Title page

Title: Maternal early pregnancy obesity and depressive symptoms during and after pregnancy

Running title: Early pregnancy obesity and depressive symptoms

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Abstract

Background: Previous studies have linked maternal obesity with depressive symptoms during and after pregnancy. It remains unknown whether obesity associates with consistently elevated depressive symptoms throughout pregnancy, predicts symptoms postpartum when accounting for antenatal symptoms, and if co-morbid hypertensive and diabetic disorders add to these associations. We addressed these questions in a sample of Finnish women whom we followed during and after pregnancy.

Methods: Early pregnancy body mass index, derived from the Finnish Medical Birth Register and hospital records in 3234 PREDO study participants, was categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.99 kg/m^2), overweight (25-29.99kg/m^2) and obese (≥30 kg/m^2) groups. The women completed the Center for Epidemiological Studies Depression Scale biweekly during pregnancy, and at 2.4 (SD=1.2) and/or 28.2 (SD=4.2) weeks after pregnancy.

Results: In comparison to normal weight women, overweight and obese women reported higher levels of depressive symptoms and had higher odds of clinically significant depressive symptoms during (23% and 43%, respectively) and after pregnancy (22% and 36%, respectively). Underweight women had 68% higher odds of clinically significant depressive symptoms after pregnancy. Overweight and obesity also predicted higher depressive symptoms after pregnancy in women not reporting clinically relevant symptomatology during pregnancy. Hypertensive and diabetic disorders did not explain or add to these associations.

Conclusions: Maternal early pregnancy overweight and obesity and depressive symptoms during and after pregnancy are associated. Mental health promotion should be included as an integral part

of lifestyle interventions in early pregnancy obesity and extended to benefit also overweight and underweight women.

Keywords: early pregnancy body mass index; antenatal depression; postpartum depression; pregnancy disorders

Introduction

In 2014, 14.9% of the world's adult population of women were obese (body mass index [BMI] ≥30 kg/m^2), including women of reproductive age (NCD-RisC 2016). The global prevalence of obesity is expected to increase to 21% by 2025 (NCD-RisC 2016). Convincing evidence shows that maternal pre-pregnancy/early pregnancy obesity poses multiple health risks during pregnancy and at delivery, including hypertension-spectrum pregnancy disorders (O'Brien *et al.* 2003; Rahman *et al.* 2015), and gestational diabetes (Torloni *et al.* 2009).

Growing evidence suggests that maternal obesity not only increases the risk for physical health hazards, but is also associated with poorer mental health during and after pregnancy. According to one meta-analysis, obese women had a 43% and 21% higher odds for reporting clinically relevant symptoms of depression during pregnancy than normal weight (BMI 18.5-24.99 kg/m^2) or overweight (25-29.99 kg/m^2) women, respectively (Molyneaux *et al.* 2014). The meta-analysis also showed that obese women had a 30% and 20% higher odds of reporting clinically relevant symptoms of depression after pregnancy than normal and overweight women, respectively (Molyneaux *et al.* 2014).

In agreement with this meta-analysis, findings from a more recent study of over 7000 US women reported that in comparison to normal weight women overweight women had 31% and obese women had 65% higher odds for reporting clinically relevant depressive symptoms during pregnancy (Venkatesh *et al.* 2016). In another study of over 13000 UK women, obese, but not overweight women, had 39% higher odds than had normal weight women for reporting clinically relevant depressive symptoms during pregnancy (Molyneaux *et al.* 2016a). Yet, another study of over 5000 women from Australia, Ireland, New Zealand and UK reported that only in women with high socio-economic status (SES), obese, but not overweight women, had 116% higher odds than had than normal weight women for reporting clinically relevant depressive symptoms during

pregnancy (Molyneaux *et al.* 2016b). This study did not find significant differences in depressive symptoms between obese, overweight and normal weight women in the low SES group or when high and low SES groups were combined (Molyneaux *et al.* 2016b). In a series of smaller scale studies from different countries and ethnic groups the pattern of findings is more mixed with some reporting associations between overweight and/or obesity and depressive symptoms (Bogaerts *et al.* 2013; Dotlic *et al.* 2014; Mina *et al.* 2015; Nagl *et al.* 2016; Ruhstaller *et al.* 2017; Salehi-Pourmehr *et al.* 2017), others reporting null associations (Ertel *et al.* 2015; Sahrakorpi *et al.* 2017) or associations with even lower levels of depressive symptoms during pregnancy (Ertel *et al.* 2015). In the more recent studies that have focused on depressive symptoms after pregnancy the pattern of findings is also mixed with other studies reporting associations between overweight and/or obesity and depressive symptoms (Mina *et al.* 2015; Salehi-Pourmehr *et al.* 2017), while other studies report that they are unrelated (Ruyak *et al.* 2016; Sahrakorpi *et al.* 2017).

However, significant caveats in the previous studies hinder conclusions about validity of the findings. None of the studies measured depressive symptoms on multiple occasions throughout pregnancy. In only seven (Rallis *et al.* 2007; Ban *et al.* 2012; Christian *et al.* 2012; Ertel *et al.* 2012; Van Poppel *et al.* 2012; Mina *et al.* 2015; Ruyak *et al.* 2016) of the studies on postpartum depressive symptoms, were depressive symptoms during pregnancy taken into account. As over 40% of women with clinically relevant depressive symptoms during pregnancy continue to suffer from these symptoms after pregnancy (Evans *et al.* 2012), it remains unclear if the effects of obesity on postpartum depressive symptoms reflect continuity of symptoms during pregnancy or if obesity is predictive of the onset of symptomatology after pregnancy. Further, the often co-morbid hypertension-spectrum pregnancy disorders and/or gestational diabetes were taken into account in only one (Mina *et al.* 2015) of the studies on symptoms during pregnancy and in two of the studies on postpartum symptoms (Sundaram *et al.* 2012; Mina *et al.* 2015). Hence, it remains unknown if

the associations between pre-pregnancy/early pregnancy obesity and depressive symptoms are explained by these hypertensive and diabetic disorders. Finally, in only four (Fowles *et al.* 2011; Lukose *et al.* 2014; Mina *et al.* 2015; Molyneaux *et al.* 2016b) studies out of the 40 focusing on depressive symptoms during pregnancy, and in only one (Mina *et al.* 2015) of the studies out of the 20 focusing on postpartum depressive symptoms was weight measured (in two studies weight was measured in a subsample (Xuto *et al.* 2012; Salehi-Pourmehr *et al.* 2017)); in the other studies it was self-reported, even years after delivery, which carries bias (Stommel & Schoenborn 2009) and may result in misclassification of women into different BMI categories.

To address these critical knowledge gaps in the literature, we tested in a large sample of pregnant Finnish women if early pregnancy BMI derived from the Finnish Medical Birth Register (MBR) (Gissler & Haukka 2004) was associated with depressive symptoms reported by the mother biweekly during pregnancy from the 12^{th} until the 39^{th} gestational week or delivery, and twice at 2.4 and 28.2 weeks after delivery. We also tested if maternal early pregnancy BMI predicted clinically relevant postpartum-onset depressive symptoms. Finally, we tested if any of these associations were driven by maternal hypertensive or diabetic pre-pregnancy or pregnancy disorders, or if these disorders added to the effects of maternal early pregnancy BMI.

Methods

Participants

The participants were from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study (Girchenko *et al.* 2017). Figure 1 presents a flow chart of the current study participants and sample attrition. The PREDO study enrolled 4785 pregnant women, of whom 4777 (8 miscarriages or stillbirths according to child birth date data from hospital records or MBR) gave birth to a singleton live child between 2006 and 2010. Of note, of the total number of 5332

enrolled participants who consented to participate, the 537 who withdrew participation or could not be traced, and hence were not included in the PREDO study sample, may include miscarriages or stillbirths not identified via hospital records or the MBR owing to missing child birth date data.

The women were recruited to the study when they visited antenatal clinics at one of the ten study hospitals in Southern and Eastern Finland for their first ultrasound screen between 12+0 and 13+6 weeks+days of gestation. The PREDO study comprises two subsamples. First, a community-based subsample who were enrolled regardless of their risk factor status for preeclampsia and intrauterine growth restriction. They comprise 3698 women who gave birth to a live child (among the 3702 women in this subsample there were 4 miscarriages or stillbirths). Second, to increase the number of women with pre-eclampsia and intrauterine growth restriction in our sample, we recruited a subsample with a known risk factor status for pre-eclampsia and intrauterine growth restriction, including obesity; they comprised 1079 women who gave birth to a live child (among the 1083 women in this subsample there were 4 miscarriages or stillbirths). As shown in Figure 1, of the 4745 women who gave birth to a live-born infant and had data on early pregnancy BMI and pre-pregnancy and pregnancy disorders, data on depressive symptoms during pregnancy were available in 3372 (71.1%). Of them, 3234 (95.9%) had data on depressive symptoms both during pregnancy and at an average of 2.4 (SD=1.2) and/or 28.2 (SD=4.2) weeks after pregnancy. This sample of 3234 women formed the analytic sample of the current study.

The women in the analytic sample were older than the participating women with a live-born infant who did not have data on depressive symptoms both during and after pregnancy ($p<0.001$), were more often primiparous ($p<0.001$) and had less often preeclampsia ($p<0.05$). The groups did not differ in the other maternal, obstetric or perinatal characteristics (all p-values>0.11).

The study protocol was approved by the Ethics Committee of Obstetrics and Gynaecology and Children and Psychiatry of the Helsinki and Uusimaa Hospital District and by the participating hospitals. All participants provided written informed consent.

Measures

Maternal early pregnancy BMI and hypertensive and diabetic pre-pregnancy and pregnancy disorders

Data were extracted from the Finnish MBR (Gissler & Haukka 2004) and/or the maternity care cards and hospital records. Each individual diagnosis was further verified by a clinical jury for the subsample recruited based on their known risk factor status of preeclampsia and intrauterine growth restriction (Figure 1).

Early pregnancy BMI was calculated from weight and height measured by a nurse at the first visit to the antenatal clinic, in our sample on average 8+4 (SD=1+3) weeks+days of gestation when pregnancy weight gain is still minimal, and categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.99 kg/m^2), overweight (25-29.99kg/m^2), and obese (≥30 kg/m^2) groups according to the World Health Organization criteria (World Health Organization 2000).

Gestational diabetes was defined as fasting, 1h or 2h plasma glucose during a 75g oral glucose tolerance test ≥5.1, 10.0 or 8.5 mmol/L, respectively; pre-eclampsia as blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic in two consecutive measurements and proteinuria ≥0.3 g/24 hours; gestational hypertension as blood pressure ≥hypertension 140 mmHg systolic and/or ≥90 mmHg diastolic in a women who was normotensive before 20 weeks of gestation.

We also identified women with Type 1 diabetes (none of the women had type 2 diabetes) and with chronic hypertension defined as blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic or medication for hypertension before 20 weeks of gestation.

Depressive symptoms during and after pregnancy

The Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977) was completed by the women biweekly up to 14 times throughout pregnancy starting from 12+0-13+6 gestation weeks+days until 38+0-39+6 gestation weeks+days or delivery, and at 2.4 (SD=1.2) and/or 28.2 (SD=4.2) weeks after pregnancy. The 20 CES-D questions were rated on a scale from none (0) to all the time (3). Higher scores indicate more depressive symptoms during the past week and a sumscore of ≥16 indicates clinically relevant depressive symptoms (Radloff 1977; Vilagut *et al.* 2016). The CES-D has been used extensively and validated in pregnant populations (Maloni *et al.* 2005; Nast *et al.* 2013). In our sample, the CES-D (Cronbach`s α=.88 to .92 in the 14 biweekly measurement points during pregnancy and the two measurement points after pregnancy) showed high internal consistency (Lahti *et al.* 2017).

Covariates and confounders

These included maternal age at delivery (years), smoking during pregnancy (did not smoke/quit during first trimester/smoked throughout pregnancy), parity (primiparous/multiparous), child's gestational age (weeks), birth weight (g) and sex (girls/boy) with data extracted from medical records and/or MBR; maternal alcohol use during pregnancy (yes/no), maternal leisure-time physical activity (PA) during pregnancy (categorized into 3 groups: not at all/less than once a month/1 to 2 times per month; approximately once a week/2 to 3 times per week; 4 to 5 times per week/approximately every day), and education level (basic/secondary vs. tertiary) were self-reported in early pregnancy.

Statistical analysis

First, by using linear mixed and generalized mixed model regression analyses, we tested if depressive symptoms levels across the biweekly measurements from 12+0 to 39+6 weeks+days of gestation/delivery varied between overweight, obese and underweight women in comparison to normal weight women. We also tested if changes in depressive symptoms levels across the biweekly measurements during pregnancy varied between these groups. Associations with depressive symptoms were tested in two separate models with depressive symptoms treated both as continuous (biweekly scores were square root transformed to improve linear model fitting and then transformed to SD units using the mean of the biweekly CES-D scores across 12-39 gestational weeks to facilitate interpretation but still retaining the within time-variation), and as dichotomized at the clinical cutoff ≥ 16. Early pregnancy BMI groups (using normal weight as the comparison group) and gestational week (values compressed to even weeks) main effects were entered first into the regression equation as between-person time invariant and within-person time-varying predictors, respectively. We thereafter added BMI group x gestation week interaction terms into the model. Random effects were allowed in the model to account for individual differences in the intercept and in the gestational week -related slopes (this model provided the best model fit based on Akaike Information Criterion in comparison to models defining random intercept or random slope only). We specified unstructured covariance and autoregressive (AR1) error covariance matrices for the linear mixed models with the continuous depressive symptoms as the outcome, and unstructured covariance matrix and binomial reference distribution for the generalized linear mixed models with clinically relevant depressive symptoms dichotomized variables as the outcome. We repeated the analyses by replacing depressive symptoms during pregnancy and gestational week with depressive symptoms after pregnancy and the time point (expressed in a number of weeks after pregnancy), when reporting these symptoms postpartum, respectively. We carried out the analyses

on depressive symptoms after pregnancy in all women in the analytic sample, and then we excluded women who reported clinically relevant depressive symptoms during pregnancy (mean of CES-D scores across 12-39 gestational weeks ≥ 16) to study postpartum-onset clinically relevant symptomatology.

We then tested if maternal hypertensive and diabetic pre-pregnancy and pregnancy disorders were associated with maternal depressive symptoms during and after pregnancy in models where early pregnancy BMI variables were replaced by disorders (no disorders was used as the referent). To study if any BMI effects were confounded by maternal hypertensive and diabetic pre-pregnancy and pregnancy disorders, we reran the early pregnancy BMI models by adjusting for having any vs. no disorders. Finally, we tested if the effects of hypertensive and diabetic pre-pregnancy and pregnancy disorders added to the effects of maternal early pregnancy BMI, by testing the effects of having any vs. no hypertensive and diabetic pre-pregnancy and pregnancy disorders on depressive symptoms during and after pregnancy in the different BMI groups.

We present all findings as adjusted for the covariates and show unstandardized estimates representing mean differences in depressive symptoms in SD units and odds ratios for having depressive symptoms scores above the clinical cutoff and their 95% Confidence Intervals. All p-values are two-tailed.

Results

Table 1 shows sample characteristics according to maternal BMI groups for the analytic sample of 3234 women. The median number of depressive symptoms ratings during pregnancy was 13 (interquartile range 12-14); 79.6% of the women had two or less missing depressive symptoms ratings during pregnancy. Of the 3234 women, 2382 (73.7%) had depressive symptoms data at both

follow-ups at 2.4 and 28.2 weeks after pregnancy, and 852 (22.3%) had depressive symptoms data at either follow-up. Supplemental Figure 1 shows the number of women with missing data on depressive symptoms during and after pregnancy

Maternal depressive symptoms during pregnancy (intraclass correlations 0.46 to 0.80, all p-values < 0.0001) and after pregnancy (intraclass correlation 0.53, p< 0.0001) were significantly correlated. The mean of the depressive symptoms sumscores across 12-39 gestational weeks was significantly correlated with the mean of the two or the only sumscore after pregnancy (intraclass correlation 0.66, p < 0.0001). Of the 3234 women with depressive symptoms data both during and after pregnancy, 677 (20.9%) had clinically relevant symptoms during pregnancy and 620 (19.2%) had clinically relevant symptoms after pregnancy. Of the 677 women with clinically relevant symptoms during pregnancy, 361 (53.3% of 677) continued to have clinically relevant symptoms after pregnancy. Of the 2557 (79.1%) women who did not have clinically relevant depression symptoms during pregnancy, 259 (10.1% of 2557) had clinically relevant symptoms after pregnancy.

Maternal early pregnancy BMI groups and depressive symptoms during pregnancy

In the model adjusted for maternal age at delivery, education, parity, physical activity, smoking and alcohol use during pregnancy as between person time-invariant covariates and gestation week as a within-person time-varying covariate, obese and overweight women, in comparison to the normal weight women reported higher levels of depressive symptoms during pregnancy (Table 2, first column). Figure 2 (Panel A) shows that the levels of depressive symptoms remained stably higher throughout pregnancy in the overweight and obese groups, and there were no significant BMI group x gestation week interactions. None of these group differences in depressive symptoms levels changed when we made further adjustments for maternal hypertensive or diabetic pre-pregnancy or pregnancy disorders (all p-values<0.002). When maternal depressive symptoms during pregnancy

were dichotomized at the clinical cutoff, maternal early pregnancy overweight was associated with 1.23-fold (95% CI 1.02, 1.48, p-values=0.03 after all covariate adjustments) and maternal obesity with 1.43-fold (1.15, 1.77, p-values<0.001 after all covariate adjustments) odds for clinically relevant depressive symptoms during pregnancy compared to normal weight women. Figure 2 (Panel B) shows that the proportion of women with clinically relevant depressive symptoms was consistently higher throughout pregnancy in the overweight and obese groups, in comparison to normal weight group, and there were no significant BMI group x gestation week interactions. Underweight women did not differ significantly from the normal weight women in depressive symptoms during pregnancy (Table 2, first column; Figure 2 Panels A and B).

These group differences did not change when we excluded women who reported a history of physician-diagnosed depression before pregnancy or those who were enrolled to the study based on their known risk-factor status for pre-eclampsia or intrauterine growth restriction (p-values<0.01).

Maternal early pregnancy BMI groups and maternal depressive symptoms after pregnancy

In the model adjusted for maternal age at delivery, education, parity, physical activity, smoking and alcohol use during pregnancy, child's gestation length, birth weight and sex as between person time-invariant covariates and time (2.4 and 28.2 weeks after pregnancy) as a within-person time-varying covariate, obese and overweight women in comparison to the normal weight women reported higher levels of depressive symptoms after pregnancy (Table 2, middle column). Figure 2 (Panel B) shows that these group differences remained stable after pregnancy and there were no BMI group x time interactions. None of these group differences in depressive symptoms levels changed when we made further adjustments for maternal hypertensive or diabetic pre-pregnancy or pregnancy disorders (p-values<0.0003). When depressive symptoms were dichotomized at the clinical cutoff, overweight women had 1.22-fold (1.00, 1.49, p-values=0.05 after all covariate

adjustments) and obese women had 1.36-fold (1.07, 1.71, p-values=0.01 after all covariate adjustments) odds for reporting clinically relevant depressive symptoms after pregnancy compared to normal weight women. The odds to report clinically relevant depressive symptoms after pregnancy was 1.68-fold (1.13, 2.53, p-values=0.01 after all covariate adjustments) for the underweight women compared to normal weight women. Figure 2 (Panel B) shows that the proportion of women with clinically relevant depression symptoms after pregnancy remained stably higher for overweight, obese and underweight women in comparison to normal weight women and there were no BMI group x time interactions.

Table 2 (third column) shows that the depressive symptoms levels were also higher for overweight and obese women in comparison to normal weight women, even when we excluded women who reported clinically relevant depressive symptoms during pregnancy from the analyses. In the women, who did not report clinically relevant depressive symptoms during pregnancy, overweight and obesity did not, however, predict clinically relevant depressive symptoms after pregnancy (p-values >0.45; data not shown).

These group differences did not either change when we excluded women who reported a history of physician-diagnosed depression before pregnancy or those who were enrolled to the study based on their known risk-factor status for pre-eclampsia and intrauterine growth restriction (p-values<0.03).

Maternal hypertensive and diabetic pre-pregnancy and pregnancy disorders and maternal depressive symptoms during and after pregnancy

Supplemental Table 1 shows that maternal hypertensive and diabetic pre-pregnancy and pregnancy disorders were not significantly associated with depressive symptoms during or after pregnancy when we made adjustments for maternal early pregnancy BMI (p-values>0.23). There were not

either any significant differences in depressive symptoms during or after pregnancy between women with and without any hypertensive and diabetic pre-pregnancy and pregnancy disorders when these differences were tested separately in the normal weight, underweight, overweight or obese groups (Supplemental Table 2).

Discussion

Our study shows that maternal early pregnancy overweight and obesity are associated with consistently higher levels of depressive symptoms throughout pregnancy and consistently higher proportion and odds to report symptoms that are clinically relevant. Of the overweight and obese women nearly 23% and 27%, respectively, reported clinically relevant symptomatology during pregnancy, in comparison to 19% of normal weight women. The odds for clinically relevant symptomatology during pregnancy were 23% and 43% higher for overweight and obese women, respectively, in comparison to those who were normal weight.

Maternal early pregnancy overweight and obesity also increased the odds to report clinically relevant symptoms after pregnancy by 22% and 36%, respectively. Importantly, our study revealed that this risk was also increased for underweight women by 68%. While early pregnancy overweight and obesity were significantly associated with higher depressive symptoms levels also in women without clinically relevant depressive symptomatology during pregnancy, the associations with clinically relevant symptoms after pregnancy did not reach significance in this subgroup.

Our study also showed that maternal hypertensive and diabetic pre-pregnancy and pregnancy disorders did not explain any of the early pregnancy BMI effects. These disorders did not either add to the effects of maternal early pregnancy BMI. Rather, our study showed that any significant

associations between hypertensive and diabetic pre-pregnancy and pregnancy disorders were accounted for by the maternal early pregnancy BMI.

Our study has many strengths. Unlike in any of the previous studies, we measured depressive symptoms consecutively throughout and after pregnancy. Second, we studied the associations in a large sample of which a subset was chosen to increase the incidence of pre-eclampsia and intrauterine growth restriction resulting in an increased statistical power to test associations of early pregnancy BMI and hypertensive and diabetic pre-pregnancy and pregnancy disorders with repeatedly measured depressive symptoms. A related strength of our study is that early pregnancy weight and height were extracted from antenatal clinical measurements and pre-pregnancy and pregnancy disorders were derived from medical records and for a subset verified by a clinical jury. In only a handful of the previous studies have weight or height been measured (Fowles *et al.* 2011; Lukose *et al.* 2014; Mina *et al.* 2015; Molyneaux *et al.* 2016b) and in only one of the previous studies (Sundaram *et al.* 2012) have these pre-pregnancy and pregnancy disorders been taken into account. Finally, sample attrition during follow-up was minor, and we were able to account for a number of relevant covariates.

A major study limitation relates to not knowing what the biological mechanisms are that underpin these associations. These may relate to alterations in hypothalamic-pituitary-adrenocortical (HPA) axis activity and inflammatory markers that are related to maternal BMI (Lindsay & Nieman 2005; McEwan *et al.* 2009; Denison *et al.* 2010; Duthie & Reynolds 2013; Godfrey *et al.* 2017). Emerging data suggest that alterations in HPA-axis activity and inflammation may also be associated with maternal depressive symptoms or distress during pregnancy (Haeri *et al.* 2013; Shelton *et al.* 2014). While these same mechanisms may account for the associations with depressive symptoms after pregnancy (Brunton & Russell 2008; Anderson & Maes 2013; O'Hara &

McCabe 2013), it remains unknown what role do changes in glucocorticoids, estradiol and progesterone, that take place after parturition, play in these associations. And, what is the role of other factors implicated in obesity and depression, such as leptin, tryptophan and vitamin D (Anderson & Maes 2013).

Also genetic and epigenetic factors may underlie the associations between obesity and depression. Twin studies suggest that the genetic component of depression is partially shared with obesity (Afari *et al.* 2010; Jokela *et al.* 2016). According to a recent systematic review of genome-wide association and candidate gene studies pleiotropic genes, such as the *FTO* gene, may underlie (Amare *et al.* 2017), but findings are however, inconsistent (Walter *et al.* 2015). Also interactions between genotype, such as the *FTO* gene, depression and BMI have been reported (Clarke *et al.* 2015; Rivera *et al.* 2017). On the other hand, both depression (Osborne *et al.* 2016; Chen *et al.* 2017; Edvinsson *et al.* 2017) and BMI (Dick *et al.* 2014; Ligthart *et al.* 2016) have been associated with DNA methylation changes at specific genetic loci, including genes regulating inflammatory function.

Behavioral mechanisms may also be involved, including sleep problems and pain that may be aggravated in higher BMI pregnancies and that may induce more depressed feelings. In addition, unhealthy diet and low physical exercise may be involved (Nascimento *et al.* 2012; Jacka & Berk 2013). We lack data on the women's dietary patterns and our measure of physical activity was self-reported. Future studies will need to unravel if these mechanisms are involved. As the association between obesity and depression is suggested to be bi-directional (Luppino *et al.* 2010), we cannot rule out the possibility of reverse causality between BMI and depressive symptoms either.

Other study limitations relate to generalizability from our findings to other groups who are different from our sample. Because a subset of women with risk factors for preeclampsia and intrauterine growth restriction was recruited in our study, our sample has a higher proportion of obese women

and a higher prevalence of preeclampsia and gestational hypertension, compared to the general population of pregnant Finnish women (Girchenko *et al.* 2017). Further, even though the attrition in our sample was minor, it was selective: the women in the analytic sample were older, more often primiparous and less often had preeclampsia than participating women with a live-born infant without data on depressive symptoms both during and after pregnancy. Finally, although we were able to control for a number of potential covariates, we cannot entirely exclude the possibility of residual confounding.

To conclude, maternal early pregnancy overweight and obesity are associated with higher levels of and proportion and odds to report clinically relevant depressive symptoms during and after pregnancy. Early pregnancy underweight women also have higher risk of clinically significant depressive symptoms after pregnancy. Hypertensive and diabetic pre-pregnancy and pregnancy disorders do not explain or add to these associations. Our findings showing that obese and underweight women are vulnerable to depressive symptoms suggest mental health needs to be considered as part of routine antenatal care. Existing lifestyle interventions in pregnant overweight and obese women have focused on dietary and physical activity behavior change without considering maternal mental health (Poston *et al.* 2015). Our findings suggest that it would be beneficial to take into account the depressive symptoms of the obese women since depression might hinder the effectiveness of the interventions. This will not only benefit the health and wellbeing of women during and after pregnancy, but the offspring as well, as maternal early pregnancy underweight, overweight, obesity and depressive symptoms during and after pregnancy may increase the offspring's risk of adverse perinatal and physical health and neurodevelopmental (Reynolds *et al.* 2013; Rahman *et al.* 2015; Lahti *et al.* 2017) outcomes in later life.

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References

Afari N, Noonan C, Goldberg J, Roy-Byrne P, Schur E, Golnari G, Buchwald D (2010). Depression and obesity: Do shared genes explain the relationship? *Depression and Anxiety* **27**, 799–806.

Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT (2017). The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Translational Psychiatry* **7**, e1007.

Anderson G, Maes M (2013). Postpartum depression: psychoneuroimmunological underpinnings and treatment. *Neuropsychiatric Disease and Treatment* **Volume 9**, 277.

Ban L, Gibson JE, West J, Fiaschi L, Oates MR, Tata LJ (2012). Impact of socioeconomic deprivation on maternal perinatal mental illnesses presenting to UK general practice. *British Journal of General Practice* **62**, 671–678.

Bogaerts AF, Devlieger R, Nuyts E, Witters I, Gyselaers W, Guelinckx I, Van den Bergh BR (2013). Anxiety and depressed mood in obese pregnant women: a prospective controlled cohort study. *Obesity facts* **6**, 152–164.

Brunton PJ, Russell J a (2008). The expectant brain: adapting for motherhood. *Nature reviews. Neuroscience* **9**, 11–25.

Chen D, Meng L, Pei F, Zheng Y, Leng J (2017). *A review of DNA methylation in depression*. *Journal of Clinical Neuroscience*

Christian LM, Iams JD, Porter K, Glaser R (2012). Epstein-Barr virus reactivation during pregnancy and postpartum: effects of race and racial discrimination. *Brain Behav Immun* **26**, 1280–1287.

Clarke T-K, Hall LS, Fernandez-Pujals AM, MacIntyre DJ, Thomson P, Hayward C, Smith

BH, Padmanabhan S, Hocking LJ, Deary IJ, Porteous DJ, McIntosh AM (2015). Major depressive disorder and current psychological distress moderate the effect of polygenic risk for obesity on body mass index. *Translational Psychiatry* **5**, e592.

Denison FC, Roberts KA, Barr SM, Norman JE (2010). Obesity, pregnancy, inflammation, and vascular function. *Reproduction* **140**, 373–385.

Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, Meduri E, Morange PE, Gagnon F, Grallert H, Waldenberger M, Peters A, Erdmann J, Hengstenberg C, Cambien F, Goodall AH, Ouwehand WH, Schunkert H, Thompson JR, Spector TD, Gieger C, Trégouët DA, Deloukas P, Samani NJ (2014). DNA methylation and body-mass index: A genome-wide analysis. *The Lancet* **383**, 1990–1998.

Dotlic J, Terzic M, Babic D, Vasiljevic N, Janosevic S, Janosevic L, Pekmezovic T (2014). The Influence of Body Mass Index on the Perceived Quality of Life during Pregnancy. *Applied Research in Quality of Life* **9**, 387–399.

Duthie L, Reynolds RM (2013). Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: Influences on maternal and fetal outcomes. *Neuroendocrinology* **98**, 106–115.

Edvinsson Å, Bränn E, Hellgren C, Freyhult E, White R, Kamali-Moghaddam M, Olivier J, Bergquist J, Boström AE, Schiöth HB, Skalkidou A, Cunningham JL, Sundström-Poromaa I (2017). Lower inflammatory markers in women with antenatal depression brings the M1/M2 balance into focus from a new direction. *Psychoneuroendocrinology* **80**, 15–25.

Ertel KA, Kleinman K, Van Rossem L, Sagiv S, Tiemeier H, Hofman A, Jaddoe VW V, Raat H (2012). Maternal perinatal depression is not independently associated with child body mass index in the generation r study: Methods and missing data matter. *Journal of Clinical Epidemiology* **65**, 1300–1309.

Ertel KA, Silveira ML, Pekow PS, Dole N, Markenson G, Chasan-Taber L (2015). Prepregnancy body mass index, gestational weight gain, and elevated depressive symptoms in a Hispanic cohort. *Health Psychology* **34**, 274–278.

Evans J, Melotti R, Heron J, Ramchandani P, Wiles N, Murray L, Stein A (2012). The timing of maternal depressive symptoms and child cognitive development: A longitudinal study. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **53**, 632–640.

Fowles ER, Timmerman GM, Bryant M, Kim S (2011). Eating at fast-food restaurants and dietary quality in low-income pregnant women. *Western journal of nursing research* **33**, 630–651.

Girchenko P, Lahti M, Tuovinen S, Savolainen K, Lahti J, Binder EB, Reynolds RM, Entringer S, Buss C, Wadhwa PD, Hämäläinen E, Kajantie E, Pesonen A-K, Villa PM, Laivuori H, Räikkönen K (2017). Cohort Profile: Prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. *International journal of epidemiology* **46**, 1380–1381g.

Gissler M, Haukka J (2004). Finnish health and social welfare registers in epidemiological research. *Norsk Epidemiologi* **14**, 113–120.

Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW V, Eriksson JG, Broekman BFP (2017). Influence of maternal obesity on the long-term health of offspring. *The Lancet Diabetes & Endocrinology* **5**, 53–64.

Haeri S, Baker AM, Ruano R (2013). Do pregnant women with depression have a pro-inflammatory profile? *Journal of Obstetrics and Gynaecology Research* **39**, 948–952.

Jacka FN, Berk M (2013). Depression, diet and exercise. *The Medical journal of Australia* **199**, S21–S23.

Jokela M, Berg V, Silventoinen K, Batty GD, Singh-Manoux A, Kaprio J, Davey Smith G,

Kivimäki M (2016). Body Mass Index and Depressive Symptoms: Testing for Adverse and Protective Associations in Two Twin Cohort Studies. *Twin Research and Human Genetics* **19**, 306–311.

Lahti M, Savolainen K, Tuovinen S, Pesonen A-K, Lahti J, Heinonen K, Hämäläinen E, Laivuori H, Villa PM, Reynolds RM, Kajantie E, Räikkönen K (2017). Maternal Depressive Symptoms During and After Pregnancy and Psychiatric Problems in Children. *Journal of the American Academy of Child & Adolescent Psychiatry* **56**, 30–39.e7.

Ligthart S, Marzi C, Aslibekyan S, Mendelson MM, Conneely KN, Tanaka T, Colicino E, Waite LL, Joehanes R, Guan W, Brody JA, Elks C, Marioni R, Jhun MA, Agha G, Bressler J, Ward-Caviness CK, Chen BH, Huan T, Bakulski K, Salfati EL, Fiorito G, Wahl S, Schramm K, Sha J, Hernandez DG, Just AC, Smith JA, Sotoodehnia N, Pilling LC, Pankow JS, Tsao PS, Liu C, Zhao W, Guarrera S, Michopoulos VJ, Smith AK, Peters MJ, Melzer D, Vokonas P, Fornage M, Prokisch H, Bis JC, Chu AY, Herder C, Grallert H, Yao C, Shah S, McRae AF, Lin H, Horvath S, Fallin D, Hofman A, Wareham NJ, Wiggins KL, Feinberg AP, Starr JM, Visscher PM, Murabito JM, Kardia SLR, Absher DM, Binder EB, Singleton AB, Bandinelli S, Peters A, Waldenberger M, Matullo G, Schwartz JD, Demerath EW, Uitterlinden AG, van Meurs JBJ, Franco OH, Chen Y-DI, Levy D, Turner ST, Deary IJ, Ressler KJ, Dupuis J, Ferrucci L, Ong KK, Assimes TL, Boerwinkle E, Koenig W, Arnett DK, Baccarelli AA, Benjamin EJ, Dehghan A (2016). DNA methylation signatures of chronic low-grade inflammation are associated with complex diseases. *Genome Biology* **17**, 255.

Lindsay JR, Nieman LK (2005). The hypothalamic-pituitary-adrenal axis in pregnancy: Challenges in disease detection and treatment. *Endocrine Reviews* **26**, 775–799.

Lukose A, Ramthal A, Thomas T, Bosch R, Kurpad A V, Duggan C, Srinivasan K (2014). Nutritional factors associated with antenatal depressive symptoms in the early stage of pregnancy

among urban South Indian women. *Maternal and child health journal* **18**, 161–170.

Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry* **67**, 220–229.

Maloni JA, Park S, Anthony MK, Musil CM (2005). Measurement of antepartum depressive symptoms during high-risk pregnancy. *Research in Nursing and Health* **28**, 16–26.

McEwan M, Lins RJ, Munro SK, Vincent ZL, Ponnampalam AP, Mitchell MD (2009). Cytokine regulation during the formation of the fetal-maternal interface: Focus on cell-cell adhesion and remodelling of the extra-cellular matrix. *Cytokine and Growth Factor Reviews* **20**, 241–249.

Mina TH, Denison FC, Forbes S, Stirrat LI, Norman JE, Reynolds RM (2015). Associations of mood symptoms with ante- and postnatal weight change in obese pregnancy are not mediated by cortisol. *Psychological Medicine* **45**, 3133–3146.

Molyneaux E, Pasupathy D, Kenny LC, McCowan LME, North RA, Dekker GA, Walker JJ, Baker PN, Poston L, Howard LM (2016b). Socio-economic status influences the relationship between obesity and antenatal depression: Data from a prospective cohort study. *Journal of Affective Disorders* **202**, 124–127.

Molyneaux E, Poston L, Ashurst-Williams S, Howard LM (2014). Obesity and Mental Disorders During Pregnancy and Postpartum: A Systematic Review and Meta-analysis. *Obstetrics and gynecology* **123**, 857–867.

Molyneaux E, Poston L, Khondoker M, Howard LM (2016a). Obesity, antenatal depression, diet and gestational weight gain in a population cohort study. *Archives of women's mental health*

Nagl M, Steinig J, Klinitzke G, Stepan H, Kersting A (2016). Childhood maltreatment and pre-pregnancy obesity: a comparison of obese, overweight, and normal weight pregnant women.

Archives of Women's Mental Health **19**, 355–365.

Nascimento SL, Surita FG, Cecatti JG (2012). Physical exercise during pregnancy. *Current Opinion in Obstetrics and Gynecology* **24**, 387–394.

Nast I, Bolten M, Meinlschmidt G, Hellhammer DH (2013). How to measure prenatal stress? A systematic review of psychometric instruments to assess psychosocial stress during pregnancy. *Paediatric and Perinatal Epidemiology* **27**, 313–322.

NCD Risk Factor Collaboration (2016). Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *The Lancet* **387**, 1377–1396.

O'Brien TE, Ray JG, Chan WS (2003). Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology (Cambridge, Mass.)* **14**, 368–374.

O'Hara MW, McCabe JE (2013). Postpartum depression: current status and future directions. *Annu.Rev.Clin.Psychol.* **9**, 379–407.

Osborne L, Clive M, Kimmel M, Gispen F, Guintivano J, Brown T, Cox O, Judy J, Meilman S, Braier A, Beckmann MW, Kornhuber J, Fasching PA, Goes F, Payne JL, Binder EB, Kaminsky Z (2016). Replication of Epigenetic Postpartum Depression Biomarkers and Variation with Hormone Levels. *Neuropsychopharmacology* **41**, 1648–1658.

Van Poppel MNM, Hartman MA, Hosper K, Van Eijsden M (2012). Ethnic differences in weight retention after pregnancy: The ABCD study. *European Journal of Public Health* **22**, 874–879.

Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, Hayes L, Khazaezadeh N, Nelson SM, Oteng-Ntim E, Pasupathy D, Patel N, Robson SC, Sandall J, Sanders TAB, Sattar N, Seed PT, Wardle J, Whitworth MK, Briley AL (2015). Effect of a behavioural intervention in

obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *The Lancet Diabetes & Endocrinology* **3**, 767–777.

Radloff LS (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement* **1**, 385–401.

Rahman MM, Abe SK, Kanda M, Narita S, Rahman MS, Bilano V, Ota E, Gilmour S, Shibuya K (2015). Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **16**, 758–770.

Rallis S, Pgd B, Skouteris H, Wertheim EH, Paxton SJ (2007). Predictors of Body Image During the First Year Postpartum : A Prospective Study Predictors of Body Image During the First Year Postpartum : A Prospective Study. **242**

Reynolds RM, Allan KM, Raja E a, Bhattacharya S, McNeill G, Hannaford PC, Sarwar N, Lee AJ, Norman JE (2013). Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *Bmj* **347**, f4539.

Rivera M, Locke AE, Corre T, Czamara D, Wolf C, Ching-Lopez A, Milaneschi Y, Kloiber S, Cohen-Woods S, Rucker J, Aitchison KJ, Bergmann S, Boomsma DI, Craddock N, Gill M, Holsboer F, Hottenga JJ, Korszun A, Kutalik Z, Lucae S, Maier W, Mors O, Muller-Myhsok B, Owen MJ, Penninx BWJH, Preisig M, Rice J, Rietschel M, Tozzi F, Uher R, Vollenweider P, Waeber G, Willemsen G, Craig IW, Farmer AE, Lewis CM, Breen G, McGuffin P (2017). Interaction between the FTO gene, body mass index and depression: Meta-analysis of 13701 individuals. *British Journal of Psychiatry* **211**, 70–76.

Ruhstaller KE, Elovitz MA, Stringer M, Epperson CN, Durnwald CP (2017). Obesity and the association with maternal mental health symptoms. *Journal of Maternal-Fetal and Neonatal Medicine*

Ruyak SL, Lowe NK, Corwin EJ, Neu M, Boursaw B (2016). Prepregnancy Obesity and a Biobehavioral Predictive Model for Postpartum Depression. *Journal of Obstetric, Gynecologic & Neonatal Nursing*

Sahrakorpi N, Koivusalo SB, Stach-Lempinen B, Eriksson JG, Kautiainen H, Roine RP (2017). "The burden of pregnancy"; heavier for the heaviest? The changes in health related quality of life (HRQoL) assessed by the 15D instrument during pregnancy and postpartum in different body mass index groups: A longitudinal survey. *Acta Obstetricia et Gynecologica Scandinavica* **96**, 352–358.

Salehi-Pourmehr H, Mohammad-Alizadeh S, Jafarilar-Agdam N, Rafiee S, Farshbaf-Khalili A (2017). The association between pre-pregnancy obesity and screening results of depression for all trimesters of pregnancy, postpartum and 1 year after birth: a cohort study. *Journal of Perinatal Medicine*

Shelton M, Schminkey D, Groer M (2014). Relationships Among Prenatal Depression, Plasma Cortisol, and Inflammatory Cytokines. *Biological research for nursing* **17**, 1–8.

Stommel M, Schoenborn CA (2009). Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHIS 2001-2006. *BMC public health* **9**, 421.

Sundaram S, Harman JS, Peoples-Sheps MD, Hall AG, Simpson SH (2012). Obesity and postpartum depression: Does prenatal care utilization make a difference? *Maternal and Child Health Journal* **16**, 656–667.

Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O (2009). Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **10**, 194–203.

Venkatesh KK, Riley L, Castro VM, Perlis RH, Kaimal AJ (2016). Association of Antenatal Depression Symptoms and Antidepressant Treatment With Preterm Birth. *Obstetrics & Gynecology* **127**, 926–933.

Vilagut G, Forero CG, Barbaglia G, Alonso J (2016). Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *PloS one* **11**, e0155431.

Walter S, Kubzansky LD, Koenen KC, Liang L, Tchetgen Tchetgen EJ, Cornelis MC, Chang S-C, Rimm E, Kawachi I, Glymour MM (2015). Revisiting Mendelian randomization studies of the effect of body mass index on depression. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* **168B**, 108–15.

World Health Organization (2000). *Obesity: preventing and managing the global epidemic: report of a WHO consultation*. vol 894. WHO: Geneva.

Xuto P, Sinsuksai N, Piaseu N, Nityasuddhi D, Phupong V (2012). A Causal Model of Postpartum Weight Retention among Thais. *Pacific Rim International Journal of Nursing Research* **16**, 48–63.

Figure captions

Figure 1. Flow chart of the participants and sample attrition of the PREDO-study.

Figure 2. Maternal depressive symptoms measured by using the Center for Epidemiological Studies Depression Scale (CES-D) during and after pregnancy in early pregnancy body mass index (BMI) groups. Panel A represents the mean of CES-D scores at the biweekly measurement points between 12+0-13+6 and 38+0-39+6 gestational weeks+days, and at 2.4 and 28.2 weeks after pregnancy in the early pregnancy BMI groups. Panel B represents the proportion of women scoring 16 or above at the biweekly measurement points between 12+0-13+6 and 38+0-39+6 gestational weeks+days, and at 2.4 and 28.2 weeks after pregnancy in the early pregnancy BMI groups. P-values refer to BMI group x gestation week and BMI group x timepoint after pregnancy interactions derived from the linear or generalized linear mixed model analyses.

Supplemental Figure 1. Frequency of participants who did and did not fill in the Center for Epidemiological Studies Depression Scale (CES-D) during and after pregnancy.

Table 1. Characteristics of the sample according to maternal early pregnancy weight groups (N=3234).

	Maternal early pregnancy body mass index (kg/m^2)				
	< 18.5	**18.5-24.99**	**25-29.99**	**≥ 30**	
	Underweight n=106	**Normal weight n=2065**	**Overweight n=633**	**Obese n=430**	
	Mean (SD)/ n (%)	**Mean (SD)/ n (%)**	**Mean (SD)/ n (%)**	**Mean (SD)/ n (%)**	**P**
Maternal characteristics					
Early pregnancy weight (kg)	49.8 (3.7)	60.6 (6.2)	74.0 (6.5)	94.5 (12.5)	<0.001
Height (m)	1.67 (0.06)	1.66 (0.06)	1.65 (0.06)	1.66 (0.06)	0.001
Early pregnancy body mass index (kg/m^2)	17.9 (0.5)	21.9 (1.7)	27.0 (1.4)	34.5 (4.0)	<0.001
Age at delivery (years)	30.2 (4.9)	31.7 (4.6)	32.0 (4.7)	32.2 (5.0)	<0.001
Education, n (%)					<0.001
Lower secondary or less	47 (44.3%)	711 (34.5%)	304 (48.1%)	237 (55.1%)	
Upper secondary	23 (21.7%)	545 (26.4%)	162 (25.6%)	112 (26.0%)	
Tertiary	36 (34.0%)	806 (39.1%)	166 (26.3%)	81 (18.8%)	
Data not available, n	0	3	1	0	
Parity, n (%)					0.86
Primiparous	44 (41.5%)	856 (41.5%)	250 (39.7%)	173 (40.2%)	
Multiparous	62 (58.5%)	1205 (58.5%)	379 (60.3%)	257 (59.8%)	
Data not available, n	0	4	4	0	
Smoking during pregnancy, n (%)					0.48
No	99 (93.4%)	1941 (94.0%)	582 (92.1%)	401 (93.5%)	
Quit during first trimester	2 (1.9%)	59 (2.9%)	28 (4.4%)	15 (3.5%)	
Smoked throughout pregnancy	5 (4.7%)	65 (3.1%)	22 (3.5%)	13 (3.0%)	
Data not available, n	0	0	1	1	
Alcohol use during pregnancy, n (%)					0.001
No	97 (92.4%)	1690 (82.6%)	543 (84.7%)	387 (88.6%)	
Yes	8 (7.6%)	355 (17.4%)	97 (15.5%)	48 (11.3%)	
Data not available, n	1	20	8	5	
Leisure-time physical activity, n (%)					<0.001
I do not exercise; less than once a month; 1 to 2 times per month	27 (25.7%)	354 (17.3%)	135 (21.6%)	114 (26.8%)	
Approximately once a week; 2 to 3 times per week	56 (53.3%)	1301 (63.7%)	389 (62.1%)	263 (61.7%)	

4 to 5 times per week; approximately every day	22 (21.0%)	386 (18.9%)	102 (16.3%)	49 (11.5%)	
Data not available, n	1	24	7	4	
Hypertension spectrum disorders, n (%)					<0.001
Normotensive	101 (95.3%)	1901 (92.1%)	537 (84.8%)	301 (70.0%)	
Gestational hypertension	2 (1.9%)	64 (3.1%)	27 (4.3%)	43 (10.0%)	
Pre-eclampsia	2 (1.9%)	55 (2.7%)	35 (5.5%)	27 (6.3%)	
Chronic hypertension	1 (0.9%)	45 (2.2%)	34 (5.4%)	59 (13.7%)	
Gestational diabetes, n (%)					<0.001
No	104 (98.1%)	1962 (95.0%)	529 (83.6%)	295 (68.6%)	
Yes	2 (1.9%)	103 (5.0%)	104 (16.4%)	135 (31.4%)	
Type 1 diabetes, n (%)					0.06
No	105 (99.1%)	2058 (99.7%)	625 (98.7%)	427 (99.3%)	
Yes	1 (0.9%)	7 (0.3%)	8 (1.3%)	3 (0.7%)	
History of physician diagnosed depression before pregnancy, n (%)					0.000
No	82 (82.8%)	1777 (91.1%)	530 (88.6%)	345 (84.4%)	
Yes	17 (17.2%)	174 (8.9%)	68 (11.4%)	64 (15.6%)	
Data not available, n	7	114	35	21	
Depressive symptoms during pregnancy					
Sumscore	12.1 (6.8)	11.0 (6.2)	11.8 (6.3)	12.7 (6.8)	<0.001
Sumscore ≥ 16, n (%)	27 (25.5%)	391 (18.9%)	145 (22.9%)	114 (26.5%)	0.001
Depressive symptoms after pregnancy					
Sumscore	11.0 (7.2)	9.7 (6.6)	10.7 (7.2)	11.6 (8.1)	<0.001
Sumscore ≥ 16, n (%)	28 (26.4%)	359 (17.4%)	131 (20.7%)	102 (23.7%)	0.002
Child characteristics					
Gestational age (weeks)	39.9 (1.3)	39.9 (1.5)	39.8 (1.8)	39.8 (1.7)	0.43
Birth weight (g)	3370.8 (475.7)	3504.2 (499.7)	3547.3 (548.6)	3658.4 (550.8)	<0.001
Sex, boys, n (%)	47 (44.3%)	1058 (51.2%)	307 (48.5%)	251 (58.5%)	0.005
Data not available, n	0	0	0	1	

Note. Frequencies and percentages refer to valid N of variable.

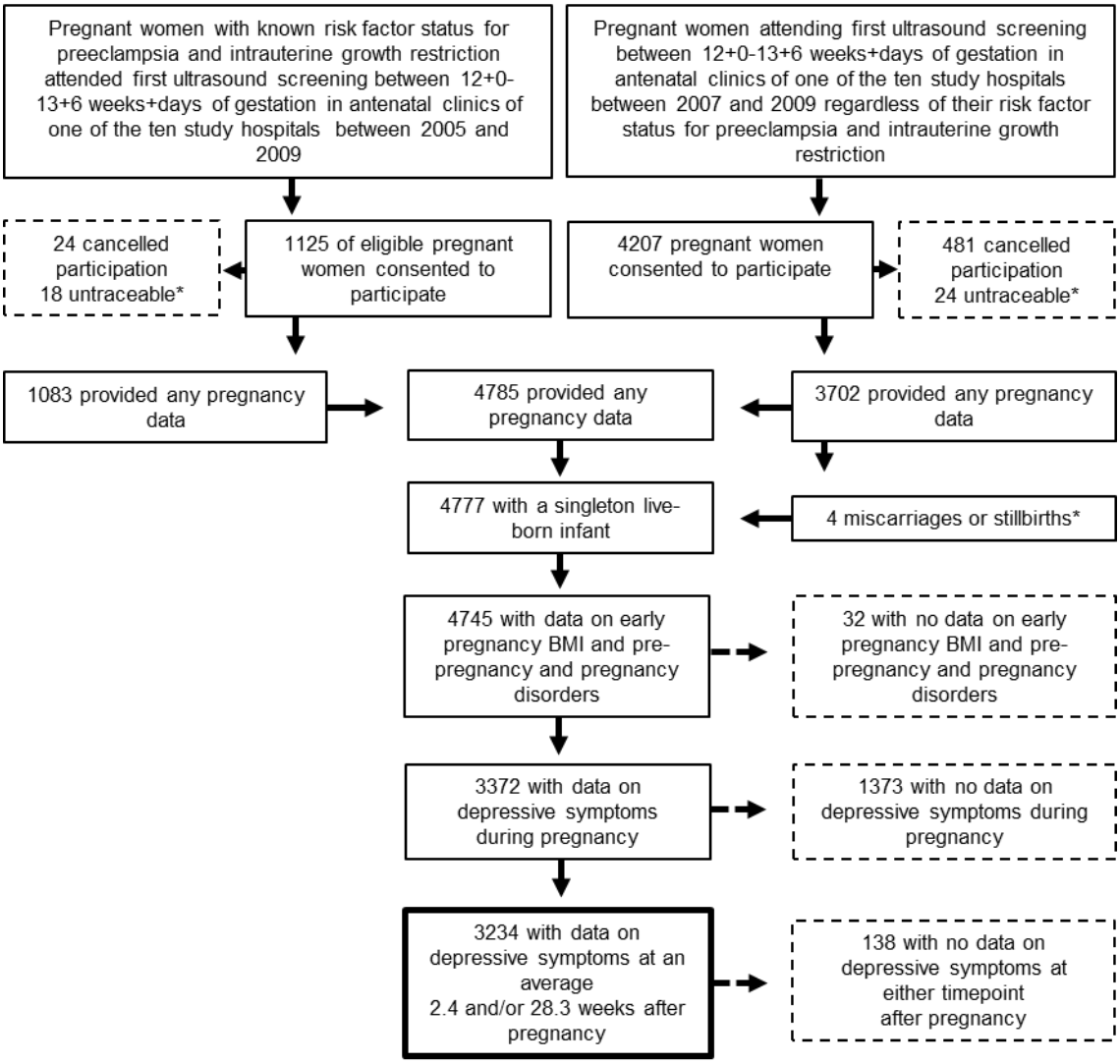
Table 2. Associations between early pregnancy body mass index (BMI) and depressive symptoms during and after pregnancy.

	Center for Epidemiological Studies Depression Scale (CES-D) in Standard Deviation units								
	During pregnancy in all women (N=3234)			**After pregnancy in all women** (N=3234)			**After pregnancy in women without clinically relevant symptoms during pregnancy (CES-D < 16)** (N=2557)		
	Mean difference	95% Confidence Interval	P[a]	Mean difference	95% Confidence Interval	P[a]	Mean difference	95% Confidence Interval	P[a]
Early pregnancy BMI group									
Normal weight (BMI 18.5-24.99 kg/m^2)	Referent			Referent			Referent		
Underweight (BMI <18.5 kg/m^2)	0.11	-0.05, 0.26	0.18	0.13	-0.02, 0.29	0.09	-0.02	-0.20, 0.16	0.85
Overweight (BMI 25-29.99 kg/m^2)	0.10	0.03, 0.17	0.005	0.14	0.07, 0.21	0.0002	0.09	0.01, 0.17	0.03
Obese (BMI ≥30 kg/m^2)	0.19	0.11, 0.28	<0.0001	0.20	0.11, 0.29	<0.0001	0.11	0.01, 0.21	0.03

Note. The analyses during pregnancy are adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy as time-invariant between person covariates and gestation week as time-varying within-person covariate; The analyses after pregnancy are adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy, child's gestational age, birth weight and sex as time-invariant between-person covariates and timepoint after pregnancy as time-varying within-person covariate.

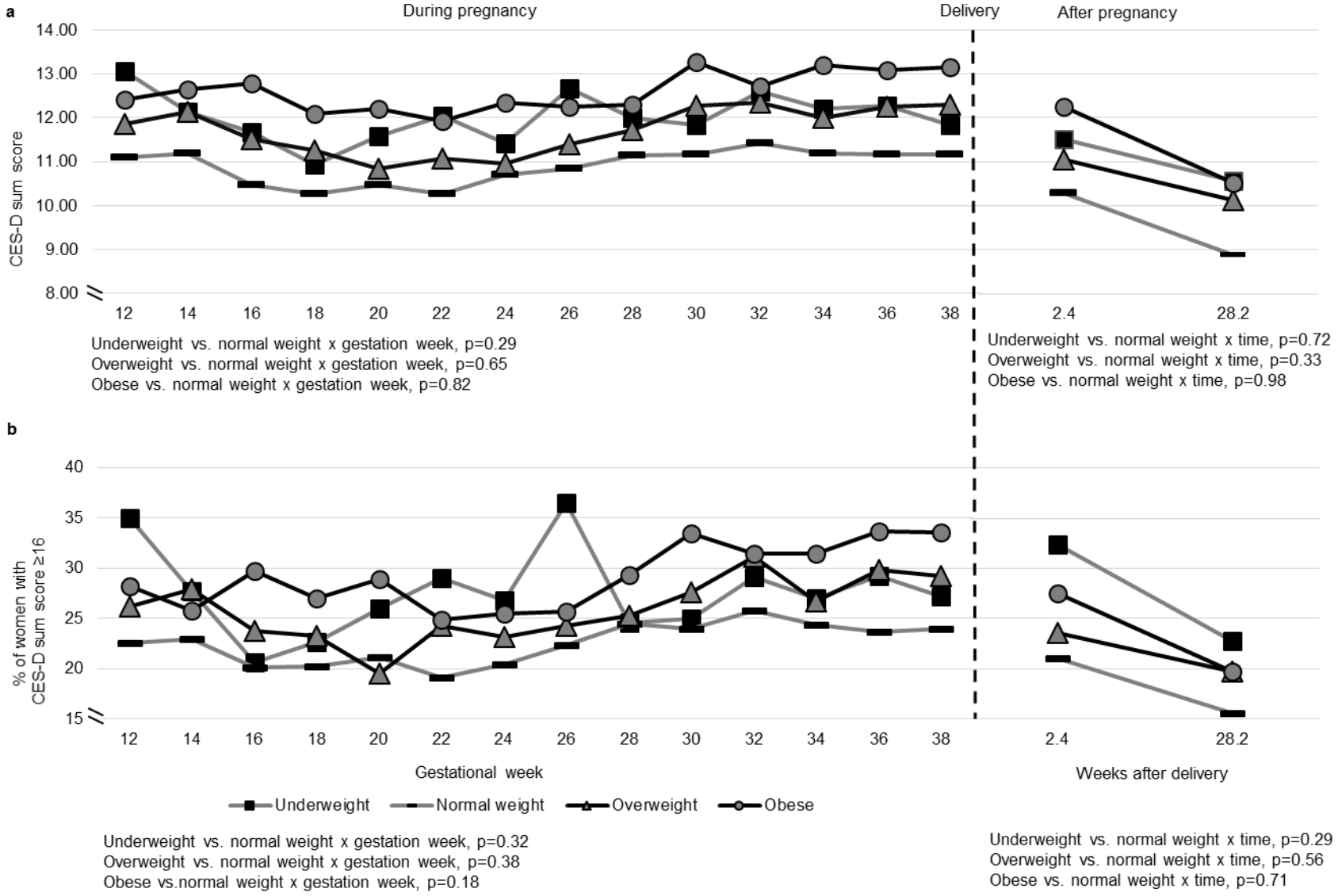
[a]Exact p-values are given unless they are below 0.0001

Figure 1.



*Note Those who cancelled participation or could not be traced may include miscarriages or stillbirths not identified via hospital records or the MBR owing to missing child birth date data.

Figure 2.


a
During pregnancy
Delivery
After pregnancy
CES-D sum score
14.00
13.00
12.00
11.00
10.00
9.00
8.00
12 14 16 18 20 22 24 26 28 30 32 34 36 38
2.4 28.2
Underweight vs. normal weight x gestation week, p=0.29
Overweight vs. normal weight x gestation week, p=0.65
Obese vs. normal weight x gestation week, p=0.82
Underweight vs. normal weight x time, p=0.72
Overweight vs. normal weight x time, p=0.33
Obese vs. normal weight x time, p=0.98
b
% of women with CES-D sum score ≥16
40
35
30
25
20
15
12 14 16 18 20 22 24 26 28 30 32 34 36 38
2.4 28.2
Gestational week
Weeks after delivery
Underweight
Normal weight
Overweight
Obese
Underweight vs. normal weight x gestation week, p=0.32
Overweight vs. normal weight x gestation week, p=0.38
Obese vs.normal weight x gestation week, p=0.18
Underweight vs. normal weight x time, p=0.29
Overweight vs. normal weight x time, p=0.56
Obese vs. normal weight x time, p=0.71

Supplemental Table 1. Associations between hypertensive and diabetic pre-pregnancy and pregnancy disorders and depressive symptoms during and after pregnancy.

	During pregnancy in all women (N=3234)			**After pregnancy in all women** (N=3234)			**After pregnancy in women without clinically relevant symptoms during pregnancy (CES-D <16)** (N=2557)		
	Mean difference	95% Confidence Interval	P[a]	Mean difference	95% Confidence Interval	P[a]	Mean difference	95% Confidence Interval	P[a]
Pre-pregnancy and pregnancy disorders:									
No disorder	Referent			Referent			Referent		
Any disorder	0.06	-0.01, 0.13	0.11	0.09	0.02, 0.17	0.02	0.09	0, 0.17	0.04
Gestational hypertension	0.02	-0.12, 0.16	0.77	0.04	-0.10, 0.17	0.61	0.05	-0.10, 0.21	0.50
Preeclampsia	0.12	-0.02, 0.27	0.10	0.12	-0.02, 0.27	0.10	0.15	-0.02, 0.31	0.09
Chronic hypertension	-0.04	-0.19, 0.09	0.49	-0.01	-0.15, 0.13	0.90	0.01	-0.14, 0.16	0.88
Gestational diabetes	0.05	-0.04, 0.14	0.32	0.08	-0.01, 0.18	0.08	0.07	-0.04, 0.17	0.21
Type 1 diabetes	0.12	-0.25, 0.49	0.53	0.11	-0.28, 0.50	0.57	0.01	-0.44, 0.44	0.98

Note. Model is adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy, time (gestation week) in the analyses during pregnancy; Model is adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy, child's gestational age, birth weight, sex, and time (measurement point at an average of two weeks and six months after pregnancy) in the analyses after pregnancy.

[a]Exact p-values are given unless they are below 0.0001

Supplemental Table 2. Differences between women with none or any hypertensive or diabetic pre-pregnancy and pregnancy disorders in depressive symptoms during and after pregnancy when these differences are tested in different categories of body mass index (BMI**).**

	Center for Epidemiological Studies Depression Scale (CES-D) in Standard Deviation units								
	During pregnancy in all women (N=3234)			**After pregnancy in all women** (N=3234)			**After pregnancy in women without clinically relevant symptoms during pregnancy (CES-D <16)** (N=2557)		
	Mean difference	95% Confidence Interval	P	Mean difference	95% Confidence Interval	P	Mean difference	95% Confidence Interval	P
Underweight (BMI <18.5 kg/m^2)									
Any disorder vs. no disorder	-0.31	-1.02, 0.40	0.39	-0.11	-0.83, 0.60	0.76	-0.03	-0.84, 0.79	0.94
Normal weight (BMI 18.5-24.99 kg/m^2)									
Any disorder vs. no disorder	-0.01	-0.13, 0.10	0.82	0.05	-0.07, 0.17	0.38	0.07	-0.06, 0.20	0.32
Overweight (BMI 25-29.99 kg/m^2)									
Any disorder vs. no disorder	0.11	-0.03, 0.25	0.11	0	-0.15, 0.15	0.96	0.01	-0.15, 0.18	0.91
Obese (BMI ≥30.00 kg/m^2)									
Any disorder vs. no disorder	-0.04	-0.19, 0.11	0.60	0.02	-0.15, 0.20	0.95	0.04	-0.15, 0.23	0.66

Note. The analyses during pregnancy are adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy as time-invariant between person covariates and gestation week as time-varying within-person covariate; The analyses after pregnancy are adjusted for maternal age at delivery, maternal education, parity, maternal physical activity, smoking and alcohol use during pregnancy, child's gestational age, birth weight and sex as time-invariant between-person covariates and timepoint after pregnancy as time-varying within-person covariate.

Supplemental Figure 1.