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The moderating role of depression in the association between hypertension during pregnancy and birth outcomes

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ABSTRACT

Objective: Investigate how hypertension during pregnancy (HDP) and depression during pregnancy (DDP) independently and jointly affect infant birth outcomes.
Methods: This population-based, retrospective cohort study included a sample of 68,052 women who participated in PRAMS 2016–2018 survey. Poisson regression was used for adjusted relative risks (aRRs).
Results: Compared to women without HDP and DDP, aRRs for PTB and LBW among women with both HDP and DDP are 2.04 (95% CI 1.73, 2.42) and 2.84 (95% CI 2.27, 3.56), respectively, albeit lower than the expected joint effect of risk.
Conclusion: DDP may modify the association between HDP and PTB, LBW.

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KEYWORDS
Hypertension; depression; preterm birth; pregnancy; low birth weight

Introduction

Hypertensive disorders of pregnancy (HDP), including chronic hypertension, gestational hypertension, pre-eclampsia/eclampsia, and chronic hypertension with superimposed pre-eclampsia, occur in approximately 5% to 10% of pregnancies (1). It accounts for nearly 16% of maternal deaths and is considered the single leading cause of maternal mortality in industrialized countries (2). Numerous studies have linked HDP with adverse birth outcomes such as preterm birth (PTB), low birth weight (LBW), and small-for-gestational-age (SGA) (3–5). The effects of HDP on birth outcomes were more evident from the second to third trimester of pregnancy (6–9), and women with pre-eclampsia or eclampsia usually had highest risk of PTB and LBW compared to women with other types of HDP (10–12). Furthermore, some studies found pre-eclampsia was associated with large-for-gestational-age (LGA), although the direction of the association was inconsistent (13,14).

Recent research also recognized the importance of depression during pregnancy (DDP) as a risk factor associated with adverse birth outcomes (15,16). Major depressive disorder complicates up to 12.7% of pregnancies and as many as 37% of women have at least some depressive symptoms during their pregnancies (17,18). However, evidence on the association between DDP and adverse birth outcomes is inconclusive (17,19,20). Mixed results were also observed regarding the impact of DDP on PTB and SGA across different racial/ethnic subgroups (21,22), but few studies investigated the association between depression and LGA (23,24).

Despite the cumulative evidence supporting the independent effect of HDP and DDP on birth outcomes, the joint effect of HDP and DDP has rarely been studied. Few existing studies investigating such joint effect on birth outcomes are mostly based on small sample sizes and address the effect of other types of psychological problems (e.g., stress, anxiety) on birth outcomes (25,26). The aims of the present study were to examine 1) the independent association between HDP or DDP and LBW, PTB, SGA, and LGA; and 2) whether DDP modifies the association between HDP and birth outcomes in a large, U.S. population-based cohort study. We hypothesized that HDP and DDP would independently and jointly increase the risk of adverse birth outcomes.

Materials and methods

Study population

We conducted a population-based, retrospective cohort study on the effect of HDP and DDP on birth

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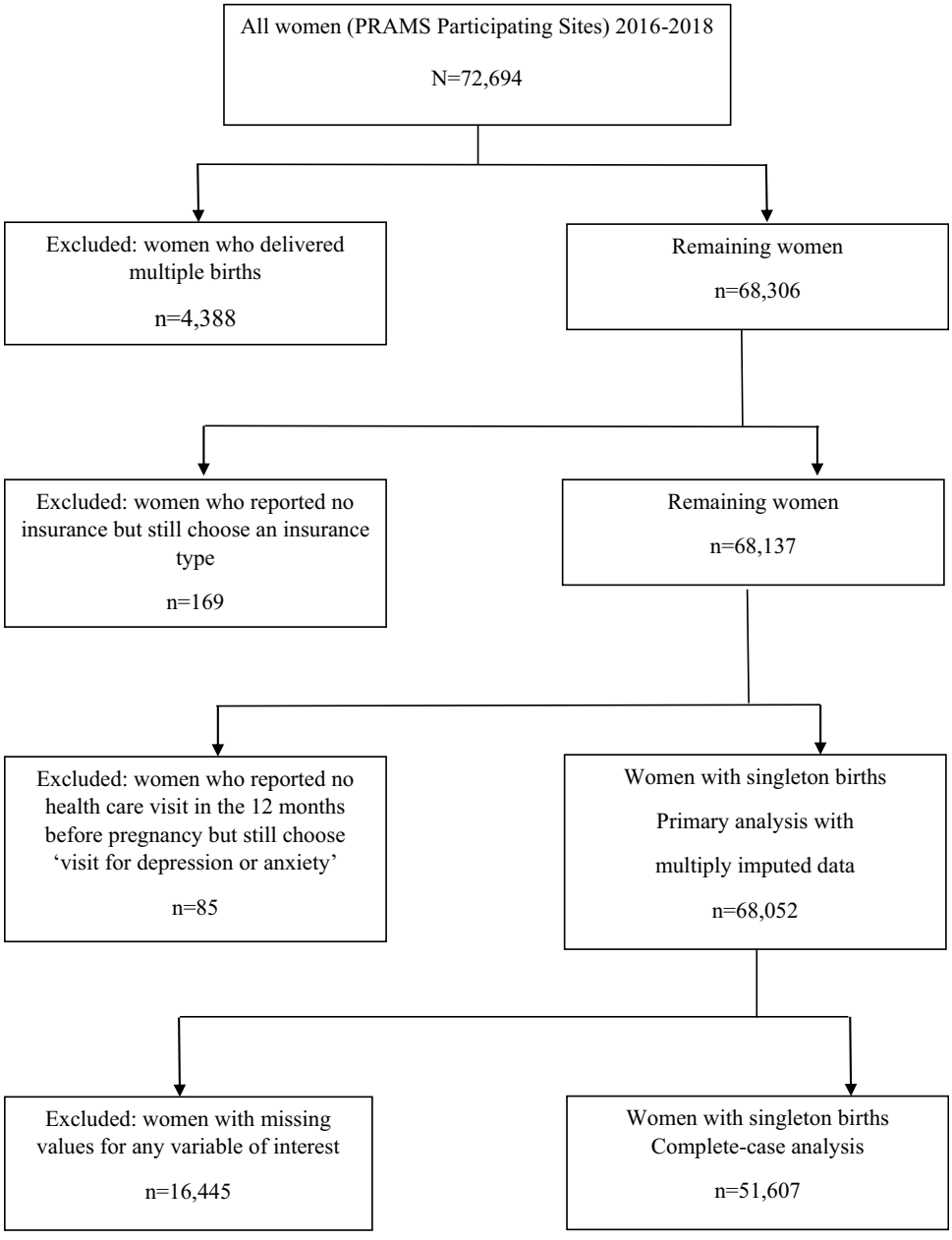

Figure 1. Exclusion criteria for sample.

outcomes. This study was based on data from the Phase 8 (2016–2018) survey of Pregnancy Risk Assessment Monitoring System (PRAMS). The Centers for Disease Control and Prevention (CDC) and state health departments jointly developed the PRAMS to identify high-risk women and infants and monitor their health status (27). PRAMS is currently used to assess about 83% of all U.S. births and collects information on maternal characteristics, behaviors, and experiences prior to conception, during pregnancy, and after delivery (27). Data are collected from a selected sample of women who had a recent live birth from each state by mail first and subsequently by a telephone interview if there is no response to repeated mailings. PRAMS data are also linked with birth certificate data which provide additional demographic and medical information for analysis (27). All women who completed the Phase 8 questionnaire ($n = 72,694$) with singleton births were eligible for the present study ($n = 68,306$). After excluding women who did not answer questions in the questionnaire with skip patterns appropriately for the insurance ($n = 169$) and healthcare visit variables ($n = 85$), our primary analytical sample included 68,052 women with 16,445 of them having missing data that were imputed for analysis (Figure 1).

Outcomes

Our outcomes of interest include PTB, LBW, SGA, and LGA. The World Health Organization (WHO) defines PTB as all births delivered at less than 37 weeks of completed gestation, and LBW as birth weights less than 2500 g (28). SGA and LGA were determined in the birth certificate based on 10th percentile and below or 90th percentile and above for gestational age and weight, respectively.

Exposure

The primary exposure in this study was HDP, and the potential effect modifier was DDP. These two variables were assessed in the PRAMS questionnaire through the question "During your most recent pregnancy, did you have any of the following health conditions?" (29) Women who checked the responses "high blood pressure (that started during this pregnancy), pre-eclampsia or eclampsia" or "depression" were considered positive for these conditions.

Covariates

We selected potential confounders based on the 10% change-in-estimate criterion and clinical relevance (30). Based on prior research, confounders that are associated with HDP and birth outcomes include maternal age, race/ethnicity, education level, cigarette use during last 3 months of pregnancy (yes or no), total household income in the 12 months before delivery, maternal pre-pregnancy body mass index (BMI), maternal weight gain, history of preterm birth (yes or no), infant sex (male or female), health insurance, prenatal care adequacy, and visit for depression or anxiety in the 12 months before pregnancy (yes or no) (31,32). Cigarette use, income, maternal BMI, health insurance and visit for depression or anxiety in the 12 months before pregnancy information were self-reported via the PRAMS questionnaire. Information on the remaining confounders was retrieved from the birth certificates.

For our analysis, maternal age was grouped to four categories: "less than 20 years," "20 to 29 years," "30–34 years" and "35 years and older." Education level was categorized as "less than high school," "high school graduate" and "college and above." Race was recoded to five categories: "White," "Black," "Asian," "other non-White" and "mixed race." In accordance with the American College of Obstetricians and Gynecologists (ACOG) guidelines on weight gain during pregnancy, maternal weight gain was categorized as "meet recommendation," "under recommendation" and "exceed recommendation" (33). Prenatal care adequacy was assessed by the Kotelchuck Index from birth certificate data, and categorized as "inadequate (received <50% of expected visits)," "intermediate (50%–79%)," "adequate (80%–109%)" and "adequate plus (≥110%)" (34). Total household income 12 months before delivery was recoded to "$20000 and less," "$20000 to $ 40000" and "more than $40000." Type of health insurance was categorized as "private/ACA (Affordable Care Act)," "Medicaid or other government insurance only," "other," "Medicaid and other" and "no insurance." BMI was categorized as "underweight or normal weight (<25 kg/m^2)," "overweight (25 – <30 kg/m^2)," and "obese (≥30 kg/m^2)."

Statistical analysis

We examined differences in sample characteristics by hypertension status during pregnancy using the Rao-Scott chi-square test for all (categorical) variables. Weighted percentages were used to describe the sample characteristics. We used modified Poisson regression model with robust error variance to examine the relationship between birth outcomes and HDP and DDP (35). We chose Poisson regression because of the retrospective cohort study design to estimate the relative risk (RR). The modified Poisson model leads to narrower confidence intervals (CIs) compared with a simple Poisson model (35). The following covariates were included in multivariable analysis to estimate the adjusted risk ratios (aRR): maternal age, race, education level, annual total household income, BMI, weight gain during pregnancy, previous preterm births, insurance type, diabetes during pregnancy, smoking in the last 3 months of pregnancy, infant sex, prenatal care adequacy, and healthcare visit for depression or anxiety 12 months before pregnancy. We performed interaction testing, including the estimation of both additive and multiplicative interaction effects, by adding an interaction term between HDP and DDP to a separate adjusted Poisson model for each of the four birth outcomes (36). Using a format proposed by Knol and VanderWeele (37), we reported aRRs and measures of interaction on both additive (relative excess risk due to interaction [RERI]) and multiplicative scales (ratio of RRs) with CIs and p-values. These estimates were generated using "interactionR" (38), an open-source R package based on Knol and VanderWeele's format, and the delta method from Hosmer and Lemeshow for the estimation of CIs of RERI (39). About 24% of the original sample had at least one missing values. Removing these observations from the analysis could result in biased parameter estimates. Therefore, we

used multiple imputation by chained equations ($m = 20$) to account for missing data (40). A sensitivity analysis using complete-case analysis ($n = 51{,}607$) was also conducted to compare the estimated effects of HDP within the strata of DDP between complete-case analysis and the primary analysis with multiply-imputed data ($n = 68{,}052$). All statistical analyses were performed using R statistical software (version 4.0.2) and R Studio software (version 1.3.1073). The "survey" package was used to account for the weighting and survey design. $\alpha = 0.05$ was considered statistically significant. The study protocol was reviewed by the Saint Louis University Institutional Review Board and was classified as exempt.

Results

The primary analysis using multiply-imputed data included 68,052 women who participated in PRAMS and had a singleton birth during 2016–2018. Of the sample, 11.7% had HDP, 11.8% had DDP, and 2.5% had both HDP and DDP (weighted percentages). Compared to women without HDP, those who had HDP are more likely to be younger than 20 years old or 35 years or older, of Black or mixed race, obese, had lower proportion of college and above level of education and lower annual total household income, had gestational weight gain exceeding recommendation, had a previous preterm birth, used Medicaid or other government insurance, had diabetes during pregnancy, smoked during pregnancy, had inadequate prenatal care, had DDP and sought care for depression or anxiety 12 months before pregnancy (Table 1).

Tables 2 and 3 present the aRRs with CIs and p-values for the interaction between HDP and DDP on the risk of PTB and LBW, SGA, and LGA, respectively. Comparing women with HDP to those without HDP, the risk of PTB was 1.58 (95% CI 1.30, 1.92) in women with DDP and 2.58 (95% CI 2.34, 2.83) in women without DDP; the risk of LBW was 1.96 (95% CI 1.54, 2.50) in women with DDP and 4.03 (95% CI 3.59, 4.54) in women without DDP (Table 2); the risk of SGA was 1.27 (95% CI 1.02, 1.57) in women with DDP and 1.50 (95% CI 1.34, 1.67) in women without DDP; the risk of LGA was 0.92 (95% CI 0.70, 1.21) in women with DDP and 0.84 (95% CI 0.74, 0.96) in women without DDP (Table 3).

The RERIs for PTB, LBW, and SGA were below 0, which indicated negative interaction across strata of DDP on an additive scale. However, these measures were not statistically significant, including the positive one for LGA. The measure of interaction on multiplicative scale, the ratios of RRs, were 0.61 (95% CI 0.50, 0.76), 0.49 (95% CI 0.37, 0.63), 0.85 (95% CI 0.67, 1.08) and 1.10 (95% CI 0.81, 1.48) for PTB, LBW, SGA, and LGA, respectively. The former two were statistically significant ($p < 0.01$), indicating negative interaction effects on the multiplicative scale for PTB and LBW. This means that the estimated joint effect of HDP and DDP was smaller than the product of the estimated independent effect of HDP and DDP.

The estimated effects of HDP within the strata of DDP using complete-case data were consistent to the results of our primary analyses in terms of magnitude and direction, which did not change the interpretations of the findings (Table 4).

Discussion

Our study found that women with HDP compared to those without, had increased risk of PTB, LBW, SGA but reduced risk of LGA, after controlling for confounders. The findings confirmed our hypothesis and were consistent with previous work (3–5). We observed that DDP increased the risk of PTB, LBW, and SGA, though not statistically significant for SGA. Our findings were also in line with a previous study that reported no additive interaction effect of HDP and DDP on birth outcomes (41). However, the adverse effects on birth outcomes among women with both conditions were lower than expected. We observed negative interaction of HDP and DDP on multiplicative scale for the risk of PTB and LBW. The joint effects were even lower than the independent effects of HDP on the risk of PTB, LBW, and SGA.

Although the causes of HDP and DDP among pregnant women are not well understood, some well-accepted pathophysiology for both HDP and DDP implicate shared physiological pathways. The abnormality of placentation that leads to reduced transfer of oxygen and nutrients to the developing fetus might trigger the maternal inflammatory response including endothelial dysfunction and increased blood pressure (42). Recent studies have also shown that inflammation was associated with depressive symptoms and adverse birth outcomes (43,44). Thus, women who have both HDP and DDP are possibly at greater risk of adverse birth outcomes than those with only one condition.

Despite the increasing prevalence of depression among pregnancy-related hospitalizations, providers may address conditions such as hypertension or diabetes during pregnancy first. However, in many cases, they would ignore or delaying the treatment of depression when patients having both depression and other medical conditions (45). The untreated DDP may lead to adverse birth outcomes and serious long-term effects

Table 1. Characteristics of study sample by hypertension status (unweighted $n = 68,052$).

Characteristics	Hypertension during pregnancy Weighted % (95% CI) Yes (11.7%)	No (88.3%)	p-value*
Maternal age			<0.01
<20 (years)	6.0 (5.2, 6.9)	4.2 (3.9, 4.4)	
20–29	47.4 (45.8, 49.0)	47.8 (47.2, 48.4)	
30–34	27.5 (26.1, 28.9)	30.1 (29.6, 30.7)	
≥35	19.1 (17.9, 20.4)	17.9 (17.5, 18.4)	
Race			<0.01
White	67.1 (65.6, 68.5)	69.9 (69.4, 70.4)	
Black	20.9 (19.6, 22.2)	14.2 (13.8, 14.6)	
Asian	3.1 (2.7, 3.6)	6.3 (6.1, 6.6)	
Other nonwhite	5.3 (4.7, 6.0)	6.7 (6.4, 7.0)	
Mixed race	3.6 (3.1, 4.2)	3.0 (2.8, 3.2)	
Education level			<0.01
Less than high school	12.4 (11.4, 13.4)	12.2 (11.8, 12.6)	
High school graduate	27.3 (25.9, 28.9)	23.3 (22.7, 23.8)	
College and above	60.3 (58.7, 61.9)	64.5 (63.9, 65.1)	
Annual total household income			<0.01
≤$20,000	32.1 (30.6, 33.7)	27.2 (26.7, 27.8)	
$20,000–$40,000	21.2 (19.8, 22.6)	20.7 (20.1, 21.2)	
>$40,000	46.7 (45.1, 48.4)	52.1 (51.5, 52.7)	
BMI			<0.01
Underweight or normal weight	33.3 (31.8, 34.9)	52.8 (52.2, 53.4)	
Overweight	26.4 (25.0, 27.9)	25.2 (24.7, 25.8)	
Obesity	40.3 (38.7, 41.9)	22.0 (21.5, 22.5)	
Weight gain during pregnancy			<0.01
Meet recommendation	22.4 (21.1, 23.7)	31.0 (30.5, 31.6)	
Under recommendation	24.2 (22.8, 25.5)	27.1 (26.5, 27.6)	
Exceed recommendation	53.5 (51.9, 55.1)	41.9 (41.3, 42.5)	
Previous preterm births			<0.01
No	95.3 (94.7, 95.9)	96.8 (96.6, 97.0)	
Yes	4.7 (4.1, 5.3)	3.2 (3.0, 3.4)	
Insurance type			<0.01
Private/ACA**	46.2 (44.5, 47.8)	50.1 (49.4, 50.7)	
Medicaid or other government insurance only	38.9 (37.3, 40.5)	35.2 (34.6, 35.8)	
Other insurance	4.6 (4.0, 5.4)	5.2 (4.9, 5.5)	
Medicaid and other insurance	8.6 (7.7, 9.6)	7.2 (6.9, 7.6)	
No insurance	1.7 (1.4, 2.2)	2.3 (2.1, 2.5)	
Diabetes during pregnancy			<0.01
No	82.5 (81.3, 83.7)	92.3 (92.0, 92.6)	
Yes	17.5 (16.3, 18.7)	7.7 (7.4, 8.0)	
Smoking in the last 3 months of pregnancy			<0.01
No	90.0 (89.0, 91.0)	92.1 (91.7, 92.4)	
Yes	10.0 (9.0, 11.0)	7.9 (7.6, 8.3)	
Infant sex			0.63
Male	51.4 (49.8, 53.0)	51.0 (50.4, 51.6)	
Female	48.6 (47.0, 50.2)	49.0 (48.4, 49.6)	
Prenatal care adequacy			<0.01
Inadequate	12.2 (11.2, 13.3)	11.7 (11.4, 12.2)	
Intermediate	7.8 (7.0, 8.7)	11.3 (11.0, 11.7)	
Adequate	34.7 (33.1, 36.3)	47.8 (47.2, 48.4)	
Adequate plus	45.3 (43.7, 46.9)	29.1 (28.6, 29.7)	
Visit for depression or anxiety 12 months before pregnancy			<0.01
No	90.5 (89.6, 91.4)	92.8 (92.4, 93.1)	
Yes	9.5 (8.6, 10.4)	7.2 (6.9, 7.6)	
Depression during pregnancy			<0.01
No	78.5 (77.2, 79.8)	89.6 (89.2, 89.9)	
Yes	21.5 (20.2, 22.8)	10.4 (10.1, 10.8)	

*P-value for Rao-Scott chi-square test.
**Affordable Care Act.

on children (23,46). However, only few prior studies have been conducted that examined depression as an effect modifier in the association between HDP and adverse birth outcomes (41). In a prospective cohort study in Canada of 2,763 women, Horsley et al (25) observed that the joint impact of HDP and depression on shorter gestational age at birth increased as depressive symptoms became greater. Findings from Horsley et al were limited by low incidence of DDP and over-sampled white, married women with high socioeconomic status. Similarly, Mogos and colleagues (41) reported that HDP and depression jointly increased risk of intrauterine growth restriction (IUGR), stillbirth, and PTB, although HDP was the

Table 2. Interaction between hypertension and depression during pregnancy on the risk of preterm birth (PTB) and low birth weight (LBW), PRAMS, 2016–2018 ($n = 68{,}052$).

	PTB			LBW		
	No Depression	Depression	Effect of depression within the strata of hypertension	No Depression	Depression	Effect of depression within the strata of hypertension
Birth outcomes	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P
No Hypertension	1.00 (Reference)	1.29 (1.13,1.48); 0.0003	1.29 (1.13,1.48); 0.0003	1.00 (Reference)	1.45 (1.21, 1.73); <0.01	1.45 (1.21, 1.73); <0.01
Hypertension	2.58 (2.34,2.83); <0.01	2.04 (1.73,2.42); <0.01	0.79 (0.66,0.95); 0.01	4.03 (3.59, 4.54); <0.01	2.84 (2.27, 3.56); <0.01	0.70 (0.56, 0.88); 0.002
Effect of hypertension within the strata of depression	2.58 (2.34,2.83); <0.01	1.58 (1.30,1.92); <0.01		4.03 (3.59, 4.54); <0.01	1.96 (1.54, 2.50); <0.01	

*Adjusted risk ratio and 95% confidence interval.
**Analysis adjusted for maternal age, race, education level, annual total household income, BMI, weight gain during pregnancy, previous preterm births, insurance type, diabetes during pregnancy, smoking in the last 3 months of pregnancy, infant sex, prenatal care adequacy, visit for depression or anxiety 12 months before pregnancy.
Measure of interaction on additive scale for PTB: RERI (95% CI) = −0.83 (−1.24, −0.41); $P = 1.00$
Measure of interaction on multiplicative scale for PTB: ratio of RRs (95% CI) = 0.61 (0.50, 0.76); $P < 0.01$.
Measure of interaction on additive scale for LBW: RERI (95% CI) = −1.64 (−2.35, −0.93); $P = 1.00$
Measure of interaction on multiplicative scale for LBW: ratio of RRs (95% CI) = 0.49 (0.37, 0.63); $P < 0.01$.

Table 3. Interaction between hypertension and depression during pregnancy on the risk of small-for-gestational-age (SGA) and large-for-gestational-age (LGA), PRAMS, 2016–2018 ($n = 68{,}052$).

	SGA			LGA		
	No Depression	Depression	Effect of depression within the strata of hypertension	No Depression	Depression	Effect of depression within the strata of hypertension
Birth outcomes	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P	RR (95% CI)*,**; P
No Hypertension	1.00 (Reference)	1.10 (0.97, 1.24); 0.15	1.10 (0.97, 1.24); 0.15	1.00 (Reference)	0.98 (0.84, 1.13); 0.76	0.98 (0.84, 1.13); 0.76
Hypertension	1.50 (1.34, 1.67); <0.01	1.39 (1.13, 1.71); 0.002	0.93 (0.75, 1.16); 0.52	0.84 (0.74, 0.96); 0.01	0.90 (0.70, 1.15); 0.41	1.07 (0.82, 1.40); 0.64
Effect of hypertension within the strata of depression	1.50 (1.34, 1.67); <0.01	1.27 (1.02, 1.57); 0.03		0.84 (0.74, 0.96); 0.01	0.92 (0.70, 1.21); 0.57	

*Adjusted risk ratio and 95% confidence interval.
**Analysis adjusted for maternal age, race, education level, annual total household income, BMI, weight gain during pregnancy, previous preterm births, insurance type, diabetes during pregnancy, smoking in the last 3 months of pregnancy, infant sex, prenatal care adequacy, visit for depression or anxiety 12 months before pregnancy.
Measure of interaction on additive scale for SGA: RERI (95% CI) = −0.20 (−0.53, 0.12); $P = 0.89$
Measure of interaction on multiplicative scale for SGA: ratio of RRs (95% CI) = 0.85 (0.67, 1.08); $P = 0.17$.
Measure of interaction on additive scale for LGA: RERI (95% CI) = 0.08 (−0.19, 0.36); $P = 0.28$
Measure of interaction on multiplicative scale for LGA: ratio of RRs (95% CI) = 1.10 (0.81, 1.48); $P = 0.55$.

Table 4. Effect of hypertension during pregnancy within the strata of depression during pregnancy comparing complete-case data and multiply-imputed data.

	Complete-case data ($n = 51,607$)		Multiply-imputed data ($n = 68,052$)	
	Depressed	Not Depressed	Depressed	Not Depressed
Birth outcomes	aRR(95%CI)*,**		aRR(95%CI)*,**	
Preterm birth	1.59 (1.31,1.92)	2.59 (2.35,2.85)	1.58 (1.30,1.92)	2.58 (2.34,2.83)
Low birth weight	1.98 (1.55,2.53)	4.08 (3.62,4.58)	1.96 (1.54, 2.50)	4.03 (3.59, 4.54)
Small for gestational age	1.27 (1.02,1.58)	1.50 (1.34,1.67)	1.27 (1.02, 1.57)	1.50 (1.34, 1.67)
Large for gestational age	0.91 (0.69,1.20)	0.84 (0.74,0.96)	0.92 (0.70, 1.21)	0.84 (0.74, 0.96)

*Adjusted risk ratio and 95% confidence interval.

**Analysis adjusted for maternal age, race, education level, annual total household income, BMI, weight gain during pregnancy, previous preterm births, insurance type, diabetes during pregnancy, smoking in the last 3 months of pregnancy, infant sex, prenatal care adequacy, visit for depression or anxiety 12 months before pregnancy.

main driving factor of the joint association over a 58-million nationwide inpatient sample. However, the cross-sectional nature of the study and failure to adjust for important confounders may have biased the study results.

The antagonistic joint effect of HDP and DDP on birth outcomes in our study was unexpected. One possible explanation is that the diagnosis of depression in women before or during pregnancy or the diagnosis of both HDP and DDP may lead to more medical screening, monitoring by the healthcare providers, and improved prenatal care that results in better pregnancy outcomes compared to healthy mothers (45). In other words, the joint effect may not be attenuated by the condition (depression) itself, but the additional care or medication. Because specific information on medication and treatment received (e.g., type, procedure, duration) for depression is not available in our dataset, failing to control for these variables as confounders may bias the results toward the null value. In addition, failure to account for the severity of HDP in the study may have biased our results as well.

The strength of this study rests in its use of a large population-based sample of women across the U.S and the availability of hypertension and depression status during pregnancy as well as information on many potential confounders. The large sample size ensured sufficient statistical power to detect significant associations and increased precision in the risk estimates. Our study adds to the existing evidence by investigating the joint effect of HDP and DDP on major adverse birth outcomes, which is rarely examined in prior research. However, there are some limitations of the present study. Firstly, the presence of HDP and DDP were self-reported by simply checking options of a single question. It may underestimate the extent of HDP and DDP due to lack of information on severity and duration of the conditions. Additionally, the specific timing of onset of HDP and the diagnosis of DDP is not available in the PRAMS data. Previous studies have shown a stronger association between HDP and elevated risks of adverse birth outcomes in mid-to-late pregnancy (6,7,9). A recent meta-analysis indicated that the risk of LBW was higher when depression was assessed in the first trimester compared to the risk measured in the second or third trimester (47). It was also found that depressive symptoms were higher at the beginning and end of pregnancy (48), and worsening symptoms during pregnancy may be associated with increased risks of adverse pregnancy outcomes (49). Besides, the onset of HDP or DDP may increase the risk of the other, which may further complicate their effects on birth outcomes (50). Therefore, given the effect of timing on varying risks of birth outcomes in existing evidence, future studies measuring HDP and DDP over time as pregnancy progresses are warranted. Similarly, potential information bias may be due to the self-report nature of the survey and birth certificate data. However, the misclassification of our data is likely non-differential which would bias the point estimates toward the null value. Future research using validated measurement for more objective data is warranted. Secondly, there may be an issue of residual confounding with our study findings due to lack of some behavioral risk factors during pregnancy (e.g., alcohol and substance use) and other relevant pregnancy history (e.g., history of LBW, stillbirth). In addition, the generalizability of this study should be interpreted with caution due to selection bias introduced by missing data. However, we addressed missingness with multiple imputation and our estimated effects of HDP within the strata of DDP from complete-case analysis were similar to those from the multiply-imputed analysis. Nevertheless, the proportion of African American women in our sample was still slightly greater than the national average for 2016–2018 (13.9% vs. 12%) (51), which could possibly explain the high incidence of HDP in our sample because African Americans are more likely than Whites to suffer from

hypertension. The final limitation is information bias resulting from misclassification of annual total household income, although we expected it would have a neglectable effect on our results.

This study confirmed findings from previous studies that women with HDP were at significantly higher risks of PTB, LBW, and SGA compared with women who do not have HDP. This highlighted the importance of early detection and management of HDP to reduce these adverse birth outcomes. We also found a significant independent effect of DDP on PTB and LBW but an unexpected antagonistic joint effect of HDP and DDP. Nonetheless, the joint effect on outcomes was greater than the independent effect of DDP on some adverse pregnancy outcomes. This highlighted the importance of depression screening among women with medical conditions for timely treatments and incentivized the development of tailored interventions in advance to maximize maternal and fetal outcomes. Future studies should examine the physiologic and pathological pathways through which depression and the concurrence of HDP and DDP affect pregnancy outcomes, as well as the persistent racial disparities in pregnancy outcomes.

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Data availability statement

The data that support the findings of this study are openly available via a data application to PRAMS at https://www.cdc.gov/prams/prams-data/researchers.htm.

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