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Maternal depression and inflammation during pregnancy

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Background. Maternal depression during pregnancy increases the risk for adverse developmental outcomes in children. However, the underpinning biological mechanisms remain unknown. We tested whether depression was associated with levels of and change in the inflammatory state during pregnancy, if early pregnancy overweight/obesity or diabetes/hypertensive pregnancy disorders accounted for/mediated these effects, and if depression added to the inflammation that typically accompanies these conditions.

Methods. We analyzed plasma high-sensitivity C-reactive protein (hsCRP) and glycoprotein acetyls at three consecutive stages during pregnancy, derived history of depression diagnoses before pregnancy from Care Register for Healthcare (HILMO) ($N = 375$) and self-reports ($N = 347$) and depressive symptoms during pregnancy using the Center for Epidemiological Studies Depression Scale completed concurrently to blood samplings ($N = 295$). Data on early pregnancy body mass index (BMI) and diabetes/hypertensive pregnancy disorders came from medical records.

Results. Higher overall hsCRP levels, but not change, during pregnancy were predicted by history of depression diagnosis before pregnancy [HILMO: mean difference (MD) = 0.69 standard deviation (s.d.) units; 95% confidence interval (CI) 0.26–1.11, self-report: MD = 0.56 s.d.; 95% CI 0.17–0.94] and higher depressive symptoms during pregnancy (0.06 s.d. per s.d. increase; 95% CI 0.00–0.13). History of depression diagnosis before pregnancy also predicted higher overall glycoprotein acetyls (HILMO: MD = 0.52 s.d.; 95% CI 0.12–0.93). These associations were not explained by diabetes/hypertensive disorders, but were accounted for and mediated by early pregnancy BMI. Furthermore, in obese women, overall hsCRP levels increased as depressive symptoms during pregnancy increased ($p = 0.006$ for interaction).

Conclusions. Depression is associated with a proinflammatory state during pregnancy. These associations are mediated by early pregnancy BMI, and depressive symptoms during pregnancy aggravate the inflammation related to obesity.

Introduction

Maternal depression during pregnancy, including major depressive disorder (MDD), dysthymia, and depressive symptoms, is a major pregnancy complication carrying prevalence rates of 7–20% (Lahti *et al.*, 2017; Woody *et al.*, 2017). Maternal depression not only hinders the maternal quality of life, but is often accompanied by overweight/obesity (Kumpulainen *et al.*, 2018), diabetes and hypertensive pregnancy disorders (Fenton and Stover, 2006), and shows high continuity postpartum (Kumpulainen *et al.*, 2018). Maternal depression during pregnancy also associates with poorer fetal growth and preterm birth (Jarde *et al.*, 2016) and increases child risk for inflammation, allergies, asthma, poorer neurodevelopment, and psychopathology (Plant *et al.*, 2016; Lahti *et al.*, 2017; Van den Bergh *et al.*, 2017; Flanigan *et al.*, 2018; Tuovinen *et al.*, 2018).

However, the biological mechanisms underlying the transmission of these effects from the mother to her child remain vague. In addition to depression-related changes in placental

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*Dr Lahti-Pulkkinen and Dr Girchenko had equal contribution and are the joined first authors.

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structure and function (Raikkonen *et al.*, 2015; Reynolds *et al.*, 2015; Lahti-Pulkkinen *et al.*, 2018), stress axes, oxidative stress, and nutrition (Glover, 2015; Van den Bergh *et al.*, 2017), it has been suggested that depression may aggravate maternal proinflammatory state set forth in pregnancy (Leff-Gelman *et al.*, 2016) and link maternal depression with child development (Glover, 2015; Van den Bergh *et al.*, 2017).

By using the Newcastle Ottawa Scale (NOS) (Herzog *et al.*, 2013; Wells *et al.*, 2014*a*, 2014*b*; Anthony and Lin, 2018), we systematically assessed the quality of evidence of the scant previous studies that have tested if depression is associated with inflammation during pregnancy. Online Supplementary Table ST1 provides a summary of the study characteristics, main findings and NOS quality of evidence assessment. Online Supplementary Table ST2 provides further details of the NOS assessment and criteria for cross-sectional (Herzog *et al.*, 2013; Anthony and Lin, 2018) and online Supplementary Table ST3 for cohort studies (Wells *et al.*, 2014*a*, 2014*b*). The NOS assessment of the reviewed studies highlights the limited quality of available evidence: of the 10 reviewed studies 40% were defined as 'poor' (Scrandis *et al.*, 2008; Azar and Mercer, 2013; Cheng and Pickler, 2014; Gustafsson *et al.*, 2018), 50% as 'fair' (Christian *et al.*, 2009; Cassidy-Bushrow *et al.*, 2012; Haeri *et al.*, 2013; Simpson *et al.*, 2016; Osborne *et al.*, 2018), and 10% as 'good' (Blackmore *et al.*, 2011) based on the NOS assessment. Online Supplementary Table ST1 also shows that the findings are mixed with some studies showing that maternal depression is associated with higher levels of a number of inflammatory markers studied and some reporting null associations. In the only study providing good quality of evidence, MDD diagnosis and depressive symptoms at 18 and 32 gestational weeks were not significantly associated with interleukin (IL)-6 or tumor necrosis factor α (TNF-α) measured at these same gestational weeks (Blackmore *et al.*, 2011). There were no longitudinal associations across time between depression and inflammation either (Blackmore *et al.*, 2011). Our review, thus, highlights the need for further studies with good quality of evidence to either refute or confirm the hypothesis that depression aggravates the proinflammatory state set forth in pregnancy.

Apart from the limited quality of evidence, there are also critical knowledge gaps in the existing literature. The studies are based on small samples limiting statistical power, and all but two (Blackmore *et al.*, 2011; Azar and Mercer, 2013) have reported cross-sectional correlations, even if depression and/or inflammation would have been measured at more than one gestational stage. In addition to the above-mentioned good quality study (Blackmore *et al.*, 2011), the other, small-scale study reporting longitudinal associations showed in 27 women that an increase in depressive symptoms from 7–10 to 16–20 gestational weeks was associated with higher IL-6 at 16–20 gestational weeks, but the increase was not associated with C-reactive protein (CRP) or TNF-α (Azar and Mercer, 2013). A further knowledge gap relates to the limited evidence available on depression diagnoses: all of the previous studies have focused on depressive symptoms and only three (Blackmore *et al.*, 2011; Haeri *et al.*, 2013; Osborne *et al.*, 2018) have additionally studied depression diagnoses. Moreover, since convincing evidence shows associations between depression and obesity in pregnant populations (Molyneaux *et al.*, 2014; Kumpulainen *et al.*, 2018); and inflammatory state in pregnancy is aggravated in response to obesity (Choi *et al.*, 2013), most studies on depression and inflammation during pregnancy have accounted for pre-pregnancy overweight/obesity (Christian *et al.*, 2009; Blackmore *et al.*, 2011; Cassidy-Bushrow *et al.*, 2012; Haeri *et al.*, 2013; Simpson *et al.*, 2016; Osborne *et al.*, 2018). However, few studies have considered diabetes and hypertensive pregnancy disorders (Azar and Mercer, 2013; Haeri *et al.*, 2013; Simpson *et al.*, 2016; Osborne *et al.*, 2018) even though these conditions are associated with depression (Fenton and Stover, 2006), often complicate overweight/obese pregnancies (Ovesen *et al.*, 2011) and associate with increased inflammation as well (Rebelo *et al.*, 2013; Pantham *et al.*, 2015). Finally, none of the studies has tested whether depression adds to the inflammatory effects of overweight/obesity, diabetes, and hypertensive pregnancy disorders.

To address these knowledge gaps, we tested the hypotheses that (1) history of depression diagnoses before pregnancy, derived from healthcare registry, and (2) from self-reports, and (3) higher levels of depressive symptoms reported during pregnancy were associated with higher levels of and increases in plasma high-sensitive CRP (hsCRP) and glycoprotein acetyls measured across three consecutive stages during pregnancy. We also tested the hypotheses that early pregnancy body mass index (BMI), diabetes, and hypertensive pregnancy disorders accounted for and, at least partially mediated these associations, and tested if depression added to the inflammation that accompanies these conditions.

We focused on two proinflammatory biomarkers: hsCRP and glycoprotein acetyls, because they both have long half-lives and indicate systemic, low-grade chronic inflammation (Ritchie *et al.*, 2015). HsCRP is among the most commonly used inflammatory biomarkers in research. Vast evidence in the general population supports its longitudinal associations with depression (Copeland *et al.*, 2012; Valkanova *et al.*, 2013; Huang *et al.*, 2019) and cardiovascular mortality (Li *et al.*, 2017). Glycoprotein acetyls are, in turn, a novel inflammatory biomarker. It is a composite signal of changes in multiple circulating glycoproteins. Glycoprotein acetyls predict the risk of infectious illnesses (Ritchie *et al.*, 2015). Importantly, both hsCRP and glycoprotein acetyl levels rise markedly during pregnancy (Wang *et al.*, 2016), making them suitable candidate biomarkers for our study.

Method

Sample

The participants came from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) Study, described in detail elsewhere (Girchenko *et al.*, 2017). Briefly, in 2005–2009, 1079 pregnant women were enrolled in the clinical subsample of the PREDO when they arrived for their first ultrasound screening at 12–13 weeks of gestation. Of them, 969 had one or more and 110 none of the known risk factors for pre-eclampsia and intrauterine growth restriction (IUGR). The study sites comprised 10 hospitals in Southern and Eastern Finland.

Of the 1079 women, 420 underwent venous blood sampling at one to three consecutive stages during pregnancy; due to economic constraints, blood was sampled only at three study hospitals. Because of large within-individual variation in the levels of hsCRP and glycoprotein acetyls across the three samplings, we did not impute missing data ($n = 41$ with one or two missing blood samples).

Hence, our sample comprised 379 women providing three blood samples taken at the median (interquartile range) 13.0 (12.6–13.4), 19.3 (19.0–19.7), and 27.0 (26.6–27.6) gestational

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weeks. Health registry data on the history of depression diagnoses before pregnancy were available for 375 women (two women had no data available and two women who received depression diagnosis during pregnancy were excluded); 347 had data on self-reported history of depression diagnosis before pregnancy (29 did not complete the questionnaire and 3 did not specify when they were diagnosed); and 295 women reported depressive symptoms concurrently to the three blood samplings during pregnancy (84 did not complete the symptom questionnaire). Women with these three analytic samples differed from women of the entire sample only in two respects: they were more often younger than 40 years, and less often reported a history of depression diagnosis before pregnancy (Table 1).

All participants signed written informed consents. The PREDO study protocol was approved by ethics committees of the Helsinki and Uusimaa Hospital District. All study procedures were in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Inflammation

The participants came for blood sampling from antecubital vein between 19:00 to 21:00 h, after having fasted for at least 10 h. Plasma was separated immediately. Ethylenediaminetetraacetic acid plasma samples were stored at −80 °C until analyzed. The hsCRP concentration (mg/L) was analyzed with a Beckman-Coulter CRP immunoturbidometric assay and Olympus AU680 analyzer (Beckman Coulter Inc., CA, USA). The intra-assay variation (CV%) of the method in our laboratory was between 2.6% ($n = 10$, mean 1.20 mg/L) and 0.7% ($n = 10$, mean 65 mg/L) and inter-assay variations were (CV%) 3.5% ($n = 30$, mean 1.07 mg/L), 1. 2% ($n = 30$, mean 11.5 mg/L), and 2.9% ($n = 30$, mean 73 mg/L). The limit of detection of the hsCRP method is 0.02 mg/L and the functional sensitivity was better than 0.1 mg/L. Glycoprotein acetyls (mmol/L) were analyzed using a high-throughput nuclear magnetic resonance metabolomics platform (1HNMR spectra, Nightingale Ltd.; Espoo, Finland) (Soininen *et al.*, 2015).

Depression

We derived depression diagnoses from the Care Register for Healthcare (HILMO), comprising diagnoses of all inpatient hospitalizations in Finland since 1969 and outpatient hospitalizations and specialized treatments since 1998; participants were born 1959–1989. Depression diagnoses were identified with the International Classification of Diseases, Tenth-Revision (ICD-10) codes F32–F33, F341 since 1996 and with ICD-9 codes 2961, 2968A, and 3004A in 1987–1995. No women had bipolar disorder in our sample. The median time interval between the last hospital discharge with depression and conception was 3.1 years (interquartile range = 1.9–6.7 years).

In early pregnancy, the women answered the question '*Have you ever been diagnosed by a physician with depression?*' followed by a question on when they were diagnosed.

Starting from 12–13 gestational weeks, the women completed the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The 20 CES-D questions describe depressive symptoms during the past week, rated from none (0) to all (3) of the time. The women completed the CES-D biweekly up to 14 times until 38–39 gestational weeks or delivery. This allowed us to identify the measurements that matched the closest to the three blood samplings for inflammatory biomarkers; for each sampling, we identified two CES-D scores closest to the sampling date. We used the average of these two scores at the three sampling points in our analyses.

Higher CES-D scores indicate more depressive symptoms, and 16 points or more represent probable clinical depression (Radloff, 1977). The CES-D is a well-established measure of depression, and it has been validated in pregnant women (Lahti *et al.*, 2017).

Covariates and moderators

Early pregnancy BMI, calculated from weight [kilograms (kg)] and height [meters (m)] measurements verified at the first antenatal clinic visit [mean = 8.5, standard deviation (S.D.) = 1.5 gestational weeks)], was derived from medical records [overweight (25–29.99 kg/m^2)/obese (⩾30 kg/m^2)/normal weight (⩽24.99 kg/m^2) (WHO, 2000)]. Diagnoses of diabetes (type 1 diabetes/gestational diabetes/no diabetes) and hypertensive (chronic hypertension/pre-eclampsia/gestational hypertension/normotension) pregnancy disorders were derived from medical records and the diagnoses were verified by a clinical jury. Additional covariates included age (<40 *v.* ⩾40 years) and smoking during pregnancy (did not smoke *v.* quit during first trimester/smoked throughout pregnancy), derived from medical records and Finnish Medical Birth Register, and antenatal alcohol use (yes/no) and education level (basic/secondary *v.* tertiary), which were reported in early pregnancy.

Statistical analyses

The primary data analytic tool was linear mixed-model regression with hsCRP and glycoprotein acetyls at the three sampling points during pregnancy, analyzed in separate models, as time-varying within-person outcomes. History of depression diagnoses before pregnancy from HILMO and self-reports were treated as time-invariant between-person predictors, and depressive symptoms at the three points matching the blood sampling points as a time-varying within-person predictor. In addition to treating depressive symptoms during pregnancy as continuous, we conducted analyses treating the symptoms as a binary variable indicating probable clinical depression (CES-D ⩾ 16). All depression indicators were assessed in separate mixed models, which included a gestational week at blood sampling as a time-varying within-person predictor and those covariates that were significantly associated with hsCRP and/or glycoprotein acetyls. Interactions of depression (diagnoses or symptoms) × gestational week at blood samplings were added into the models to test if depression predicted changes in hsCRP or glycoprotein acetyls during pregnancy.

We then tested if overweight/obesity, diabetes, or hypertensive pregnancy disorders accounted for any effects of depression on inflammation by including the main effects of these conditions into separate mixed-model equations. If the effect sizes of depression attenuated after adjustment for these conditions, we further tested for mediation with the bootstrapping method using 5000 resamples and bias corrected 95% confidence intervals. These analyses were performed only if the other criteria for mediation were also met: (1) the depression indicator was associated with the condition that attenuated the association and (2) the condition in question was associated with the inflammation marker in question. Finally, to study if depression added to the inflammatory effects of overweight/obesity, diabetes or hypertensive pregnancy disorders, we included interaction terms depression ×

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Table 1. Characteristics of the sample

	Entire sample ($N = 1079$)		Sample with 3 high-sensitivity C-reactive protein blood samples and data on the history of depression diagnosis before pregnancy from HILMO ($N = 375$)			Sample with 3 high-sensitivity C-reactive protein blood samples and data on depression diagnosis before pregnancy from self-reports ($N = 347$)			Sample with 3 high-sensitivity C-reactive protein blood samples and data on depressive symptoms reported concurrently to the blood samplings during pregnancy ($N = 295$)		
	Mean/*N* (S.D./%)	Range	Mean/*N* (S.D./%)	Range	P1	Mean/*N* (S.D./%)	Range	P2	Mean/*N* (S.D./%)	Range	P3
Age (years)	33.2 (5.8)	17.2–47.4	32.6 (5.2)	19.5–47.4	0.14	32.6 (5.1)	19.5–47.4	0.08	32.6 (5.1)	20.3–47.4	0.11
<40 years, *n* (%)	902 (83.6%)		337 (89.9%)		0.003	312 (89.9%)		0.006	265 (89.8%)		0.008
⩾40 years, *n* (%)	177 (16.4%)		38 (10.1%)			35 (10.1%)			30 (10.2%)		
Data not available, *n* (%)	0		0			0			0		
Education					0.71			0.46			0.79
Lower secondary or lower	483 (46.1%)		181 (48.7%)			169 (48.7%)			139 (47.1%)		
Upper secondary or tertiary	564 (53.9%)		191 (51.3%)			178 (51.3%)			156 (52.9%)		
Data not available, *n* (%)	32		3			0			0		
Data not available, *n* (%)	0		0			0			0		
Smoking during pregnancy					0.49			0.46			0.80
No	1025 (95.4%)		351 (93.9%)			324 (93.6%)			277 (94.2%)		
Quit during first trimester	39 (3.6%)		17 (4.6%)			17 (4.9%)			14 (4.8%)		
Smoked throughout pregnancy	11 (1.0%)		6 (1.6%)			5 (1.5%)			3 (1.0%)		
Data not available, *n* (%)	4		1			1			1		
Alcohol use during pregnancy					0.23			0.30			0.10
No	776 (71.9%)		295 (86.0%)			285 (85.6%)			252 (87.2%)		
Yes	158 (14.6%)		48 (14.0%)			48 (14.4%)			37 (12.8%)		
Data not available, *n* (%)	145		32			14			6		
Body mass index in early pregnancy(kg/m^2)	27.4 (6.5)	17.2–55.0	27.1 (6.6)	17.6–55.0	0.44	27.1 (6.7)	17.6–55.0	0.46	26.7 (6.7)	17.7–55.0	0.10
Normal weight (<24.99 kg/m^2)	503 (46.6%)		183 (48.8%)		0.15	171 (49.3%)		0.26	153 (51.9%)		0.08
Overweight (25–29.99 kg/m^2)	193 (17.9%)		78 (20.8%)			69 (19.9%)			58 (19.7%)		
Obese (⩾30 kg/m^2)	383 (35.5%)		114 (30.4%)			107 (30.8%)			84 (28.5%)		
Data not available, *n* (%)	0		0			0			0		
Hypertensive disorders in pregnancy					0.87			0.32			0.37
Normotension	705 (65.5%)		237 (63.2%)			222 (64.1%)			192 (65.1%)		
Gestational hypertension	108 (10.0%)		36 (9.6%)			34 (9.8%)			31 (10.5%)		
Pre-eclampsia	98 (9.1%)		37 (9.9%)			33 (9.5%)			24 (8.1%)		
Chronic hypertension	168 (15.6%)		65 (17.3%)			58 (16.7%)			48 (16.3%)		

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Data not available, *n* (%)	0		0			0			0		
Diabetes disorders in pregnancy					0.66			0.60			0.20
No	818 (75.8%)		288 (76.8%)			268 (77.2%)			233 (79.0%)		
Gestational diabetes	239 (22.2%)		78 (20.8%)			72 (20.8)			55 (18.6%)		
Type 1 diabetes	22 (2.0%)		9 (2.4%)			7 (2.0%)			7 (2.4%)		
Data not available, *n* (%)	0		0			0			0		
History of depression diagnosis before pregnancy					0.81			0.64			0.20
From HILMO											
No	1033 (96.1%)		357 (95.2%)			329 (95.1%)			281 (95.9%)		
Yes	39 (3.6%)		18 (4.8%)			17 (4.9%)			12 (4.1%)		
Data not available, *n* (%)	4		0			1			2		
From self-reports					0.04			0.04			0.07
No	827 (89.6%)		322 (93.3%)			324 (93.4%)			261 (93.2%)		
Yes	96 (10.4%)		23 (6.7%)			23 (6.6%)			19 (6.8%)		
Data not available, *n* (%)	156		30			0			15		
Depressive symptoms during pregnancy											
Continuous score (mean of reports at 3 blood sampling points)	11.61 (7.05)	0.5–44.7	11.51 (7.11)	0.3–45.0	0.72	11.54 (7.15)	0.33–45.0	0.76	10.58 (10.5)	0.33–45.0	0.78
Binary score (continuous score⩾16, probable clinical depression)					0.80			0.99			0.87
No	609 (78.9%)		229 (78.7%)			221 (78.9%)			231 (78.3%)		
Yes	163 (21.1%)		62 (21.3%)			59 (21.1%)			64 (21.7%)		
Data not available, *n* (%)	307		84			67			0		
High-sensitivity C-reactive protein (mg/L), median (interquartile range)											
First sampling point (11.1–16.7 gestational weeks)	3.81 (2.18–7.34)	0.23–32.70	3.83 (2.22–7.40)	0.23–32.70	0.86	3.80 (2.12–7.34)	0.23–32.70	0.94	3.80 (2.12–7.11)	0.23–31.49	0.90
Data not available, *n* (%)	669		0			0			0		
Second sampling point (17.1–22.9 gestational weeks)	4.53 (2.42–8.69)	0.31–60.65	4.56 (2.37–8.95)	0.31–60.65	0.83	4.50 (2.33–8.71)	0.31–60.65	0.83	4.30 (2.30–7.97)	0.31–60.65	0.48
Data not available, *n* (%)	674		0			0			0		
Third sampling point (25.3–31.1 gestational weeks)	3.95 (2.11–6.91)	0.19–61.07	3.81 (2.05–6.93)	0.19–61.07	0.68	3.73 (2.00–6.59)	0.19–28.15	0.39	3.72 (1.98–6.37)	0.22–26.10	0.39
Data not available, *n* (%)	677		0			0			0		
Glycoprotein acetyls (mmol/L)[a]											
First sampling point (11.1–16.7 gestational weeks)	1.26 (0.16)	0.89–1.85	1.27 (0.16)	0.89–1.85	0.40	1.26 (0.16)	0.89–1.85	1.0	1.25 (0.15)	0.89–1.85	0.42

(*Continued*)

Table 1. (*Continued.*)

	Entire sample ($N = 1079$)		Sample with 3 high-sensitivity C-reactive protein blood samples and data on the history of depression diagnosis before pregnancy from HILMO ($N = 375$)			Sample with 3 high-sensitivity C-reactive protein blood samples and data on depression diagnosis before pregnancy from self-reports ($N = 347$)			Sample with 3 high-sensitivity C-reactive protein blood samples and data on depressive symptoms reported concurrently to the blood samplings during pregnancy ($N = 295$)		
	Mean/*N* (S.D./%)	Range	Mean/*N* (S.D./%)	Range	P1	Mean/*N* (S.D./%)	Range	P2	Mean/*N* (S.D./%)	Range	P3
Data not available, *n* (%)	680		31			31			24		
Second sampling point (17.1–22.9 gestational weeks)	1.34 (0.18)	0.94–2.14	1.35 (0.17)	1.0–2.14	0.44	1.35 (0.17)	1.0–2.14	0.45	1.34 (0.17)	1.0–2.14	>0.999
Data not available, *n* (%)	679		31			31			24		
Third sampling point (25.3–31.1 gestational weeks)	1.45 (0.18)	1.06–2.25	1.45 (0.18)	1.06–2.25	1.0	1.44 (0.17)	1.06–2.25	0.45	1.44 (0.17)	1.06–2.25	0.47
Data not available, *n* (%)	688		31			31			24		

Depressive symptoms during pregnancy in the entire sample are reported as the mean of all available observations, and for the analytic samples as the mean of depressive symptom scores measured at the time of the three blood samplings during pregnancy.
P1 reflects *p* value from the analyses exploring the difference between the entire sample ($N = 1079$) and the sample with data on the history of depression diagnosis before pregnancy derived from HILMO ($N = 375$).
P2 reflects *p* value from the analyses exploring the difference between the entire sample ($N = 1079$) and the sample with data on the history of depression diagnosis before pregnancy derived from self-reports ($N = 348$).
P3 reflects *p* value from the analyses exploring the difference between the entire sample ($N = 1079$) and the sample with data on depressive symptoms reported (Center for Epidemiological Studies Depression Scale) at the time of the three blood samplings during pregnancy ($N = 295$).
HILMO refers to Care Register for Healthcare.
[a]For glycoprotein acetyls, the analytic samples comprised 344, 317, and 271 women with three blood samples with glycoprotein acetyls and history of depression diagnosis before pregnancy from HILMO and from self-reports and depressive symptoms reported concurrent to the blood samplings during pregnancy, respectively.

normal weight/overweight/obesity, depression × diabetes disorders, and depression × hypertensive disorders into the mixed-model equations.

For mixed-models, we used variance components covariance structure and defined a random intercept and random slope for time, i.e. gestational week at blood sampling. Because hsCRP and CES-D distributions were skewed, we normalized hsCRP with logarithm and CES-D with square root transformations. To facilitate interpretation, we transformed all continuous variables to standard deviation (S.D.) units (for time-varying variables we used the mean of the three data points during pregnancy and its S.D. to retain within-person variation). To facilitate clinical interpretation, we also provide test statistics in raw units of hsCRP and glycoprotein acetyls.

We conducted sensitivity analyses by excluding measurements of hsCRP and glycoprotein acetyls taken within a month preceding or following acute infectious disease diagnoses derived from HILMO to ascertain that acute infection did not affect our results. The sensitivity analyses included 879–1112 hsCRP and 808–1020 glycoprotein measurements out of the 885–1125 available samples. Infectious illnesses were identified with diagnostic codes as described elsewhere (Lund-Sorensen *et al.*, 2016; Kohler *et al.*, 2017).

Results

Background characteristics

Table 1 shows the sample characteristics. HsCRP and glycoprotein acetyls were inter-correlated (Pearson r's $\geqslant 0.38$, $p < 0.001$) and showed high rank-order stability across pregnancy ($r \geqslant 0.75$ for hsCRP and $r \geqslant 0.72$ for glycoprotein). Online Supplementary Figure ST1 shows that levels of hsCRP (panel A) and glycoprotein acetyls (panel B) changed during pregnancy; change in hsCRP was A-shaped, whilst glycoprotein acetyls increased linearly across pregnancy. HILMO and self-reported history of depression diagnosis before pregnancy showed concordance ($\kappa = 0.47$, $p < 0.001$), and both were associated with higher levels of depressive symptoms during pregnancy [diagnosis from HILMO: mean difference(MD) = 1.00 S.D., 95% CI 0.44–1.56, $p = 0.001$; diagnosis from self-reports: MD = 1.09 S.D., 95% CI 0.64–1.53, $p < 0.001$) and with higher prevalence of probable clinical depression during pregnancy (diagnosis from HILMO: 66.7% *v.* 19.4%, $p < 0.001$; diagnosis from self-reports: 57.9% *v.* 18.4%, $p < 0.001$).

Online Supplementary Table ST4 shows that women with lower education, who were overweight or obese in early pregnancy or had chronic hypertension, pre-eclampsia, or gestational diabetes had higher overall hsCRP and glycoprotein acetyl levels. HsCRP levels were also higher and changed less across pregnancy in women younger than 40 years ($\beta = 0.013$ in older and $\beta = -0.006$ in younger women; $p = 0.01$ for age × time interaction). Glycoprotein acetyls increased more across pregnancy in overweight than normal weight women ($\beta = 0.08$ in overweight and $\beta = 0.07$ in normal weight women; $p = 0.01$ for normal weight *v.* overweight × time interaction). Smoking, alcohol use during pregnancy or type 1 diabetes was not associated with hsCRP or glycoprotein acetyls (online Supplementary Table ST4).

Depression and inflammation during pregnancy

Table 2 shows that hsCRP levels were 0.69 S.D. [mean difference in raw units (MD) = 4.11, 95% confidence interval (CI) 2.54–

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5.69 mg/L] and 0.56 S.D. (MD = 2.44, 95% CI 1.12–3.77 mg/L) higher in women with compared to those without a history of depression diagnosis before pregnancy derived from HILMO and self-reports, respectively; hsCRP levels were also 0.28 S.D. (MD = 1.02, 95% CI 0.17–1.88 mg/L) higher in women with compared to those without probable clinical depression during pregnancy, and 0.06 S.D. higher per each S.D. increase in these symptoms during pregnancy. Glycoprotein acetyls were 0.52 S.D. (MD = 1.02, 95% CI 0.17–1.88 mg/L) higher in women with compared to those without a history of depression diagnosis from HILMO and 0.25 S.D. (MD = 0.05, 95% CI 0.003–0.09 mg/L) higher in women with compared to those without probable clinical depression during pregnancy. All associations, except for probable clinical depression during pregnancy with glycoprotein acetyls, remained significant when adjusted for age and education (Table 2) and when adjusted for diabetes and hypertensive pregnancy disorders (online Supplementary Table ST5). However, all associations became non-significant when adjusted for early pregnancy BMI (Table 2). In the models where depression no longer associated with hsCRP, overweight (MD = 0.54 S.D. between normal weight *v.* overweight, 95% CI 0.31–0.97) and obesity (MD = 1.01 S.D. between normal weight *v.* obesity, 95% CI 0.80–1.22) remained significant predictors of hsCRP (respective values for glycoprotein acetyls were MD = 0.73 S.D., 95% CI 0.51–0.97 and MD = 0.93 S.D., 95% CI 0.51–1.18). Figures 1–2 display that there were no depression × gestational week at blood sampling interactions.

The exclusion of hsCRP and glycoprotein measurements taken within one month preceding or following diagnosed infectious diseases did not change the associations (online Supplementary Table ST6).

Mediation

Online Supplementary Figures ST2–ST4 show that early pregnancy BMI mediated the following effects on hsCRP: history of depression diagnosis before pregnancy from HILMO and from self-reports, and depressive symptoms reported during pregnancy. Online Supplementary Figure ST5 shows that BMI also mediated the effect of history of depression diagnosis before pregnancy from HILMO on glycoprotein acetyls. We did not test other possible mediation effects, as the criteria for mediation tests were not met.

Additive effects

We found one significant interaction: depressive symptoms during pregnancy interacted significantly with normal weight *v.* obesity in the analysis of hsCRP ($p = 0.006$ for interaction; $p = 0.57$ for depressive symptoms × normal weight *v.* overweight interaction). Figure 3 shows that higher depressive symptoms during pregnancy were associated with higher hsCRP levels in obese women, but not in overweight or normal weight women. This may reflect that below BMI 30 kg/m^2 hsCRP increased with increasing BMI, but at BMI 30 kg/m^2 and above hsCRP plateaued showing no further increase (online Supplementary Fig. ST6).

Discussion

We found that depression was associated with higher levels of hsCRP and glycoprotein acetyls during pregnancy. The findings for hsCRP were consistent and significant across the different information sources of depression; whether history of depression diagnosis before pregnancy was derived from HILMO or self-reports, or whether depressive symptoms were reported during pregnancy concurrent to the three consecutive blood samplings, and treated either as a continuous or a binary variable, the latter indicating probable clinical depression during pregnancy. The pattern of findings on glycoprotein acetyls was also consistent across the different information sources, but reached conventional significance levels for the history of depression diagnosis before pregnancy derived from HILMO and for the probable clinical depression reported during pregnancy.

While hsCRP and glycoprotein acetyl levels changed modestly during pregnancy, the associations between depression and these inflammatory biomarkers did not vary across pregnancy. The level of these inflammatory biomarkers has, however, been shown to be markedly higher among women who are than who are not pregnant (Wang *et al.*, 2016). In line, another study has reported that in pregnant women the mean hsCRP levels were above 10 mg/L at 10.6 gestational weeks (Berggren *et al.*, 2015), and yet another study has reported that over 50% of non-pregnant 31-year-old women have hsCRP values below 1.0 mg/L (Liukkonen *et al.*, 2011).

Our findings associating depression with higher inflammation among pregnant women correspond with meta-analytic findings from the general population showing longitudinal associations between depression and higher hsCRP and IL-6 levels (Valkanova *et al.*, 2013). Furthermore, in our study, the degree of inflammation related to depression was of comparable magnitude to the inflammation associated with early pregnancy overweight, gestational diabetes, and pre-eclampsia. Only the effects of early pregnancy obesity exceeded the degree of depression-related inflammation during pregnancy. In raw units, mean differences in hsCRP levels between women with and without depression diagnosis before pregnancy and with and without probable clinical depression during pregnancy were between 1.02 and 4.11 mg/L. This magnitude of inflammation is comparable to the degree of inflammation that has been suggested to increase cardiovascular disease risk moderately in the general population (Li *et al.*, 2017). These findings suggest that depression is associated with a higher proinflammatory state during pregnancy, bearing at least moderate clinical relevance to maternal health and possibly fetal development. To our knowledge, our prospective study is the largest on this topic in sample size thus far, and the first to show such associations using the information on depression derived from different sources and three consecutive stages during pregnancy.

The associations between the different depression measures with hsCRP and glycoprotein acetyls were independent of age, education, diabetes, and hypertensive pregnancy disorders. However, early pregnancy BMI accounted for and mediated the effects of depression diagnosis before pregnancy and depressive symptoms during pregnancy on inflammation. The mediation via BMI is not surprising, since early pregnancy overweight/obesity and antenatal depression are highly interrelated (Molyneaux *et al.*, 2014; Kumpulainen *et al.*, 2018). Nevertheless, since depression and obesity show continuity across time (Simmonds *et al.*, 2016; Kumpulainen *et al.*, 2018), and the depression-BMI-association is bi-directional (Luppino *et al.*, 2010), we cannot disentangle whether overweight/obesity preceded depression, or *vice versa*. Therefore, the mediation findings must be interpreted with caution.

We also found that depressive symptoms during pregnancy added to the inflammatory effects of obesity: among obese women, who had already approximately 1 S.D. higher hsCRP levels

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Table 2. Associations of a history of depression diagnosis before pregnancy derived from the Care Register for Healthcare (HILMO) and self-reports, and depressive symptoms and probable clinical depression reported during pregnancy with high-sensitivity C-Reactive protein and glycoprotein acetyls across the three measurement points during pregnancy

	Model 1			Model 2			Model 3		
	Estimate in S.D. units[a]	95% CI	*p*	Estimate in S.D. units[a]	95% CI	*p*	Estimate in S.D. units[a]	95% CI	*p*
High-sensitivity C-reactive protein (S.D. units) (outcome)									
History of depression diagnosis before pregnancy (yes *v.* no)									
From HILMO	0.69	0.26–1.11	0.002	0.50	0.08–0.92	0.02	0.16	−0.21 to 0.53	0.40
From self-reports	0.56	0.17–0.94	0.005	0.47	0.10–0.85	0.01	0.28	−0.05 to 0.60	0.09
Depressive symptoms during pregnancy									
Continuous score (S.D. units)	0.06	0.00–0.13	0.05	0.06	0.00–0.13	0.05	0.05	−0.01 to 0.11	0.14
Binary score (continuous score⩾16, probable clinical depression *v.* continuous score<16, no probable clinical depression)	0.28	0.03–0.53	0.03	0.28	0.04–0.52	0.02	0.20	−0.01 to 0.42	0.06
Glycoprotein acetyls (S.D. units) (outcome)									
History of depression diagnosis before pregnancy (yes *v.* no)									
From HILMO	0.52	0.12–0.93	0.01	0.42	0.01–0.84	0.04	0.04	−0.32 to 0.39	0.84
From self-reports	0.30	−0.06 to 0.66	0.10	0.24	−0.11 to 0.60	0.18	0.04	−0.26 to 0.34	0.78
Depressive symptoms during pregnancy									
Continuous score (S.D. units)	0.05	−0.01 to 0.11	0.10	0.05	−0.01 to 0.11	0.10	0.04	−0.02 to 0.09	0.23
Binary score (continuous score⩾16, probable clinical depression *v.* continuous score<16, no probable clinical depression)	0.25	0.02–0.46	0.04	0.25	0.02–0.48	0.03	0.19	−0.008 to 0.38	0.06

Model 1 is unadjusted for covariates but includes the gestational week when blood was sampled as a within-person time-varying predictor, Model 2 is Model 1 + age and education, Model 3 is Model 2 + body mass index in early pregnancy [categorized as normal weight (<25 kg/m^2), overweight (25–29.99 kg/m^2) and obese (⩾30 kg/m^2)].

[a]Estimates and 95% confidence intervals (95% CI) reflect differences between those with and without a history of depression diagnosis before pregnancy or with and without probable clinical depression during pregnancy in high-sensitivity C-reactive protein (hsCRP) and glycoprotein acetyls in standard deviation (S.D.) units or change in S.D. units in hsCRP and glycoprotein acetyls per S.D. unit change in the continuous depressive symptom scores during pregnancy.

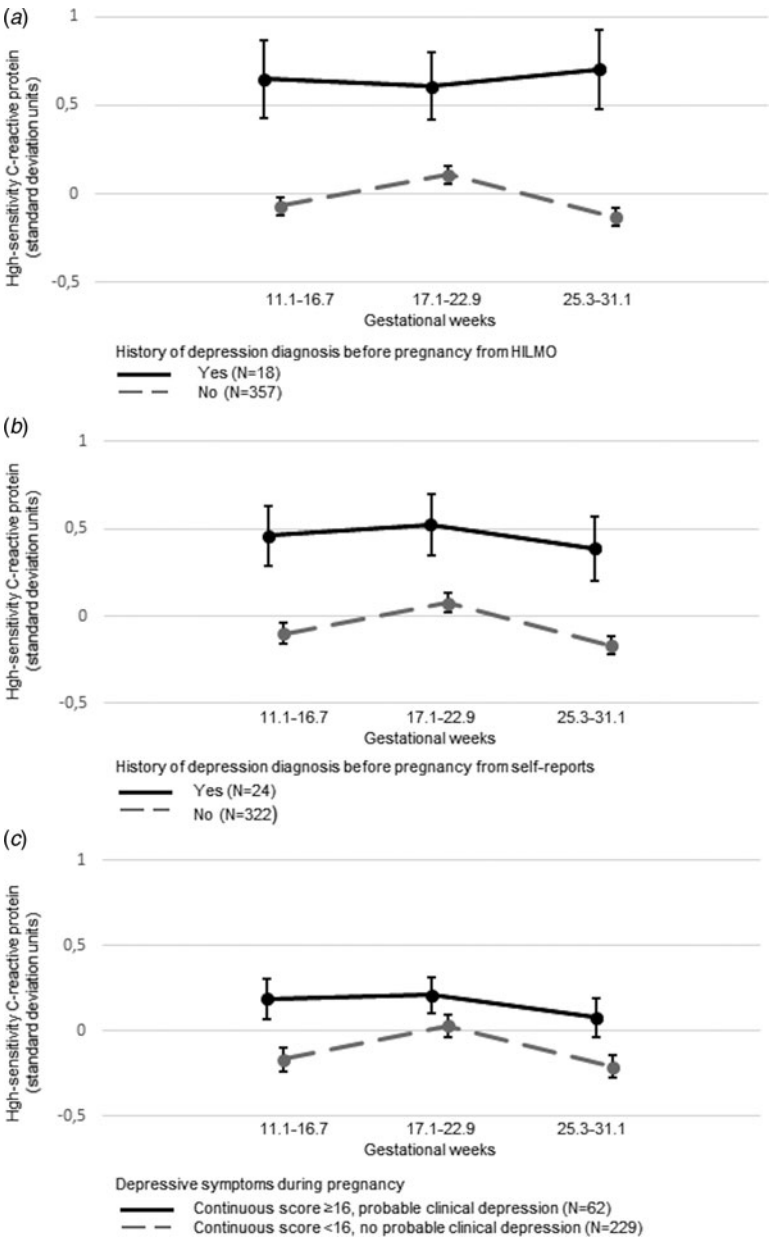
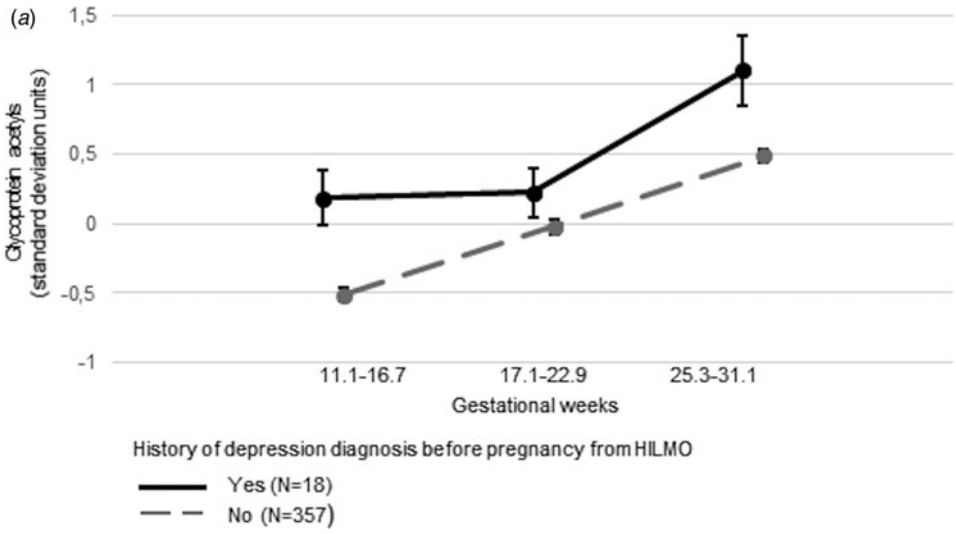


Fig. 1. Associations between history of depression diagnosis before pregnancy from the Care Register for Healthcare (HILMO) (panel A; $p = 0.37$ for interaction with gestational week at blood sampling) and from self-reports (panel B; $p = 0.99$ for interaction with gestational week at blood sampling) and probable clinical depression during pregnancy (panel C; $p = 0.62$ for interaction with gestational week at blood sampling) and high-sensitivity C-reactive protein across the three measurement points during pregnancy.

throughout pregnancy, hsCRP increased further by 0.19 S.D. by each S.D. increase in depressive symptoms during pregnancy. In overweight and normal weight women, this was not true. Based on the nature of the association we found between BMI and hsCRP, we speculate that the strong linear association between BMI and hsCRP between 20 and 30 kg/m^2 leaves no room for depression to independently predict hsCRP in normal weight and overweight women. However, our data suggest that in obese women hsCRP reaches a ceiling: at 30 kg/m^2 and above hsCRP levels plateau, remain consistently high, no longer increasing with increasing BMI. This leaves room for the effects of depressive symptoms, which increase inflammation in obese women even further. Corresponding interactions between obesity and depression on inflammation have also been reported in non-pregnant populations (Ladwig *et al.*, 2003), but our findings are inconsistent with findings from one study of pregnant women that were ethnically diverse from our sample (Cassidy-Bushrow *et al.*, 2012).

Obesity is a well-known proinflammatory state (Choi *et al.*, 2013; Pantham *et al.*, 2015) with the perturbation of intestinal microbiota and changes in intestinal permeability being potential triggers of inflammation (Cox *et al.*, 2015). The secretion of inflammatory cytokines from adipose tissue leads to overexpression of pro-inflammatory cytokines (Hotamisligil, 2006). Obesity indeed mediated most effects of depression on inflammation in our study. However, since inflammation levels increased even further in obese women with higher depressive symptoms during pregnancy, also other factors associated with both depression and inflammation may have contributed to our findings. Genetics and epigenetics and their interactions may contribute, since depression has been associated with both the single-nucleotide polymorphisms and expression of genes regulating inflammatory function (Barnes *et al.*, 2017; Mahajan *et al.*, 2018). These factors may also contribute to the interactions between obesity and depression on inflammation, since evidence suggests shared genetic origins of obesity and depression (Wray

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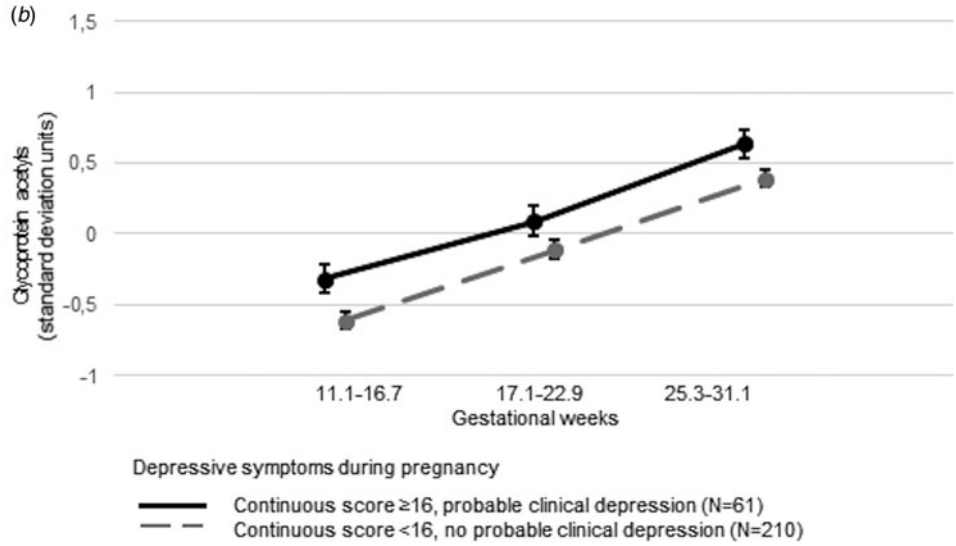


Fig. 2. Associations between (1) history of depression diagnosis before pregnancy from the Care Register for Healthcare (HILMO) (panel A; $p = 0.60$ for interaction with gestational week at blood sampling) and (2) probable clinical depression during pregnancy (panel C; $p = 0.70$ for interaction with gestational week at blood sampling) and glycoprotein acetyls across the three measurement points during pregnancy.

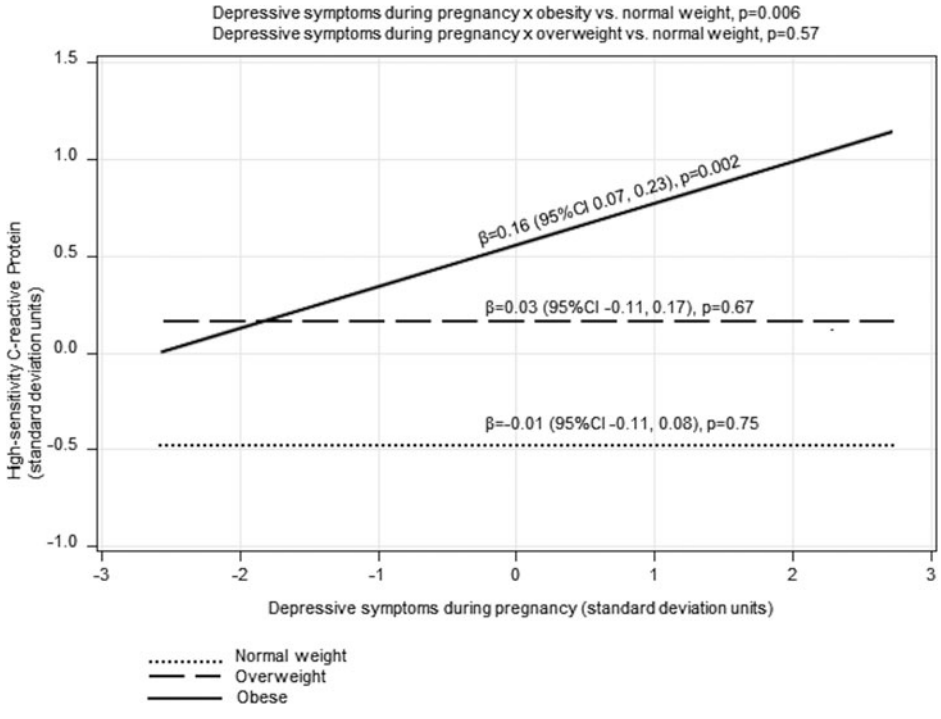


Fig. 3. Associations between depressive symptoms during pregnancy and high-sensitivity C-reactive protein during pregnancy in women who in early pregnancy were normal weight [body mass index (BMI) < 25 kg/m^2), overweight (BMI 25–29.99 kg/m^2), or obese (BMI ⩾ 30 kg/m^2).

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et al., 2018). Hypothalamic–pituitary–adrenal (HPA) axis activity may also be involved. Glucocorticoids regulate inflammation by exacerbating the secretion of pro-inflammatory cytokines and acute phase proteins (Pariante, 2017) and have both pro- and anti-inflammatory effects in the brain (Walker and Spencer, 2018). Glucocorticoid functioning is also closely associated with depression and obesity (Stetler and Miller, 2011; Boggero *et al.*, 2017; Milaneschi *et al.*, 2019). Findings in smaller subsamples of the PREDO study suggest that depressive symptoms during pregnancy are associated with placental mRNA level changes in genes regulating HPA axis function (Raikkonen *et al.*, 2015; Reynolds *et al.*, 2015). The gut microbiota-brain axis functioning is also intertwined with inflammatory processes, and changes in its function are associated with depression (Alam *et al.*, 2017). Furthermore, depression, obesity and inflammation are each also associated with poorer nutrition, insufficient sleep, physical inactivity, and substance use (Lai *et al.*, 2014; Lai *et al.*, 2015; Ironson *et al.*, 2018; Stubbs *et al.*, 2018; Milaneschi *et al.*, 2019). A large Mendelian randomization study found that while CRP concentrations were associated with depression, genetic variation regulating CRP was not (Wium-Andersen *et al.*, 2014). This finding argues against a causal pathway from inflammation to depression and suggests that a common 'residual confounding' factor may possibly underlie the associations found. Hence, the proinflammatory effects of depression and obesity likely stem from multiple contributory factors. Our findings emphasize the need for further studies on these pathways specifically during pregnancy.

Strengths of our study include a large sample size compared to the previous studies, which often included less than 100 participants. We had data on depression from different sources and hsCRP and glycoprotein acetyls were measured at three consecutive stages during pregnancy, which no previous study has had. Furthermore, many previous studies on depression and inflammation during pregnancy utilized very rapidly degrading inflammatory markers, most commonly IL-6. HsCRP is an acute-phase protein with a longer half-life than IL-6 (Wirtz *et al.*, 2000) and glycoprotein acetyls display even slower kinetics than hsCRP. Thus, we were able to obtain more stable estimates of the participants' inflammatory state across pregnancy (Ritchie *et al.*, 2015). While the increases in hsCRP and glycoprotein acetyls in pregnancy (Wang *et al.*, 2016) suggest they are suitable markers of antenatal inflammation, having data also on other inflammatory biomarkers would have given further insight on the associations of depression and antenatal inflammation. Since glycoprotein acetylation is a mix of a range of proteins (Ritchie *et al.*, 2015), we would also have benefited from data on the specific protein levels. It would also have been informative to have cortisol data to indicate HPA axis activity and other biomarkers that are triggered by inflammation.

The study limitations also include that our sample comprised women at risk for pre-eclampsia and IUGR and that blood samples were available only for a subsample. Furthermore, although diagnostic data from HILMO were available for 99.5% of women with three blood samples, self-reported diagnostic data were available for 91.6% and depressive symptoms were reported by 77.8% of the women. The analytic samples comprised women who were younger and less often self-reported a history of depression diagnoses before pregnancy. These factors limit generalizations of our findings to other samples.

In conclusion, our study showed that depression is associated with a proinflammatory state during pregnancy. These associations are mediated by early pregnancy BMI, and depressive symptoms during pregnancy aggravate the inflammation related to obesity.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719001909.

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Conflict of interest. None.

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