heterozygous displayed intermediate scores (Fig. 2B and C). Similar trends were observed at the other time points (Fig. 2A and D).

Post-hoc analyses on individual *SERPINA6* SNPs in relation to peripartum depression scores in the subset of women without previous psychiatric history are displayed in Table 3. Bonferroni-adjusted significant associations of rs8022616 with depressive symptoms in gestational week 17 and postpartum week six were found. Presence of two or one copy of the minor allele (G) was associated with higher self-rated depression scores in gestational week 17 (Fig. 3A) and postpartum week six (Fig. 3C), respectively.

Associations between EPDS scores and SNPs in *HSD3B2* in the entire sample (Table S3), and in *CRH*, *CRHBP*, *CRHR1*, *HSD3B2* and *NR3C1* in the sample without previous mental health problems (Table S4), were found but not explored. These results were not considered robust as they were not significant in both the SKAT and likelihood ratio analyses.

3.3. Association of HPA-axis hormones with SNPs in HPA-axis genes

The relationship between SNPs in HPA-axis genes and cortisol and cortisone levels were investigated in two different sub-studies at different time points. As displayed in Table 4, the strongest association was the one between *CRH* and CAR AUCg. This association was driven by three SNPs in the *CRH* gene; rs 1,870,392 (B = −188 nmol/l*min, β = −0.24, p = 0.011), rs 11,990,370 (B = −165 nmol/l*min, β = −0.31, p = 0.001), and rs 11,996,294 (B = −75 nmol/l*min, β = −0.22, p = 0.023) where, across all three SNPs, the minor allele was associated with lower CAR AUCg in the third trimester.

A number of additional statistically significant associations were noted between HPA-axis genes and hormones, but we only followed up on the two SNPs that had been associated with self-rated depression. The *HSD11B1 was* associated with pregnancy serum cortisone levels, evening pregnancy saliva cortisol level, pregnancy CAR AUCi, and CAR Δ cortisol. However, post-hoc analyses revealed no association between *HSD11B1* rs12565406 and these HPA-axis hormones.

SERPINA6 was associated with pregnancy serum cortisol and pregnancy morning saliva cortisol. Using the additive model, *SERPINA6* rs8022616 was associated with pregnancy serum cortisol (B = 71.4 mmol/l, β = 0.17, p = 0.016) and pregnancy morning saliva cortisol (B = 25.9 mmol/l, β = 0.17, p = 0.016); with increasing

Table 1
Descriptive statistics of the study population (n = 1629) and the subset of women without previous self-reported mental health problems (n = 692).

		All women (*n* = 1629)		Women with no pre-pregnancy mental health problems (*n* = 692)	
			Mean ± SD or n (%)	n	Mean ± SD or n (%)
Age, years		1611	31.4 ± 4.6	690	31.4 ± 4.2
BMI, kg/m^2		1461	23.9 ± 4.2	691	24.0 ± 4.2
Parity, before delivery	Nulliparous	1589	710 (44.7)	683	311 (45.5)
	One child		620 (39.0)		271 (39.7)
	Two children		216 (13.6)		86 (12.6)
	Three or more children		43 (2.7)		15 (2.2)
Education	High school	1462	1133 (77.5)	692	559 (80.8)
	University		329 (22.5)		133 (19.2)
Pre-pregnancy mental health problems[a]	No	1461	692 (47.4)	692	692 (100)
	Yes		769 (52.6)		0
Breastfeeding postpartum week six	Yes, exclusively	1520	1141 (75.1)	616[b]	490 (79.5)
	Yes, partially		264 (17.4)		88 (14.3)
	No		115 (7.6)		38 (6.0)
Partner support	Yes, plenty	1509	917 (60.8)	615[b]	374 (60.8)
	Yes, a little		551 (36.5)		228 (37.1)
	No		41 (2.7)		13 (2.1)
Sleep duration postpartum week six		1510	6.5 ± 1.3	614[b]	6.5 ± 1.2
Women with depressive symptoms	Gestational week 17	1449	162 (9.9)	686	31 (4.5)
	Gestational week 32	1469	186 (11.4)	670	39 (5.6)
	Postpartum week six	1515	188 (11.5)	614[b]	30 (4.7)
	Postpartum month six	1420	155 (9.5)	589[b]	22 (3.5)

Percentages are given in relation to available responses.
[a] Defined as self-reported pre-pregnancy contact with psychologist or psychiatrist, or self-reported history of depression.
[b] Women with antenatal depression according to EPDS scores in gestational week 17 and 32 excluded, i.e. women with the *de novo* postpartum onset.

Table 2
Likelihood ratio test results on *HSD11B1* SNPs, using an additive model, in relation to EPDS scores in gestational week 17 and 32 and postpartum week six and month six in the total sample (n = 1629).

HSD11B1 SNPs	EPDS gestational week 17	EPDS gestational week 32	EPDS postpartum week 6	EPDS postpartum month 6
	p	*p*	*p*	*p*
rs846908	0.145	0.442	0.751	0.814
rs701950	***0.014***	***0.045***	0.989	0.537
rs12565406	***0.018***	***0.0028***[a]	***0.0015***[a]	***0.029***
rs10863782	0.780	0.282	0.151	***0.034***
rs11119328	0.848	0.408	0.621	0.546
rs4844488	0.312	0.142	***0.024***	0.980
rs10863785	0.981	0.835	0.169	0.546
rs3753519	0.841	0.742	0.896	0.333

Analyses in gestational week 17 and 32 were adjusted for age, BMI, parity, educational level, and pre-pregnancy psychiatric history. In addition to these risk factors, analyses in the postpartum period were also adjusted for breastfeeding, partner support and sleep duration.
[a] The significance threshold was set to $p = 0.00625$, following Bonferroni's correction for multiple testing.

number of copies of the minor allele (G), increasing serum and saliva cortisol concentrations were noted. None of the other HPA-axis hormones were associated with *SERPINA6* rs8022616.

4. Discussion

Stress-related genetic polymorphisms were investigated in relation to peripartum depression symptoms and stress hormones. Statistically significant findings included SNPs in the hydroxysteroid 11-beta dehydrogenase 2 (*HSD11B1*) gene in relation to self-rated depression scores in postpartum week six among all participants, and serpin family A member 6 (*SERPINA6*) gene at the same time-point among women with *de novo* onset postpartum depression. SNPs in these genes were also associated with stress hormone levels during pregnancy.

Depression during pregnancy and the postpartum period is a multifactorial psychiatric disorder, in which both constitutive and environmental factors influence each other and contribute to risk and resilience (Yim et al., 2015). The present study investigated the contribution of common genetic variants in HPA-axis genes to perinatal depression, taking into account psychosocial and demographic factors which are often overlooked in biological studies (i.e., age, parity, education, previous psychiatric history, breastfeeding, partner support, and sleep pattern duration), in a population-based sample of prospectively followed women. We found associations of SNPs in *HSD11B1* and *SERPINA6,* genes that are involved in HPA-axis regulation, with antenatal and postpartum depression, as well as HPA-axis hormone levels. Unfortunately, the small sample sizes for the hormonal analyses precluded any further gene-hormone-PPD pathway analyses.

Response to endogenous and exogenous stressors can influence vulnerability to develop psychiatric disorders, including PPD (Yim et al., 2015). Pregnancy, delivery and the postpartum period can indeed act as triggering factors or stressors per se. The stress response system, especially the HPA-axis, undergoes notable changes over the peripartum period, reflected in changes in hormone levels and feedback mechanisms. Variations in the adjustment of the HPA-axis in the perinatal period have indeed been associated with PPD, at the hormonal (Iliadis et al., 2015a, b; Iliadis et al., 2016) and transcriptomic (Katz et al., 2012) levels.

Regarding genetic studies, common variants in the glucocorticoid (*NR3C1*) and type 1 corticotropin-releasing hormone (*CRHR1*) receptors have been associated with increased risk of PPD in a relatively small clinical sample (Engineer et al., 2013). However, we and others have not been able to replicate this finding, even in larger samples (Costas et al., 2010; El-Ibiary et al., 2013; Schneider et al., 2014; Stergiakouli et al., 2014). On the contrary, the present study provides evidence for association of SNPs in the *HSD11B1* gene, located on chromosome 1, encoding the enzyme 11β- HSD1 (Henley and Lightman, 2011), with peripartum depression. Particularly, the G allele of the SNP rs12565406 in the *HSD11B1* gene was associated with antenatal depression at gestational week 32 and postpartum depression at six weeks postpartum, after adjustment for psychosocial and demographic covariates.

The mechanism by which the genetic make-up of 11β-HSD1 impacts on hormonal levels is not known. The 11β-HSD1 protein is expressed in

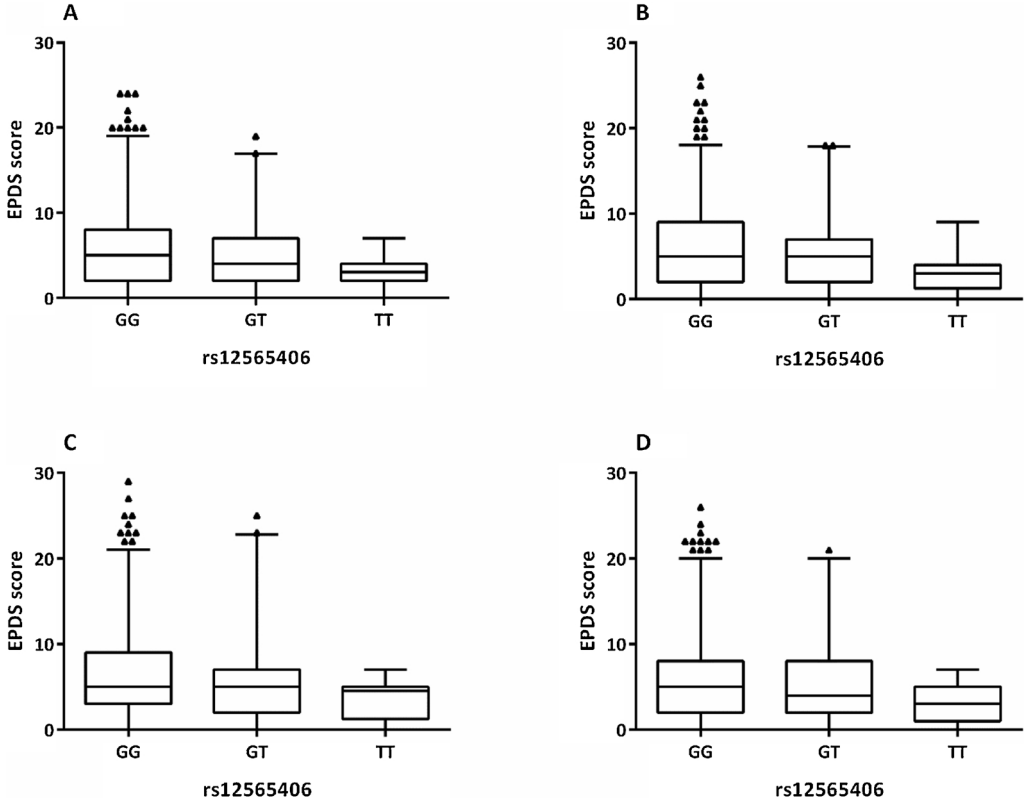

Fig. 2. Boxplots of self-rated depression scores (EPDS) in relation to *HSD11B1* rs12565406 genotypes in gestational week 17 (A), gestational week 32 (B), postpartum week six (C), and postpartum month six (D) in the total sample (n = 1629).

Table 3
Likelihood ratio test results on *SERPINA6* SNPs, using an additive model, in relation to EPDS scores in gestational week 17 and 32 and postpartum week six and month six in the subset of women without previous mental health problems (n = 692 in gestational week 17 and 32). Findings in postpartum week six and postpartum month six represent women with *de novo* onset of postpartum depression, as women with depressive symptoms during pregnancy were excluded in these analyses (n = 635).

SERPINA6 SNPs	EPDS gestational week 17	EPDS gestational week 32	EPDS postpartum week 6	EPDS postpartum month 6
	p	*p*	*p*	*p*
rs941601	0.902	0.701	0.886	0.264
rs8022616	***0.0090***[a]	0.212	***0.0007***[a]	0.078
rs11627241	0.811	0.713	0.801	0.787
rs1998056	0.822	0.974	0.188	0.260

Analyses in gestational week 17 and 32 were adjusted for age, BMI, parity, educational level, and pre-pregnancy psychiatric history. In addition to these risk factors, analyses in the postpartum period were also adjusted for breast-feeding, partner support and sleep duration.

[a] The significance threshold was set to $p = 0.0125$, following Bonferroni's correction for multiple testing.

many tissues, including the hypothalamus and pituitary gland, and takes part in the regulation of the central HPA-axis activity and glucocorticoid response (Tomlinson et al., 2004). It exerts enzymatic activity by catalyzing the production of cortisol from inactive cortisone, and vice versa. A positive correlation has been found between 11β-HSD1 levels in urine and symptoms of major depression in women (Raven and Taylor, 1998), and a common genetic variant in *HSD11B1* (rs11119328) has been associated with late-night salivary cortisol levels as well as risk of developing a depressing episode in non-pregnant subjects (Dekker et al., 2012). We have previously reported, in a subset of the present population-based sample, that neuroticism mediates the impact of *HSD11B1* SNP rs12565406 on the risk for PPD (Iliadis et al., 2017). In pregnant subjects, distress during pregnancy was associated with elevated methylation of the *HSD11B2*, a different form of the enzyme also involved in the cortisol-cortisone conversion (Monk et al., 2016). Recently, Räikkönen et al., reported that maternal depression during pregnancy could alter glucocorticoid action in the placenta, via upregulation of *HSD11B1* and *NR3C1* mRNA levels, and this could affect offspring's regulatory behavior (Raikkonen et al., 2015). Hellgren et al. reported a positive correlation of the cortisone to cortisol ratio, as a functional marker of the enzyme, and birth weight, but only in women with psychiatric morbidity (Hellgren et al., 2016). In the present study, SNPs in *HSD11B1* (but not rs12565406) were associated with pregnancy cortisone, cortisol awakening response and evening cortisol, thus calling for future studies to investigate their functional role and whether genetic-driven HPA-axis imbalance predisposes to depression, or if individuals with a certain genetic make-up cannot successfully counterbalance other mechanisms associated with PPD by timely and successfully adjusting their HPA-axis activity.

PPD is not only a multifactorial disorder; it also encompasses various sub-types and trajectories, with distinct phenotypes and correlates (Fredriksen et al., 2017; Putnam et al., 2017). To investigate genetic vulnerability to develop *de novo* peripartum depression, we performed additional analyses, including only women without previous mental health problems for the pregnancy time-points, and for the postpartum time-points, no depression during pregnancy either. In these analyses, an association was found between PPD and polymorphisms in the *SERPINA6* gene; SNP rs8022616 was associated with depressive symptoms at gestational week 17 and at six weeks postpartum among women with de novo onset of postpartum depression. Regarding *SERPINA6*, located on chromosome 14 and encoding the corticosteroid binding globulin (CBG) protein (Henley and Lightman, 2011), SNPs in this gene have been linked to a cluster of somatic and psychiatric symptoms, including pain, anxiety and depression (Holliday et al.,

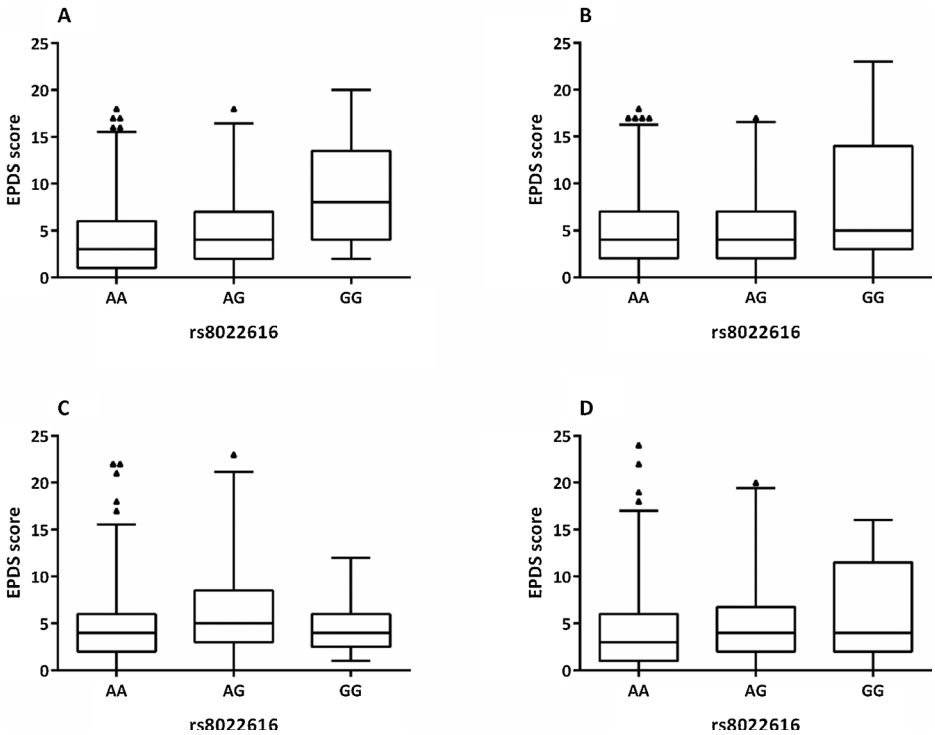

Fig. 3. Boxplots of self-rated depression scores (EPDS) in relation to *SERPINA6* rs8022616 genotypes in gestational week 17 (A), gestational week 32 (B), postpartum week six (C), and postpartum month six (D) in the subset of women without previous mental health problems (n = 692). Findings in postpartum week six (C) and postpartum month six (D) represent women with *de novo* onset of postpartum depression (n = 635), as women with depressive symptoms during pregnancy were excluded in these analyses.

2010). Particularly, a recent genome-wide association meta-analysis indicated that a small proportion of plasma cortisol was accounted for by SERPINA6 (Bolton et al., 2014). Other studies have also found evidence for altered cortisol levels in individuals with rare mutations in this gene (Gagliardi, Ho, & Torpy, 2010) or in carriers of specific *SERPINA6* variants, only identified in a Chinese population thus far (Lin et al., 2012). In the present study, *SERPINA6* variations were also associated with serum and salivary morning cortisol levels during pregnancy, indicating a potential effect on the regulation of the HPA-axis. We can therefore speculate that variants in *SERPINA6* may, through their effect on HPA-axis functioning, partly explain the heightened risk for developing PPD. Moreover, the fact that no *HSD11B1* SNP was associated with symptoms of peripartum depression in these sub-samples suggests differential genetic vulnerability to *de novo* PPD. However, only self-reported data on previous contact with a psychiatrist or psychologist, or previous history of depression was available, thus calling for future studies to investigate genetic factors in women with psychiatric history. This would further contribute to define PPD, to distinguish it from non-peripartum depression and to develop specific treatments.

4.1. Methodological strengths and limitations

The present study has a strong psychobiological rationale that motivates the choice of the selected genes and included a relatively large sample with sufficient power to be informative in relation to the expected effect sizes. Coverage of the genetic variance at the pathway-level allowed a comprehensive analysis of the HPA-axis though coverage for some of the genes was low. The relation between genetic make-up and endocrine measures, although assessed at single time-points and in smaller sub-samples, is of relevance to identifying functional correlates of SNPs. Validated screening instruments have been employed; however, the covariates were retrospectively assessed. The sample is highly homogenous and population-based, nevertheless participation rate was relatively low in the BASIC study, including around 20% of the population, often more educated and with a relatively high proportion of women with previous mental health problems. The relatively high percentage of women who self-reported pre-pregnancy mental health history is in line with the literature on lifetime prevalence of affective disorders among women. However, it is also important to note that, contact with a psychologist/psychiatrist, which was used to assess mental health history, does not always correspond to a diagnosis of depression or another psychiatric disorder, but more often to temporary psychological distress and subclinical symptoms. Mental health assistance in Sweden is socially accepted/taboo-free and offered at a low price by the public health and social care system. Indeed, in the Swedish health care system, women may have met with psychologists for termination of pregnancy, infertility problems, fear of childbirth, and stress-related problems. Further confirming the representativeness of the total sample, the proportion of women with peripartum depressive symptoms varied between 9.5% 11.5%, which is in line with the reported figures in the literature being between 13% and 19% (O'Hara and McCabe, 2013). Furthermore, in order to address a potential overrepresentation of women with history of symptoms of affective disorders, who showed greater interest in participating in the study, women with pre-pregnancy mental health history were excluded in the second set of analyses. Thus, the present study focused on peripartum depression according to its latest definition according to the DSM-V.

A strength of the study is the analyses which were performed, encompassing only those without previous mental health problems. Despite the design, which is population-based, one could hypothesize that cases of very severe depression would be less likely to fill out the web-based surveys, rendering the findings more applicable to more moderate PPD cases. Moreover, women who use nicotine, who are more often depressed in general, may have refrained from providing a saliva sample as they had to abstain from smoking or moist snuffs prior to the test. Population stratification at the genetic level was addressed by excluding women reporting non-Caucasian origin; however, region of origin within Northern Europe was not taken into account (Salmela et al., 2008). Finally, the significance threshold was not corrected for multiple-testing, although the genetic and statistical analyses have been hypothesis-driven; this calls for independent replications in larger samples. However, key findings were confirmed using a dual statistical approach and potentially interesting results were reported and interpreted. As correction for multiple testing can contribute to type II

Table 4
SKAT analyses on gene SNP-sets in relation to hypothalamus-pituitary-adrenal axis hormones in pregnancy and the postpartum period in subsets. Some of the women participated in two independent sub-studies as part of the BASIC framework, in which various HPA-axis measures were evaluated. Cases and controls selected from the large genotyped sample (n = 1629) were studied regarding salivary cortisol awakening response in gestational week 35–39 (n = 134), salivary evening cortisol levels in gestational week 36 (n = 168) and postpartum week 6 (n = 139), as well as blood cortisol and cortisone levels in gestational week 35–39 (n = 216).

	Serum cortisol pregnancy (n = 199)	Serum cortisone pregnancy (n = 199)	Serum cortisol/ cortisone ratio pregnancy (n = 199)	Awakeni-ngsaliva cortisol pregnancy (n = 199)	CAR AUCg pregnancy (n = 109)	CAR AUCi pregnancy (n = 109)	CAR peak cortisol pregnancy (n = 119)	CAR Δ cortisol pregnancy (n = 106)	Evening saliva cortisol pregnancy (n = 168)	Evening saliva cortisol post-partum (n = 1-39)
CRH	0.338	0.608	0.404	0.338	***0.002***	0.776	0,619	0,701	0.944	0.596
CRHBP	0.057	0.404	0.172	0.059	0.553	0.962	0,600	0,947	0.114	0.070
CRHR1	0.532	0.968	0.654	0.526	0.303	0.222	0,291	0,721	***0.008***	0.391
CRHR2	0.472	0.611	0.528	0.463	***0.044***	0.250	***0,027***	0,275	0.561	0.422
CYP17-A1	0.737	0.864	0.848	0.710	0.849	0.766	0,405	0,355	0.352	0.798
CYP21-A2	0.408	0.521	0.709	0.408	0.143	0.323	0,731	0,420	0.315	0.317
FKBP5	0.061	0.986	0.316	0.061	0.446	0.640	0,093	0,334	0.287	0.804
HSD11-B1	0.383	***0.049***	0.492	0.385	0.051	***0.015***	0,978	***0,026***	***0.029***	0.053
HSD11-B2	0.749	0.875	0.933	0.735	0.918	0.643	0,877	0,441	0.460	0.609
HSD3-B1	0.712	0.577	0.503	0.712	1.000	0.460	0,597	0,727	0.701	1.000
HSD3-B2	0.375	0.412	0.351	0.375	0.347	0.774	0,571	0,047	0.345	0.349
MC2R	0.588	0.982	0.979	0.591	0.159	0.413	0,596	0,250	0.308	0.345
NR3C1	0.428	0.542	0.179	0.438	0.219	0.591	0,250	0,773	0.092	0.476
NR3C2	0.219	0.789	0.847	0.210	0.370	0.841	0,803	0,528	0.112	0.538
POMC	0.767	0.401	0.985	0.767	0.515	0.375	0,855	0,558	0.487	0.389
SERPIN-A6	***0.035***	0.204	0.201	***0.035***	0.407	0.518	0,231	0,565	0.731	0.684

Analyses in gestational week 17 and 32 were adjusted for age, BMI, parity, educational level, and pre-pregnancy psychiatric history. In addition to these risk factors, analyses in the postpartum period were also adjusted for breastfeeding, partner support and sleep duration. CAR = cortisol awakening response, AUC = area under the curve.

errors, the present study can be considered exploratory compared to previous studies (Costas et al., 2010; El-Ibiary et al., 2013; Engineer et al., 2013; Schneider et al., 2014; Stergiakouli et al., 2014).

4.2. Conclusion

The present results point to putative genetic risk factors for PPD related to the HPA axis, while taking into account psychosocial and demographic factors. Moreover, associations were observed between HPA-axis hormones and genetic variants. It is plausible that, if replicated, findings of this study could contribute to the early identification of vulnerable individuals and provide insights for new treatment options.

Role of the funding source

The funding source had no role in the study design, data collection and interpretation, and results reporting.

Conflict of interest

Sundström-Poromaa I., M.D., Ph.D., serves occasionally on advisory boards or act as invited speaker at scientific meetings for MSD, Novo Nordisk, Bayer Health Care, and Lundbeck A/S. Skalkidou A, M.D., Ph.D., has occasionally been invited as a speaker at scientific meetings for Biotekna, Ferring and Merck. The other authors report no financial relationships with commercial interests. All authors have no conflict of interest related to this work

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The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.02.002.

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