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Maternal prenatal hair cortisol is associated with prenatal depressive symptom trajectories

Paula Mustonen[a,b,*], Linnea Karlsson[a,b], Eeva-Leena Kataja[a,b], Noora M. Scheinin[a,c], Susanna Kortesluoma[a,d], Bárbara Coimbra[e], Ana João Rodrigues[e], Nuno Sousa[e], Hasse Karlsson[a,c]

[a] FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Finland
[b] Department of Child Psychiatry, University of Turku and Turku University Hospital, Turku, Finland
[c] Department of Psychiatry, University of Turku and Turku University Hospital, Turku, Finland
[d] Institute of Biomedicine, University of Turku, Finland
[e] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

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ABSTRACT

Maternal prenatal cortisol levels have been inconsistently associated with self-reports of prenatal psychological distress (PD). Previous research has linked hair cortisol concentration (HCC) evaluating cumulatively the previous months with cross-sectional PD measures that usually cover the past week(s), which may lead to misleading conclusions on their relations. We aimed to investigate how maternal HCC relates to cumulative PD measures across pregnancy.

Methods: Subjects (N = 595) were drawn from the FinnBrain Birth Cohort Study. Maternal HCC was measured from hair samples collected at gestational week (gwk) 24 (HCC1, n = 467) and at delivery (HCC2, n = 222). As HCC1 and HCC2 comprised mostly of different subjects, they were considered as independent populations. Maternal PD assessments at gwks 14, 24, and 34 were the Edinburgh Postnatal Depression Scale (EPDS), the anxiety subscale of the Symptom Checklist (SCL-90), the Pregnancy-Related Anxiety Questionnaire -Revised2 (PRAQ-R2), and a daily hassles scale. Cumulative PD comprised of the mean scores of two consecutive assessments (mean1 = gwks 14 and 24; mean2 = gwks 24 and 34). In addition, EPDS and SCL scores were modelled by using growth mixture modelling to identify symptom trajectory categories. Regression models were adjusted for age, body mass index, education and use of selective serotonin/serotonin-norepinephrine reuptake inhibitor medication.

Results: In the adjusted regression model, higher HCC2 was related to the "consistently elevated" prenatal depressive symptoms trajectory in comparison to "consistently low" (β = .71, p = .021) and "low and increasing" (β = .82, p = .011) symptom trajectories. Additionally, the cumulative mean (mean 1) of daily hassles in relationships was associated with HCC1 (β = 0.25, p = .004). General or pregnancy-related anxiety symptoms were unrelated to HCC after adjustment for the covariates.

Conclusions: The assessment of cumulative or trajectory measures of PD can reveal important associations with maternal prenatal HCC, even though the associations are generally weak. Of the different dimensions of PD, prenatal trajectories of depressive symptoms were most consistently linked with end-pregnancy HCC levels.

1. Introduction

Maternal prenatal psychological distress (PD) is associated with offspring development and health outcomes (O'Donnell and Meaney, 2017; van den Bergh et al., 2017) as well as with altered offspring brain structure, function and connectivity (van den Bergh et al., 2018). Fetal exposure to altered maternal cortisol levels is considered to be one of the major mediators of these effects (Entringer et al., 2015; Rakers et al., 2017), while data linking maternal prenatal cortisol concentrations with both maternal symptoms of prenatal PD and different child outcomes are inconsistent (Seth et al., 2016; Zijlmans et al., 2015). One possible reason for this incongruence is the methodological mismatch when short-term measurements, such as salivary or plasma cortisol, are used to reflect longer term cortisol homeostasis (Cherak et al., 2018; Seth et al., 2016; Zijlmans et al., 2015).

Hair cortisol concentration (HCC) as a marker of long-term cortisol

* Corresponding author: University of Turku, FinnBrain Birth Cohort Study, Lemminkäisenkatu 3 a, Teutori Building, 20014, Turun yliopisto, Finland.
E-mail address: pmmust@utu.fi (P. Mustonen).

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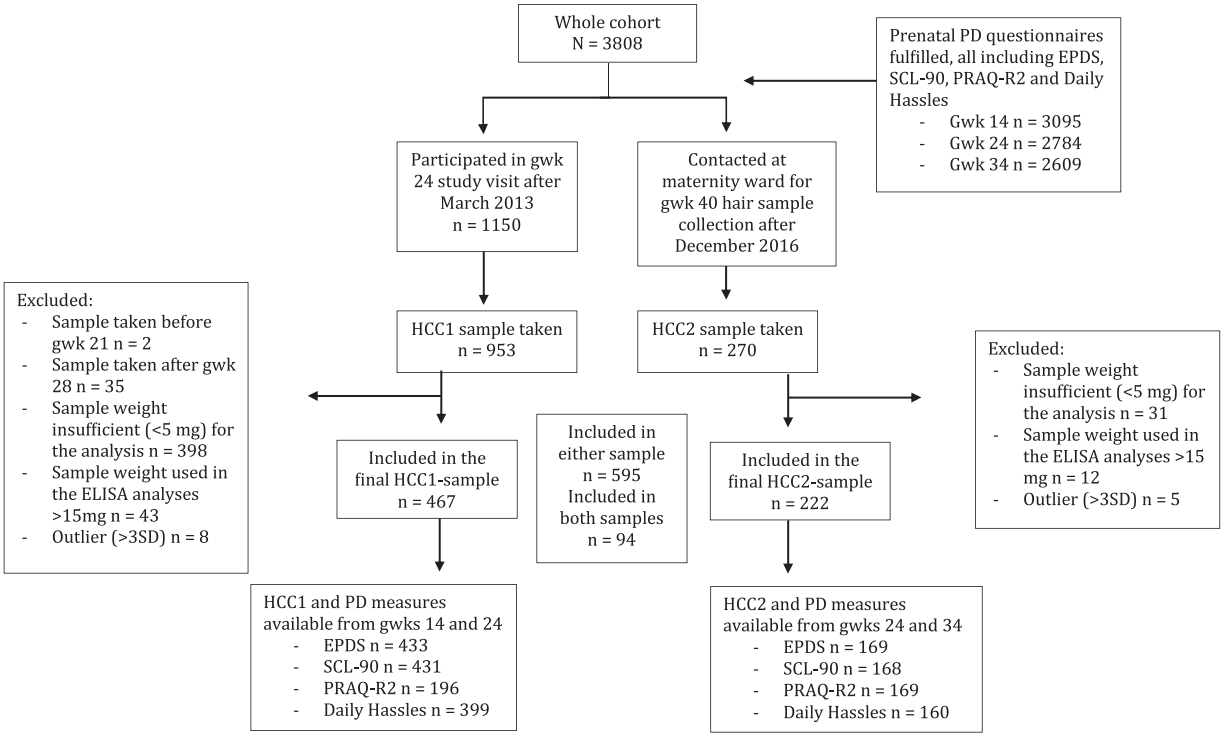

Fig. 1. Flow chart of the study design.
Notes of abbreviations: PD = psychological distress; EPDS = the Edinburgh Postnatal Depression Scale; SCL-90 = the Symptom Checklist −90; PRAQ-R2 = the Pregnancy-related Anxiety Questionnaire -Revised2; gwk = gestational week; HCC1 = hair cortisol concentration measured at gwk 24; HCC2 = hair cortisol concentration measured 1–3 days after delivery.

secretion has been presented as a solution to mitigate this challenge and thus far, there are nine studies assessing the associations between prenatal PD and HCC (Bowers et al., 2018; Duffy et al., 2018; Orta et al., 2018; for a review, see Mustonen et al., 2018). However, the existing research yields rather inconsistent information on the associations between self-reported symptoms of PD and HCC, and only three of the nine studies have found HCC to be associated with some type of PD (Hoffman et al., 2016; Kalra et al., 2007; Orta et al., 2018).

Several factors can affect functioning of the hypothalamic-pituitary-adrenal (HPA) axis and not all symptoms of prenatal PD are likely to be associated with increased long-term cortisol levels. The type, levels, duration and timing of prenatal PD most likely matter. On the other hand, utilizing HCC poses a novel challenge regarding temporal dynamics, as we are measuring cortisol exposure over several months with HCC, while PD questionnaires often assess distress symptoms during the previous days or weeks (Braig et al., 2015b; Scharlau et al., 2017).

One way to overcome these methodological issues is to analyze the PD symptom trajectories across time. The mean scores of several timepoints can be used as a crude estimate of cumulative stress over time, and a more fine-tuned version is to utilize latent growth mixture modelingmodelling (Muthén and Muthén, 2000) to identify distinct groups with different trajectories of self-reports of PD (e.g., Korja et al., 2018). According to our knowledge, however, no previous studies in pregnant or non-pregnant populations have assessed the associations between HCC and PD trajectories reflecting the longitudinal course of PD. Additionally, very few have utilized cumulative scores of repetitive measures of PD (Scharlau et al., 2017).

Of note, cortisol levels increase normally up to 2–3-fold towards the end of pregnancy, largely because placental corticotropin-releasing hormone (CRH) secretion is enhanced by a positive feedback loop of the HPA axis (Jung et al., 2011). Additionally, the efficacy of placental 11β-HSD2 enzyme functioning in converting cortisol into its inactive metabolites is significant in protecting the fetus from excessive levels of maternal cortisol (Reynolds, 2013). Importantly, the 11β-HSD2 activity can be diminished by PD (Janssen et al., 2016). In addition to the overall cortisol levels rising towards the end of pregnancy, the reactivity of the HPA axis functioning attenuates during the last trimester (de Weerth and Buitelaar, 2005; Howland et al., 2017). As these normative physiological changes occur in cortisol secretion towards the end of pregnancy, cross-sectional measures of PD have limitations in explaining the variance in end-of-pregnancy HCC. In line with this, previous research reports associations between PD symptoms and HCC only in mid-pregnancy assessments (Hoffman et al., 2016; Kalra et al., 2007; Orta et al., 2018) and not when HCC has been measured postpartum (Braig et al., 2015b; Duffy et al., 2018).

The aim of this study was to assess the associations between maternal prenatal HCC and different types and timelines of maternal prenatal PD symptoms. First, we examined cross-sectional associations between recent PD measures and HCC measured at the same time. Second, we assessed cumulative PD as the mean of two consecutive PD measures to better match the timeline the HCC measures reflect. Third, we identified distinct trajectories of depressive and anxiety symptoms throughout pregnancy. PD was measured longitudinally throughout the pregnancy by repeated assessments. HCC was measured cross-sectionally in mid- and the end of pregnancy from two largely distinct study populations. We first hypothesized that cumulative PD measures and trajectories of PD symptoms across pregnancy are predictors of maternal HCC. Second, if associations with cross-sectional (recent or cumulative) PD symptoms would be seen, we expected them to be more pronounced in mid-pregnancy than in the end of pregnancy. Third, we anticipated the type of PD to matter in whether associations with HCC are observed.

2. Methods

2.1. Study population

The study subjects were drawn from the FinnBrain Birth Cohort

Study, a population-based longitudinal pregnancy cohort (www.finnbrain.fi; Karlsson et al., 2018). Consecutive pregnant women attending a routine ultrasound at the gestational week (gwk) 12 were recruited to the study between December 2011 and April 2015 at three sites in Turku, Finland and the Åland Islands, Finland. Parent(s) participating in the study gave their written informed consent. The number of women recruited in the whole cohort was 3808. The participation rate was 66% of those informed about the project. The attrition rate during pregnancy was 8.1% (Karlsson et al., 2018).

This study was carried out with a sub-population of women who donated hair samples at second trimester (gwk 24) study visits (excluded if gwks at sample taking were < 21 or > 28, N = 2 and 35, respectively) and/or at the delivery ward 1–3 days after giving birth (excluded if gwks < 34, N = 0) (Fig. 1). The overall participation rate for the gwk 24 study visit was approximately 44% of all the 3808 mothers in the Cohort (Karlsson et al., 2018). Collection of gwk 24 hair samples begun at March 2013, after which hair samples were collected from consecutive Cohort subjects who gave their consent and had adequately hair for sample collection. The collection of gwk 40 hair samples began in December 2014.

2.2. Measures

2.2.1. Hcc

Maternal hair samples were collected at gwk 24 (hereafter HCC1) and after delivery (hereafter HCC2). A strand of hair at least 5 cm long was cut from a standardized area of the posterior vertex region of the head as close to the scalp as possible (Greff et al., 2018; Sauvé et al., 2007). Hair samples were stored in foil in a dry place protected from light according to good research practise, Finnish legislation and data protection until the analyses. The analyses were performed at Life and Health Sciences Research Institute (ICVS), University of Minho, Portugal. For the analysis, a 5 cm segment was cut from samples with adequate length to cover the past 5 months [based on an estimate of 1 cm growth per month (Greff et al., 2018)]; and 5–15 mg of each sample was analysed.

The hair segments were washed in isopropanol for 3 min three times and finely minced using surgical scissors. For extraction of cortisol, 1.5 ml of methanol was added to each sample and the samples were incubated at 55 °C for 24 h. After centrifuging at 10,000 rpm for 2 min, the supernatant was transferred to a new vial. Methanol was evaporated at 60 °C under a constant stream of nitrogen until samples were dried completely. Finally, 0.15 ml of phosphate buffer was added and 50 µl of each sample was analysed with ELISA (IBL International Cortisol Saliva ELISA) following the manufacturer's procedure. All samples were analysed in duplicates and the mean intra-assay coefficients of variation for HCC1 was 3.2% (SD 3.1, range 0.00–14.9 %). For HCC2, the mean coefficient of variation was 2.8% (SD 2.5, range 0.00–12.5 %).

In total, N = 953 maternal hair samples were collected at gwk 24 study visits (82% of the mothers from the beginning of the hair sample collection). For the gwk 40 sample collection, 296 mothers were contacted personally at the delivery ward with 91% of them (N = 270) donating a hair sample. The exclusion of samples outside the weight range of 5–15 mg (HCC1 n = 441 samples excluded, HCC2 n = 43 samples excluded) was based on sensitivity analyses suggesting that both very low and very high sample weights were related to increased sample weight -related HCC variance. Final numbers after all exclusions were: N = 467 samples for HCC1 and N = 222 for HCC2 (Fig. 1). Of the 467 participants in HCC1 population, 20.1% (94 subjects) were also included in HCC2. Still, as the HCC1 and HCC2 populations comprised mostly different subjects, they were treated as independent samples and the trajectory approach was not applied to HCC measures.

2.2.2. Prenatal PD measures

Prenatal psychological distress was measured by using several standardized self-report research questionnaires that assess different subtypes of PD. Questionnaires assessing depressive, anxiety and pregnancy-related anxiety symptoms and stressfulness of daily experiences were sent to subjects repeatedly at three assessment points during pregnancy; at gestational weeks 14, 24, and 34. The research questionnaires were either mailed to the subjects or they could be filled in online. Depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987), general anxiety symptoms with the Symptom Checklist −90, anxiety subscale (SCL-90; Derogatis et al., 1973; Holi et al., 1998), pregnancy-specific anxiety with the Pregnancy-Related Anxiety Questionnaire –Revised (PRAQ-R2; Huizink et al., 2016, 2004), and the stressfulness of daily experiences with the modified Daily Hassles scale (Korpela et al., 2008). The time spans that the questionnaires assess are one week for EPDS, one month for SCL-90 and three months for Daily Hassles. The instructions of PRAQ-R2 do not specify the time span but ask the subject to rate "what best describes your situation". The Cronbach α values for EPDS, SCL-90 and PRAQ-R2 at gwks 14, 24, and 34 were between 0.82–0.86. Stressful daily life experiences were assessed with three separate items from the Daily Hassles scale [hassles related to social relationships (DH1), work (DH2), and money (DH3)] each rated on a four-point Likert-scale on how much concerns the hassles induced in daily life.

The continuous total sum scores for EPDS, SCL-90, and PRAQ-R2 were utilized. Missing values of individual items were imputed with the mean of the other item responses of the study subject, with a maximum of 1/3 of missing responses/questionnaire being acceptable for being included in the data set. As HCC was estimated to measure long-term cortisol levels during the previous 5 months, the means of questionnaire sum scores of the previous two timepoints [(gwks 14 + 24) / 2 = mean1 and (gwks 24 + 34) / 2 = mean2] were calculated to correspond with HCC24 and HCC40, respectively, to assess cumulative scores of the self-reported PD symptoms. As the questionnaires assess PD symptoms from one week to three months, the time span depicted by the mean of two questionnaires assessed ten weeks apart from each other varies from approximately 2.5 months to 5 months. Means were calculated only when data from both timepoints were available for each questionnaire, which affected particularly PRAQ-R2 values, where the questionnaire was added in the gwk 14 questionnaires only in June 2014 ($N_{PRAQ\ gwk14}$ = 333, $N_{PRAQ\ gwk24}$ = 615, and $N_{PRAQ\ gwk34}$ = 573). In addition, Latent Growth Mixture Modelling (LGMM; Muthén and Muthén, 2000) was utilized to model the trajectories of maternal prenatal symptoms of depression and general anxiety (the EPDS and SCL-90, respectively; for details see paragraph 2.3) as these symptoms were assessed three times during pregnancy among the whole sample with questionnaires with eligible psychometric properties thus enabling their modelling with LGMM.

2.2.3. Covariates

Several potential maternal and hair-related covariates were selected based on prior research (Braig et al., 2015a; Stalder et al., 2017). Data on potential covariates were available from questionnaires (gwks 14 and 34) and from the Finnish Medical Birth Register administered by the National Institute of Health and Welfare (www.thl.fi) (Table 1).

Data on maternal age (years) at delivery (categorized as < 25, 25–35 and > 35), pre-pregnancy body mass index (BMI, kg/m^2; categorized as ≤ 20, 20,01–25, 25,01–30 and > 30), smoking during pregnancy (0 = "not at all", 1 = "yes, before knowing about the pregnancy", 2 = "yes, smoking throughout pregnancy"), sex of the child (girl/boy), and gestational weeks at delivery were drawn from the Finnish Medical Birth Register.

Self-report questionnaires were used to obtain information on other covariates including maternal educational level [categorized as "Low" (high school/vocational, < 12 years), "Medium" (polytechnics), or "High" (university degree or comparable], parity (dichotomized as primiparous vs others), marital status (dichotomized as married/domestic partnership vs others), ethnicity (dichotomized as Caucasian vs others), use of medications [assessed at gwk 14 for the HCC1 group and

Table 1
Descriptives and confounding factors.

	HCC1 (N = 467) mean (SD) / N (%)	HCC2 (N = 222) mean (SD) / N (%)
Maternal covariates		
Age at delivery (years)	31.1 (4.3)	30.6 (4.2)
Age in 3 categories		
< 25	27 (5.8)	16 (7.2)
25–35	324 (69.4)	162 (73.0)
> 35	116 (24.8)	44 (19.8)
BMI before pregnancy (kg/m2)	24.5 (4.4)	24.5 (4.8)
BMI in 4 categories		
≤20	37 (7.9)	18 (8.1)
20,01 - 25	269 (57.6)	126 (56.8)
25,01 - 30	114 (24.4)	53 (23.9)
> 30	42 (9.0)	21 (9.5)
Education		
High school / vocational (< 12years)	107 (22.9)	63 (28.4)
Polytechnics	162 (34.7)	61 (27.5)
University	178 (38.1)	81 (36.5)
Parity		
Nulliparous	261 (55.9)	134 (60.4)
Others	184 (39.4)	72 (32.4)
Marital status		
Married/domestic partnership	414 (89.5)	186 (83.8)
Others	26 (5.6)	16 (7.2)
Ethnicity		
Caucasian	447 (95.7)	204 (91.9)
Others	0	0
Medication use		
SSRI/SNRI use		
No	421 (90.1)	167 (75.2)
Yes	20 (4.3)	3 (1.8)
Inhaled/topical corticosteroids		
No	420 (89.9)	162 (73.0)
Yes	21 (4.5)	8 (3.6)
Systemic anti-inflammatory drugs		
No	435 (93.1)	169 (76.1)
Yes	6 (1.3)	0 (0)
Substance use		
Alcohol		
No	330 (70.7)	151 (68.0)
Yes, before knowing about pregnancy	59 (12.6)	31 (14.0)
Yes[a]	51 (10.9)	16 (7.2)
Smoking		
No	419 (89.7)	196 (88.3)
Yes, before knowing about pregnancy	33 (7.1)	15 (6.8)
Yes	9 (1.9)	7 (3.2)
Drugs		
No	436 (93.4)	195 (87.8)
Yes	2 (0.4)	4 (1.8)
Gender of the fetus		
Girl	235 (50.3)	102 (45.9)
Boy	231 (49.5)	119 (53.6)
Gestational weeks at delivery	39.6 (1.9)	39.7 (1.4)
Hair and hair sample related attributes		
Gestational weeks at sample taking	24.5 (1.0)	39.9 (1.4)
Season at sample taking		
Spring	142 (30.4)	58 (26.1)
Summer	123 (26.3)	57 (25.7)
Autumn	119 (25.5)	22 (9.9)
Winter	83 (17.8)	85 (38.3)
Hair color		
Blond	173 (37.0)	98 (44.1)
Dark	282 (60.4)	123 (58.7)
Hair washing		
< 4 times /week	330 (70.7)	165 (74.3)
> 4 times /week	127 (27.2)	56 (25.2)
Hair dying		
No	88 (18.8)	59 (26.6)
Yes	379 (81.2)	162 (73.0)
Sample weight (mg)	9.9 (3.1)	11.2 (3.3)
Hair cortisol concentration (pg/mg)	19.8 (34.6)	20.5 (19.9)

Notes of abbreviation: HCC1 = hair cortisol concentration measured at gestational week 24; HCC2 = hair cortisol concentration measured 1–3 days after delivery; BMI = body mass index.

[a] 70% of subjects with continuous alcohol use during pregnancy reported using alcohol less than monthly and for 52%, the amount was less than 0.5 units per time.

gwk 34 for the HCC2 group; selective serotonin (and noradrenalin) reuptake inhibitors (SSRI/SNRI; yes/no), inhaled/topical corticosteroids (yes/no), systemic anti-inflammatory drugs (yes/no)], substance use during the index pregnancy [based on both gwk 14 and 34 questionnaires; alcohol (0 = "not at all", 1 = "yes, before knowing about the pregnancy" and 2 = "yes") and illicit drugs (yes/no)]. The hair-related attributes that were considered were hair color (blond/dark), hair dying (yes/no), frequency of hair washing (more or less frequently than 4 times per week), and the season of sample taking ("Winter" from December to February, "Spring" from March to May, "Summer" from June to August, and "Autumn" from September to November) (Braig et al., 2015a).

2.3. Statistical analyses

The HCC data were examined for outliers and values > 3 standard deviations (SD) above the mean were excluded from the final analyses (N = 8 for HCC1 and N = 5 for HCC2; Stalder et al., 2013). According to common practise, natural logarithmic transformations were performed on the HCC data to reduce skewness. However, raw concentration values are provided when presenting the mean values of HCC (see Tables 1 and 4). All the analyses were performed separately for HCC1 and HCC2 as they comprised different populations. We first tested the correlations between HCC and different PD measures to select which PD measures to include as independent variables in the adjusted models. For those with suggestive of statistically significant associations ($p < 0.1$), we then carried on to the adjusted models. Based on literature on possible biological relevance (Braig et al., 2015a; Stalder et al., 2017) and statistical associations between the potential confounders with both HCC and PD, the covariates were included in the models in a stepwise manner. The first step (Model1) was adjusted for maternal education, age and BMI. In the second step (Model 2), maternal use of SSRI/SNRI medication was added as a covariate. Analysis of covariance (ANCOVA) was used in the modelling.

In addition to the confounders selected in the final models, HCC was also associated with seasonality, marital status, use of systemic anti-inflammatory drugs and use of illicit drugs. However, as these factors were unrelated to PD measures, they were not included in the final models. Further, sensitivity analyses excluding subjects reporting the use of anti-inflammatory or illicit drugs did not alter the results on the relations between PD and HCC1/2, thus these subjects were retained in the data analyses.

To be able to assess the influence of attrition, the subjects were compared with both 1) all Cohort participants and 2) those who had provided a hair sample but whose sample was excluded from the analyses: no differences in any of the PD measures were noted (see Appendix A). Moreover, no differences in any of the covariates were noted between the latter group and the final study population (Appendix A). Comparison with the whole Cohort population revealed that subjects not providing hair samples were younger [mean age 30.1 (SD 4.8) vs 30.9 (SD 4.4) years, respectively, $p > 0.001$], less educated (vocational 40.0% vs 28.1%, polytechnics 27.9% vs 33.6% and university level 32.0% vs 38.3%, respectively, $p > 0.001$), and reported

the use of SSRI/SNRIs in the end of pregnancy less frequently (2.3% vs 4.1%, p = .026) than the subjects in the final HCC1/2 populations (Appendix A).

LGMM was used to model the trajectories of depressive and general anxiety symptoms from gwk 14 to gwk 34. Pregnancy-related anxiety symptoms could not be modelled with LGMM as the number of subjects with all three measures was too low. The psychometric properties of Daily Hassles scale precluded its inclusion in this type of modelling. Growth curves of symptoms were estimated for each individual, separately for each symptom category, and then prototypic curves were identified for the whole sample. The aim was to select latent curves, i.e., the developmental patterns in symptoms that most optimally describe the data and are also interpretable. Individual item scores were used in the models, and participants with missing data were incorporated in the analyses with maximum likelihood under the missing-at-random assumption (Graham, 2009), in order to minimize bias (Nagin, 2005). LGMM was performed among subjects with both PD questionnaire data and the relevant HCC1 or HCC2 measurement.

First, the factor structures of prenatal PD questionnaires were examined separately for depressive and anxiety symptoms using structural equation modelling. The longitudinal Confirmatory Factor Analysis of the EPDS and SCL-90 showed good fit with the data (see Appendix B).

In the LGMM, the numbers of maternal prenatal PD latent classes, separately for EPDS and SCL-90 scores, were determined by increasing the number of classes in separate analyses and observing the change in statistical indices. Bayesian Information Criterion (BIC; where lower value indicates better model fit; Nylund et al., 2007), Entropy (values > 0.80 indicating excellent accuracy; Lubke and Muthén, 2007) and posterior probabilities of class memberships (i.e., the probability of an individual belonging to a group; a score of 0.80 or above is preferred; Nagin, 2005) were used for decision making (see Appendix B for statistical fit indices). Also, theoretical and clinical interpretability of the class solutions where used when selecting the best model.

For EPDS LGMM, all the statistical indices continued to improve and/or were satisfactory up to a 4-group model in both HCC1 and HCC2 samples (See Appendix B). The 4-group solution was also clinically interpretable, and retained satisfactory latent group sizes, so this was selected to model the trajectories of maternal depressive symptoms in both samples. For SCL-90 LGMM, a 3-group solution was the best fit with the data in HCC1 sample, whereas in the HCC2 sample 2- and 4-group solutions appeared to fit better (see Appendix B). Statistical analyses with both 2- and 4-class solutions were performed but as the unadjusted associations between the group variable and HCC2 were similar with both solutions (data not shown), the analyses were continued with the 2-class variable with larger group sizes. The group labeling and group sizes of the selected models are described in Figs. 2a-d. The groups with highest overall level of PD symptoms were selected as reference groups in pairwise comparisons.

The statistical analyses were performed using SPSS v.24 apart from the LGMM, which was performed using Mplus 6 (Muthén and Muthén, 2000).

3. Results

3.1. Sample characteristics

Participant sociodemographics, hair sample characteristics, and descriptive information on the covariates, PD measurements and HCC are described in Table 1. For all subjects (i.e the populations of both HCC1 and HCC2 pooled together), the mean age was 30.9 (SD 4.3) years and maternal prepregnancy BMI was 24.5 (SD 4.5) kg/m^2. The educational level of 28.1% of the mothers was elementary school, 33.6% had vocational/undergraduate education and 38.3% had an educational degree comparable to a university degree. In all, 4.3% of mothers in the HCC1 population had SSRI/SNRI use in early pregnancy and 1.8% of the mothers in the HCC2 population used them in late pregnancy.

The mean HCC was higher in HCC2 samples when compared to HCC1 samples [20.5 (SD 19.9) pg/mg vs 19.8 (SD 34.6) pg/mg, respectively; p = .002].

Both in the HCC1 and HCC2 populations, four separate subgroups for different prenatal EPDS symptom trajectories were identified ("Consistently low", "Moderate and slightly increasing", "Moderate and steeply increasing", and "High and decreasing" in the HCC1 sample and "Consistently low", "Low and increasing", "Low and steeply increasing", and "Consistently elevated" in HCC2). Moreover, two separate subgroups for SCL-90 symptom trajectories with HCC1 and three for HCC2 were identified ("Consistently low" and "High and decreasing" in HCC1 and "Consistently low", "Low and steeply increasing", and "High and decreasing" in HCC2). Mean levels of PD symptoms are described for each trajectory category in Figs. 2a-d.

3.2. Associations between HCC and cross-sectional, recent PD

First, we analysed the associations between the individual PD scores/timepoint and HCCs assessed approximately at the same time (cross-sectional, recent PD). No associations were observed between any type of recent PD and HCC at neither assessment point (β's between −0.075 and 0.12, p´s between 0.11 and 0.94; for details, see Table 2).

3.3. Associations between HCC and cumulative mean of PD

We further assessed a cumulative prevalence of symptoms composing a mean score of two previous questionnaire timepoints, i.e. mean1 and mean2 scores (cumulative mean of PD, see Table 2). HCC1 was associated with both PRAQ-R2 mean1 (β = −0.028, p = .034) and DH1 mean1 (β = 0.22, p = .013). The other measures (EPDS, SCL-90, DH2, and DH3) were not associated with HCC1 (β´s between −0.024 and 0.016, p's between 0.27 and 0.83; see Table 2). None of the PD mean2 variables (EPDS, SCL-90, PRAQ-R2, DH1–3) were related to HCC2 (β's between −0.11 and 0.057, p's between 0.090 and 0.97; see Table 2), although the association between HCC2 and EPDS mean2 approached statistical significance (β = 0.036, p = .090) and was thus included in the adjusted models according to our analysis plan.

The mean1 of DH1 was associated with HCC1 also after adjusting for all the covariates in the Models 1 and 2 (β = 0.25 in both, p's < 0.005, see Table 3). The direction of association between PRAQ-R2 mean1 and HCC1 was negative also in Models 1 and 2 and thus differed from other dimensions of PD, but it did not reach statistical significance (β´s −0.028 and −0.025, p's 0.083 and 0.093, respectively). No association was observed between EPDS mean2 and HCC2 in the adjusted models (β's 0.034 and 0.031, p's 0.12 and 0.18).

3.4. Associations between HCC and trajectories of depressive and anxiety symptoms across pregnancy

HCC2 was found to be elevated in relation to continuously higher levels of depressive symptoms (Adj R^2 = 0.025, p = .043, see Table 4). In particular, the mothers in the "Consistently elevated" group presented with higher HCC than mothers in both the "Consistently low" (β = −0.54, p = .016 for the contrast) and the "Low and increasing" (β = −0.55, p = .026 for the contrast) groups. The associations between the EPDS trajectories and HCC1 only approached statistical significance (Adj R^2 = 0.008, p = .082) and no differences were seen in either HCC1 or HCC2 between the different SCL-90 trajectory groups (see Table 4).

The association between HCC2 and EPDS trajectories remained after adjusting for maternal education, age and BMI in Model 1 (p value for the EPDS trajectory variable = 0.035, for the whole model Adj R^2 = 0.053, p = .026; see Table 4). The association between the EPDS trajectory variable and HCC2 was influenced by the inclusion of maternal use of SSRI/SNRI's (Model 2) (p changing from 0.035 in Model

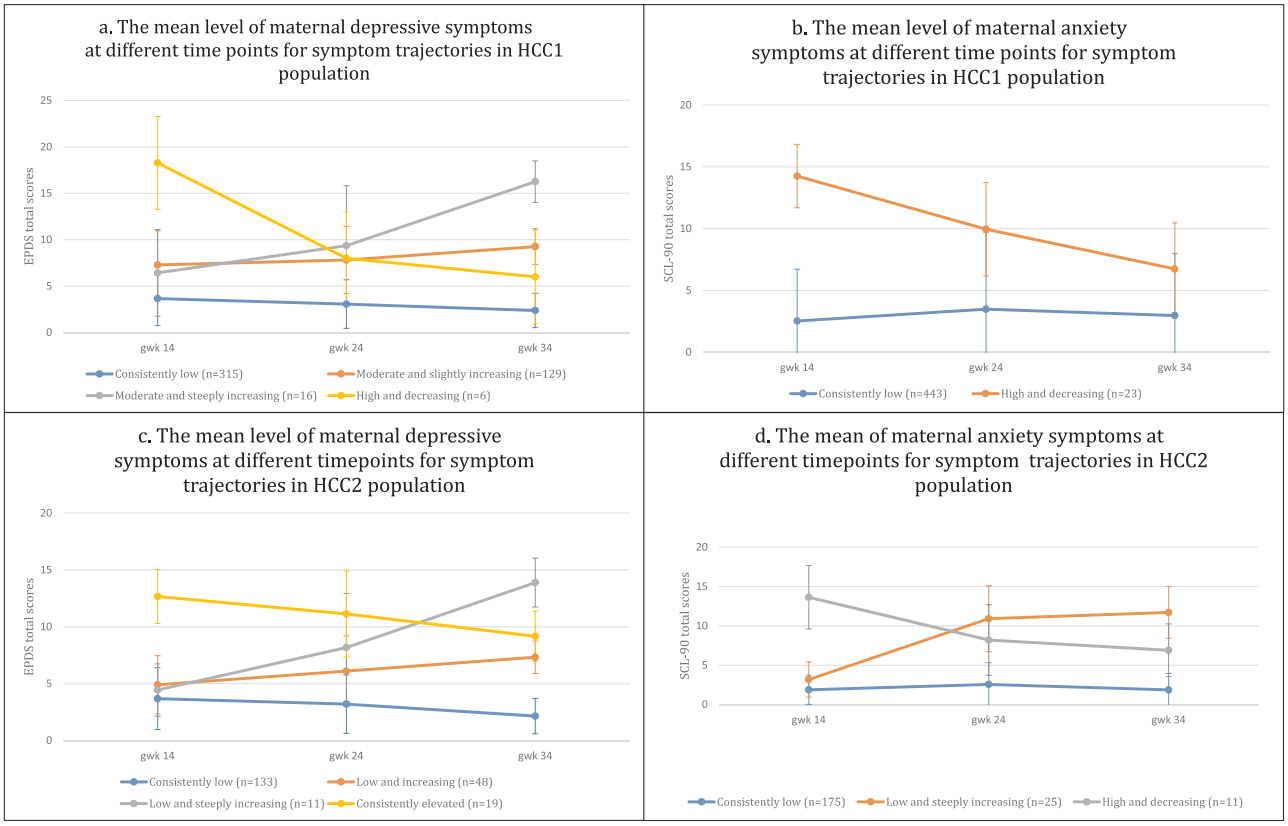

Fig. 2. (a) The mean level of maternal depressive symptoms at different time points for symptom trajectories in HCC1 population. (b). The mean level of maternal anxiety symptoms at different time points for symptom trajectories in HCC1 population. (c). The mean level of maternal depressive symptoms at different timepoints for symptom trajectories in HCC2 population. (d). The mean of maternal anxiety symptoms at different timepoints for symptom trajectories in HCC2 population. Notes of abbreviation: HCC1 = hair cortisol concentration measured at gwk 24; gwk = gestational week; HCC2 = hair cortisol concentration measured 1–3 days after delivery; EPDS = the Edinburgh Postnatal Depression Scale; SCL-90 = the Symptom Checklist −90, anxiety subscale. The populations of HCC1 (Fig. 2a and 2b) and HCC2 (Fig. 2c and 2d) are comprised of independent samples.

1–0.065 in Model 2), but the distinct groups still predicted HCC2 [HCC2 higher in "Consistently elevated" group in comparison to "Consistently low" (β = −0.71, p = .021) and "Low and increasing" (β = −0.82, p = .011) groups]. Model 2 for EPDS trajectories explained 6.4% of the variance in HCC2 (p = .032). For HCC1 and EPDS trajectories, no statistically significant associations were observed in the adjusted models, although the beta estimates were similar in direction and magnitude to those observed with EPDS and HCC2 (see Table 4).

4. Discussion

The current study aimed at examining the associations between maternal prenatal HCC and long-term indicators of maternal prenatal PD. According to our knowledge, this is the first study to utilize a trajectory approach in modelling the course of maternal psychological distress symptoms over time to assess the associations between HCC and PD, either in pregnant or in non-pregnant study populations. The results support our first *a priori* hypothesis that trajectories of PD across pregnancy were associated with long-term secretion of cortisol, as the mothers in the subgroup with the highest levels of depressive symptoms had 3.5–4.2 % higher end-of-pregnancy HCC than the mothers in the subgroups with low levels of overall prenatal depressive symptoms. HCC measured at gwk 24 did not differ depending on the depression or anxiety symptom trajectory group.

As associations with end-of-pregnancy HCC were only observed using the trajectory-approach, that approach seems to provide novel information on the relations between PD and long-term cortisol secretion during pregnancy. The subgroup of mothers with "Low and steeply increasing" depressive symptoms had comparably high (mean 13.8, SD 2.1) total scores on the EPDS at gwk 34, but maybe because of the lower symptom levels in early- and mid-pregnancy, i.e. the proportionately short time of symptom presentation, their HCC2 was not elevated. This also supports the hypothesis that the chronicity of the prenatal symptoms is relevant when HPA axis functioning is investigated. In turn, altered functioning of the HPA axis could also contribute to the persistence of PD symptoms.

The trajectory approach was perhaps better-suited to be used in comparison with HCC2 than HCC1, as the PD trajectories were assessed from all time-points until the end of pregnancy and thus, the mid-pregnancy HCC should have been able to predict symptoms emerging later in time to show associations. However, it can be argued that the HPA axis of subjects with continuously low or mid-level symptoms would be primed to function in a different manner than that of subjects with steeper increase or decrease in symptom prevalence.

A trajectory approach to PD symptoms has not previously been utilized in studies with cortisol measurements but latent groups identified based on different trajectories in maternal prenatal PD have been associated with alterations in offspring behavior. In a study by Kataja et al. (2018), 8-month-old infants were less prone to disengage their attention from fearful (vs. happy and neutral) faces when their mothers belonged to groups with more chronically elevated perinatal depressive symptoms. This supports the hypothesis that chronicity of depressive symptoms could induce more pronounced physiological responses that could be observed as alterations in long-term cortisol levels, and thus be associated with offspring outcomes.

Concordant with our second hypothesis, when assessed cross-sectionally with cumulative measures, associations between HCC and prenatal PD measures were observed in mid-pregnancy but not in the

Table 2
Correlations between HCC and cross-sectional recent and cumulative means of prenatal PD.

	HCC1			HCC2		
	β	p	N	β	p	N
EPDS						
Recent[a]	0.014	0.24	457	0.027	0.15	172
Cumulative[b]	0.016	0.27	433	**0.036**†	**0.090**	169
SCL-90						
Recent[a]	0.016	0.17	455	0.003	0.89	172
Cumulative[b]	0.015	0.27	431	0.003	0.89	168
PRAQ-R2						
Recent[a]	0.001	0.88	457	−0.002	0.85	172
Cumulative[b]	**−0.028***	**0.034**	196	−0.006	0.65	169
Daily Hassles						
Worries about relationships (DH1)						
Recent[a]	0.12	0.11	436	−0.009	0.94	169
Cumulative[b]	**0.22***	**0.013**	399	−0.11	0.46	160
Worries about work (DH2)						
Recent[a]	0.020	0.76	436	−0.075	0.39	169
Cumulative[b]	−0.024	0.73	399	0.005	0.97	160
Worries about money (DH3)						
Recent[a]	−0.022	0.72	436	0.060	0.57	169
Cumulative[b]	0.015	0.83	399	0.057	0.64	160

Notes of abbreviation: PD = psyhological distress; HCC1 = hair cortisol concentration measured at gwk 24; gwk = gestational week; HCC2 = hair cortisol concentration measured 1–3 days after delivery; EPDS = the Edinburgh Postnatal Depression Scale; SCL-90 = the Symptom Checklist −90; PRAQ-R2 = the Pregnancy-related Anxiety Questionnaire -Revised2.
[a] total scores from single timepoints; gwk 24 questionnaires in comparison to HCC1 and gwk 34 questionnaires in comparison to HCC2.
[b] mean 1 (gwk 14 and 24 questionnaires) in comparison to HCC1 and mean 2 (gwk 24 and 34 questionnaires) in comparison to HCC2.

end of pregnancy as was expected based on the pregnancy-related alterations in HPA axis functioning. Maternal HCC was higher in mothers who reported more worries about relationships during the first and second trimesters and lower with more pregnancy-related anxiety. This is in line with previous literature (Hoffman et al., 2016; Kalra et al., 2007; Orta et al., 2018) and further supports the hypothesis that the HPA axis would be more reactive to distress in early- and mid-pregnancy. This is also consistent with our third hypothesis that the type of PD affects both whether or not associations are observed as well as the direction of the association.

The observed negative association between pregnancy-related anxiety and HCC in the unadjusted models could be explained by the general notion of anxiety disorders being associated with decreased HCC (Stalder et al., 2017) but on the other hand, some pregnancy-related concerns in early pregnancy may also be expected and reflect normal adaptation. Worries about relationships and pregnancy-related anxiety can be argued to be especially relevant during this period of getting ready for the transition to parenthood (Huizink et al., 2017). The characteristics of pregnancy-related anxiety are not comprehensively understood but it seems to differ significantly from general anxiety and in some studies only pregnancy-specific anxiety was associated with altered short-term cortisol levels (Beijers et al., 2010; Dahlerup et al., 2018; van den Heuvel et al., 2018). In addition, in our data these measures had more variance in symptom prevalence in comparison to depressive or general anxiety symptoms, which could account for the associations to be observable (see Appendix C). However, adjustment with the selected covariates led to the association between pregnancy-related anxiety and HCC falling below the statistical significance level.

Importantly, the associations observed between HCC and PD measures were generally weak. For example, worries about relationships only accounted for 2.1% of the variance in HCC1 in the adjusted model. The observed magnitudes of associations are not surprising as a recent *meta*-analysis comprising mainly non-pregnant study populations also reported no associations between HCC and self-reported PD when all types of PD were reviewed pooled together (Stalder et al., 2017). As the HPA axis reactivity alters during pregnancy, findings with large effect sizes in pregnant populations would be surprising. Thus, our results highlight the importance of assessing different types of PD separately and, importantly, offer novel information on the importance of utilizing long-term approaches in PD assessments, better paralleling with HCC measurements. This would be important to be taken into account in future studies despite the overall small effect sizes.

Adjusting for maternal use of SSRI/SNRI medication weakened the associations between depressive symptoms and HCC. This is in line with literature as there are direct effects of SSRI medication on HPA axis functioning and most evidence suggest their use to dampen HPA axis activity (Hinkelmann et al., 2012; Knorr et al., 2012; Ruhé et al., 2015). Thus, the direct effects of the use of SSRI/SNRI medication could weaken the observed positive association between HCC and depressive symptoms. However, in our data the use of SSRI/SNRI medication was associated with elevated HCC in mid-pregnancy. This could be due to the subjects with continued antidepressant use during pregnancy having more severe depressive symptoms fulfilling diagnostic criteria of a major depressive disorder. The severity of the symptoms/disorder could be the reason for the association with increased long-term cortisol levels.

Variance in HCC was different for the populations with HCC1 and HCC2 samples. It can be hypothesized that the physiological pregnancy-related changes decrease the interindividual variance in long-term

Table 3
Adjusted models for cumulative means of prenatal PD.

	UNADJUSTED				MODEL 1[a]				MODEL 2[b]			
	Adj R^2	β	p	N	Adj R^2	β	p	N	Adj R^2	β	p	N
PD symptom cumulative means explaining HCC1												
MODEL A: Daily hassles mean1	0.009†		0.082	399	0.017†		0.083	394	0.021†		0.057	388
Worries about relationships (DH1)		**0.22***	**0.013**			**0.25****	**0.005**			**0.25****	**0.004**	
Worries about work (DH2)		−0.024	0.73			−0.022	0.76			−0.036	0.62	
Worries about money (DH3)		0.015	0.83			−0.003	0.97			0.016	0.83	
MODEL B: PRAQ-R2 mean1	**0.018***		**0.034**	195	0.024		0.13	192	**0.044***		**0.046**	190
PRAQ-R2		**−0.028***	**0.034**			−0.025†	0.083			−0.024†	0.093	
PD symptom cumulative means explaining HCC2												
MODEL C: EPDS mean2	0.011†		0.090	169	**0.049***		**0.045**	162	0.044†		0.069	160
EPDS		0.036†	0.090			0.034	0.12			0.031	0.18	

Notes of abbreviation: PD = psychological distress; HCC1 = hair cortisol concentration measured at gwk 24; gwk = gestational week; HCC2 = hair cortisol concentration measured 1–3 days after delivery; EPDS = the Edinburgh Postnatal Depression Scale; PRAQ-R2 = the Pregnancy-related Anxiety Questionnaire -Revised2.
[a] Model 1 adjusted for maternal education, maternal body mass index and maternal age.
[b] Model 2 adjusted for covariates in Model 1 and maternal use of SSRI/SNRI medication.

Table 4
Adjusted models for trajectories of prenatal depressive symptoms.

		UNADJUSTED				MODEL 1[a]				MODEL 2[b]			
PD symptom trajectories explaining HCC1	mean (SD) HCC1 (pg/mg)	Adj R^2	β	p	N	Adj R^2	β	p	N	Adj R^2	β	p	N
MODEL A1: EPDS Trajectories (HCC1)		0.008†		0.082	466	0.011		0.15	442	0.016†		0.081	435
EPDS trajectory variable				0.082				0.077				0.13	
Consistently low	19.12 (36.82)		−0.62	0.14	315		−0.67	0.11			−0.61	0.14	
Moderate and slightly increasing	20.52 (30.08)		−0.41	0.33	129		−0.44	0.30			−0.40	0.34	
Moderate and steeply increasing	18.89 (13.53)		−0.31	0.52	16		−0.45	0.36			−0.43	0.38	
High and decreasing	24.71 (16.61)		ref		6		ref				ref		
MODEL A2: SCL trajectories (HCC1)					466								
SCL-90 trajectory variable		- 0.001		0.42									
Consistently low	19.62 (34.96)		−0.18	0.42	443								
High and decreasing	18.83 (15.83)		ref		23								
PD symptom trajectories explaining HCC2	mean (SD) HCC2 (pg/mg)	Adj R^2	β	p	N	Adj R^2	β	p	N	Adj R^2	β	p	N
MODEL B1: EPDS Trajectories (HCC2)		**0.025***		**0.043**	211	**0.053***		**0.026**	200	**0.064***		**0.032**	162
EPDS trajectory variable				**0.043**				**0.035**				0.065	
Consistently low	18.62 (19.84)		**−0.54***	**0.016**	133		**−0.53***	**0.023**			**−0.71***	**0.021**	
Low and increasing	19.52 (17.82)		**−0.55***	**0.026**	48		**−0.64***	**0.012**			**−0.82***	**0.011**	
Low and steeply increasing	25.91 (16.46)		−0.082	0.81	11		−0.064	0.86			−0.37	0.41	
Consistently elevated	29.16 (25.77)		ref		19		ref				ref		
MODEL B2: SCL trajectories (HCC2)													
SCL-90 trajectory variable		−0.008		0.83	211								
Consistently low	19.71 (19.16)		0.17	0.59	175								
Low and steeply increasing	24.70 (26.77)		0.19	0.57	25								
High and decreasing	16.84 (14.30)		ref		11								

Notes of abbreviation: PD = psychological distress; HCC1 = hair cortisol concentration measured at gwk 24; gwk = gestational week; HCC2 = hair cortisol concentration measured 1–3 days after delivery; EPDS = the Edinburgh Postnatal Depression Scale; SCL-90 = the Symptom Checklist −90; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin-norepinephrine reuptake inhibitors.

[a] Model 1 adjusted for maternal education, maternal body mass index and maternal age.

[b] Model 2 adjusted for covariates in Model 1 and maternal use of SSRI/SNRI medication.

cortisol levels towards the end of pregnancy. However, similar correlations between important covariates and HCC were observed in both HCC1 and HCC2 samples, which strengthens the reliability of the data.

In our study, 5 cm hair segments were used, thus, the possibility of wash-out effects may not be excluded (Dettenborn et al., 2012; Kirschbaum et al., 2009). However, as wash-out effect is not related to prenatal PD and it has not affected the observed associations among the first 0–6 cm (Luo et al., 2012; Steudte et al., 2011), it should not compromise the interpretation of our data. In our data, HCC was not associated with hair-related attributes such as hair dying or hair washing. A sensitivity analysis adjusting for hair dying (> 70% of subjects having their hair dyed) was also performed without any of the main findings being significantly altered, thus we consider the factor not to have biased the findings.

This study has several strengths. First, the relatively large number of study subjects allowed statistical power to observe mild associations between PD measures and HCC. Utilizing latent growth modelling as a measure for the long-term course of PD offers a novel approach to studying these phenomena while being easily applicable. In this study, several types of PD were assessed in a longitudinal setting and the measured types of distress were selected on a basis of being relevant during the prenatal period. A wide array of potential covariates was available for examination. In addition, HCC was measured at two different timepoints to assess the effects of timing on how self-reported PD measures are reflected as alterations in HPA axis functioning.

Limitations of the study should also be considered. As the study population comprised of a normal population with only some subjects with higher levels of PD symptoms, the number of subjects for example in some symptom trajectory groups was rather low. This may have resulted in existing group differences remaining unobserved or individual values having excessive effects. Ensuring adequate group sizes was an important factor in assessing the fits of different models that were identified from the data and careful consideration was applied when assessing the statistical and clinical fit of each model. The possible influence of any outlier values was controlled by careful exclusion of those subjects. Although longitudinal data was collected for the PD measures, the two different timepoints of HCC were assessed as two independent samples, as the number of women with both HCC measures was too low for the purposes of this study. Longitudinal HCC data might have given more insight into the trajectories and change in cortisol secretion patterns in relation to the trajectories of prenatal PD. The time spans of which the questionnaires assessed varied from one week (EPDS) to three months (Daily Hassles) which is important to note especially when interpreting the results of recent PD. The time spans of cumulative means of PD correspond relatively well with the time frame of HCC.

Relatively many subjects were excluded due to inadequate hair sample size. This was not related to the characteristics of the study subjects but rather to factors in the hair collection procedure and in post hoc analysis the included and excluded subjects did not differ in any of the PD measures or the main covariates. In line with our previous Cohort description (Karlsson et al., 2018), the subjects with more data available have higher educational level and are slightly older, but importantly, the final study population and the whole FinnBrain Study Cohort population did not differ in terms of the PD exposure. Not having data on other hair steroids such as hair cortisone precluded more detailed analyses on the HPA axis functioning and more comprehensive steroid profiles (Scharlau et al., 2017). The study population was ethnically homogenous, which may limit the generalizability of the results to multi-ethnic populations, but it also reduces effects of uncontrolled variation.

One of the main rationales in studying PD and its endocrine correlates is to further understand the mechanisms by which PD can affect fetal programming. In this study, we focus on measuring cumulative secretion of cortisol, but it is evident that the mechanisms involved are far more complex. Alternative pathways by which maternal PD could affect the development of the fetus were recently reviewed by Huizink and de Rooij (2018) and they include, for instance, mechanisms

concerning the maternal sympathetic nervous system (Levine et al., 2016), neurotransmitters, especially serotonin (St-Pierre et al., 2016), epigenetics (Cao-Lei et al., 2017), intestinal microbiome (O'Mahony et al., 2017), immunological system (Schepanski et al., 2018), and cognitive processes (Kataja et al., 2017).

5. Conclusions

By using modelling that illustrates long-term or cumulative maternal PD, we were able to add novel aspects to the existing literature on how PD is related to HCC. Different types of PD seem to be differentially related to HCC, albeit with generally weak associations. However, our notion of consistently elevated depressive symptoms being linked with end-pregnancy HCC should be further investigated, as it appears that the prenatal symptom course is especially relevant in comparison to short-term symptomatology. In the future HCC studies in both pregnant and non-pregnant populations should consider the compatibility of timelines reflected by the different measures is advised. Longitudinal, multimodal and transgenerational studies are required to assess the potential programming effects altered maternal long-term cortisol levels have on offspring development.

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendixes A–C Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104383.

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