

## **Risk Factors for Postpartum Relapse in Women at Risk of Postpartum Psychosis: The Role of Psychosocial Stress and the Biological Stress System**

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**Abstract**

**Background:** Postpartum psychosis is the most severe psychiatric disorder associated with childbirth, and the risk is particularly high for women with a history of bipolar disorder, schizoaffective disorder or those who have suffered a previous episode of postpartum psychosis. Whilst there is a lot of evidence linking stress to psychosis unrelated to childbirth, the role of stress in the onset of postpartum psychosis has not been fully investigated.

**Methods:** A prospective longitudinal study of 112 pregnant women, 51 at risk of postpartum psychosis because of a DSM-IV diagnosis of bipolar disorder (n=41), schizoaffective disorder (n=6) or a previous postpartum psychosis (n=4) and 61 healthy women with no past or current DSM-IV diagnosis and no family history of postpartum psychosis. Women were followed up from the third trimester of pregnancy to 4 weeks' post partum. Women at risk who had a psychiatric relapse in the first 4 weeks' post partum (AR-unwell) (n=22), were compared with those at risk who remained well (AR-well) (n=29) on measures of psychosocial stress (severe childhood maltreatment and stressful life events) and antenatal biology (cortisol and inflammatory biomarkers).

**Results:** Logistic regression analyses revealed that severe childhood maltreatment ( $OR=4.9$ , 95% CI 0.5-49.2) and higher daily cortisol in the third trimester of pregnancy ( $OR=3.7$ , 95% CI 1.2-11.6) predicted psychiatric relapse in the first 4 weeks' post partum in women at risk of postpartum psychosis after adjusting for clinical and sociodemographic covariates.

**Conclusion:** The current study provides evidence for the role of psychosocial stress and the biological stress system in the risk of postpartum relapse in women at risk of postpartum psychosis.

**Keywords:** Postpartum Psychosis; Childhood Maltreatment; Stressful Life Events; Cortisol; Inflammatory Markers; Perinatal

## 1 Introduction

Postpartum (or puerperal) psychosis (PP) is the most severe psychiatric disorder associated with childbirth (Jones et al., 2014), but it remains unclear why some women at risk become unwell after giving birth while others remain well. Whilst there is substantial evidence linking stress to psychosis unrelated to gestation, and despite the fact that pregnancy and childbirth are themselves potential stressors (Robertson et al., 2004), the role of stress in PP has not been fully investigated.

PP typically occurs within the first few weeks following delivery, although onset is often within days of childbirth (Heron et al., 2007). Whilst PP is relatively rare, occurring in 1-2 per 1000 deliveries in the general population (Jones, 2012), the risk is greatly increased for women with a diagnosis of bipolar disorder, schizoaffective disorder and/or a personal or family history of PP, with up to 50% experiencing an episode of PP after giving birth (Dean et al., 1989; Di Florio et al., 2013; Doyle et al., 2012; Jones and Craddock, 2001; Wesseloo et al., 2016).

It is well established that psychosocial stress and the biological stress system play a role in the aetiology and course of affective and non-affective psychoses unrelated to childbirth. Indeed, there is considerable evidence of an association between both childhood maltreatment and more recent stressful life events (i.e., occurring in the months prior to illness onset) and psychosis unrelated to gestation (e.g., Beards et al., 2013; Lex et al., 2017; Varese et al., 2012), and it has been suggested that the biological stress system might be one of the mechanisms underlying this association. Genetic predisposition and early environmental factors, such as perinatal stress and childhood trauma, can contribute to Hypothalamic Pituitary Adrenal (HPA) axis dysregulation and stress-related brain alterations, resulting in a heightened sensitivity to subsequent psychosocial stress and an increased risk for later psychopathology (Heim and Nemeroff, 1999, 2001; Pruessner et al., 2017; Read et al., 2001, 2014; Walker and Diforio, 1997; Walker et al., 2008). Support for this theory has come from studies showing an association between childhood trauma and altered HPA axis function (e.g., Bernard et al., 2017; Bunea et al., 2017; Heim et al., 2000, 2001, 2002), as well as evidence of cortisol dysregulation in individuals with affective and non-affective psychoses unrelated to gestation. Indeed,

research has shown a specific pattern of cortisol dysregulation in these disorders, characterized by increased cortisol levels during the day and a blunted Cortisol Awakening Response (CAR) (Belvederi Murri et al., 2016; Mondelli et al., 2010). Furthermore, this pattern of Hypothalamic Pituitary Adrenal (HPA) axis activation has also been reported in individuals at risk for psychosis, prior to illness onset (Collip et al., 2011; Day et al., 2014; Walker et al., 2013), and particularly in those who become unwell (Labad et al., 2015). The immune response, an important component of the stress system, has also been implicated in the development of affective and non-affective psychoses unrelated to childbirth, with increased inflammatory markers found in both patients with bipolar disorder and those with psychosis (Mondelli et al., 2011, 2015; Mørch et al., 2016).

To date, only a few studies have investigated some of these psychosocial and biological factors in relation to PP, with the majority finding no association between psychosocial factors, such as childhood adversity or stressful life events, and the onset of PP (Dowlatshahi and Paykel, 1990; Marks et al., 1991; McNeil, 1988; Perry et al., 2016; Warselius et al., 2019). However, these studies mainly had small sample sizes, used cross sectional designs, did not use questionnaires that have been validated to assess traumatic and stressful life events or did not examine experience of childhood neglect. On the other hand, there is emerging evidence of immune system dysregulation in women with PP (Dazzan et al., 2018). Indeed, research has shown that, compared with healthy postpartum women and non-postpartum women, women with PP failed to show the normal postpartum T cell increases, whilst showing upregulation of immune system-related monocyte genes and elevated monocyte and cytokine levels (Bergink et al., 2013; Kumar et al., 2017; Sathyanarayanan et al., 2019). Furthermore, we recently found that, compared with women at risk of PP who remained well in the post partum, women with PP showed reductions in regional brain volumes and cortical surface area, similar to those seen in individuals with psychosis unrelated to gestation (Fusté et al., 2017). Taken together, these findings provide evidence to suggest that multiple biological factors might play a role in the onset of PP.

Nevertheless, there is a lack of research examining the role of psychosocial and biological factors *together* in the onset of PP. Indeed, much of the research to date has examined the role of individual risk factors. However, given our understanding of psychoses unrelated to gestation it is likely that multiple biological and psychological factors are involved in increasing the risk for PP. Only one study to date, by our group, has examined psychosocial and biological stress together in relation to PP (Aas et al., 2020). We showed that, at 3-4 months post partum, women with PP experienced more recent stressful life events, had higher levels of perceived stress and immune system (c-reactive protein) and HPA axis (daily cortisol) hyperactivation, compared with healthy postpartum women. Interestingly, we also found that women at risk of PP who remained well in the postpartum had stress and immune activation levels that were intermediate between those of women with PP and healthy women, suggesting that these factors might represent trait markers for severe postpartum mental illness, which are then exacerbated in those women who go on to become unwell (Aas et al., 2020). However, only a prospective study, examining these factors prior to the onset of PP, can answer this question.

In order to do this, the current study examined both psychosocial and biological measures of stress in a prospective longitudinal study of women at risk of PP, because of a diagnosis of bipolar disorder, schizoaffective disorder or a previous history of PP. Women were then followed-up to ascertain who did and did not have a psychiatric relapse in the postpartum period. We measured maternal childhood trauma, stressful life events and cortisol levels and immune markers in the third trimester of pregnancy. We hypothesized that, compared with women at risk of PP who remained well following the delivery (AR-well), women at risk of PP who relapsed (AR-unwell) would be more likely to 1) have experienced severe childhood trauma, 2) have experienced stressful life events during pregnancy and 3) show dysregulation of the biological stress system similar to that reported in affective and non-affective psychoses unrelated to childbirth, that is, a blunted CAR and increased daily cortisol and inflammatory markers (Belvederi Murri et al., 2016; Mondelli et al., 2010, 2015).

## **2 Methods and Materials**

### **2.1 Design**

This study is part of the Psychiatry Research and Motherhood (PRAM) Study, a prospective longitudinal study, in which a group of pregnant women at risk of developing PP (AR) and a control group of healthy pregnant women (HC) were recruited and followed-up from 25 weeks' gestation to 4 weeks' post partum. Maternal sociodemographics, clinical information, stress experiences (severe childhood maltreatment, stressful life events and intimate partner violence) and biological measures of stress (HPA axis function and inflammatory markers) were assessed in the late second or third trimester of pregnancy (baseline assessment). Clinical information and stressful life events in pregnancy were assessed again at 6 days' and/or 8 weeks' post partum (for the period between the baseline assessment and 4 weeks' post partum). Ethical approval was granted by Camberwell St Giles Ethics Committee (REC: 10/H0807/14). All participants provided written informed consent.

### **2.2 Sample**

The sample comprised 112 women: 51 women at risk of PP recruited from perinatal mental health services in London and 61 healthy pregnant women recruited from King's College London Obstetric Services or from advertisements in local GP practices. Women were considered at risk if they had a DSM-IV diagnosis of bipolar disorder (n=41, 80%), schizoaffective disorder (n=6, 12%) or had suffered a previous episode of PP (n=4, 8%) (Table 1). Healthy controls (HCs) were required to be free from any lifetime DSM-IV diagnosis and have no first-degree relatives with a history of PP.

Inclusion criteria for all women were:  $\geq 18$  years of age, singleton pregnancy and ability to communicate in English. Women were excluded if they had any uterine anomalies or known severe obstetric complications in the index pregnancy, were unable to have an MRI scan, were unlikely to keep their child or, for the AR group, were too unwell to participate.

## 2.3 Measures

### 2.3.1 Sociodemographic and clinical assessment

Sociodemographic data, including maternal age, ethnicity, education, employment and marital status were collected at baseline (median=26.9 weeks, range 22.0-38.3 weeks) (see supplementary file).

Current and past DSM-IV Axis I disorders were assessed at baseline and at 8 weeks' post partum using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I-CV: First, 1996). Information obtained at diagnostic interview was supplemented with participants' medical notes. Consensus meetings were held with senior psychiatrists to confirm participants' diagnosis and to determine their antenatal and postnatal clinical status.

The AR women were classified as having a psychiatric relapse (AR-unwell) if, in the first 4 weeks' post partum they a) met DSM-IV diagnostic criteria for a psychotic, manic or hypomanic, depressive or mixed episode; or b) had a combination of DSM-IV symptoms that, whilst not meeting diagnostic criteria, impacted on their daily functioning (e.g., their ability to care for the baby or themselves) and/or were of sufficient intensity to require a change in treatment (either pharmacological or management plan). This broader definition was used to capture all affective relapse events, as all of the AR women were closely monitored by perinatal mental health services and most took psychotropic medication to either prevent the onset of frank PP or to treat the symptoms as soon as they developed in order to prevent them from worsening, and thus we expected that progression to full-blown psychosis would be a rarer event in this group (as indeed we found). Women were then classified as having a severe relapse if, in the first 4 weeks' post partum, they experienced psychotic, manic, mixed symptoms, and/or psychiatric hospitalization (Wesseloo et al., 2016). The 4-week time frame was chosen according to the DSM-IV postpartum-onset specifier (American Psychiatric Association, 1994).

We measured symptom severity at baseline using the Positive and Negative Syndrome Scale (PANSS: Kay et al., 1987), the Young Mania Rating Scale (YMRS: Young et al., 1978) and the Hamilton

Depression Rating Scale (HAM-D: Hamilton, 1960). Furthermore, women were classified as having a psychiatric relapse at any time *during pregnancy* (antenatal relapse) using the same definition as above (i.e., symptoms that met DSM-IV diagnostic criteria or a combination of DSM-IV symptoms that, whilst not meeting diagnostic criteria, impacted on the woman's daily functioning and/or required a change in treatment).

Information about age at illness onset, duration of illness, lifetime number of admissions, previous episodes of PP and medication use was collected at baseline and/or 8 weeks' post partum (see supplementary file).

Obstetric information, including parity, pregnancy-related medical conditions (e.g., gestational diabetes, hypertension) and mode of delivery, and information about maternal physical health, including medical conditions (e.g., metabolic disorder, endocrine disorder), pre-pregnancy Body Mass Index (BMI) and alcohol and cigarette use during pregnancy, was collected at baseline and/or at 6 days' and/or 8-weeks' post partum (see supplementary file).

Clinical, sociodemographic, health and obstetric data for the AR and HC groups are presented in Table 1. The HC group were significantly more likely to be employed ( $\chi^2_{(1)}=4.3, p=.04$ ) and to be married or cohabiting ( $\chi^2_{(1)}=5.7, p=.02$ ) than the AR group. Furthermore, the HC group were significantly more likely to have consumed alcohol during pregnancy ( $\chi^2_{(1)}=11.3, p<.01$ ), whilst the AR group were significantly more likely to have smoked during pregnancy ( $\chi^2_{(1)}=5.3, p=.04$ ), and had a significantly higher BMI ( $U=1751.5, z=2.5, p=.01$ ).

### **2.3.2 Experience of Severe Childhood trauma**

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q: Bifulco et al., 2005) was administered at baseline to assess experience of childhood maltreatment (physical abuse, sexual abuse, antipathy and neglect) and parental loss and separation prior to the age of 17 years. The

questionnaire has previously been found to have good reliability and validity, showing concordance with the CECA interview (Bifulco et al., 2005). The CECA.Q has been widely used in research of patients with psychosis unrelated to gestation (e.g., Aas et al., 2012) and with women during pregnancy (e.g., Lara et al., 2015) (see supplementary file).

### ***2.3.3 Experience of Stressful life events***

The List of Threatening Experiences Questionnaire (LTE-Q: Brugha and Cragg, 1990) was administered at baseline and again at 8 weeks' post partum to assess maternal experience of stressful life events during pregnancy. This questionnaire has been used in research in psychosis and bipolar disorder unrelated to gestation (e.g., Hosang et al., 2012; Mondelli et al., 2010), and with pregnant and postpartum women (e.g., Willie et al., 2016). We added a question about experience of major pregnancy-related problems (e.g., pre-eclampsia, decreased fetal movement) (see supplementary file).

The modified pregnancy version of the Composite Abuse Scale - Short (CAS - Pregnancy Version: Hegarty, 2007) was administered at baseline to assess intimate partner violence (IPV). This version assesses experience of sexual, physical and severe abusive partner (i.e., husband, partner or boy/girlfriend) behaviour in the 12 months prior to pregnancy and during pregnancy (up to baseline). The questionnaire has been used previously in research with pregnant women (e.g., Lockwood Estrin et al., 2019) (see supplementary file).

### ***2.3.4 Maternal Antenatal Stress-related Biology***

#### ***2.3.4.1 Salivary cortisol***

Saliva samples were obtained in the third trimester (median=32.7 weeks, range 28.1-38.7 weeks). Participants were instructed to collect six samples, using Salivette sampling devices (Sarstedt, UK), at awakening, at 15, 30 and 60 minutes after awakening, at 12pm and 8pm to measure CAR and daily cortisol. Salivary cortisol was measured using a high sensitivity ELISA kit (Salimetrics Europe Ltd, UK). The inter- and intra-assay CV ranged from 8 to 11% and 6 to 10%, respectively. Additional

sampling and analysis protocol details are described in Osborne et al. (2018) and the supplementary file.

#### **2.3.4.2 Inflammatory markers**

Blood samples were collected between 12pm and 3pm in the third trimester (median=29.4 weeks, range 25-38 weeks) to measure high sensitivity C-Reactive Protein (hsCRP), Interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, Tumor Necrosis Factor (TNF $\alpha$ ), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Monocyte Chemoattractant Protein 1 (MCP-1) and Interferon Gamma (INF- $\gamma$ ). Serum hsCRP was measured using an ELISA kit (PZ Cormay, Poland); the assay was analyzed in batches on the Cobas Mira (intra- and inter-assay CV were 2.96 % and 3.85 % respectively). Serum cytokine levels were measured using a cytokine chip array kit (Randox Laboratories, UK); the kit uses a sandwich chemiluminescent immunoassay, described previously (Di Nicola et al., 2013; Osborne et al., 2018). For IL-1 $\alpha$ , IL-4, IL-10 and INF- $\gamma$ , >50% of the sample was at the lowest detectable level of the assay, so these measures were not included in the analyses.

#### **2.4 Statistical analyses**

Statistical analyses were performed in SPSS Statistics Version 24 (IBM Ltd, UK). For all statistical tests, data were first examined for outliers, normality of distribution and homogeneity of variance. Where necessary, data were log-transformed prior to analysis, with raw data presented in tables and figures. Where data did not benefit from transformation non-parametric statistical tests were used.

Firstly, the AR-unwell group were compared with the AR-well group; secondly, *all* of the AR group were compared with the HC group. In univariate analyses, group comparisons of continuous data were made using the independent samples t-test. For non-parametric data, the Mann-Whitney U test was used. Pearson's chi-square ( $\chi^2$ ) test of the independence of variables was used for the analysis of categorical data.

Pearson's correlation ( $r_p$ ) was used for the analysis of association between parametric continuous variables, and Spearman's correlation ( $r_s$ ) was applied to non-parametric continuous variables, or between dichotomous and continuous variables that did not meet parametric assumptions. Point-biserial correlation coefficients ( $r_{pb}$ ) were used for associations between a true dichotomous variable and continuous variable that allowed parametric analysis. Phi ( $\Phi$ ) statistics are reported for association between two dichotomous variables.

Logistic regression was used in follow-up analyses to examine potential predictors for psychiatric relapse in the first 4 weeks' post partum whilst controlling for the effects of covariates. The bootstrap method (with 1000 samples) was used for regression analyses.

### 3 Results

#### 3.1 Sociodemographic, health, obstetric and clinical characteristics

In the AR group, 22 (43.1%) women had a psychiatric relapse (AR-unwell): 9 (40.9%) had symptoms of depression or depression and anxiety, 8 (36.4%) had manic or hypomanic symptoms, 4 (18.2%) had psychotic symptoms and 1 (4.5%) had mixed symptoms. Of the 22 women who had a psychiatric relapse, 13 (59.1%) had symptoms that met DSM-IV diagnostic criteria and 9 (40.9%) had symptoms that, whilst not meeting diagnostic criteria, impacted on their daily functioning and/or were of sufficient intensity to require a change in treatment. Of the 22 women who had a psychiatric relapse, 9 (40.9%) had a severe relapse. Twenty-nine (56.9%) of the AR group remained symptom free in the 4 weeks following the delivery (AR-well).

The AR-unwell group were significantly less likely to be employed ( $\chi^2_{(1)}=6.3, p=.01$ ), more likely to have a medical condition ( $\chi^2_{(1)}=4.0, p=.05$ ) and a pregnancy-related medical condition ( $\chi^2_{(1)}=5.5, p=.02$ ), compared with the AR-well group. There were no other differences between the AR groups in sociodemographic, health or obstetric characteristics. Compared with the AR-well group, the AR-unwell group were significantly more likely to have had a psychiatric relapse during pregnancy

( $\chi^2_{(1)}=10.6, p<.01$ ). Furthermore, the AR-unwell group had significantly higher HAM-D ( $U=431.5, z=3.3, p<.01$ ), PANSS negative ( $U=340.0, z=2.4, p=.02$ ), general ( $U=430.5, z=3.3, p<.01$ ) and total ( $U=432.5, z=3.3, p<.01$ ) scores at baseline than the AR-well group. There were no differences between the two groups in YMRS or PANSS positive scores at baseline, and the groups did not differ in antenatal medication use. Furthermore, there were no significant differences between the groups in diagnosis at recruitment, age at illness onset, duration of illness, number of lifetime admissions or previous history of PP (Table 2), and no differences in maternal postpartum medication use (supplementary material: Table A.1).

### **3.2 Women at risk of PP who relapsed were more likely to have experienced severe childhood trauma**

In support of our hypothesis, the AR-unwell group were significantly more likely than the AR-well group to have experienced severe childhood maltreatment (physical abuse, sexual abuse, antipathy and neglect) prior to the age of 17 ( $\chi^2_{(1)}=4.3, p=.04$ ). There was no significant difference between the two groups in parental loss or separation prior to the age of 17 (Table 3).

### **3.3 Women at risk of PP who relapsed were not more likely to have experienced stressful life events during pregnancy**

Contrary to what we hypothesized, there was no significant difference between the two groups in the percentage of women who experienced stressful life events during pregnancy. The AR-unwell group were, however, significantly more likely to perceive stressful life events as being more distressing ( $t_{(32)}=2.2, p=.04$ ) (Table 3).

In the 12 months prior to pregnancy, one (5.3%) of the AR-unwell group and two (7.4%) of the AR-well group experienced IPV. During pregnancy, none of the AR-unwell group and one (3.7%) of the AR-well group experienced IPV (Table 3). Owing to the small numbers no statistical analyses were performed.

### **3.4 Women at risk of PP who relapsed were more likely to show dysregulation of the biological stress system**

Whilst there was no significant difference between the two groups in their CAR (AUC<sub>i</sub>), in line with our hypothesis, the AR-unwell group had significantly higher diurnal cortisol levels compared with the AR-well group (AUC<sub>g</sub>, nmol/L:  $t_{(32)}=2.8$ ,  $p<.01$ ). In terms of individual time-points, the AR-unwell group had significantly higher cortisol levels at midday ( $t_{(32)}=2.8$ ,  $p<.01$ ) and 8pm ( $t_{(32)}=2.4$ ,  $p=.03$ ) compared with those in the AR-well group (Table 3; Figures 1a,b).

However, contrary to our hypothesis that the AR-unwell group would have increased inflammatory markers, there were no significant differences between the two groups in IL-1 $\beta$ , IL-2, IL-6, IL-8, TNFa, VEGF, EGF or hsCRP; there was only a trend for a significant difference in MCP-1 levels, with the AR-unwell group having lower MCP-1 ( $t_{(41)}=2.0$ ,  $p=.053$ ) (Table 3).

The two groups did not differ in gestational age at saliva collection (median=32.7 vs 33.0,  $U=146.5$ ,  $z=0.8$ ,  $p=.81$ ) or blood acquisition (median=29.9 vs 28.9,  $U=296$ ,  $z=1.3$ ,  $p=.19$ ).

### **3.5 Follow-up analyses of predictors of psychiatric relapse in the first 4 weeks' post partum in women at risk of PP**

Logistic regression analyses were conducted to examine whether maternal psychosocial and biological measures of stress that had shown between-group differences predicted psychiatric relapse in the first 4 weeks' post partum in the AR groups after adjusting for sociodemographic, health and clinical characteristics (Table 4).

Factors that had shown between-group differences were included in logistic regression analyses. As HAM-D and PANSS negative, general and total scores were intercorrelated *and/or* correlated with antenatal relapse (supplementary material: Table A.2), HAM-D and PANSS negative, general and total scores were not included in the regression analyses, leaving antenatal relapse as a measure of

antenatal psychopathology. Furthermore, as the number of women with a perceived distress score that could be included in the regression analyses was small ( $n=22$ ) and perceived distress was correlated with antenatal relapse, perceived distress was not included in regression analyses.

We first assessed the amount of variance explained by each of the factors individually. Maternal childhood maltreatment accounted for 13% of the variance between the AR-unwell and AR-well groups ( $\beta=1.3$ , Wald statistic=4.1,  $p=.02$ ,  $OR=3.8$ , 95% CI [1.0-13.7], model  $\chi^2_{(1)}=4.4$ ,  $p=.04$ ). Daily cortisol accounted for 26% of the variance between the AR groups ( $\beta=1.1$ , Wald statistic=5.2,  $p=.01$ ,  $OR=2.9$  CI [1.2-7.1], model  $\chi^2_{(1)}=7.1$ ,  $p<.01$ ). Finally, the sociodemographic, health and clinical covariates that had shown between-group differences (namely, employment status, chronic medical conditions, pregnancy-related medical conditions and antenatal relapse) were entered in a model together. Together they accounted for 49% of the variance between the AR groups, but only antenatal relapse and employment status were significant ( $\beta=2.0$ , Wald statistic=4.3,  $p<.01$ ,  $OR=7.7$ , 95% CI [1.1-53.7] and  $\beta=-1.5$ , Wald statistic=3.2,  $p=.04$ ,  $OR=0.2$ , 95% CI [0.04-1.1], respectively, model  $\chi^2_{(4)}=19.3$ ,  $p<.01$ ). Chronic medical conditions and pregnancy-related medical conditions were no longer significant ( $\beta=-0.9$ , Wald statistic=1.3,  $p=.24$ ,  $OR=2.5$ , 95% CI [0.5-12.4],  $\beta=1.0$ , Wald statistic=1.2,  $p=.21$ ,  $OR=2.7$ , 95% CI [0.5-16.0], respectively).

Finally, severe childhood maltreatment and daily cortisol were entered in a regression model together adjusting for antenatal relapse and employment status. The model was significant ( $\chi^2_{(4)}=16.2$ ,  $p<.01$ ) and accounted for 53% of the variance between the two AR groups. Childhood maltreatment now reached a trend for significance ( $\beta=1.6$ , Wald statistic=1.8,  $p=.08$ ,  $OR=4.9$ , 95% CI 0.5-49.2), whilst daily cortisol remained significant ( $\beta=1.3$ , Wald statistic=5.0,  $p=.01$ ,  $OR=3.7$ , 95% CI 1.2-11.6). Antenatal relapse was significant ( $\beta=2.1$ , Wald statistic=4.2,  $p=.02$ ,  $OR=8.4$ , 95% CI 1.1-65.2), however employment status was not significant ( $\beta=-0.7$ , Wald statistic=0.5,  $p=.47$ ,  $OR=0.5$ , 95% CI 0.1-3.4).

### 3.6 Comparison of women at risk of PP with healthy women

All of the women at risk of PP (AR) were compared with the healthy women (HC) in their experience of childhood trauma, stressful life events during pregnancy, IPV, and cortisol levels and inflammatory markers in the third trimester of pregnancy.

Compared with HCs, the AR group were significantly more likely to have experienced severe childhood maltreatment ( $\chi^2_{(1)}=13.7, p<.001$ ) and parental loss or separation ( $\chi^2_{(1)}=4.6, p=.03$ ) prior to the age of 17. The AR group were also significantly more likely to have experienced a stressful life event during pregnancy ( $\chi^2_{(1)}=14.3, p<.001$ ). However, there was no difference between the groups in perceived distress. In the 12 months prior to pregnancy 6.5% (3) of the AR group and none of the HC group experienced IPV. During pregnancy 2.3% (1) of the AR group and none of the HC group experienced IPV. Statistical analyses were not performed on these data. The AR group had a smaller (blunted) CAR, although the difference was not statistically significant. Furthermore, there was no difference between the groups in daily cortisol levels. Finally, the AR group had significantly higher hsCRP compared with the HC group ( $t_{(93)}=3.4, p<.01$ ), whilst the HC group had significantly higher IL-8 and VEGF ( $t_{(88)}=2.4, p=.02$  and  $t_{(88)}=2.5, p=.01$ , respectively). There were no significant differences between the groups in IL-1 $\beta$ , IL-2, IL-6, TNF $\alpha$ , EGF, MCP-1 (supplementary material: Table A.3).

## **4 Discussion**

Using a prospective longitudinal study, we demonstrated, for the first time, that experience of severe childhood maltreatment and elevated daily cortisol levels during the third trimester of pregnancy are associated with psychiatric relapse in the first 4 weeks' post partum in women at risk of PP. These findings are in line with the notion that psychosocial stress and the biological stress system are involved in the aetiology and course of both affective and non-affective psychoses unrelated to childbirth.

### **4.1 Women at risk of PP who relapsed were more likely to have experienced severe childhood trauma**

Compared with the AR-well women, the AR-unwell women were more likely to have experienced severe childhood maltreatment (physical abuse, sexual abuse, antipathy or neglect). Although this difference only reached a trend for significance when other factors were considered, the findings show that the odds of having a psychiatric relapse in the first 4 weeks' post partum were nearly 5 times higher for women at risk of PP who experienced severe childhood maltreatment than for those at risk who did not have such experience.

This finding is in line with the literature on psychosis unrelated to gestation, which has found the experience of childhood maltreatment to be associated with increased risk of developing a psychotic disorder (Varese et al., 2012), as well as research showing that childhood maltreatment is more prevalent in individuals at risk for psychosis compared with the general population, and particularly in individuals at risk who subsequently develop psychosis (e.g., Bechdolf et al., 2010; Thompson et al., 2014). However, our findings differ from those of Perry et al. (2016), who found that women at risk of PP who developed an episode of psychosis following childbirth were no more likely to have experienced sexual, physical or emotional abuse than women at risk who remained well. One possible explanation for the difference in findings is that Perry and colleagues did not explicitly ask women about their experience of severe childhood maltreatment using a specific, validated questionnaire, which we did. Instead, they relied on women voluntarily disclosing experience of abuse, which may

have resulted in underreporting (Perry et al., 2016). Furthermore, we also included women who developed symptoms of depression in the AR-unwell group (41% of the AR-unwell group had symptoms of depression/depression and anxiety). Perry et al. (2016), on the other hand, only included women who became unwell with an episode of mania, mixed affective state or affective psychosis. It could, therefore, be suggested that childhood maltreatment is predictive of postpartum depressive symptoms in women at risk of PP, but not postpartum mania or psychosis. This would, indeed, fit with the literature showing that childhood maltreatment contributes to the development, course and treatment outcome of depression, both unrelated and related to gestation (e.g., Li et al., 2016; Nanni et al., 2012; Racine et al., 2021). However, a more recent study by Perry et al. (2020) found no direct association between childhood abuse and postpartum depression in women with bipolar disorder.

#### **4.2 Women at risk of PP who relapsed were not more likely to have experienced stressful life events during pregnancy**

Interestingly, we did *not* find that the AR-unwell group were more likely than the AR-well group to have experienced stressful life events during pregnancy. This finding differs from the literature on affective and non-affective psychoses unrelated to gestation, in which stressful life events have been found to occur in the months prior to psychotic relapse (e.g., Bebbington et al., 1993; Brown and Birley, 1968; Dohrenwend et al., 1987) and in the months preceding an acute mood episode in individuals with bipolar disorder (Lex et al., 2017). On the other hand, our findings corroborate those of McNeil (1988), Marks et al. (1991) and, more recently, our own research in a different sample of women at risk of PP (Aas et al., 2020), all of which have found that women at risk of PP were no more likely to have experienced stressful life events prior to postpartum illness onset than those at risk who remained well. It could, therefore, be suggested that stressful life events play a different role in the course of postpartum and non-postpartum psychiatric illnesses. We did, however, find that the AR-unwell women were more likely than the AR-well group to perceive stressful life events during pregnancy as being more distressing. This finding, which is in line with the literature on psychosis unrelated to gestation (e.g., Trotman et al., 2014), suggests that, whilst stressful life events themselves may not represent a risk factor for psychiatric relapse, a woman's perception of stressful life events

might play a role in the onset of postpartum symptoms in women at risk of PP. It is, however, important to note that, despite being higher in the AR-unwell group, mean perceived distress scores were relatively low (4.9 out of 36). Furthermore, perceived distress was associated with antenatal relapse. It is, therefore, possible that the difference between the AR groups in perceived distress was explained by the fact the AR-unwell group were more likely to have experienced a psychiatric relapse during pregnancy. Whilst we could not explore this in the current study, it warrants further investigation.

The number of women reporting IPV was too small to test for between group differences in this study. We could not, therefore, examine whether IPV represents a risk factor for psychiatric relapse. Whilst a previous study found no association between IPV and postpartum relapse in women at risk of PP (Taylor et al 2019), a systematic review and meta-analysis reported a high prevalence and increased odds of having experienced domestic violence among women with a range of other perinatal mental disorders (Howard et al., 2013). The role of IPV in increasing the risk for psychiatric relapse in women at risk of PP, therefore, requires further research.

#### **4.3 Women at risk of PP who relapsed were more likely to show dysregulation of the biological stress system**

Compared with the AR-well group, the AR-unwell group showed elevated daily cortisol levels in the third trimester of pregnancy, particularly at midday and 8pm. To our knowledge, this is the first study measuring diurnal cortisol levels in pregnancy in women at risk of PP. Whilst there have been mixed findings in the literature on postnatal depression, with some studies suggesting an association between cortisol levels in pregnancy and depressive symptoms in the early postpartum (Handley et al., 1980) and others failing to find an association (e.g., Glynn and Sandman, 2014; Yim et al., 2009), our finding is consistent with the literature on individuals at risk of psychosis unrelated to gestation. Indeed, research has shown that HPA axis abnormalities, including higher basal cortisol levels during the day, are present in individuals at risk of psychosis unrelated to gestation prior to the onset of a psychotic illness (Collip et al., 2011; Walker et al., 2013). Furthermore, there is evidence that HPA

axis abnormalities are greater in individuals at risk who subsequently transition to psychosis compared with those at risk who do not (Walker et al., 2013). The current finding also confirms and extends our recently published data, which showed higher levels of daily cortisol in *postpartum* women with PP compared with healthy women (Aas et al., 2020). Furthermore, it suggests, for the first time, that specific alterations in HPA axis function might already be present prior to the onset of postnatal symptoms. This indicates that daily cortisol levels in the third trimester of pregnancy might represent a biological marker that could be used to identify which of the women at risk of PP are likely to relapse in the early postpartum. Interestingly, we found that the AR-unwell group did not differ from the AR-well group in terms of their CAR, which fits with our recently published study measuring cortisol levels in *postpartum* women with PP (Aas et al., 2020).

Contrary to our hypotheses, we found no differences between the two AR-groups in inflammatory markers (il-1 $\beta$ , il-2, il-6, il-8, TNFa, VEGF, EGF and hsCRP). This is surprising, given the accumulating evidence of immune system dysfunction in PP, including higher rates of both autoimmune thyroiditis and pre-eclampsia (Bergink et al., 2015, 2011), elevated cytokine and monocyte levels, and an upregulation of immune system-related monocyte genes (Bergink et al., 2013; Kumar et al., 2017; Sathyanarayanan et al., 2019). Furthermore, our group has recently demonstrated that a higher percentage of women with PP had hsCRP levels  $\geq 3$ , compared with women at risk and healthy postpartum women (46%, 37% and 15% respectively) (Aas et al., 2020). However, it must be emphasized that all of this research was conducted in women who had *already* developed an episode of PP. This suggests that, whilst immune system dysregulation might be a characteristic of PP, it is not necessarily present prior to the illness onset.

Although only reaching a trend for statistical significance, we found that the AR-unwell group had lower MCP-1 levels during pregnancy than the AR-well group. Perhaps surprisingly, this suggests a 'protective' influence of MCP-1 levels on the risk of psychiatric relapse in the first 4 weeks' post partum. This is, however, in line with the findings of Carvalho et al. (2013), who reported lower levels of MCP-1 in individuals with depression who did not subsequently respond to treatment.

Furthermore, our group has recently found lower levels of MCP-1 whole blood mRNA expression in treatment-resistant depressed patients compared with non-resistant patients (unpublished). Nevertheless, given that MCP-1 was the only inflammatory marker to differ between the groups, and that the difference only reached a trend for significance, it is important to interpret this finding with caution. Additional research in larger samples is needed in order to gain a better understanding of the role of MCP-1 in the risk of psychiatric relapse in women at risk of PP.

#### **4.4 Clinical characteristics**

We also found that the AR-unwell group were more likely to have had a psychiatric relapse during pregnancy. Whilst not the focus of the current paper, this finding is in line with previous studies of Bergink et al. (2012) and Taylor et al. (2019), both of which found relapse during pregnancy to be a predictor of relapse in the postpartum in women at risk of PP. Together these findings suggest that psychiatric relapse during pregnancy could represent a predictor for psychiatric relapse in the postpartum in women at risk of PP.

Finally, it should be noted that we found no association between a history of PP and an increased risk of psychiatric relapse in the postpartum. This is surprising given the previous reports of higher relapse rates for women with a history of PP (e.g., Bergink et al., 2012; Dean et al., 1989; Wesseloo et al., 2016). This could be due to the fact we used a broader definition of postpartum episodes and that only 17.6% of the women at risk had a ‘severe relapse’ (i.e., psychotic, manic, mixed symptoms, and/or psychiatric hospitalization), possibly because in this study women who had experienced a previous episode of PP might have been more closely monitored by perinatal mental health services, given their increased risk, and so were less likely to become unwell.

#### **4.5 Strength and limitations**

This study has a number of strengths. To our knowledge, it is the first longitudinal study to follow women at risk of PP prospectively from pregnancy through to 8 weeks’ post partum in order to examine the role of multiple psychosocial and biological measures of stress in an attempt to build a

more comprehensive picture of risk factors for a postpartum relapse in these women. Participants were assessed using in-depth clinical, psychosocial and biological measures, including standardized questionnaires, such as the CECA.Q (Bifulco et al., 2005). To our knowledge, this is the first time a validated measure of childhood maltreatment has been used to assess maternal experience of childhood trauma, including severe abuse and neglect, in women at risk of PP. Furthermore, we collected extensive descriptive data to provide a detailed picture of the sample. In addition, diagnostic interviews were supplemented by clinical notes and discussed in consensus meetings with senior psychiatrists to confirm participant diagnoses.

Despite the strengths there are also limitations which should be considered. The sample size is relatively small and, although we had a high participant retention rate, not all of the participants completed every assessment, resulting in an even smaller number for some of the analyses. Thus, it is possible that some of the associations failed to reach statistical significance due to a lack of power to detect differences. These findings should, therefore, be replicated in future research using larger samples. Second, whilst a key strength of the study is the investigation of multiple psychosocial and biological risk factors, this has resulted in multiple comparisons, which might have increased the likelihood that some of the findings occurred by chance. However, given that this is a new field of study, we chose not to apply strict corrections throughout the analyses in favour of leniency as a first step, in order to identify new areas for future research. Another important aspect to consider is that women at risk of PP were recruited from specialist perinatal mental health services, and so were closely monitored throughout their pregnancy and the postpartum period. This is likely to have contributed to the fact that fewer of the women at risk became unwell and developed full-blown psychosis (i.e., less than the expected 50% of women at risk reported to become unwell in the postpartum (e.g., Di Florio et al., 2013; Doyle et al., 2012; Jones and Craddock, 2001)). While it was, of course, incredibly beneficial to the women's mental health and functioning that the care from perinatal services reduced the progression to full-blown psychosis, this meant we had to use a broader definition of PP to capture relapse of affective symptoms in the immediate postpartum. Consistent

with this approach, we found that 43% of the AR group developed an affective relapse in the first 4 weeks' post partum.

**In conclusion**, the current study provides evidence for the role of psychosocial stress and the biological stress system in the onset of postpartum symptoms in women at risk of PP. If confirmed, the findings point to maternal antenatal cortisol as a biological marker that could be used to identify which women at risk of PP are more likely to experience a psychiatric relapse, and highlight the importance of implementing interventions, such as mindfulness-based stress reduction, aimed at reducing them. Furthermore, screening women at risk for the experience of severe childhood maltreatment and psychiatric relapse during pregnancy could provide further information about which of these women will go on relapse in the postpartum period and would, therefore, benefit from increased support throughout pregnancy.

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### **Author contributions**

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### **Appendix A. Supplementary Material**

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**Table 1: Sample characteristics in the AR and HC groups**

	AR (n=51)	HC (n=61)	Significance Testing
Age (years), M (SD)	32.7 (5.5)	33.3 (4.7)	$t_{(110)} = 0.6, p = .54$
Ethnicity, white, % (n)	60.8 (31)	77.0 (47)	$\chi^2_{(1)} = 3.5, p = .06$
Education, degree or higher, % (n)	72.5 (37)	82.0 (50)	$\chi^2_{(1)} = 1.4, p = .23$
<b>Employment status, employed or student, % (n)</b>	<b>64.7 (33)</b>	<b>82.0 (50)</b>	$\chi^2_{(1)} = 4.3, p = .04$
<b>Marital status, married or cohabiting, % (n)</b>	<b>70.6 (36)</b>	<b>88.5 (54)</b>	$\chi^2_{(1)} = 5.7, p = .02$
<b>Cigarette use in pregnancy, % (n)</b>	<b>15.7 (8)</b>	<b>3.3 (2)</b>	$\chi^2_{(1)} = 5.3, p = .04^1$
<b>Alcohol use in pregnancy, % (n)</b>	<b>7.8 (4)</b>	<b>34.4 (21)</b>	$\chi^2_{(1)} = 11.3, p < .01$
<b>BMI, M (SD)<sup>a</sup></b>	<b>25.8 (5.3)</b>	<b>23.1 (3.3)</b>	$U = 1751.5, z = 2.5, p = .01$
Pregnancy-related medical conditions, % (n) <sup>b</sup>	51.2 (22)	32.4 (11)	$\chi^2_{(1)} = 2.7, p = .10$
Parity, nulliparous, % (n)	64.7 (33)	52.5 (32)	$\chi^2_{(1)} = 1.7, p = .19$
Mode of delivery, non-instrumental, % (n) <sup>c</sup>	52.1 (25)	60.7 (37)	$\chi^2_{(1)} = 0.8, p = .37$
Diagnosis at recruitment:		-	-
Bipolar Disorder, % (n)	80.4 (41)	-	-
<i>Bipolar Disorder Type I, % (n)</i>	80.5 (33)	-	-
<i>Bipolar Disorder Type II, % (n)</i>	17.1 (7)	-	-
<i>Cyclothymic Disorder, % (n)</i>	2.4 (1)	-	-
Schizoaffective Disorder, % (n)	11.8 (6)	-	-
<i>Bipolar Type, % (n)</i>	66.7 (4)	-	-
<i>Depressive Type, % (n)</i>	33.3 (2)	-	-
Psychosis NOS*, % (n)	7.8 (4)	-	-
Age (years) at illness onset, M (SD) <sup>d</sup>	19.9 (6.6)	-	-
Duration of illness (years), M (SD)	12.7 (6.2)	-	-
Lifetime number of admissions, % (n):		-	-
0	29.4 (15)	-	-
1	27.5 (14)	-	-
2	21.6 (11)	-	-
3	13.7 (7)	-	-
4	5.9 (3)	-	-
5	2.0 (1)	-	-
Previous history of postpartum psychosis, % (n)	23.5 (12)	-	-
Antenatal relapse, % (n)	60.8 (31)	-	-
Type of symptoms in pregnancy**:		-	-
<i>Depressive and/or anxiety symptoms, % (n)</i>	77.4 (24)	-	-
<i>Manic/hypomanic symptoms, % (n)</i>	9.7 (3)	-	-
<i>Changing symptoms, % (n)</i>	12.9 (4)	-	-
HAM-D Score at baseline, M (SD) <sup>e</sup>	6.1 (4.8)	-	-
YMRS Score at baseline, M (SD) <sup>f</sup>	1.7 (2.2)	-	-
PANSS Positive Score at baseline, M (SD) <sup>e</sup>	7.3 (1.0)	-	-
PANSS Negative Score at baseline, M (SD) <sup>e</sup>	7.8 (2.6)	-	-
PANSS General Score at baseline, M (SD) <sup>e</sup>	19.7 (4.3)	-	-
PANSS Total Score at baseline, M (SD) <sup>e</sup>	34.8 (6.4)	-	-
Any psychotropic medication during pregnancy, % (n) <sup>d</sup>	68.6 (35)	-	-
Psychotropic medication at baseline, % (n):	54.9 (28)	-	-
<i>Antidepressants at baseline, % (n)</i>	21.5 (6)	-	-
<i>Sertraline, % (n)</i>	50.0 (3)	-	-
<i>Mirtazapine, % (n)</i>	33.3 (2)	-	-
<i>Escitalopram, % (n)</i>	16.7 (1)	-	-
<i>Antipsychotics at baseline, % (n)</i>	82.1 (23)	-	-
<i>Quetiapine, % (n)</i>	52.2 (12)	-	-
<i>Quetiapine XL, % (n)</i>	4.3 (1)	-	-
<i>Olanzapine, % (n)</i>	30.4 (7)	-	-
<i>Risperidone, % (n)</i>	8.7 (2)	-	-
<i>Aripiprazole, % (n)</i>	4.3 (1)	-	-
<i>Mood stabilisers at baseline, % (n)</i>	25.0 (7)	-	-
<i>Lithium, % (n)</i>	71.4 (5)	-	-
<i>Lamotrigine, % (n)</i>	28.6 (2)	-	-

<sup>a</sup>AR = 46, HC = 59; <sup>b</sup>AR = 43, HC = 34; <sup>c</sup>AR = 48, HC = 61; <sup>d</sup>AR = 50; <sup>e</sup>AR = 48; <sup>f</sup>AR = 47;

<sup>1</sup>Fisher's exact reported

\* Women who have only had a previous PP

\*\* Depression and/or anxiety: Depression n=18; Depression & anxiety n=6 (1 of whom depression & anxiety not concurrent); Changing symptoms: 1 participant had mixed symptoms followed by depressive symptoms, 1 had anxiety followed by manic/hypomanic symptoms, 1 had manic/hypomanic symptoms followed by depressive symptoms and 1 had depression and anxiety followed by manic symptoms

**Table 2: Sample characteristics in the AR-unwell and AR-well groups**

	AR-unwell (n=22)	AR-well (n=29)	Significance Testing
Age (years), M (SD)	31.4 (5.7)	33.7 (5.3)	$t_{(49)} = 1.5, p = .15$
Ethnicity, white, % (n)	50.0 (11)	69.0 (20)	$\chi^2_{(1)} = 1.9, p = .17$
Education, degree or higher, % (n)	63.6 (14)	79.3 (23)	$\chi^2_{(1)} = 1.5, p = .21$
<b>Employment status, employed or student, % (n)</b>	<b>45.5 (10)</b>	<b>79.3 (23)</b>	<b><math>\chi^2_{(1)} = 6.3, p = .01</math></b>
Marital status, married or cohabiting, % (n)	59.1 (13)	79.3 (23)	$\chi^2_{(1)} = 2.5, p = .12$
Cigarette use in pregnancy, % (n)	18.2 (4)	13.8 (4)	$\chi^2_{(1)} = 0.2, p = .71^1$
Alcohol use in pregnancy, % (n)	4.5 (1)	10.3 (3)	$\chi^2_{(1)} = 0.6, p = .63^1$
BMI, M (SD) <sup>a</sup>	25.1 (5.6)	26.2 (5.1)	$U = 218.0, z = 0.9, p = .39$
<b>Medical condition, % (n)</b>	<b>59.1 (13)</b>	<b>31.0 (9)</b>	<b><math>\chi^2_{(1)} = 4.0, p = .05</math></b>
<b>Pregnancy-related medical conditions, % (n)<sup>b</sup></b>	<b>72.2 (13)</b>	<b>36.0 (9)</b>	<b><math>\chi^2_{(1)} = 5.5, p = .02</math></b>
Parity, nulliparous, % (n)	59.1 (13)	69.0 (20)	$\chi^2_{(1)} = 1.9, p = .56$
Mode of delivery, non-instrumental, % (n) <sup>c</sup>	55.0 (11)	50.0 (14)	$\chi^2_{(1)} = 0.1, p = .73$
Diagnosis at recruitment:			$\chi^2_{(2)} = 3.7, p = .15^1$
Bipolar Disorder, % (n)	68.1 (15)	89.6 (26)	
<i>Bipolar Disorder Type I, % (n)</i>	80.0 (12)	80.8 (21)	
<i>Bipolar Disorder Type II, % (n)</i>	13.3 (2)	19.2 (5)	
<i>Cyclothymic Disorder, % (n)</i>	6.7 (1)	0.0 (0)	
Schizoaffective Disorder, % (n)	18.2 (4)	6.9 (2)	
<i>Bipolar Type, % (n)</i>	50.0 (2)	100.0 (2)	
<i>Depressive Type, % (n)</i>	50.0 (2)	0.0 (0)	
Psychosis NOS*, % (n)	13.6 (3)	3.4 (1)	
Age (years) at illness onset, M (SD) <sup>d</sup>	20.7 (7.0)	18.7 (6.0)	$U = 253.0, z = 1.1, p = .28$
Duration of illness (years), M (SD)	12.6 (6.3)	12.8 (6.2)	$t_{(48)} = 0.1, p = .93$
Lifetime number of admissions, % (n):			$\chi^2_{(5)} = 2.5, p = .86^1$
0	27.3 (6)	31.0 (9)	
1	22.7 (5)	31.0 (9)	
2	27.3 (6)	17.2 (5)	
3	18.2 (4)	10.3 (3)	
4	4.5 (1)	6.9 (2)	
5	0.0 (0)	3.4 (1)	
Previous history of postpartum psychosis, % (n)	27.3 (6)	20.7 (6)	$\chi^2_{(1)} = 0.3, p = .58$
<b>Antenatal relapse, % (n)</b>	<b>86.4 (19)</b>	<b>41.4 (12)</b>	<b><math>\chi^2_{(1)} = 10.6, p &lt; .01</math></b>
Type of symptoms in pregnancy**:			-
<i>Depressive and/or anxiety symptoms, % (n)</i>	68.4 (13)	91.7 (11)	-
<i>Manic/hypomanic symptoms, % (n)</i>	10.5 (2)	8.3 (1)	-
<i>Changing symptoms, % (n)</i>	21.1 (4)	0.0 (0)	-
<b>HAM-D Score at baseline, M (SD)<sup>e</sup></b>	<b>8.7 (4.8)</b>	<b>4.4 (4.0)</b>	<b><math>U = 431.5, z = 3.3, p &lt; .01</math></b>
YMRS Score at baseline, M (SD) <sup>f</sup>	2.3 (2.4)	1.3 (2.0)	$U = 334.5, z = 1.6, p = .11$
PANSS Positive Score at baseline, M (SD) <sup>e</sup>	7.5 (1.5)	7.1 (0.4)	$U = 287.5, z = 0.5, p = .60$
<b>PANSS Negative Score at baseline, M (SD)<sup>e</sup></b>	<b>8.9 (3.9)</b>	<b>7.1 (0.4)</b>	<b><math>U = 340.0, z = 2.4, p = .02</math></b>
<b>PANSS General Score at baseline, M (SD)<sup>e</sup></b>	<b>21.9 (4.6)</b>	<b>18.3 (3.5)</b>	<b><math>U = 430.5, z = 3.3, p &lt; .01</math></b>
<b>PANSS Total Score at baseline, M (SD)<sup>e</sup></b>	<b>38.3 (8.1)</b>	<b>32.4 (3.5)</b>	<b><math>U = 432.5, z = 3.3, p &lt; .01</math></b>
Any psychotropic medication during pregnancy, % (n) <sup>d</sup>	81.8 (18)	60.7 (17)	$\chi^2_{(1)} = 2.6, p = .11$
Psychotropic medication at baseline, % (n)	59.1 (13)	51.7 (15)	$\chi^2_{(1)} = 0.3, p = .60$
<i>Antidepressants at baseline, % (n)</i>	38.5 (5)	6.7 (1)	-
<i>Sertraline, % (n)</i>	40.0 (2)	100.0 (1)	-
<i>Mirtazapine, % (n)</i>	40.0 (2)	0.0 (0)	-
<i>Escitalopram, % (n)</i>	20.0 (1)	0.0 (0)	-
<i>Antipsychotics at baseline, % (n)</i>	92.3 (12)	73.7 (11)	-
<i>Quetiapine, % (n)</i>	58.3 (7)	45.5 (5)	-
<i>Quetiapine XL, % (n)</i>	8.3 (1)	0.0 (0)	-
<i>Olanzapine, % (n)</i>	16.7 (2)	45.5 (5)	-
<i>Risperidone, % (n)</i>	8.3 (1)	9.0 (1)	-
<i>Aripiprazole, % (n)</i>	8.3 (1)	0.0 (0)	-
<i>Mood stabilisers at baseline, % (n)</i>	15.4 (2)	33.4 (5)	-
<i>Lithium, % (n)</i>	50.0 (1)	80.0 (4)	-
<i>Lamotrigine, % (n)</i>	50.0 (1)	20.0 (1)	-

<sup>a</sup> AR-unwell = 19, AR-well = 27; <sup>b</sup> AR-unwell = 18, AR-well = 25; <sup>c</sup> AR-unwell = 20, AR-well = 28; <sup>d</sup> AR-unwell = 22, AR-well = 28; <sup>e</sup> AR-unwell = 19, AR-well = 29;<sup>f</sup> AR-unwell = 19, AR-well = 28<sup>1</sup>Fisher's exact reported

\*Women who have only had a previous PP

Depression and/or anxiety: Depression n=18; Depression & anxiety n=6 (1 of whom depression & anxiety not concurrent); Changing symptoms = 1 participant had mixed symptoms followed by depressive symptoms, 1 had anxiety followed by manic/hypomanic symptoms, 1 had manic/hypomanic symptoms followed by depressive symptoms and 1 had depression and anxiety followed by manic symptoms.

**Table 3: Psychosocial and biological comparisons in the AR-unwell and AR-well groups**

	AR-unwell (n=22)	AR-well (n=29)	Significance Testing
<b>Severe childhood maltreatment (physical abuse, sexual abuse, antipathy or neglect), % (n)<sup>a</sup></b>	<b>72.2 (13)</b>	<b>40.7 (11)</b>	$\chi^2_{(1)} = 4.3, p = .04$
Types of severe childhood maltreatment:			-
Physical abuse, % (n) <sup>b</sup>	18.8 (3)	3.7 (1)	-
Sexual abuse, % (n) <sup>c</sup>	36.8 (7)	20.7 (6)	-
Antipathy, % (n) <sup>d</sup>	47.1 (8)	14.8 (4)	-
Neglect, % (n) <sup>d</sup>	41.2 (7)	14.8 (4)	-
Parental loss or separation, % (n) <sup>e</sup>	47.6 (10)	31.0 (9)	$\chi^2_{(1)} = 1.4, p = .23$
Experience of a stressful life event in pregnancy, % (n) <sup>f</sup>	82.4 (14)	76.9 (20)	$\chi^2_{(1)} = 0.2, p = 1.0^1$
<b>Perceived distress from stressful life events in pregnancy, M (SD)<sup>g</sup></b>	<b>4.9 (2.9)</b>	<b>3.1 (1.9)</b>	$t_{(32)} = 2.2, p = .04$
Intimate partner violence in 12 months prior to pregnancy, % (n) <sup>h</sup>	5.3 (1)	7.4 (2)	-
Intimate partner violence during pregnancy, % (n) <sup>b</sup>	0.0 (0)	3.7 (1)	-
IL-1 $\beta$ (ng/L), M (SD) <sup>i</sup>	1.0 (0.7)	1.0 (0.6)	$t_{(41)} = 0.5, p = .59$
IL-2 (ng/L), M (SD) <sup>i</sup>	1.4 (0.9)	1.2 (0.8)	$t_{(31.9)} = 0.7, p = .50^2$
IL-6 (ng/L), M (SD) <sup>i</sup>	0.6 (0.4)	0.9 (1.5)	$t_{(41)} = 0.7, p = .51$
IL-8 (ng/L), M (SD) <sup>i</sup>	1.2 (0.7)	1.4 (0.7)	$t_{(41)} = 0.6, p = .52$
TNF $\alpha$ (ng/L), M (SD) <sup>i</sup>	1.0 (0.5)	1.3 (1.0)	$t_{(40.2)} = 1.1, p = .24^2$
VEGF (ng/L), M (SD) <sup>i</sup>	3.4 (6.0)	2.1 (0.9)	$t_{(41)} = 0.7, p = .51$
EGF (ng/L), M (SD) <sup>i</sup>	16.6 (16.4)	13.2 (16.8)	$t_{(41)} = 0.5, p = .63$
MCP-1 (ng/L), M (SD) <sup>i</sup>	34.1 (18.9)	45.5 (20.0)	$t_{(41)} = 2.0, p = .053$
hsCRP (mg/L), M (SD) <sup>j</sup>	7.7 (5.9)	8.3 (12.8)	$t_{(40)} = 0.5, p = .64$
AUC <sub>i</sub> (nmol/L), M (SD) <sup>k</sup>	-1.8 (191.9)	-13.2 (180.7)	$t_{(29)} = 0.2, p = .87$
<b>AUC<sub>g</sub> (nmol/L), M (SD)<sup>l</sup></b>	<b>102.2 (34.0)</b>	<b>72.7 (26.8)</b>	$t_{(32)} = 2.8, p < .01$
Awakening (nmol/L), M (SD) <sup>l</sup>	11.1 (6.3)	10.0 (5.4)	$t_{(32)} = 0.2, p = .82$
12pm (nmol/L), M (SD) <sup>l</sup>	9.4 (3.3)	6.4 (2.9)	$t_{(32)} = 2.8, p < .01$
8pm (nmol/L), M (SD) <sup>l</sup>	5.1 (3.2)	2.8 (1.3)	$t_{(17.0)} = 2.4, p = .03^2$

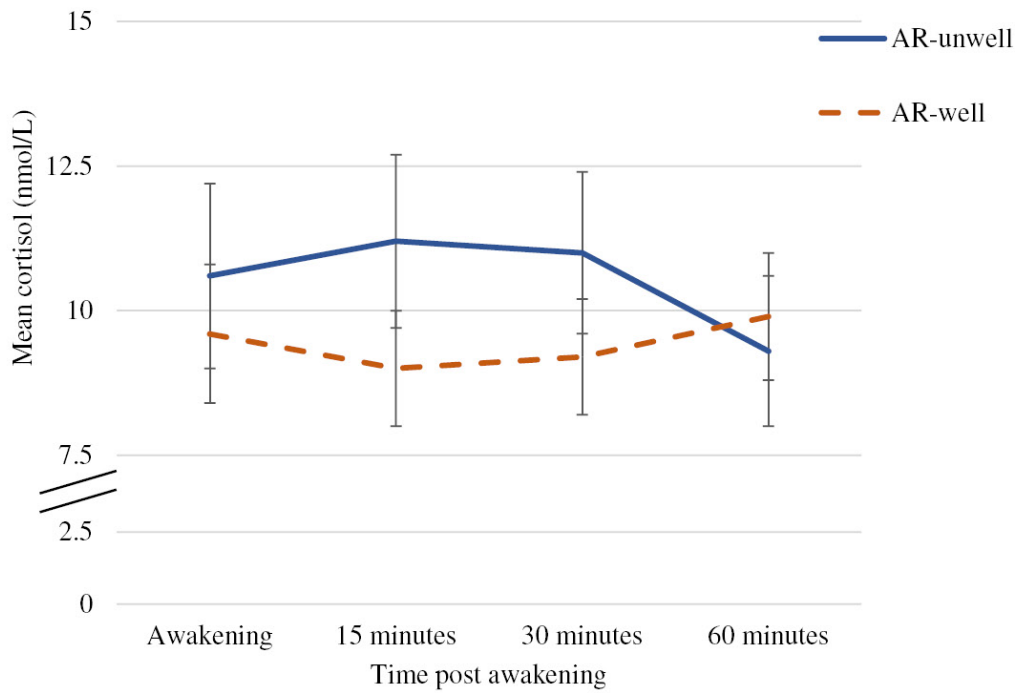
<sup>a</sup> AR-unwell = 18, AR-well = 27; <sup>b</sup> AR-unwell = 16, AR-well = 27; <sup>c</sup> AR-unwell = 19, AR-well = 29;

<sup>d</sup> AR-unwell = 17, AR-well = 27; <sup>e</sup> AR-unwell = 21, AR-well = 29; <sup>f</sup> AR-unwell = 17, AR-well = 26;

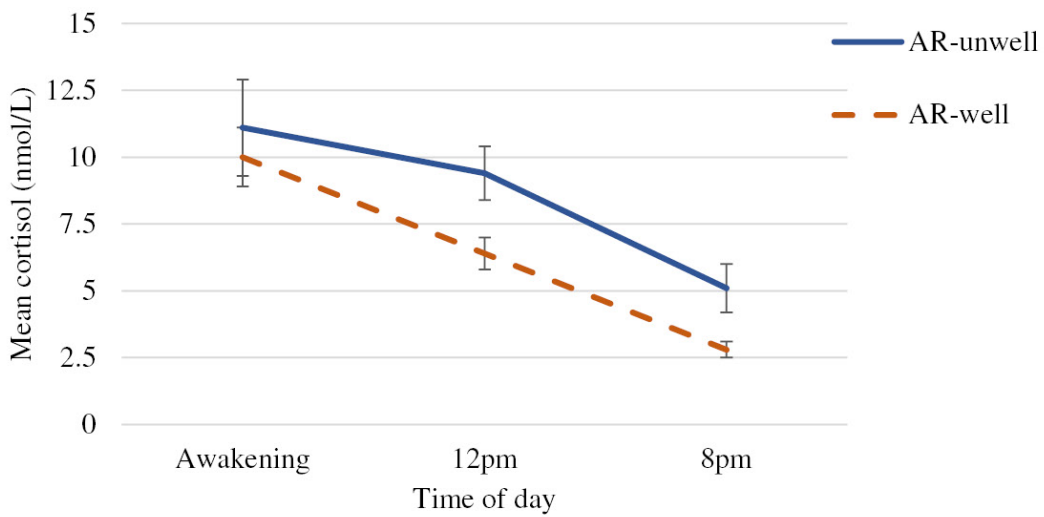
<sup>g</sup> AR-unwell = 14, AR-well = 20; <sup>h</sup> AR-unwell = 19, AR-well = 27; <sup>i</sup> AR-unwell = 19, AR-well = 24;

<sup>j</sup> AR-unwell = 20, AR-well = 22; <sup>k</sup> AR-unwell = 14, AR-well = 17; <sup>l</sup> AR-unwell = 12, AR-well = 22

<sup>1</sup>Fisher's exact reported; <sup>2</sup>Levenes presented



**Figure 1a: Cortisol awakening response in the AR-unwell and AR-well groups**



**Figure 1b: Daily cortisol levels in the AR-unwell and AR-well groups**

**Table 4: Predictors of psychiatric relapse in the first 4 weeks' post partum in women at risk of PP**

		$\chi^2$	<i>df</i>	<i>p</i>	Nagelkerke <b>R<sup>2</sup></b>
1 <sup>st</sup> Model	Severe childhood maltreatment	4.4	1	.04	.13
2 <sup>nd</sup> Model	Daily cortisol	7.1	1	<.01	.26
3 <sup>rd</sup> Model	Employment status Chronic medical condition Pregnancy-related medical condition Antenatal relapse	19.3	4	<.01	.49
4 <sup>th</sup> Model	Severe Childhood maltreatment Daily cortisol Employment status Antenatal relapse	16.2	4	<.01	.53

## **Appendix A - Supplementary Material**

### **Sociodemographic and clinical assessment**

Maternal age in years; ethnicity, dichotomized as “white” or “Black, Asian and Minority Ethnic Groups (BAME)”; education, dichotomized as “A-Level and Higher” or “Vocational/GCSE and lower”; employment, dichotomized as “Employed/student” (including women who were on maternity or sick leave) or “Unemployed/full-time mother”; marital status, dichotomized as “Married/cohabiting” or “Single with/without partner”, were collected at baseline.

Age at illness onset in years; duration of illness in years; lifetime number of admissions, ranging from 0-5 admissions; previous episodes of PP, dichotomized as “No previous episodes” or “One or more previous episodes”; medication use, dichotomized as any “Yes” or “No”, were collected at baseline and/or 8 weeks’ post partum.

Parity, dichotomized as “Nulliparous” (i.e., no children) or “Primi-/Multiparous” (i.e., one or more child/children); pregnancy-related medical conditions (e.g., gestational diabetes, hypertension), dichotomized as any “Yes” or “No”; mode of delivery, dichotomized as “Non-instrumental” or “Instrumental” (including elective/emergency c-section, forceps or ventouse); medical conditions (e.g., metabolic disorder, endocrine disorder), dichotomized as any “Yes” or “No”; pre-pregnancy Body Mass Index (BMI); alcohol use, dichotomized as “Never/monthly or less” or “2-4 times a month or more”; cigarette use during pregnancy, dichotomized as any “Yes” or “No”, were assessed at baseline and/or at 6 days’ and/or 8-weeks’ post partum.

### **Childhood trauma**

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q; Bifulco et al., 2005) was administered to assess retrospectively maternal experience of childhood maltreatment (including physical abuse, sexual abuse, antipathy and neglect) and parental loss and separation prior to the age of 17 years.

For the current study, the most conservative cut-off scores, suggested to be the optimum cut-off for association with adult disorders (Bifulco et al., 2005), were used to dichotomise CECA.Q responses into severe and no/non-severe categories for physical abuse, sexual abuse, antipathy and neglect. For the analyses, a binary childhood maltreatment variable was created. Presence of severe childhood maltreatment was rated if participants had experienced any severe physical abuse, sexual abuse, antipathy or neglect (0 = no/non-severe childhood maltreatment, 1 = severe childhood maltreatment). A binary variable was also created for any parental loss and separation, with loss and separation rated if participants had experienced the death of either or both parents and/or separation from either or both parents for  $\geq 6$  months prior to the age of 17 (0 = no parental loss or separation, 1 = parental loss or separation).

### **Stressful life events**

The List of Threatening Experiences Questionnaire (LTE-Q: Brugha and Cragg, 1990) was administered to assess maternal experience of stressful life events during pregnancy.

For the analyses, experience of stressful life events during pregnancy was dichotomized as either absent (0 = no stressful life events during pregnancy) or present (1 = stressful life events during pregnancy). The questionnaire also assesses perceived distress from the stressful life events. Participants who responded 'yes' to any of the items were then asked to indicate how distressing it was for them at the time on a 3-point scale (1 = not too bad; 2 = moderately bad; 3 = very bad). The scores were summed for each participant to create a total score (ranging from 1 to 36), with higher scores indicating higher levels of distress.

### **Intimate partner violence**

The modified pregnancy version of the Composite Abuse Scale – Short (CAS – Pregnancy Version: Hegarty, 2007) was administered to assess intimate partner violence (IPV). This modified version assesses experience of sexual, physical and severe abusive partner (i.e., husband, partner or boy/girlfriend) behaviour in the 12 months prior to pregnancy and during pregnancy.

For the analyses, experience of IPV was dichotomized as either absent (0 = no intimate partner violence) or present (1 = intimate partner violence) if the women had experienced  $\geq 1$  act of abuse.

### **Salivary cortisol**

Saliva samples were obtained in the third trimester, at awakening, at 15, 30 and 60 minutes after awakening, at 12pm and 8pm.

The formula for the area of a trapezoid (Pruessner et al., 2003) was used to calculate (i) Cortisol Awakening Response (CAR) (AUC<sub>i</sub>) using the four samples acquired within the first hour of waking, and (ii) diurnal cortisol secretion (AUC<sub>g</sub>) using awakening, midday and evening samples.

## Supplementary Tables

**Table A.1: Psychotropic medication use in the first month post partum in the AR-unwell and AR-well groups**

	AR-unwell (n=20)	AR-well (n=28)	Significance Testing
Psychotropic medication in 1 <sup>st</sup> month post partum, % (n)	90.0 (18)	75.0 (21)	$\chi^2_{(1)} = 1.7, p = .27^1$
<i>Antidepressants, % (n)</i>	25.0 (5)	3.6 (1)	-
<i>Sertraline, % (n)</i>	40.0 (2)	100.0 (1)	-
<i>Mirtazapine, % (n)</i>	40.0 (2)	0.0 (0)	-
<i>Duloxetine, % (n)</i>	20.0 (1)	0.0 (0)	-
<i>Antipsychotics, % (n)*</i>	80.0 (16)	67.9 (19)	-
<i>Quetiapine, % (n)</i>	43.7 (7)	26.3 (5)	-
<i>Olanzapine, % (n)</i>	37.5 (6)	47.4 (9)	-
<i>Risperidone, % (n)</i>	12.5 (2)	26.3 (5)	-
<i>Aripiprazole, % (n)</i>	6.3 (1)	0.0 (0)	-
<i>Mood stabilisers, % (n)</i>	20.0 (4)	21.4 (6)	-
<i>Lithium, % (n)</i>	25.0 (1)	83.3 (5)	-
<i>Lamotrigine, % (n)</i>	50.0 (2)	16.7 (1)	-
<i>Carbamazepine, % (n)</i>	25.0 (1)	0.0 (0)	-
<i>Benzodiazepines, % (n)*</i>	10.0 (2)	0.0 (0)	-
<i>Clonazepam, % (n)</i>	50.0 (1)	0.0 (0)	-
Continued psychotropic medication from 3 <sup>rd</sup> Trimester, % (n) <sup>a</sup>	77.8 (14)	60.9 (14)	-
Started psychotropic medication in 1 <sup>st</sup> month post partum, % (n) <sup>a</sup>	22.2 (4)	30.4 (7)	-

<sup>a</sup>AR-unwell = 18, AR-well = 23

<sup>1</sup>Fishers Exact presented

\*Information about medication type was missing for one participant who was taking antipsychotics and benzodiazepines

**Table A.2: Correlations in the AR-unwell and AR-well groups**

	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>N</b>
<b>1 Employment status</b>	-											51
<b>2 Chronic medical condition</b>	-.19	-										51
<b>3 Pregnancy-related medical conditions</b>	-.03	.03	-									43
<b>4 Antenatal relapse</b>	-.09	.21	<b>.49**</b>	-								51
<b>5 HAM-D</b>	-.09	.25	<b>.42**</b>	<b>.51***</b>	-							48
<b>6 PANSS Negative</b>	<b>-.41**</b>	.06	-.08	.11	.15	-						48
<b>7 PANSS General</b>	<b>-.29*</b>	.22	.12	<b>.49***</b>	<b>.75***</b>	<b>.34*</b>	-					48
<b>8 PANSS Total</b>	<b>-.36*</b>	.20	.05	<b>.39**</b>	<b>.72***</b>	<b>.51***</b>	<b>.97***</b>	-				48
<b>9 Severe childhood maltreatment</b>	-.09	-.01	.12	.10	.19	-.24	.18	.08	-			45
<b>10 Perceived Distress</b>	-.01	.29	.13	<b>.40*</b>	.28	.09	.28	.30	.20	-		34
<b>11 Daily cortisol (AUCg)</b>	-.27	.02	.23	.01	.11	.24	.08	.13	-.01	-.13	-	34

\* p < .05, \*\* p < .01, \*\*\* p < .001

**Table A.3: Psychosocial and biological comparisons in the AR and HC groups**

	AR (n=51)	HC (n=61)	Significance Testing
<b>Severe childhood maltreatment (physical abuse, sexual abuse, antipathy or neglect), % (n)<sup>a</sup></b>	<b>53.3 (24)</b>	<b>18.6 (11)</b>	$\chi^2_{(1)} = 13.7, p < .001$
Types of severe childhood maltreatment:			-
Physical abuse, % (n) <sup>b</sup>	9.3 (4)	9.8 (6)	-
Sexual abuse, % (n) <sup>c</sup>	27.1 (13)	3.3 (2)	-
Antipathy, % (n) <sup>d</sup>	27.3 (12)	8.5 (5)	-
Neglect, % (n) <sup>d</sup>	25.0 (11)	11.9 (7)	-
<b>Parental loss or separation, % (n)<sup>e</sup></b>	<b>38.0 (19)</b>	<b>19.7 (12)</b>	$\chi^2_{(1)} = 4.6, p = .03$
<b>Experience of a stressful life event in pregnancy, % (n)<sup>f</sup></b>	<b>79.1 (34)</b>	<b>41.7 (25)</b>	$\chi^2_{(1)} = 14.3, p < .001$
Perceived distress from stressful life events in pregnancy, M (SD) <sup>g</sup>	3.1 (2.1)	3.9 (2.5)	$U = 519.0, z = 1.5, p = .14$
Intimate partner violence in 12 months prior to pregnancy, % (n) <sup>h</sup>	6.5 (3)	0.0 (0)	-
Intimate partner violence during pregnancy, % (n) <sup>i</sup>	2.3 (1)	0.0 (0)	-
IL-1 $\beta$ (ng/L), M (SD) <sup>j</sup>	1.0 (0.7)	1.3 (1.0)	$t_{(88)} = 1.4, p = .15$
IL-2 (ng/L), M (SD) <sup>j</sup>	1.3 (0.9)	1.7 (1.5)	$t_{(88)} = 1.4, p = .18$
IL-6 (ng/L), M (SD) <sup>k</sup>	0.8 (1.1)	0.6 (0.7)	$t_{(87)} = 1.4, p = .16$
<b>IL-8 (ng/L), M (SD)<sup>j</sup></b>	<b>1.3 (0.7)</b>	<b>2.2 (1.7)</b>	$t_{(80.8)} = 2.4, p = .02^1$
TNF $\alpha$ (ng/L), M (SD) <sup>j</sup>	1.1 (0.8)	1.1 (0.9)	$t_{(88)} = 0.5, p = .63$
<b>VEGf (ng/L), M (SD)<sup>j</sup></b>	<b>2.7 (4.0)</b>	<b>3.2 (2.3)</b>	$t_{(88)} = 2.5, p = .01$
EGF (ng/L), M (SD) <sup>j</sup>	14.7 (16.5)	16.0 (25.5)	$t_{(88)} = 0.9, p = .40$
MCP-1 (ng/L), M (SD) <sup>j</sup>	40.5 (20.2)	47.8 (40.9)	$t_{(76.7)} = 0.2, p = .83^1$
<b>hsCRP (mg/L), M (SD)<sup>l</sup></b>	<b>8.0 (10.0)</b>	<b>4.3 (5.7)</b>	$t_{(93)} = 3.4, p < .01$
AUC <sub>i</sub> (nmol/L), M (SD) <sup>m</sup>	-8.0 (182.8)	58.2 (237.9)	$t_{(76)} = 1.3, p = .19$
AUC <sub>g</sub> (nmol/L), M (SD) <sup>n</sup>	83.1 (32.4)	86.3 (30.8)	$t_{(77)} = 0.5, p = .65$
Awakening (nmol/L), M (SD) <sup>n</sup>	10.3 (5.7)	11.1 (4.7)	$t_{(65.4)} = 0.9, p = .35^1$
12pm (nmol/L), M (SD) <sup>n</sup>	7.4 (3.3)	6.9 (2.7)	$t_{(77)} = 0.7, p = .48$
8pm (nmol/L), M (SD) <sup>n</sup>	3.6 (2.4)	4.2 (4.0)	$t_{(77)} = 0.2, p = .87$

<sup>a</sup> AR = 45, HC = 59; <sup>b</sup> AR = 43, HC = 61; <sup>c</sup> AR = 48, HC = 61; <sup>d</sup> AR = 44, HC = 59; <sup>e</sup> AR = 50, HC = 61; <sup>f</sup> AR = 43, HC = 60; <sup>g</sup> AR = 34, HC = 25;

<sup>h</sup> AR = 46, HC = 31; <sup>i</sup> AR = 43, HC = 31; <sup>j</sup> AR = 43, HC = 47; <sup>k</sup> AR = 43, HC = 46; <sup>l</sup> AR = 42, HC = 53; <sup>m</sup> AR = 31, HC = 47; <sup>n</sup> AR = 34, HC = 45

<sup>1</sup>Levenes presented

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