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1 **Low serum placental lactogen at term predicts postnatal symptoms of depression and**  
2 **anxiety in women delivering female infants**

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11

12 Running title: Serum placental lactogen predict postnatal depression

13 **Abstract**

14 **Background.** Placental endocrine insufficiency may increase the risk of depression and  
15 anxiety during pregnancy and/or after birth. This study investigated the association between  
16 serum human placental lactogen (hPL) and measures of perinatal mental health, accounting  
17 for selective serotonin-reuptake inhibitor (SSRI) usage.

18 **Method.** Caucasian women with singleton, term pregnancies recruited at their pre-surgical  
19 appointment prior to an elective caesarean section (ELCS) were studied. Serum hPL levels in  
20 maternal blood collected at recruitment were measured by ELISA. Depression and anxiety  
21 scores were derived from Edinburgh Postnatal Depression Scale (EPDS) and the trait  
22 subscale of the State-Trait Anxiety Inventory (STAI) questionnaires completed at recruitment  
23 and three postnatal time points. Data was analysed by unadjusted and adjusted multiple linear  
24 regression.

25 **Results.** In adjusted linear regressions, term maternal serum hPL levels were negatively  
26 associated with postnatal EPDS and STAI score ten weeks postnatal for mothers who had  
27 girls ( $B = -.367$ ,  $p = .022$ , 95% CI  $-.679$ ,  $-.056$ ; and  $B = -.776$ ,  $p = .030$ , 95% CI  $-1.475$ ,  $-.077$   
28 respectively). Excluding women prescribed SSRIs strengthened the relationship at 10 weeks  
29 and uncovered an earlier association between hPL and mood scores within one week of  
30 delivery (EPDS  $B = -.357$ ,  $p = .041$ , 95% CI  $-.698$ ,  $-.015$ ; and STAI  $B = -.737$ ,  $p = .027$ , 95% CI  
31  $-1.387$ ,  $-.086$ ). In mothers who had boys, there were no associations between hPL and mood  
32 scores at any time point.

33 **Conclusion.** Low hPL predicted postnatal depression and anxiety symptoms exclusively in  
34 mothers of girls. Insufficiency in hPL may contribute to maternal mood symptoms.

35

36 **Key words:** human placental lactogen, sex differences, postnatal depression, postnatal  
37 anxiety

38 **1. Introduction**

39 During pregnancy, women are highly vulnerable to perinatal mental health problems, with  
40 depression and anxiety among the most common (Bauer et al., 2014) and associated with  
41 substantial morbidity to both mother and child (Stewart, 2011). Poor mental health in  
42 pregnancy is strongly linked to postnatal depression, both having negative effects on mother–  
43 child interactions and child development in the short and longer term (Brand and Brennan,  
44 2009; Kinsella and Monk, 2009). A recent study in the UK estimated that maternal mental  
45 health disorders have a long-term cost to UK society of £8.1 billion for each one-year cohort  
46 of births with nearly three-quarters of this cost relating to adverse impacts on the child (Bauer  
47 et al., 2014). Despite the considerable clinical, financial and emotional burden to society, and  
48 the reporting of many risk factors, the biological mechanisms are unknown. Consequently, our  
49 ability to predict which women will experience significant mental health symptoms related to  
50 pregnancy is severely limited.

51 Hormonal changes represent prime candidates linking pregnancy to the higher vulnerability  
52 for depression because their levels change dramatically, driven in part by the placenta acting  
53 as an endocrine organ (Burton and Fowden, 2015). The human placenta is the source of 102  
54 polypeptide hormones contributing to the co-ordinated induction and maintenance of maternal  
55 physiology and behaviour (Liu et al., 2018). Studies in rodent models directly demonstrate the  
56 importance of prolonged exposure to oestrogen, progesterone, and the lactogenic hormones  
57 prolactin and placental lactogens in the induction of maternal care behaviours (Creeth et al.,  
58 2019). To date there is little direct evidence from human studies to support altered levels of a  
59 specific pregnancy hormone in perinatal depression or anxiety. However, there is indirect  
60 evidence to suggest that lactogenic signalling may be important. Human placental lactogen  
61 (hPL) is coded for by three separate genes with the majority of term hPL derived from the  
62 human chorionic somatomammotropin 1 (CSH1) gene (Männik et al., 2010). hPL is present at  
63 considerably higher levels than the pituitary hormone prolactin in the maternal serum at term  
64 (5–7 vs. 0.15–0.18 µg/ml) (Newbern and Freemark, 2011) and both hormones bind and  
65 activate the prolactin receptor (Gurtunca and Sperling, 2017). Maternal serum hPL levels and  
66 placental *hPL* expression have previously been demonstrated to be significantly reduced in  
67 pregnancies complicated by fetal growth restriction (Männik et al., 2010; Roh et al., 2005). We  
68 reported an association between lower maternal serum hPL and being born small for  
69 gestational age (Janssen et al., 2016b). Fetal growth restriction is more common when  
70 mothers experience prenatal depression (Diego et al., 2009). Maternal obesity has been  
71 associated with decreased placental *hPL* expression at term (Vakili et al., 2013) potentially as  
72 a consequence of changes in the interactions between key regulatory elements at the gene  
73 locus (Jin et al., 2018). Maternal obesity is a risk factor for maternal depression and anxiety

74 (Molyneaux et al., 2014). Decreased maternal serum levels of prolactin (Gurtunca and  
75 Sperling, 2017), have been reported in human mothers with postnatal depression symptoms  
76 (Groer and Morgan, 2007; Ingram et al., 2003). Maternal serum levels of prolactin have been  
77 inversely correlated with anxiety scores during pregnancy (Asher et al., 1995). We reported  
78 lower placental *hPL* gene expression in term placenta from women with clinically diagnosed  
79 depression and women self-reporting clinically significant symptoms of depression (Janssen  
80 et al., 2016a). In this 2016 study, we were not able to compare depression symptoms to serum  
81 levels of hPL as either the sample numbers were too low or the data was not collected. An  
82 additional factor which may have not been considered in previous studies in the confounder  
83 of antidepressant usage in pregnancy. Selective serotonin reuptake inhibitors (SSRIs), which  
84 are commonly prescribed in pregnancy to manage mood symptoms (Dubovicky et al., 2017),  
85 have a lactogenic activity (Goodnick et al., 2005), potentially masking any relationship  
86 between placental lactogens levels and mood symptoms

87 The aims of this study were to investigate the relationship between maternal serum levels of  
88 hPL in term pregnancies and both maternally reported symptoms of depression and anxiety.  
89 A sensitivity analyses was performed to further understand the relationship between mood  
90 symptoms and hPL levels. These analyses were performed using data from the Grown in  
91 Wales cohort (Janssen et al., 2018).

## 92 **2. Method**

### 93 *2.1 Cohort*

94 Full ethical approval for the Grown in Wales (GiW) Study cohort (Janssen et al., 2018) was  
95 obtained from the Wales Research Ethics Committee REC reference 15/WA/0004. Research  
96 was carried out in line with the principles of the Declaration of the Helsinki as revised in 2008.  
97 Briefly, the GiW study is a longitudinal birth cohort based in South East Wales, United Kingdom  
98 that began in September 2015 and ended recruitment in November 2016. Women aged  
99 between 18 and 45 with a singleton term pregnancy without fetal abnormalities or infectious  
100 diseases were recruited at their morning pre-surgical appointment prior to an elective  
101 caesarean section (ELCS) at the University Hospital of Wales by two trained research  
102 midwives.

### 103 *2.2 Participant numbers*

104 355 women were recruited into the study and seven withdrew. hPL concentrations were  
105 available for 272 of these women of whom 251 had fully complete antenatal self-reported  
106 mental health data at term. However not all of the participants completed mental health  
107 questionnaires at all time points (Supplementary Table 2). 91% of participants in the Grown in

108 Wales cohort reported Caucasian ethnicity (Janssen et al., 2018), and the current study  
109 focused on this group of 233 women.

### 110 *2.3 Materials*

#### 111 *2.3.1 Maternal depression and anxiety symptoms*

112 Maternal mental health was measured through two self-reporting questionnaires, both  
113 validated for pre- and post-natal use. Depression was measured using the Edinburgh  
114 Postnatal Depression Scale (EPDS) which comprises of ten questions each scored between  
115 zero and three, with total scores 13 and above indicating probable depression (Cox et al.,  
116 1987; Matthey et al., 2006). Anxiety was measured using the Trait subscale of the State Trait  
117 Anxiety Index to measure general anxiety levels (Meades and Ayers, 2011; Spielberger et al.,  
118 1983). This subscale contains 20 questions scored between one and four, with final scores of  
119 40 and above indicating high anxiety levels. Both questionnaires were filled in at the pre-  
120 surgical appointment (A1), within seven days of birth (P1), ten weeks (P2) and 12 months  
121 postnatally (Y1). Missing data was addressed using participant level mean substitution for  
122 those missing <20% of data.

#### 123 *2.3.2 Selective Serotonin Re-uptake Inhibitor (SSRI) use*

124 SSRI prescription records were recorded by research midwives from the medical notes after  
125 birth.

#### 126 *2.3.3 Human placental lactogen*

127 Maternal venous serum samples were obtained at recruitment from blood taken as part of an  
128 anaesthetic review. Serum was obtained by centrifugation of maternal venous blood which  
129 was then frozen at -80°C. hPL levels were assayed in duplicate using the Leinco  
130 Technologies Human Placental Lactogen (HPL) Micro-ELISA test kit (Universal Biologicals  
131 product code T115-96 tests). Assays were performed by the NIHR Cambridge Biomedical  
132 Research Centre, Core Biochemical Assay Laboratory.

#### 133 *2.3.4 Maternal demographics and birth outcomes*

134 Maternal lifestyle and demographics were reported by the mother in the questionnaire at  
135 recruitment. Data included ethnicity, education, income, age, and whether they smoked or  
136 drank alcohol during their pregnancy. Welsh Index of Multiple Deprivation (WIMD) 2014 scores  
137 were calculated from anonymised postcodes (<http://wimd.wales.gov.uk>). Delivery information,  
138 fetal and placental biometry, body mass index at initial booking and parity were taken from the  
139 research midwives notes after birth.

140 *2.4 Statistical analysis*

141 All statistical tests were carried out in IBM SPSS Statistics Version 23. Normality was  
142 assessed using Shapiro-Wilk test, Kolmogorov-Smirnov test, histograms and normal Q-Q  
143 plots. EPDS, STAI scores and hPL concentration were all found to be not normally distributed,  
144 and therefore non-parametric tests were used going forward. Chi squared tests and  
145 Spearman's correlations were used when analysing demographic data for categorical and  
146 continuous data respectively. Both unadjusted and adjusted linear regression was used to  
147 assess the relationship between hPL and maternal perinatal mental health. Potential  
148 confounders that had a significant relationship with A1 EPDS or A1 STAI through univariate  
149 linear regressions were taken forward to a multiple linear regression with either A1 EPDS or  
150 STAI. Due to the large number of potential confounding variables, backward selection was  
151 then used to choose the final variables to include. To simplify analyses, those that were  
152 significant in either A1 EPDS or A1 STAI were taken forward to all the subsequent adjusted  
153 linear regressions to ensure the same confounders were used throughout all analysis. A  
154 sensitivity analysis was performed to determine the effect of SSRI usage during pregnancy on  
155 hPL levels. Women that were prescribed SSRIs at any point during their pregnancy were  
156 removed from the dataset and the unadjusted and adjusted multiple linear regressions were  
157 performed again. All unadjusted and adjusted linear regressions were run separately for  
158 participants who had girls and boys. Figure was created in R Studio Version 1.1.463.

159

160 **3. Results**

161 Demographics of the 233 women in this study are provided in Table 1. The relationship  
162 between these variables and maternal hPL levels are described, by either chi-squared or  
163 Spearman's correlation tests for categorical and continuous data respectively (Table 1).  
164 Serum hPL levels were significantly associated with birth weight as previously reported  
165 (Männik et al., 2010; Roh et al., 2005), head circumference and placental weight. Two  
166 maternal characteristics associated with serum hPL were maternal BMI, as reported in other  
167 studies (Vakili et al., 2013), and WIMD score. WIMD is designed to identify the small areas of  
168 Wales that are the most deprived related to multiple indicators including income, employment  
169 status, health status and educational achievement. Higher scores are associated with an  
170 increased percentage of people being treated for mental health conditions  
171 (<http://wimd.wales.gov.uk>). However, individually mental health history, education or income  
172 were not associated with serum hPL.

173 A1 EPDS and STAI scores recorded just prior to the term delivery were strongly associated  
174 with depression/anxiety scores recorded at all three postnatal time points ( $p > 0.001$  for all

175 comparisons; Supplementary Table 1). Prenatal mood scores were chosen to decide the  
176 confounding variables for testing. Maternal depression and anxiety scores were recorded at  
177 four time points. Not all of women completed all four questionnaires, with completion rate  
178 lowest at Y1 (Supplementary Table 2). The relationships between both mood scores and  
179 potential confounders were assessed using univariate linear regressions (Supplementary  
180 Table 3). Those that were significant at the  $p < .05$  level were taken forward to a multiple linear  
181 regression analysis with EPDS and STAI independently. A backward selection process was  
182 performed to choose the final confounders to enter into the adjusted model. The confounders  
183 significant with A1 EPDS at  $p < 0.05$  were 'history of mental health' and 'highest education  
184 level'. The potential confounders significant with A1 STAI at  $p < 0.05$  were 'history of mental  
185 health' and 'WIMD'. All three factors were taken forward into the adjusted linear regressions.

186 To investigate the relationship between hPL and perinatal anxiety and depression, multiple  
187 linear regression was used. Unadjusted, there was no significant associations when all  
188 participants were included (Table 2). However, when splitting analyses by fetal sex, term  
189 anxiety scores ( $p = .041$ ) and both ten week depression ( $p = .037$ ) and anxiety scores ( $p = .047$ )  
190 were significantly associated with hPL concentration when the infant was a girl but not when  
191 the infant was a boy (Table 2). After adjustment for the three confounders, the relationship  
192 between hPL and depression and anxiety scores at ten weeks postnatal for mothers of girls  
193 remained significantly negatively associated (EPDS  $p = .022$  and STAI  $p = .030$ ) (Table 2). After  
194 controlling for a history of mental health, WIMD and highest education level, hPL  
195 concentrations predicted a decrease in depression scores ( $B = -.367$ ) and more strongly in  
196 anxiety ( $B = -.776$ ) in women with girls.

197 To determine if there were an effect of SSRI usage on the relationship between hPL and  
198 maternal mental health, a sensitivity analysis was performed. Those who were prescribed  
199 SSRIs at any point during their pregnancy were removed from the analyses and the linear  
200 regressions repeated. There were 21 women prescribed SSRIs, 13 of which had boys and  
201 eight who had girls. The unadjusted linear regressions uncovered a significant association  
202 between hPL concentrations at three time points: just prior to delivery (A1), within one week  
203 of delivery (P1) and 10 weeks after delivery (P2) for both depression and anxiety when the  
204 infant was female (Table 3; Figure 1). After adjustment for the three confounders, the  
205 relationship between hPL and depression and anxiety scores at one week and ten weeks  
206 postnatal remained significantly negatively associated (Table 3). Again, this was only  
207 significant for mothers of girls and not mothers of boys. hPL predicted a larger decrease in  
208 depression scores at P2 compared to P1 ( $B = -.357$  and  $B = -.737$  respectively), and the reverse  
209 was true of anxiety scores ( $B = -.718$  and  $B = -.337$ , respectively). Sex-specific association was  
210 not related to inherent, naturally occurring differences in the levels of hPL between mothers



211 pregnant with male versus female infants (EPDS <13; male infant/without SSRIs  $8.33 \pm .3$   
212 versus female infant/without SSRIs  $8.58 \pm .3$  female;  $p=.533$ ).

213

#### 214 **4. Discussion**

215 Here we report that lower levels of maternal serum human placental lactogen (hPL) measured  
216 at term are predictive of higher maternal depression and anxiety scores postnatally, but only  
217 in women who gave birth to girls. This negative association was initially only significant for  
218 mood scores reported ten weeks after delivery. However, removing data from participants  
219 prescribed SSRIs during their pregnancy strengthened the results and additionally predicted  
220 mood scores within one week of the birth. For mothers of boys, there were no association  
221 between maternally reported symptoms of depression or anxiety with hPL.

222 This is the first study to report a sex-specific relationship between serum human placental  
223 lactogen levels and postnatal depression and anxiety symptoms. Although the unit of change  
224 was small, hPL concentrations were significantly negatively associated with postnatal  
225 depression and anxiety. Furthermore, this association was only present for women who had  
226 girls. We previously reported an association between lower expression of the *hPL* gene in the  
227 placenta of women with prenatal symptoms of depression (Janssen et al., 2016a) highlighting  
228 the same inverse relationship in two independent studies. Considerable experimental data  
229 exists to demonstrate that lactogenic hormones, both prolactin and placental lactogen, are  
230 important for the appropriate induction of maternal behaviour in rodents. In particular, infusion  
231 of placental lactogen into the brain of virgin female rodents causes them to adopt maternal  
232 behaviours whereas blocking lactogenic signalling by ablating the prolactin receptor, to which  
233 the hormone binds, results in a lack of pup-induced maternal behaviour and altered indicating  
234 a key contribution of lactogenic signalling to maternal behaviour and changes in the brain  
235 (Creeth et al., 2019). *In vivo*, placental lactogens are proposed to enter the maternal brain  
236 through the choroid plexus, which accumulates the short and long isoforms of the prolactin  
237 receptor to facilitate their entry into the brain (Augustine et al., 2003; Bridges and Hays, 2005;  
238 Grattan, 2002; Pi et al., 2003). Placental lactogens are thought to bind the prolactin receptor  
239 in the medial preoptic area (MPOA) and paraventricular nucleus (PVN) of the hypothalamus  
240 and the hippocampus (Bridges et al., 1990; Brown et al., 2017; Kokay et al., 2006; Torner et  
241 al., 2009; Vergara-Castañeda et al., 2016), regions important for maternal behaviour (Kimble  
242 et al., 1967; Stack et al., 2002). We have experimentally demonstrated, again in rodents, that  
243 altering the endocrine function of the mouse placenta alters maternal caregiving behaviour  
244 (Creeth et al., 2018) and that a smaller endocrine compartment is associated with higher levels  
245 of maternal anxiety (McNamara et al., 2018). These data suggest a causal relationship

246 between lower levels of hPL and the development of symptoms of depression and anxiety in  
247 human pregnancy because women do not undergo the appropriate brain adaptations required  
248 to initiate maternal behaviour.

249 A second important finding of this study was that removing data from women prescribed SSRIs  
250 in pregnancy strengthened the relationship between mood symptoms and hPL levels. SSRIs  
251 function by selectively binding the 5-hydroxytryptamine transporter blocking the reuptake of  
252 serotonin by pre-synaptic neurons resulting in enhanced serotonergic function in the brain  
253 (Sanguhl et al., 2009). Serotonin induces the release of prolactin-releasing factors from the  
254 hypothalamus stimulating the pituitary to release prolactin causing prolactinaemia, at least in  
255 rodents (Gil-ad et al., 1976; Kamberi et al., 1971). Although human literature is conflicting, a  
256 large pharmacoepidemiological study reported a clear association between SSRIs and a rise  
257 in serum prolactin (Petit et al., 2003). If SSRI usage is associated with prolactinaemia in  
258 pregnancy, this could explain why removing data from women prescribed SSRIs strengthened  
259 the association between mood symptoms and hPL levels. Together, these data suggest a  
260 mechanism through which placental endocrine dysfunction could increase the risk of  
261 depression in mothers both during pregnancy and immediately after birth and also suggest a  
262 mechanism through which SSRIs might function to alleviate maternal symptoms.

263 In this study we observed a sex-specific association between serum placental lactogens and  
264 postnatal mood symptoms. Although some placental hormones show inherent sex differences,  
265 such as human chorionic gonadotropin which is higher when the fetus is female (Adibi et al.,  
266 2015), we did not find significant sex-differences in the level of hPL. Lower maternal serum  
267 levels of hPL have been reported in small for gestational age pregnancies, but only when the  
268 infant was female (Lagerström et al., 1990). Similarly, maternal smoking has been associated  
269 with lower maternal hPL in mothers carrying girls but not boys (Bremme et al., 1990). These  
270 relationships may reflect sex-specific endocrine responses by the male and female placenta.

#### 271 *4.1 Limitations*

272 Both a strength and a limitation of our study is the defined nature of the cohort. Grown in Wales  
273 is set in South Wales where the majority of the population are Caucasian. We examined data  
274 exclusively from Caucasian women to avoid confounders that can be introduced by ethnic  
275 differences (Bornstein et al., 2013; Capron et al., 2018). We had too few women in our study  
276 representing distinct other ethnicities. All women in the cohort were recruited at a single site  
277 by the same two highly trained research midwives where they completed the EPDS and STAI  
278 questionnaires, and where blood was collected in advance of their planned surgery. Therefore,  
279 all women were in the same environment when responding to questionnaires and providing  
280 blood samples, and anticipating a surgical delivery. The homogenous nature of the cohort

281 provided a clear advantage uncovering the reported associations with relatively small numbers  
282 of participants. However, our findings may not apply to other ethnicities or to other modes of  
283 delivery. It will therefore be important to replicate these findings in more diverse cohorts, and  
284 across other modes of delivery. A second limitation of this study are the smaller sample sizes  
285 at the later time points (P2=124, Y1=95). The negative associations between hPL and mood  
286 were only significant in women with girls and there were higher numbers for this group at each  
287 time point. With more samples from boys, a similar association between low hPL and maternal  
288 mood symptoms may be present where the fetus is male. A third limitation is that serum hPL  
289 was measured at a single time point. We do not know whether low hPL is present at earlier  
290 time points. This knowledge has important implications for the use of hPL levels as a predictive  
291 biomarker.

## 292 **5. Conclusions**

293 This study set out to assess the relationship between maternal hPL concentrations at term  
294 and perinatal mental health measures in the Grown in Wales Study cohort. hPL serum levels  
295 at term were found to predict postnatal depression and anxiety scores. The inverse  
296 relationships between low hPL and high scores for depression and anxiety were significant for  
297 mothers who had girls, and not those who had boys. Excluding those prescribed SSRIs during  
298 pregnancy strengthened the relationship. Our data is consistent with the hypothesis that low  
299 lactogenic signalling contributes to perinatal mood disorders rescued, in part, by the  
300 prolactinaemic function of SSRIs.

301

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311

## 312 **Declarations of interest:**

313 None.

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448

449

450 **Tables**

451

452 **Table 1. Demographic and birth data for 233 participants and relationship with maternal**  
453 **hPL**

<b><i>Demographics</i></b>	<b><i>% (n) or median (IQR)</i></b>	<b><i>p</i></b>
Maternal age	33 (7)	.348
Parity	1 (1)	.109
Maternal BMI at booking	26.4 (7.3)	<b>.009**</b>
WIMD score <sup>a</sup>	1270 (1200)	<b>.002**</b>
History of mental health, % (n)		.408
No	69.5 (161)	
Yes	30.5 (71)	
SSRI use in pregnancy, % (n)		.879
No	91 (212)	
Yes	9 (21)	
SSRI use at term, % (n)		.789
No	94.8 (221)	
Yes	5.2 (12)	
Highest education level, % (n)		.443
Left before GCSE	6 (14)	
GCSE or vocational	22.7 (53)	
A-level	12.4 (29)	
University	30 (70)	
Postgraduate	26.2 (61)	
Not recorded	2.6 (6)	
Family income, % (n)		.909
<£18,000	7.3 (17)	
£18-25,000	10.3 (24)	
£25-43,000	19.3 (45)	
>£43,000	51.1 (119)	
Not recorded	12 (28)	
Smoking in pregnancy <sup>b</sup> , % (n)		.785
No	89.7 (209)	
Yes	10.3 (24)	
Alcohol in pregnancy <sup>c</sup> , % (n)		.182
No	91.4 (213)	
Yes	6.9 (16)	
Not recorded	1.7 (4)	
Season of birth, % (n)		.621
Spring	21 (49)	
Summer	23.2 (54)	
Autumn	33.9 (79)	
Winter	21.8 (51)	
Fetal sex, % (n)		.436
Female	45.5 (106)	
Male	54.5 (127)	
Gestational age (days)	274 (3)	.238
Placental weight (g)	654 (171)	<b>&lt;.001***</b>
Birth weight (g)	3500 (665)	<b>&lt;.001***</b>
Head circumference (cm)	35.5 (2.2)	<b>.002**</b>

454 Categorical data compared with hPL using chi squared tests, and continuous data with  
455 Pearson's correlations. BMI (Body Mass Index), WIMD (Welsh Index of Multiple Deprivation),



456 SSRI (Selective Serotonin Reuptake Inhibitors). Data is for 233 participants with the exception  
 457 of head circumference (n=231) and placental weight (n=228), WIMD (n=227) and BMI  
 458 (n=222).

459 <sup>a</sup> WIMD scores range from 1-1909 with higher scores indicating a small area of a lower overall  
 460 deprivation, and a low score indicative of higher overall deprivation.

461 <sup>b</sup> At any point in pregnancy

462 <sup>c</sup> Weekly at any point in pregnancy

463

464 **Table 2. Unadjusted and adjusted multiple linear regression models analysing**  
 465 **association between hPL concentration µg/ml and maternal mental health scores.**

<i>Mood scores</i>	<i>All</i>			<i>Male</i>			<i>Female</i>		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
<b>Unadjusted linear regressions</b>									
A1 EPDS	- .179	-.396, .038	.106	- .040	-.383, .303	.817	- .278	-.560, .004	.053
A1 STAI	- .172	-.587, .242	.413	.357	-.282, .996	.270	- .561	-1.100, .023	.041*
P1 EPDS	- .158	-.418, .103	.233	.005	-.409, .419	.980	.308	-.642, .026	.070
P1 STAI	- .393	-.946, .160	.162	- .349	-1.195, .497	.413	- .453	-1.190, .283	.224
P2 EPDS	- .188	-.473, .096	.193	.034	-.457, .526	.889	- .361	-.700, .022	.037*
P2 STAI	- .485	-1.107, .137	.125	- .106	-1.166, .955	.842	- .775	-1.538, .012	.047*
Y1 EPDS	- .104	-.465, .257	.567	.048	-.626, .721	.887	- .195	-.632, .241	.374
Y1 STAI	- .358	-1.166, .451	.382	.073	-1.458, 1.603	.923	- .583	-1.549, .383	.232
<b>Adjusted linear regressions</b>									
A1 EPDS	- .069	-.280, .143	.523	.094	-.233, .422	.569	- .216	-.500, .069	.136
A1 STAI	.012	-.385, .409	.953	.513	-.094, 1.119	.097	- .438	-.966, .090	.103
P1 EPDS	- .118	-.382, .146	.377	.064	-.373, .501	.771	- .311	-.660, .037	.079
P1 STAI	- .234	-.797, .329	.413	- .069	-.949, .811	.876	- .510	-1.285, .265	.193
P2 EPDS	- .101	-.375, .173	.466	.250	-.217, .716	.287	- .367	-.679, .056	.022*
P2 STAI	- .325	-.925, .274	.285	.171	-.861, 1.203	.740	- .776	-1.475, .077	.030*
Y1 EPDS	.077	-.269, .423	.659	.271	-.294, .836	.335	- .117	-.546, .311	.585
Y1 STAI	- .032	-.852, .788	.939	.420	-1.004, 1.844	.551	- .544	-1.518, .429	.429

466 A1 (at term pre-surgical appointment), P1 (up to seven days postnatally), P2 (ten weeks  
 467 postnatally), Y1 (12 months postnatally), EPDS (Edinburgh Postnatal Depression Scale), STAI

468 (Speilberger State Trait Anxiety-Trait subscale). Adjusting for history of mental health, WIMD,  
 469 and Highest education level.

470

471

472 **Table 3. Unadjusted linear regression assessing relationship between hPL and**  
 473 **perinatal mental health scores, in women not prescribed SSRIs.**

<i>Mood scores</i>	<i>All</i>			<i>Male</i>			<i>Female</i>		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
<b>Unadjusted linear regressions</b>									
A1 EPDS	- .194	-.405, .016	.070	- .045	-.381, .291	.791	- .297	-.569, .026	-. .032*
A1 STAI	- .182	-.569, .205	.356	.307	-.321, .935	.334	- .527	-1.012, .042	-. .034*
P1 EPDS	- .183	-.435, .068	.151	.045	-.356, .447	.822	- .385	-.707, .062	-. .020*
P1 STAI	- .530	-1.039, .020	.042	- .323	-1.131, .486	.427	- .728	-1.389, .066	-. .032*
P2 EPDS	- .181	-.470, .107	.216	.084	-.422, .590	.740	- .378	-.720, .037	-. .030*
P2 STAI	- .554	-1.118, .010	.054	- .177	-1.204, .850	.731	- .825	-1.477, .173	-. .014*
Y1 EPDS	- .098	-.447, .252	.580	.036	-.681, .752	.919	- .182	-.577, .213	.359
Y1 STAI	- .489	-1.237, .260	.198	- .191	-1.720, 1.338	.801	- .641	-1.496, .213	.138
<b>Adjusted linear regressions</b>									
A1 EPDS	- .090	-.301, .121	.400	.098	-.236, .432	.561	- .239	-.521, .043	.095
A1 STAI	- .025	-.413, .363	.901	.499	-.134, 1.131	.121	- .434	-.928, .060	.085
P1 EPDS	- .165	-.425, .097	.215	.040	-.402, .483	.855	- .357	-.698, .015	-. .041*
P1 STAI	- .363	-.902, .175	.184	- .059	-.941, .822	.893	- .718	-1.433, .004	-. .049*
P2 EPDS	- .069	-.350, .212	.626	.180	-.842, 1.202	.724	- .737	-1.387, .086	-. .027*
P2 STAI	- .336	-.898, .226	.238	.334	-.144, .812	.166	- .337	-.658, .016	-. .040*
Y1 EPDS	.065	-.280, .411	.708	.264	-.359, .888	.391	- .077	-.489, .334	.707
Y1 STAI	- .288	-1.076, .499	.468	.037	-1.417, 1.491	.959	- .588	-1.510, .335	.207

474 Adjusted for history of mental health, WIMD, and Highest education level.

475

476

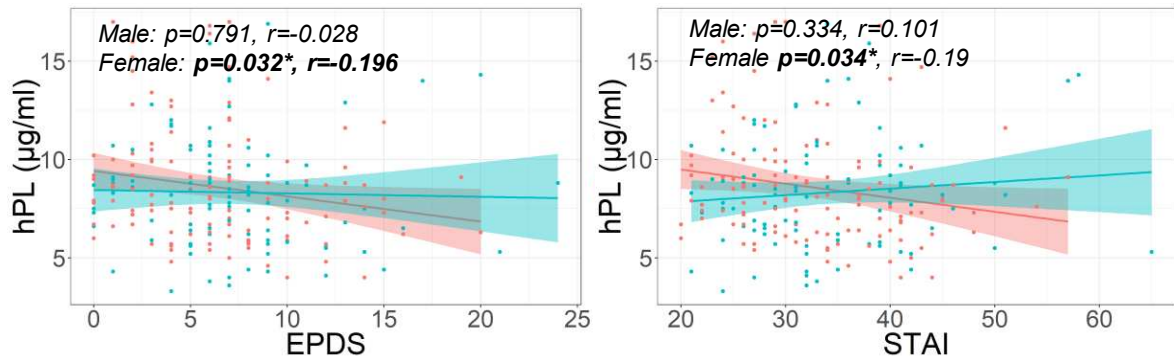
477

478 **Figure legends**

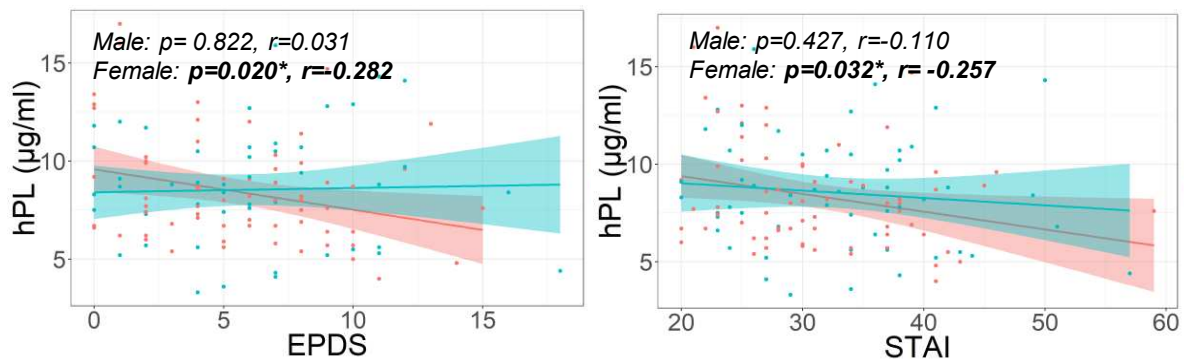
479 **Figure 1: Maternal serum hPL values correlate with EPDS and STAI scores for mothers**  
 480 **of girls**

481 Spearman's correlation of maternal serum hPL levels measured just prior to a term ELCS  
 482 delivery and perinatal mental health scores in women not prescribed SSRIs analysing male  
 483 and female data separately. Line of best fit is linear model. A1: at pre-surgical appointed prior  
 484 to delivery; P1: within one week of delivery; P2: ten weeks after delivery.

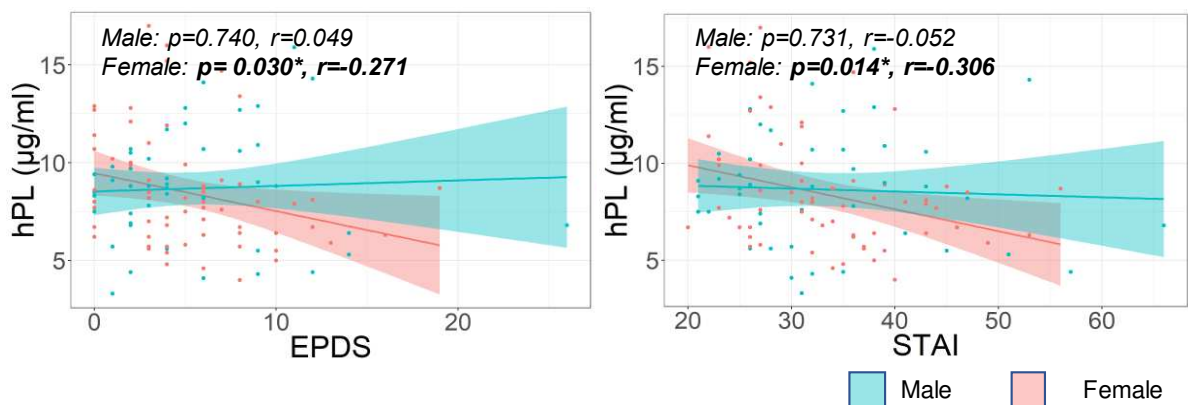
**Antenatal (term)**



**Postnatal (week one)**



**Postnatal (week 10)**



Male Female

485

486

487 **Supplementary Tables**

488

489 Supplementary Table 1: Spearman's correlations between perinatal mental health scores.

	<b>A1 EPDS</b>	<b>A1 STAI</b>	<b>P1 EPDS</b>	<b>P1 STAI</b>	<b>P2 EPDS</b>	<b>P2 STAI</b>	<b>Y1 EPDS</b>	<b>Y1 STAI</b>
<b>A1 EPDS</b>	-	-	-	-	-	-	-	-
<b>A1 STAI</b>	.722; <.001***	-	-	-	-	-	-	-
<b>P1 EPDS</b>	.644; <.001***	.595; <.001***	-	-	-	-	-	-
<b>P1 STAI</b>	.693; <.001***	.793; <.001***	.763; <.001***	-	-	-	-	-
<b>P2 EPDS</b>	.577; <.001***	.523; <.001***	.538; <.001***	.584; <.001***	-	-	-	-
<b>P2 STAI</b>	.633; <.001***	.752; <.001***	.587; <.001***	.697; <.001***	.739; <.001***	-	-	-
<b>Y1 EPDS</b>	.615; <.001***	.548; <.001***	.580; <.001***	.593; <.001***	.607; <.001***	.541; <.001***	-	-
<b>Y1 STAI</b>	.598; <.001***	.729; <.001***	.561; <.001***	.661; <.001***	.536; <.001***	.727; <.001***	.711; <.001***	-

490 (Correlation coefficient; *p* value)

491 A1 (at pre-surgical appointment), P1 (up to seven days postnatally), P2 (ten weeks  
492 postnatally), Y1 (12 months postnatally), EPDS (Edinburgh Postnatal Depression Scale), STAI  
493 (Spielberger State Trait Anxiety-Trait subscale).

494

495 Supplementary Table 2: Numbers of participants at each time point

	<b>All</b>	<b>Male</b>	<b>Female</b>
<b>A1 EPDS</b>	233	106	127
<b>A1 STAI</b>	233	106	127
<b>P1 EPDS</b>	133	62	71
<b>P1 STAI</b>	135	62	73
<b>P2 EPDS</b>	124	56	68
<b>P2 STAI</b>	122	54	68
<b>Y1 EPDS</b>	95	36	59
<b>Y1 STAI</b>	96	36	60

496

497

498 Supplementary Table 3: Univariate linear regression *p* values of potential confounders with  
499 antenatal mental health.

<b>Demographics</b>	<b>A1 EPDS <i>p</i> value</b>	<b>A1 STAI <i>p</i> value</b>
Maternal age	.347	.476
Parity	.996	.557
Maternal BMI at booking	.139	.265
WIMD score <sup>a</sup>	<b>.029*</b>	<b>.004**</b>
Highest education level Left before GCSE	<b>.033*</b>	.177

GCSE or vocational	.686	.191
A-level	.661	.131
University	<b>.025*</b>	.401
Postgraduate	<i>Ref.</i>	<i>Ref.</i>
Family income		
<£18,000	<b>.003**</b>	<b>.003**</b>
£18-25,000	.355	.182
£25-43,000	.374	.219
>£43,000	<i>Ref.</i>	<i>Ref.</i>
Smoking in pregnancy <sup>b</sup>	<b>.025*</b>	<b>.040*</b>
Alcohol in pregnancy <sup>c</sup>	.073	.069
Gestational age ( <i>days</i> )	.692	.844
History of mental health	<b>&gt;.001***</b>	<b>&gt;.001***</b>

500 *Ref.* (reference category)

501 <sup>a</sup> WIMD score ranges from 1-1909, high score indicating a small area of a lower overall  
502 deprivation, and a low score of higher overall deprivation.

503 <sup>b</sup> At any point in pregnancy

504 <sup>c</sup> Weekly at any point in pregnancy

505

506