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Association Between Pre-Pregnancy Depression/Anxiety Symptoms and Hypertensive Disorders of Pregnancy

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Abstract

Background: Depression and anxiety symptoms have been linked with hypertensive disorders during pregnancy, but these associations have not been fully elucidated. Our objective was to consider hypertension in pregnancy and its subtypes (chronic hypertension, gestational hypertension, preeclampsia) and evaluate whether the proximity of psychological symptoms to pregnancy informs any associations observed.
Methods: Pregnancy Outcomes and Community Health Study participants who provided interview data at enrollment (16–27 weeks' gestation) and whose hypertensive disorder status was abstracted from medical records were eligible for inclusion ($n = 1371$). Maternal history of depression/anxiety symptoms at four time points in the life course were ascertained via self-report at enrollment (i.e., lifetime history, 1 year prior to pregnancy, since last menstrual period, and past week). Weighted logistic regression models were used to examine depression/anxiety symptom measures in relation to hypertensive disorders (overall) and subtype.
Results: Following adjustment for maternal sociodemographic factors, smoking, and prepregnancy body mass index, prepregnancy depression or anxiety symptoms (i.e., lifetime history and 1 year prior to pregnancy) were associated with hypertensive disorders during pregnancy. Subtype analyses revealed that these associations were driven primarily by chronic hypertension (adjusted odds ratios = 2.7–3.5). Preeclampsia accompanied by preterm delivery was also linked to women's lifetime history of depression symptoms (odds ratio = 2.3, 95% confidence interval 1.0–5.2).
Conclusion: Our results suggest that the link between maternal chronic hypertension and depression/anxiety symptoms precedes pregnancy. In addition, prepregnancy history of depression/anxiety symptoms may be considered part of a risk profile for preterm preeclampsia.

Introduction

Hypertensive disorders complicate 5%–10% of pregnancies and include diagnoses of chronic hypertension (CH), gestational hypertension (GH), or preeclampsia (PE).[1,2] These disorders are the second leading cause of maternal mortality in the United States and are associated with an increased risk of stillbirth and neonatal mortality, as well as a range of maternal and infant morbidities (e.g., intrauterine growth restriction).[3–6] Given the prevalence of these disorders and the sequelae associated with them, understanding the etiology of hypertensive disorders during pregnancy represents an important public health objective.

Prepregnancy risk factors (e.g., obesity), aberrations in early placentation (e.g., incomplete spiral artery conversion), and alterations in maternal angiogenic/antiangiogenic factors during pregnancy (e.g., soluble endoglin) have been individually and collectively linked to these conditions.[7–13]

Maternal psychological functioning may be an additional factor to consider, given that among men and nonpregnant women, psychopathology can precede and increase subsequent risk for hypertensive disease.[14–18] Biologically informed investigations suggest that connections between psychological functioning and incident hypertension are plausible and likely involve alterations to several physiological processes (e.g., inflammatory, autonomic, hypothalamic-pituitary-adrenal activity).[19,20]

However, studies investigating associations between maternal psychological functioning (typically depression or anxiety symptoms) and hypertensive disorders during pregnancy have yielded equivocal results.[21–24] Several conceptual and empirical gaps in the literature may contribute to this lack of consensus. For example, studies to date have primarily focused on PE or have collapsed across hypertensive disorder subtype. Thus, associations between maternal depression or anxiety symptoms and hypertensive disorders

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during pregnancy have yet to be elucidated in detail. Additionally, the contribution of gestational age at delivery has not been fully explored within studies focusing solely on PE. Given that the etiology and severity of PE may differ when it coincides with preterm versus term delivery,[25,26] stratification of PE by gestational age may offer additional clues to associations with maternal psychological health. With respect to maternal depression or anxiety symptoms, measurement has relied upon maternal self-reports during the early weeks of pregnancy (prior to 20 weeks) as the frame of reference. However, given that maternal symptoms of depression or anxiety emerge and are exacerbated at various points in the life course, and that the onset of certain hypertensive disorder subtypes begin prior to pregnancy (i.e., CH), a more thorough investigation of issues relating to time course may be warranted.

The goal of our analysis is to address the aforementioned gaps in the literature using data from the Pregnancy Outcomes and Community Health (POUCH) study. Specifically, we aim to examine the association between depression/anxiety symptoms across the life course and hypertension disorders during pregnancy, independent of maternal demographic and pregnancy characteristics. In addition to contextualizing extant research, these efforts may help identify specific mechanisms underlying associations between maternal psychological functioning and hypertensive disorders during pregnancy.

Methods

Study population

The Pregnancy Outcomes and Community Health (POUCH) study, designed to examine etiological pathways leading to preterm delivery, enrolled 3019 women (16–27 weeks of gestation) from 52 prenatal clinics in five Michigan communities from 1998–2004. Eligibility criteria included English proficiency, maternal age ≥ 15 years, and a singleton pregnancy with no known congenital or chromosomal abnormalities or prepregnancy diabetes. A stratified sampling scheme was used to assemble the cohort and a subcohort of 1,371 women from the cohort who were studied in greater depth (e.g., medical records abstracted, biological samples assessed). The subcohort included all women who delivered preterm and a stratified sample of women who delivered at term. Additional details about the sampling scheme and the study sample are reported elsewhere.[27] To account for the stratified sampling, all analyses use sampling weights to arrive at unbiased estimates and standard errors that represent the original sampling frame. The present analysis is based upon the 1371 POUCH study subcohort women who completed a health history survey at enrollment and whose hypertensive disorder status was abstracted from medical records. This study was approved by the Michigan State University Review Board and all participating medical centers.

Measures

Depression and anxiety symptoms. Maternal history of depression/anxiety symptoms at four time points in the life course were measured via self-report at enrollment (Table 1). The time points covered (1) lifetime history (''Depression symptoms: lifetime''), which included women who endorsed ''depression with medication'' as a condition ever diagnosed by a health care provider when not pregnant, (2) one year prior to pregnancy (''Depression or anxiety symptoms: past year''), which included women who endorsed ''depression/anxiety'' as a condition that prompted a visit to a health care provider in the one year prior to pregnancy; (3) since the last menstrual period (LMP), (''Depression or anxiety symptoms: since LMP''), which included women who reported experiencing either anxiety or depression symptoms since their

Table 1. Measures of Depression/Anxiety Symptoms According to Time Points in the Life Course

Construct	*Definition*
Depression symptoms: lifetime (Required medication use and doctor diagnosis)	Endorsed ''depression that required medication'' to the following: ''I'd like to know if a health care provider ever told you that you had any of these conditions when you were not pregnant.''
Depression or anxiety symptoms: past year (Required doctor's visit)	Endorsed ''depression/anxiety'' to the following: ''In the year before this pregnancy, about how many times did you go to a doctor's office, clinic, etc., for reasons related to your health?''
Depression or anxiety symptoms: since LMP	Self-report at enrollment: depression or anxiety to the following: ''Since your last period, have you had any other medical, emotional, and/or mental health problems?'' Women who reported experiencing either anxiety or depression symptoms since their LMP were included.
Depressive symptoms: past week	Center for Epidemiologic Study Depression (CES-D) Scale Survey directions instruct participants to evaluate the extent to which a series of statements reflect their functioning ''during the past week/''
Anti-depressant/anxiety medication use: during pregnancy	Medical record evidence of any of the following: benzodiazepines, selective serotonin reuptake inhibitors, serotonin receptor antagonists, norepinephrine and dopamine reuptake inhibitors, selective serotonin 1A receptor antagonists, selective serotonin and norepinephrine reuptake inhibitors, and tricyclic anti-depressants/

LMP, last menstrual period.

LMP; and (4) within the past week, (''Depressive symptoms: past week''), which included women with scores ≥16 on the Center for Epidemiologic Study Depression scale. Labor and delivery medical record evidence of antidepressant/antianxiety medication prescription during pregnancy (''Antidepressant/antianxiety medication use: pregnancy'') was also assessed. Medications included benzodiazepines, selective serotonin reuptake inhibitors, serotonin receptor antagonists, norepinephrine and dopamine reuptake inhibitors, selective serotonin 1A receptor antagonists, selective serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants. Membership within the depression/anxiety symptom groups was not mutually exclusive.

Hypertensive disorders. Evidence of hypertensive disorders was abstracted from medical records. Diagnostic categories included: chronic hypertension (CH)—before 20 weeks' gestation a diastolic blood pressure (DBP) ≥90 mmHg or systolic blood pressure (SBP) ≥140 mmHg on at least two different calendar days, medical record diagnosis, or use of antihypertensive medication; gestational hypertension (GH)—no CH, DBP ≥90 mmHg or SBP ≥140 mmHg on at least two different calendar days after 20 weeks; and preeclampsia (PE)—GH plus evidence of proteinuria not explained by genitourinary infection, or PE superimposed on CH. Proteinuria was defined as ≥300 mg per 24 hour urine collection or 1+ protein on urine dipstick on at least two occasions after 20 weeks.

Covariates. Covariates obtained via self-report at enrollment and those reported in the literature to be associated with either depression/anxiety symptoms or hypertensive disorders during pregnancy were considered for each analytic model. These included maternal age (continuous), race/ethnicity (African American vs. white/other), smoking history (ever vs. never), parity (primiparous vs. multiparous), Medicaid Insurance status (yes vs. no), and prepregnancy body mass index (BMI) (continuous). We retained covariates that (1) altered the magnitude of the association (any direction) between any of the main exposures and outcomes by ≥10%, or (2) were associated with any of the depression/anxiety measures as well as any hypertensive disorder. All covariates with the exception of parity met these criteria.

Statistical analysis

To better contextualize any findings observed, we began by performing two sets of descriptive analyses. The first evaluated maternal and pregnancy characteristics according to hypertensive disorder status and subtype. The second evaluated the degree of overlap among the depression/anxiety symptom measures given their lack of mutual exclusivity. Next, we used separate logistic regression models to examine the association of each depression/anxiety symptom measure with the presence of any hypertensive disorder. We then used polytomous logistic regression models to examine whether any of the depression/anxiety symptom measures were associated with hypertensive disorder subtype (i.e., CH, GH, and PE). Since PE in the context of preterm and term delivery may differ in severity and etiology,[28] we performed an additional polytomous logistic regression analysis to evaluate whether depression/anxiety symptom measures were associated with PE after subdividing by timing of delivery. All models were repeated following adjustment for covariates, and all analyses (unadjusted and adjusted) employed weights to reflect the POUCH study sampling scheme. Unweighted analyses did not affect the pattern of findings (data not shown).

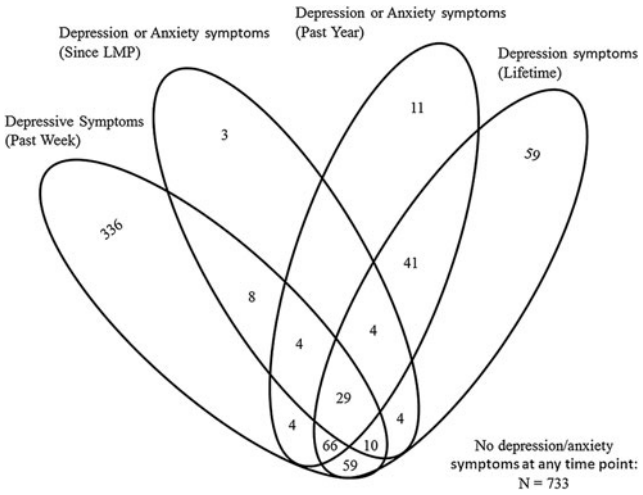

FIG. 1. Life course depression/anxiety symptom measures and their degree of overlap. Missing data: depressive symptoms (past week): $n = 6$; depression or anxiety (since last menstrual period [LMP]): $n = 1$; depression or anxiety (past year): $n = 1$.

All analyses also use time point–specific referents for the depression/anxiety symptom measures. This approach maximizes cell sizes to improve the stability of our analytic models. In addition, this approach likely conforms to clinical reality, in that measures of depression/anxiety at one point in time (e.g., prepregnancy) do not clearly suggest whether women's symptoms will reemerge at a later point in time (e.g., pregnancy). When assessing maternal risk at the beginning of pregnancy, prenatal care providers will query women about lifetime history of symptoms (yes/no) and recent history of symptoms (yes/no) and use this information to guide clinical care. While it may be useful to characterize associations with hypertensive disorders based upon evidence of symptoms at a single time point, this strategy could attenuate effect sizes. Thus, we performed a sensitivity analysis using women who were not categorized as exhibiting depression/anxiety symptoms at any time point as the referent ($n = 733$; Fig. 1) to evaluate whether alterations to any of the findings were observed.

Results

Weighted subcohort analyses from the POUCH study revealed prevalences of hypertensive disorders as follows: 9.6% overall, 3.0% CH, 4.1% GH, and 2.5% PE. Women with hypertensive disorders (all subtypes combined) had a higher mean age and BMI and were more likely to deliver preterm (Table 2). Regarding hypertensive disorder subtypes, older maternal age was associated with an increased risk of GH and CH, preterm delivery was associated with an increased risk of PE and CH, and higher prepregnancy BMI

Table 2. Maternal Demographic and Pregnancy Characteristics According to Hypertensive Disorder Presence and Subtype

			HTN disorder subtype (Total N = *149)*		
	*No HTN disorder (*N = *1222)* n *(Wt%)*	*Any HTN disorder (*N = *149)* n *(Wt%)*	*Chronic HTN (*N = *49)* n *(Wt%)*	*Gestational HTN (*N = *56)* n *(Wt%)*	*Preeclampsia (*N = *44)* n *(Wt%)*
Maternal race/ethnicity					
White/other	691 (75)	101 (79)	30 (74)	38 (80)	33 (82)
Black	531 (25)	48 (21)	19 (26)	18 (20)	11 (18)
Medicaid					
Yes	705 (50)	78 (44)	33 (49)	24 (39)	21 (47)
No	515 (50)	71 (56)	16 (51)	32 (61)	23 (53)
Smoking history (lifetime)					
None	879 (73)	100† (64)	24* (52)	41 (67)	35 (74)
Any	343 (27)	49 (36)	25 (48)	15 (33)	9 (26)
Parity					
Primiparous	510 (41)	67 (47)	14 (34)	31 (51)	22 (56)
Multiparous	711 (59)	82 (53)	35 (66)	25 (49)	22 (44)
Gestational age at delivery					
Full term (≥37 weeks)	946 (90)	90* (80)	31* (82)	42 (89)	17* (64)
Preterm (<37 weeks)	276 (10)	59 (20)	18 (18)	14 (11)	27 (36)
	M (SE)	*M (SE)*	*M (SE)*	*M (SE)*	*M (SE)*
Maternal age (years)	26.3 (0.2)	28.2* (0.6)	28.9* (1.1)	28.6* (1.0)	26.9 (1.3)
Prepregnancy BMI (kg/m^2)	26.4 (0.2)	30.0* (0.8)	31.3* (1.4)	29.6* (1.3)	28.8* (1.0)

Data weighted for the Pregnancy Outcomes and Community Health (POUCH) study sampling scheme.
Missing data: Medicaid, $n = 2$; parity, $n = 1$.
*$p < 0.05$, †$p < 0.10$ relative to the ''no HTN disorder'' group ($n = 1222$).
BMI, body mass index; HTN, hypertension; M, mean; SE, standard error; Wt%, weighted percentage.

was associated with an increased risk of every hypertensive disorder subtype. While history of maternal smoking was not significantly associated with hypertensive disorders collapsed across subtype, it was associated with an increased risk of CH (odds ratio [OR] = 2.5, 95% confidence interval [CI] 1.2–5.3).

Approximately 35% of women reported high levels of depressive symptoms during the past week, 5% reported depression or anxiety symptoms since their LMP, 12% reported depression or anxiety symptoms within the past year, 21% endorsed ''depression with medication'' as being diagnosed by a health care provider when not pregnant, and in approximately 10% of women there was medical record evidence of antidepressant/antianxiety medication use during pregnancy. Figure 1 displays the overlap in depression/anxiety symptom measures. Approximately 65% of women with depression/anxiety symptoms in the previous week were negative on all other depression/anxiety symptom measures. Among the 62 women who reported depression/anxiety symptoms since the LMP, only 11 (18%) were negative for prepregnancy depression/anxiety symptoms, suggesting new onset in the first half of pregnancy is uncommon. Among the 158 women with depression/anxiety symptoms in the previous year, only 19 (12%) did not report a lifetime history further supporting the chronicity of these symptoms. Based on medical records for the entire pregnancy, 124 women were prescribed antidepressant/antianxiety medication during pregnancy. The prevalence of maternal antidepressant/antianxiety medication prescription varied across the depression/anxiety symptom groups: 2% ($n = 16$) among the 733 women with no depression/anxiety symptoms, 2% ($n = 5$) among the 366 women with symptoms of depression/anxiety within the previous week only, and 34% ($n = 103$) among women with a history of depression/anxiety symptoms (since LMP, previous year, or lifetime).

Unadjusted and adjusted associations of depression/anxiety symptoms with any hypertensive disorder and hypertensive disorder subtype are summarized in Tables 3 and 4. Prepregnancy history of depression/anxiety symptoms (i.e., past year, lifetime) was associated with the presence of a hypertensive disorder during pregnancy (OR = 1.8, 95%CI 1.1–3.2 and OR = 1.8, 95%CI 1.1–2.9, respectively). These findings were driven by CH rather than other hypertensive disorder subtypes and remained significant following adjustment for covariates (Table 4). Antidepressant or antianxiety medication prescription during pregnancy was also associated with CH (OR = 3.4, 95%CI 1.4–8.3), but this association was attenuated in adjusted models (aOR = 2.4, 95%CI 0.9–6.4).

PE analyses that collapsed across gestational age at delivery showed no associations with any depression/anxiety symptom measure (Table 4). However, significant associations emerged after taking into account timing of delivery (Table 5). Relative to women who delivered at term with no evidence of PE, lifetime history of depression symptoms was associated with PE that co-occurred with preterm delivery

Table 3. Unadjusted Associations of Maternal Depression/Anxiety Symptoms with Hypertensive Disorder Presence and Subtype

				HTN disorder subtype (Total N = *149)*					
	*No HTN disorder (*N = *1222)*	*Any HTN Disorder (*N = *149)*		*Chronic HTN (*N = *49)*		*Gestational HTN (*N = *56)*		*Preeclampsia (*N = *44)*	
	n *(%)*	n *(%)*	*OR [95%CI]*	n *(%)*	*OR [95%CI]*	n *(%)*	*OR [95%CI]*	n *(%)*	*OR [95%CI]*
Depression symptoms[1] (lifetime)									
Yes	226 (20)	46 (31)	1.8* [1.1–2.9]	21 (45)	3.3* [1.6–7.1]	15 (31)	1.8 [0.9–3.8]†	10 (14)	0.6 [0.3–1.4]
No (ref)	995 (80)	103 (69)	—	28 (55)	—	41 (69)	—	34 (86)	—
Depression or anxiety symptoms[3] (past year)									
Yes	129 (12)	30 (19)	1.8* [1.1–3.2]	17 (35)	4.1* [1.9–8.9]	7 (15)	1.4 [0.5–3.6]	6 (8)	0.7 [0.3–1.7]
No (ref)	1092 (88)	119 (81)	—	32 (65)	—	49 (85)	—	38 (92)	—
Depression or anxiety symptoms (since LMP)									
Yes	57 (5)	5 (4)	0.8 [0.3–2.4]	3 (11)	2.2 [0.6–8.4]	1 (1)	0.2 [0.0–1.6]	1 (1)	0.3 [0.0–1.9]
No (ref)	1164 (95)	144 (96)	—	46 (89)	—	55 (99)	—	43 (99)	—
Depressive symptoms (past week)									
Yes	462 (35)	54 (29)	0.8 [0.5–1.2]	23 (36)	1.0 [0.5–2.1]	18 (24)	0.6 [0.3–1.1]	13 (31)	0.8 [0.4–1.9]
No (ref)	754 (65)	95 (71)	—	26 (64)	—	38 (76)	—	31 (69)	—
Antidepressant or anxiety medication use (during pregnancy)									
Yes	105 (10)	19 (16)	1.8† [1.0–3.5]	10 (26)	3.4* [1.4–8.3]	5 (13)	1.4 [0.5–4.1]	4 (10)	1.0 [0.3–4.1]
No (ref)	1117 (90)	130 (84)	—	39 (74)	—	51 (87)	—	40 (90)	—

Data weighted for the POUCH Study sampling scheme.

Missing data: depressive symptoms (past week): $n = 6$; depression or anxiety (since LMP): $n = 1$; depression or anxiety (past year): $n = 1$; depression or anxiety (lifetime): $n = 1$.

[1]Required doctor diagnosis and medication use.

[2]Required doctor's visit.

*$p < 0.05$, †$p < 0.10$ relative to the "no HTN disorder" group ($n = 1222$)

95%CI, 95% confidence interval; OR, odds ratio.

Table 4. Adjusted Associations of Maternal Depression/Anxiety Symptoms with Hypertensive Disorder Presence and Subtype

				HTN disorder subtype (total N = *149)*					
	*No HTN disorder (*N = *1222)*	*Any HTN disorder (*N = *149)*		*Chronic HTN (*N = *49)*		*Gestational HTN (*N = *56)*		*Preeclampsia (*N = *44)*	
	n *(%)*	n *(%)*	*aOR [95% CI]*	n *(%)*	*aOR [95%CI]*	n *(%)*	*aOR [95%CI]*	n *(%)*	*aOR [95%CI]*
Depression symptoms[1] (lifetime)									
Yes	226 (20)	46 (31)	1.5† [0.9–2.5]	21 (45)	2.7* [1.2–6.3]	15 (31)	1.7 [0.8–3.5]	10 (14)	0.6 [0.2–1.4]
No (ref)	995 (80)	103 (69)	—	28 (55)	—	41 (69)	—	34 (86)	—
Depression or anxiety symptoms[2] (past year)									
Yes	129 (12)	30 (19)	1.7† [1.0–3.0]	17 (35)	3.5* [1.5–7.8]	7 (15)	1.3 [0.5,3.5]	6 (8)	0.7 [0.2–1.8]
No (ref)	1092 (88)	119 (81)	—	32 (65)	—	49 (85)	—	38 (92)	—
Depression or anxiety symptoms (since LMP)									
Yes	57 (5)	5 (4)	0.7 [0.2–2.1]	3 (11)	1.8 [0.5–6.7]	1 (1)	0.2 [0.0–1.4]	1 (1)	0.3 [0.0–1.7]
No (ref)	1164 (95)	144 (96)	—	46 (89)	—	55 (99)	—	43 (99)	—
Depressive symptoms (past week)									
Yes	462 (35)	54 (29)	0.7 [0.4–1.2]	23 (36)	0.9 [0.4–2.0	18 (24)	0.6 [0.3–1.3]	13 (31)	0.9 [0.4–1.9]
No (ref)	754 (65)	95 (71)	—	26 (64)	—	38 (76)	—	31 (69)	—
Antidepressant or anxiety medication use (during pregnancy)									
Yes	105 (10)	19 (16)	1.4 [0.7–2.8]	10 (26)	2.4† [0.9–6.4]	5 (13)	1.1 [0.4–3.3]	4 (10)	0.9 [0.2–3.5]
No (ref)	1117 (90)	130 (84)	—	39 (74)	—	51 (87)	—	40 (90)	—

Data weighted for the POUCH study sampling scheme and adjusted for maternal race/ethnicity, Medicaid status, smoking history (lifetime), age at enrollment, and prepregnancy BMI.

Missing data: depressive symptoms (past week): $n = 6$; depression or anxiety (Since LMP): $n = 1$; depression or anxiety (past year): $n = 1$; depression or anxiety (lifetime): $n = 1$.

[1]Required doctor diagnosis and medication use.

[2]Required doctor's visit.

*$p < 0.05$, †$p < 0.10$ relative to the "no HTN disorder" group ($n = 1222$).

Table 5. Unadjusted Associations Between Maternal Depression/Anxiety Symptoms and Preeclampsia Stratified by Gestational Age at Delivery

	Full term, no PE (N = *1019*)	*Full term and PE* (N = *17*)		*Preterm, no PE* (N = *308*)		*Preterm and PE* (N = *27*)	
	n *(%)*	n *(%)*	*OR [95%CI]*	n *(%)*	*OR [95%CI]*	n *(%)*	*OR [95%CI]*
Depression symptoms[1] (lifetime)							
Yes	192 (21)	0 (0)	Cannot estimate	70 (23)	1.2 [0.8–1.6]	10 (38)	2.3* [1.0–5.2]
No (ref)	827 (79)	17 (100)	—	237 (77)	—	17 (62)	—
Depression or anxiety symptoms[2] (past year)							
Yes	116 (12)	0 (0)	Cannot estimate	37 (13)	1.0 [0.7–1.6]	6 (23)	2.1 [0.8–5.3]
No (ref)	903 (88)	17 (100)	—	270 (87)	—	21 (77)	—
Depression or anxiety symptoms (since LMP)							
Yes	48 (5)	0 (0)	Cannot estimate	13 (4)	0.8 [0.4–1.5]	1 (4)	0.7 [0.1–5.2]
No (ref)	971 (95)	17 (100)	—	294 (96)	—	26 (96)	—
Depressive symptoms (past week)							
Yes	391 (34)	5 (31)	0.9 [0.3–3.0]	112 (38)	1.2 [0.9–1.5]	8 (30)	0.8 [0.4–1.9]
No (ref)	624 (66)	12 (69)	—	194 (62)	—	19 (70)	—
Antidepressant or anxiety medication use (during pregnancy)							
Yes	84 (10)	1 (9)	0.9 [0.1–7.1]	36 (12)	1.2 [0.8–1.9]	3 (11)	1.2 [0.3–3.9]
No (ref)	935 (90)	16 (91)	—	272 (88)	—	24 (89)	—

Data weighted for the POUCH study sampling scheme.
Missing data: depressive symptoms (past week): $n = 6$; depression or anxiety (since LMP): $n = 1$; depression or anxiety (past year): $n = 1$; depression or anxiety (lifetime): $n = 1$.
[1]Required doctor diagnosis and medication use.
[2]Required doctor's visit.
*$p < 0.05$, †$p < 0.10$ relative to the ''full term, no PE'' group ($n = 1019$).
PE, preeclampsia.

(OR = 2.3, 95%CI 1.0–5.2). These findings were not driven by women whose PE was superimposed on CH ($n = 8$) and remained significant following adjustment for covariates (data not shown).

In the above analyses, women in the referent group for any given time point may have had evidence of depression/anxiety symptoms at another time point. When we reanalyzed the data using women not categorized as exhibiting depression/anxiety symptoms at any time point as the referent group ($n = 733$; Fig. 1), point estimates increased in magnitude but were not always statistically significant due to decreases in cell sizes and corresponding decreases in precision (data not shown).

Discussion

Taken together, our findings suggest that associations between maternal depression or anxiety symptoms and hypertensive disorders during pregnancy depend upon the measure and timing of maternal psychological symptoms as well as hypertensive disorder subtype. Following adjustment for covariates, findings were almost exclusively observed with the prepregnancy measures of depression or anxiety symptoms. Follow-up analyses revealed that these associations were driven primarily by CH. For PE, women's prepregnancy history of depression symptoms was associated with an increased risk of the disorder when it co-occurred with preterm delivery. Despite the fact that CH is a demonstrated risk factor for PE,[1,29] these findings were unaffected following the exclusion of women whose PE was superimposed upon preexisting CH.

In this study, we were unable to disentangle whether CH preceded symptoms of depression/anxiety (or vice versa), because both sets of symptoms likely occurred prior to the pregnancy and were not prospectively ascertained. Previous work suggests that these conditions can precede or follow one another,[14–18] but it is unclear which scenario occurs more frequently among women of reproductive age. Increasing work points to a variety of biological mechanisms that may underlie these associations, including alterations to sleep quality, hypothalamic-pituitary-adrenal axis activity, and inflammatory processes,[19,20,30] but it is similarly unclear whether the directionality of the associations is subserved by particular biological mechanisms or risk factors versus others. Irrespective of these etiologic issues, medical-related morbidities associated with hypertension are more severe in the context of depression or anxiety symptoms (e.g., functional disability),[31] and thus, furthering our understanding of how these conditions are associated with one another across the life course merits future study.

Hypertensive disorders with onset during pregnancy (≥ 20 weeks) include GH and PE, and to date, studies investigating their association with psychological functioning have focused predominantly on PE and on depression and/or anxiety (symptoms and/or diagnoses) during pregnancy. Among seven of these studies, five were positive[32–36] and two were negative;[21,23] since most did not inquire about the prepregnancy period, there is no way to know whether depression/anxiety symptoms and/or diagnoses during pregnancy represented a preexisting chronic problem. One exception was a study that used interview and prenatal records to ascertain depression/anxiety diagnosis during and prior to pregnancy and reported no association with PE for the latter.[34] We attempted to resolve discrepancies in the literature by investigating the contribution of gestational age at

delivery as an effect modifier. PE is considered to be more severe if delivery occurs spontaneously or is initiated by medical personnel within the preterm versus the term range.[25,26,37] In addition, PE that co-occurs with preterm delivery is also thought to differ etiologically from PE that co-occurs with term delivery, with the former being more likely to involve poor placentation, high maternal vascular resistance, low cardiac output, and alterations in liver enzymes.[25,37–39]

We found that links between depression/anxiety symptoms in the prepregnancy period and PE emerged following stratification by preterm delivery. However, it is important to note that sparse data led to ''zero cells'' for certain variable combinations, for example, lifetime history of depression symptoms and PE among women delivering at term (Table 5). In our study, the importance of the prepregnancy period for maternal mental health counters the hypothesis that maternal symptoms of depression/anxiety arise primarily as a consequence of PE-related pathology. However, our results are consistent with several other explanations: prepregnancy depression/anxiety symptoms and preterm PE share underlying causal factors; prepregnancy depression/anxiety symptoms affects maternal physiology that predisposes to preterm PE; and/or medication used to treat prepregnancy depression/anxiety symptoms increases the risk of preterm PE.

There are limitations to keep in mind when interpreting the study findings. Our study protocol did not include more time-consuming instruments, such as the Composite International Diagnostic Interview, that would have diagnosed depression and anxiety disorders along the life course. In addition, women were interviewed in mid pregnancy, thus we lacked self-reports of depression/anxiety symptoms with new onset in the second half of pregnancy. We did, however, capture use of antidepressant or antianxiety medications throughout pregnancy. The questions from which the depression and anxiety symptom measures were derived make it challenging to separate issues of temporality from those of comorbidity, medication use, and psychological symptom severity. For example, most associations between maternal psychological functioning and hypertensive disorders during pregnancy were limited to the prepregnancy time points. These particular measures of psychological functioning required a visit to a medical professional and/or receipt of prescription medication. Therefore, these variables may represent factors associated with access to health care, more severe depression or anxiety symptomatology, and/or direct pharmacologic effects associated with antidepressant or antianxiety medication use. However, it is unlikely that this last factor fully explains the study findings, because the inclusion of medical record evidence of medication use in adjusted analyses did not attenuate any of our findings (data not shown).

Additional factors to consider when interpreting our findings include the small cell sizes associated with some of the hypertensive disorder subtype analyses as well as the possibility that maternal self-reports of depression/anxiety symptoms were influenced by knowledge of CH status. We believe this latter issue is an unlikely explanation for the current findings given that associations were limited to a subset of depression/anxiety symptom measures. We did not measure depression/anxiety symptom chronicity or incorporate factors known to exacerbate or mitigate depressive/anxious symptomatology (e.g., stressful life events; social support). These points merit further investigation. Our study and the literature as a whole would also benefit from investigating the separate contributions of depression and anxiety to any links observed with hypertensive disorders during pregnancy. While depression and anxiety (particularly generalized anxiety disorder) are often comorbid, they differ in symptomatology and etiology.[40,41] Such differences, in turn, may be particularly illustrative in furthering our understanding of why links between these conditions and hypertensive disorders were observed in our study and those of others.

Despite these limitations, strengths of our investigation include the demographic breadth of the POUCH study sample as well as the careful ascertainment of hypertensive disorder status and subtype from medical records. Another strength is the comprehensive nature of the maternal self-reports collected at POUCH study enrollment, which, despite the caveats described above, enabled us to perform an investigation into how maternal psychological functioning across the life course may be related to hypertensive disorders overall and subtypes during pregnancy and motivate future work.

In sum, the current study adds to the growing literature linking hypertensive disorders (both within and outside of pregnancy) and maternal mental health. Given that hypertensive disease during pregnancy is associated with adverse maternal and infant morbidities as well as the development of maternal cardiovascular disease later in life,[42,43] furthering our understanding of factors contributing to the etiology of these conditions is warranted. Doing so may help us identify women who would benefit from improved and targeted surveillance efforts prior to, during, and following pregnancy.

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