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Maternal Hypertensive Disorders in Pregnancy and Postpartum Plasma B Vitamin and Homocysteine Profiles in a High-Risk Multiethnic U.S., Population

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Abstract

Background: Hypertensive disorders of pregnancy are a recognized risk factor of a woman's future cardiovascular risk. The potential role of micronutrients in mitigating hypertensive disorders is not fully understood. This study examined maternal postpartum plasma B vitamin profiles by hypertensive disorders of pregnancy in a high-risk multiethnic U.S. population.

Materials and Methods: The analyses included 2584 mothers enrolled within 3 days postpartum at the Boston Medical Center. Hypertensive disorders of pregnancy included gestational hypertension and pre-eclampsia disorders (pre-eclampsia, eclampsia, hemolysis, elevated liver enzymes, and/or low platelets syndrome) as documented in the medical records. Plasma folate, vitamin B12, and homocysteine levels were measured in blood samples collected at enrollment. Kernel density plots and multivariable regressions were used to examine the relationship between hypertensive disorders and postpartum B vitamin profiles.

Results: Of the 2584 mothers, 10% had pre-eclampsia disorders that were associated with significantly lower plasma folate (adjusted beta coefficient (aβ): −0.10; 95% CI: −0.22 to −0.06) and increased homocysteine (aβ: 0.08; 95% CI: 0.04–0.13), but not with vitamin B12 concentrations. These associations remained robust after adjusting for a range of pertinent covariables and were more pronounced in non-Hispanic Black women compared with other groups. However, gestational hypertension was not significantly associated with any postpartum biomarker.

Conclusions: We found that pre-eclampsia disorders, but not gestational hypertension, was associated with lower folate and higher homocysteine levels postpartum, especially among Black mothers. This finding, if further confirmed, may have implications for postpartum care, including attention to maternal micronutrient status to reduce and prevent hypertensive disorders in pregnancy-associated consequences in subsequent pregnancies and lifespan. Registration date: July 25, 2017; Registry website: https://clinicaltrials.gov/ct2/show/NCT03228875.

Keywords: B vitamins, biomarkers, high-risk, homocysteine, hypertension, pre-eclampsia

Introduction

Hypertensive disorders of pregnancy are a leading cause of maternal and infant morbidity and mortality in the United States and currently affects about 8% of pregnancies.[1,2] The rates of hypertensive disorders of pregnancy differ by race/ethnicity and is more common among non-Hispanic Black women compared with non-Hispanic White and Hispanic women, in parallel with high rates of chronic hypertension in non-Hispanic Black women.[3] Women with hypertensive disorders have a higher risk of recurrence in a subsequent pregnancy.[4] Furthermore, the effects of hypertensive disorders extend beyond pregnancy with long-term complications, including chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism, and

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impaired memory.[5] Thus, advancing the prevention of hypertensive disorders in pregnancy, and reducing its short- and long-term adverse effects, particularly among high-risk groups, is a key step to reduce maternal mortality and morbidity, a national priority.[4]

Existing research has explored the association between hypertensive disorders of pregnancy such as pre-eclampsia and genetic, metabolic, environmental, and psychosocial risk factors,[1] including maternal micronutrient status and vitamin intake during pregnancy.[6] Studies conducted in Iran,[7] Peru,[8] Poland,[9] and India[10] demonstrated elevated plasma levels of homocysteine and lower folate and vitamin B12 in women with pre-eclampsia.

There is a need for U.S.-based research exploring the effect of hypertensive disorders in pregnancy on postpartum micronutrient status or whether there are any racial or ethnic differences in these associations. Where possible, hypertensive disorders should also be explored on a spectrum of severity as gestation hypertension is typically considered to be a mild condition, whereas hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome is considered a severe form of pre-eclampsia.[11] Given the growing recognition of the impact of hypertensive disorders on long-term maternal cardiometabolic health in addition to pregnancy outcomes, such research is critically needed to inform prevention strategies for pre-eclampsia and appropriate postpartum care for pre-eclamptic women to prevent its recurrence. Optimizing micronutrient status is in general safe, inexpensive, and scalable.

This study explores the postpartum plasma folate, vitamin B12, and homocysteine profiles among mothers on a spectrum of hypertensive disorders during pregnancy in the Boston Birth Cohort (BBC)—a predominantly urban low-income multiethnic U.S. population. We classify women into three groups: (1) no hypertension, (2) gestational hypertension, and (3) pre-eclampsia disorders, including pre-eclampsia, eclampsia, and HELLP. We hypothesize that hypertensive disorders are associated with (i) reduced folate and (ii) higher homocysteine levels. We also explore the role of vitamin B12, which is less studied and posit that for all three biomarkers, the effect of pre-eclampsia disorders is greater than gestational hypertension.

Furthermore, we investigate racial/ethnic differences in the association between hypertensive disorders and postpartum B vitamins and homocysteine levels. Such information is critically needed to inform American College of Obstetricians and Gynecologists (ACOG) guidelines, which currently do not screen women for B vitamin or homocysteine during preconception, pregnancy, nor postpartum, and do not recommend the use of vitamins in the prevention or treatment of hypertensive disorders of pregnancy.[12] This research may also have implications for improving maternal postpartum care as well as early prevention of hypertensive disorders in subsequent pregnancies and its associated cardiometabolic consequences throughout the life course.[3,13]

Materials and Methods

The data are from the ongoing BBC study, which commenced in 1998.[14] Eligible mothers for the parent BBC study are those who had a singleton live infant (without major birth defects) at the Boston Medical Center (BMC), a large urban hospital serving a predominantly low-income racial minority inner-city patient population. As of 2016, the BBC study included 8509 mother–infant dyads enrolled postpartum at the BMC. The study protocol was approved by the institutional Review Boards of Boston Medical Center and Johns Hopkins Bloomberg School of Public Health.

This study includes 2584 mothers of the Boston Birth Cohort whose children continued to receive pediatric care at the BMC, and who had measurements of plasma B vitamin biomarkers (folate, vitamin B12, and homocysteine) in blood samples collected at postpartum enrollment. Of note, 2584 mothers had plasma folate and vitamin B12 measurements, whereas 2567 women had homocysteine measurements. The sampling frame is illustrated in Supplement Figure S1. The comparability of the study sample versus the overall sample is presented in Supplementary Table S1.

As described elsewhere,[14] hypertensive disorders of pregnancy was defined as the presence of any of the following physician diagnoses as documented in medical records: gestational hypertension, pre-eclampsia, eclampsia, or HELLP syndrome. Furthermore, we created subgroups of hypertensive disorders of pregnancy differentiating gestational hypertension from pre-eclampsia disorders—defined as pre-eclampsia, eclampsia, or HELLP syndrome. Plasma folate and vitamin B12 concentrations were measured by a commercial laboratory *via* chemiluminescent immunoassay using a MAGLUMI 2000 Analyzer (Snibe Co. Ltd.). Plasma homocysteine was measured using automatic clinical analyzers (Beckman-Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China.

The interassay coefficient of variation for all three markers are <6%.[15] Maternal B vitamin concentrations were assessed as continuous variables using (i) raw and (ii) log transformed concentrations. Other covariates included sociodemographic factors such as race/ethnicity (non-Hispanic Black [Black, African American, or Haitian], non-Hispanic White, Hispanic, and other), postpartum age (<20, 20–29, and 30+years), nativity (U.S. born vs. non-U.S. born), education (≤elementary, high school, or ≥college), marital status (unmarried vs. married), receipt of public assistance, including WIC (Women Infants and Children), Food Stamps, AFDC (Aid to Families with Dependent Children), Housing assistance or Fuel assistance (yes vs. no), and parity (nulliparous vs. multiparous).

Behavioral risk factors included cigarette smoking (never vs. any), alcohol consumption (never vs. any), and stress (mother's report of life or pregnancy as being very stressful). Biomedical factors included presence of either prepregnancy obesity (BMI ≥30 kg/m^2), or diabetes mellitus (gestational or pregestational diabetes), and chronic hypertension (prepregnancy hypertension).

All analyses were conducted using STATA version 15 (StataCorp LP, College Station, TX). Kernel density distribution plots were used to graph the distribution of maternal B vitamins by pre-eclampsia as well as maternal race/ethnic status. Unadjusted and adjusted linear regression models were used to explore the relationship between hypertensive disorders of pregnancy and maternal B vitamin plasma concentrations. Confounders included identified correlates of hypertensive disorders of pregnancy in the literature—maternal race (non-Hispanic Black vs. other groups), age, nativity, education, marital status, receipt of public assistance, parity, cigarette smoking, alcohol consumption, stress, obesity/diabetes, and chronic hypertension.[3]

Forest plots were conducted on the association of hypertensive disorders status with postpartum folate and homocysteine levels, stratified by key maternal characteristics (age, parity, race/ethnicity [non-Hispanic Black vs. other groups], smoking status and presence of obesity/diabetes).

All p values in the analyses were based on two-sided statistical tests and the Type I error rate was set at 0.05.

Results

Table 1 shows the distribution of maternal characteristics across the spectrum of hypertensive disorders in pregnancy. Women with gestational hypertension and pre-eclampsia disorders were more likely to be older, educated, under more self-reported stress, obese or diabetic, and have chronic hypertension. A full description of the study sample in comparison with all BBC study participants is presented in Supplementary Table S1 highlighting many similarities between this study sample and the entire BBC. Of note, only 3% of women in the sample had gestational hypertension, whereas 10% had pre-eclampsia disorders.

The prevalence of gestational hypertension was 3.0% among non-Hispanic Blacks, 2.0% among Hispanics, and 3.0% among others. The prevalence of pre-eclampsia disorders was 11.0% among non-Hispanic Blacks, 8.5% among Hispanics, and 8.5% among others. Further breakdown of postpartum B vitamins and homocysteine concentrations by subgroup of hypertensive disorders in pregnancy (gestational hypertension, pre-eclampsia/eclampsia, and HELLP), are presented in Supplementary Table S2.

Figure 1 highlights the kernel density of postpartum biomarkers by the hypertensive disorders of pregnancy. Women with gestational hypertension and pre-eclampsia disorders had reduced folate and vitamin B12 levels but higher homocysteine levels.

In Table 2, the differences in postpartum maternal B vitamin biomarkers across the spectrum of hypertensive disorders status in overall samples and by race/ethnicity were described. Overall, elevated levels of plasma homocysteine and lower folate and vitamin B12 were seen in women with gestational hypertension and pre-eclampsia disorders. These associations were strongest among non-Hispanic Black women. Table 3 highlights the effect of hypertensive disorders on log transformed maternal B vitamin and homocysteine biomarkers in total sample as well as by race/ethnicity, using multivariable linear regression models. In the overall sample, gestational hypertension did not have a significant association with the postpartum biomarkers.

However, the presence of pre-eclampsia disorders was significantly associated with lower plasma folate (adjusted beta coefficient [aβ]: −0.14; 95% CI: −0.22 to −0.06) but higher homocysteine (aβ: 0.08; 95% CI: 0.04–0.13) concentrations postpartum. In contrast, the relationship between pre-eclampsia disorders and vitamin B12 concentration was not significant (aβ: 0.02; 95% CI: −0.03 to 0.07). Racial/ethnic differences were also seen as the relationship between pre-eclampsia disorders and maternal B vitamin/homocysteine biomarkers was strongest in non-Hispanic Black women. Specifically, the presence of pre-eclampsia disorders was significantly associated with lower plasma folate (aβ: −0.17; 95% CI: −0.26 to −0.07) among non-Hispanic Black women only.

Pre-eclampsia disorders were associated with higher homocysteine concentrations postpartum among Hispanic (aβ: 0.18; 95% CI: 0.07–0.29) as well as non-Hispanic Black women (aβ: 0.08; 95% CI: 0.03–0.15).

Figures 2 and 3 are forest plots of the association of pre-eclampsia disorders with postpartum plasma folate and homocysteine levels, respectively, stratified by key maternal characteristics—age, parity, race/ethnicity, smoking status, and medical conditions—presence of obesity/diabetes. Subgroups of women with significant associations between pre-eclampsia disorders and postpartum plasma folate levels include women aged 20–29 years, primipara, non-Hispanic Blacks, nonsmokers, and obese/diabetic women. Of note, there was a significant interaction in the relationship between pre-eclampsia disorders and postpartum plasma folate levels among non-Hispanic Blacks versus other groups (confirming our earlier analyses by race/ethnicity). In contrast, all subgroups of women except those <30 years of age as well as current smokers and obese/diabetic women had significant associations between hypertensive disorders and postpartum homocysteine levels.

Discussion

In this multiethnic U.S. low-income population, we analyzed postpartum micronutrient biomarkers (folate, B12, and homocysteine) in relation to a spectrum of hypertensive disorders: (1) no hypertension, (2) gestational hypertension, and (3) pre-eclampsia disorders, including pre-eclampsia, eclampsia, and HELLP syndrome. We found that pre-eclampsia disorders were significantly associated with lower plasma folate and higher homocysteine concentrations postpartum, particularly among non-Hispanic Black women. In contrast, gestational hypertension, a mild form of hypertensive disorder during pregnancy, was not associated with these biomarkers.

Although pre-eclampsia disorders were a recognized risk factor of a woman's future cardiovascular risk, little is known about the underlying link and how to break it. Our findings are supportive of previous published data on the role of folate and homocysteine in cardiovascular health.[16,17] Folate and homocysteine levels are inversely correlated, and high concentrations of homocysteine are a documented risk factor for vascular disease and higher levels of homocysteine can damage endothelial cells and cause endothelial dysfunction, which is characteristic of pre-eclampsia.

Studies have demonstrated that high homocysteine in early pregnancy is a risk factor for pre-eclampsia.[16,17] In addition, elevated levels of homocysteine in women with pre-eclampsia exist from early pregnancy and remain high until postpartum.[17] In this study, given the blood samples were collected within a few days after delivery, we speculate that the samples are likely reflective of circulating folate, B12, and homocysteine levels at late pregnancy. Future studies with blood collections at preconception and specific trimesters are needed to determine if the differences might have existed before pregnancy and/or were worsened during the pregnancy.

Our study findings, if further confirmed, have a number of clinical and public health implications. First, this study underscores the importance of optimizing maternal micronutrient status during both prenatal and postnatal periods as they play an important role in cellular growth, replication, and repair; and their deficiencies have been linked with hypertensive disorders.[18] Specifically, elevated homocysteine levels are

Table 1. Characteristics of Study Mothers Who Had Measurements of Plasma B Vitamins Stratified by Pre-Eclampsia Status During Pregnancy, A Subsample of the Boston Birth Cohort

	Spectrum of hypertensive disorders of pregnancy								
	Total (N = 2584)		*No hypertension (N = 2246)*		*Gestational hypertension (N = 73)*		*Pre-eclampsia disorders*[a] *(N = 265)*		p *value*
Maternal characteristics	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	
Race/ethnicity									0.401
Non-Hispanic Black[b]	1772	69	1522	68	54	74	196	74	
Hispanic	504	20	451	20	10	14	43	16	
Other	305	12	270	12	9	12	26	10	
Missing	3	0	3	0	0	0	0	0	
Age in years									0.005
<20	252	10	228	10	6	8	18	7	
20–29	1289	50	1141	51	36	49	112	42	
30+	1043	40	877	39	31	42	135	51	
Nativity (U.S. born)									0.856
Not born in U.S.	1531	59	1336	59	43	59	152	57	
Born in U.S.	1005	39	870	39	29	40	106	40	
Missing	48	2	40	2	1	1	7	3	
Education									0.009
Less than high school	727	28	656	29	17	23	54	20	
High school/GED	932	36	781	35	29	40	122	46	
Some college and above	907	35	792	35	27	37	88	33	
Missing	18	1	17	1	0	0	1	0	
Marital status									0.487
Married	902	35	777	35	25	34	100	38	
Unmarried	1656	64	1448	64	46	63	162	61	
Missing	26	1	21	1	2	3	3	1	
Receipt of public assistance[c]									0.128
No	339	13	288	13	16	22	35	13	
Yes	2231	86	1944	87	57	78	230	87	
Missing	14	1	14	1	0	0	0	0	
Parity									0.763
Multiparous	758	29	663	30	18	25	77	29	
Primiparous	1822	71	1580	70	55	75	187	71	
Missing	4	0	3	0	0	0	1	0	
Cigarette smoking									0.830
Never smoked	2089	81	1821	81	58	79	210	79	
Ever smoked	472	18	405	18	15	21	52	20	
Missing	23	1	20	1	0	0	3	1	
Alcohol consumption									0.702
No	2308	89	2008	89	67	92	233	88	
Yes	199	8	173	8	3	4	23	9	
Missing	77	3	65	3	3	4	9	3	
High stress[d]									0.001
No	2042	79	1787	80	67	92	188	71	
Yes	529	20	447	20	6	8	76	29	
Missing	13	1	12	1	0	0	1	0	
Presence of diabetes mellitus or obesity									<0.001
No	1814	70	1626	72	40	55	148	56	
Yes	769	30	619	28	33	45	117	44	
Missing	1	0	1	0	0	0	0	0	
Chronic hypertension									<0.001
No	2414	93	2152	96	73	100	189	71	
Yes	170	7	94	4	0	0	76	29	

[a]Defined as pre-eclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome.
[b]Non-Hispanic Black includes maternal self-report as Black, African American, or Haitian.
[c]Public assistance is defined as receipt of any of the following: WIC (Women Infants and Children), food stamps, AFDC (Aid to Families with Dependent Children), housing assistance, or fuel assistance.
[d]Mother's self-report of life or pregnancy being very stressful. $p \leq 0.5$, $p \leq 0.01$, $p \leq 0.001$.

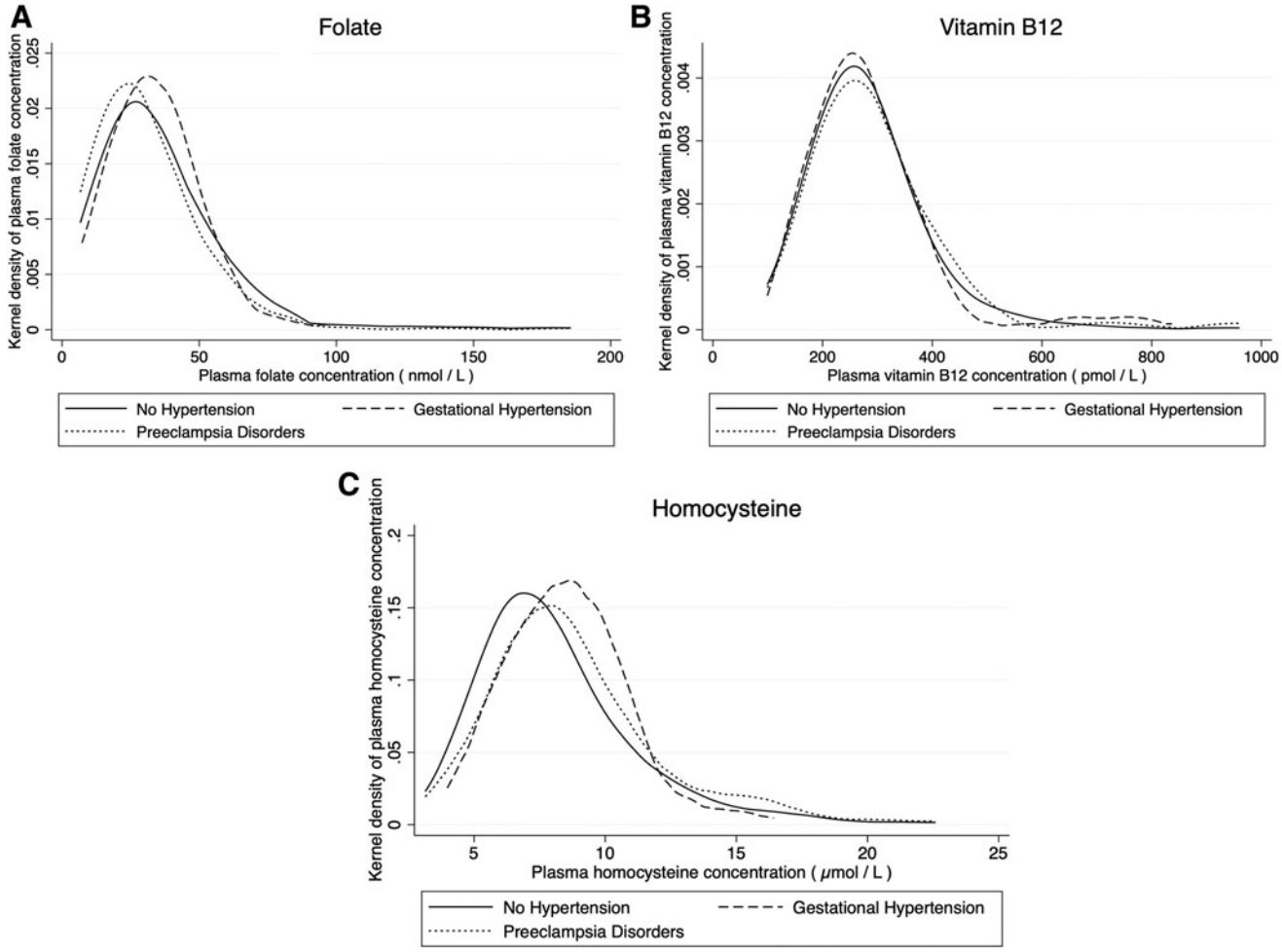

FIG. 1. Postpartum plasma folate, vitamin B12, and homocysteine distribution by spectrum of hypertensive disorders in pregnancy: **(A)** folate, **(B)** vitamin B12, and **(C)** homocysteine.

associated with higher risk of cardiovascular diseases in adults, including hypertension, arteriosclerosis, and stroke.[19,20]

Second, the use of multivitamin supplements particularly in early pregnancy has been advocated to ensure optimal perinatal outcomes and remain a relatively low-cost, safe, and feasible clinical and public health intervention for all women of childbearing age. Our prior study showed that maintaining adequate folate status until the third trimester was associated with lower risk of preterm birth—a complication of hypertensive disorders of pregnancy.[14]

Folate supplements are an effective treatment to lower homocysteine levels and folate supplementation, or fortification remains a simple and cost-effective intervention, which may prove particularly useful in preventing hypertensive disorders in the populations with low folate and/or high homocysteine status. Even in the U.S. setting with a mandatory folic acid fortification program, this study showed that among high-risk populations such as the BBC, lower folate levels, and elevated homocysteine may be a modifiable cardiovascular risk factor associated with hypertensive disorders in pregnancy.

Third, our data showed a clear linkage of lower postpartum folate levels with pre-eclampsia disorders in pregnancy, a prenatal condition. Several studies have shown the association between folic acid supplementation and pre-eclampsia.[15,21] Preconception or prenatal interventions remain key in preventing or ameliorating the risk of pre-eclampsia disorders and its associated adverse effects.[22] Given the fact that pre-eclampsia disorders in pregnancy have long-term impacts and tends to recur in subsequent pregnancies, optimal postpartum, and interpregnancy care for women with hypertensive disorders, including correction of low levels of B vitamins and elevated homocysteine, may help to reduce future risk of hypertensive disorders and cardiovascular consequences.

In the United States, women are typically discharged from the hospital on postpartum day 2–4 and ACOG recommend a single blood pressure check between 3 and 10 days postpartum for women with a hypertensive disorder of pregnancy.[11] Our findings, if further confirmed, suggest that attention to B vitamin status should be part of the early postpartum visit among women with hypertensive disorders during pregnancy. Furthermore, ACOG and the Society for Maternal Fetal Medicine (SMFM) recommend interpregnancy care for women who have a history of hypertensive disorders of pregnancy, which offers another window of opportunity to follow up B vitamin status among women with hypertensive disorders during pregnancy.

Table 2. Mean (SD) and Median (IQR) of Postpartum Plasma Folate, B12, and Homocysteine by Spectrum of Hypertensive Disorders of Pregnancy, Stratified by Race/Ethnicity

	No hypertension		*Gestational hypertension*		*Pre-eclampsia disorders*[a]		
	Mean (SD)	*Median (IQR)*	*Mean (SD)*	*Median (IQR)*	*Mean (SD)*	*Median (IQR)*	p *value*[b]
Folate							
Total ($N=2584$)	35.50 (23.83)	30.33 (24.08)	33.54 (15.71)	31.90 (18.39)	30.37 (20.07)	26.54 (22.82)	0.003
Non-Hispanic Black ($N=1775$)	34.61 (22.91)	29.45 (24.61)	30.33 (13.32)	29.97 (15.17)	29.14 (20.56)	25.35 (21.61)	0.003
Hispanic ($N=504$)	35.86 (25.06)	30.63 (21.11)	37.97 (8.70)	39.32 (15.93)	34.71 (17.60)	29.59 (20.82)	0.919
Other ($N=305$)	39.90 (26.23)	35.07 (24.88)	47.86 (25.23)	44.98 (23.73)	32.51 (19.74)	31.07 (22.82)	0.232
Vitamin B12							
Total ($N=2584$)	283.83 (109.51)	265.39 (109.27)	288.65 (123.64)	264.39 (113.14)	296.97 (132.76)	269.15 (127.02)	0.192
Non-Hispanic Black ($N=1775$)	291.75 (112.76)	272.74 (112.63)	284.79 (116.50)	260.80 (117.20)	304.40 (139.70)	274.51 (131.09)	0.312
Hispanic ($N=504$)	269.61 (106.42)	252.41 (108.59)	268.03 (84.44)	235.69 (140.84)	269.07 (118.32)	241.49 (105.68)	0.999
Other ($N=305$)	262.82 (89.25)	252.29 (91.78)	334.76 (191.38)	293.79 (55.66)	287.12 (92.33)	254.90 (107.94)	0.041
Homocysteine							
Total ($N=2567$)	8.15 (3.03)	7.51 (3.33)	8.50 (2.26)	8.49 (2.80)	8.84 (3.28)	8.13 (3.18)	0.002
Non-Hispanic Black ($N=1758$)	8.35 (3.14)	7.68 (3.44)	8.63 (2.50)	8.46 (3.43)	9.00 (3.32)	8.30 (3.60)	0.022
Hispanic ($N=504$)	7.77 (2.79)	7.25 (3.05)	8.88 (0.98)	9.15 (0.67)	8.93 (3.34)	8.01 (2.92)	0.021
Other ($N=305$)	7.66 (2.63)	7.20 (2.85)	7.31 (1.38)	7.09 (1.14)	7.46 (2.61)	6.95 (3.13)	0.865

[a]Defined as the presence of one of the following: pre-eclampsia, eclampsia, or HELLP syndrome.
[b]Test for significant difference in mean biomarker level by hypertensive disorders of pregnancy status.
IQR, interquartile range; N, number; SD, standard deviation; HELLP, hemolysis, elevated liver enzymes, low platelets.

Table 3. Crude and Adjusted Mean Difference in Postpartum Plasma Folate, B12, and Homocysteine Among Women with Pre-Eclampsia/Eclampsia/HELLP and Among Women with Gestational Hypertension as Compared with Women Without any of Those Conditions

Race/ethnicity	*Gestational hypertension*				*Pre-eclampsia disorders*[a]			
	Crude linear regression		*Adjusted*[b] *linear regression*		*Crude linear regression*		*Adjusted*[b] *linear regression*	
	β *(95% CI)*	p *value*	*a*β *(95% CI)*	p *value*	β *(95% CI)*	p *value*	*a*β *(95% CI)*	p *value*
LnFolate								
Total (*N* = 2584)	0.01 (–0.13 to 0.15)	0.909	0.01 (–0.13 to 0.15)	0.850	–0.15 (–0.22 to –0.07)	0.001	–0.14 (–0.22 to –0.06)	0.001
Non-Hispanic Black (*N* = 1775)	–0.06 (–0.22 to 0.11)	0.486	–0.06 (–0.22 to 0.11)	0.488	–0.17 (–0.26 to –0.08)	0.001	–0.17 (–0.26 to –0.07)	0.001
Hispanic (*N* = 504)	0.20 (–0.15 to 0.56)	0.257	0.18 (–0.17 to 0.53)	0.316	0.03 (–0.15 to 0.20)	0.763	0.05 (–0.13 to 0.24)	0.572
Other (*N* = 305)	0.21 (–0.17 to 0.59)	0.279	0.23 (–0.14 to 0.60)	0.222	–0.22 (–0.45 to 0.01)	0.065	–0.20 (–0.44 to 0.03)	0.089
Ln Vitamin B12								
Total (*N* = 2584)	0.01 (–0.07 to 0.10)	0.753	0.02 (–0.06 to 0.10)	0.677	0.03 (–0.01 to 0.08)	0.169	0.02 (–0.03 to 0.07)	0.392
Non-Hispanic Black (*N* = 1775)	–0.03 (–0.12 to 0.07)	0.609	–0.02 (–0.12 to 0.08)	0.738	0.03 (–0.02 to 0.07)	0.392	0.02 (–0.03 to 0.08)	0.383
Hispanic (*N* = 504)	0.01 (–0.20 to 0.23)	0.899	0.01 (–0.21 to 0.23)	0.947	0.02 (–0.13 to 0.09)	0.725	–0.03 (–0.15 to 0.08)	0.562
Other (*N* = 305)	0.20 (–0.01 to 0.42)	0.067	0.21 (–0.02 to 0.43)	0.060	0.09 (–0.04 to 0.22)	0.182	0.09 (0.05–0.23)	0.198
Ln homocysteine								
Total (*N* = 2567)	0.07 (–0.01 to 0.15)	0.096	0.06 (–0.01 to 0.14)	0.111	0.08 (0.04– 0.12)	<0.001	0.08 (0.04–0.13)	<0.001
Non-Hispanic Black (*N* = 1758)	0.05 (–0.04 to 0.15)	0.259	0.06 (–0.03 to 0.16)	0.192	0.08 (0.03– 0.13)	0.004	0.09 (0.03–0.15)	0.001
Hispanic (*N* = 504)	0.18 (–0.02 to 0.39)	0.081	0.17 (–0.04 to 0.38)	0.104	0.13 (0.03– 0.24)	0.011	0.18 (0.07– 0.29)	<0.001
Other (*N* = 305)	–0.01 (–0.22 to 0.20)	0.906	–0.01 (–0.23 to 0.20)	0.909	–0.04 (–0.16 to 0.09)	0.576	–0.05 (–0.19 to 0.08)	0.434

[a]Defined as the presence of one of the following: pre-eclampsia, eclampsia, or HELLP syndrome.
[b]Adjusted for maternal race, age, nativity, education, marital status, receipt of public assistance, parity, cigarette smoking, alcohol consumption, stress, presence of obesity or diabetes, and chronic hypertension.
aβ, adjusted beta coefficient; β, beta coefficient; Ln, natural log; N, number.

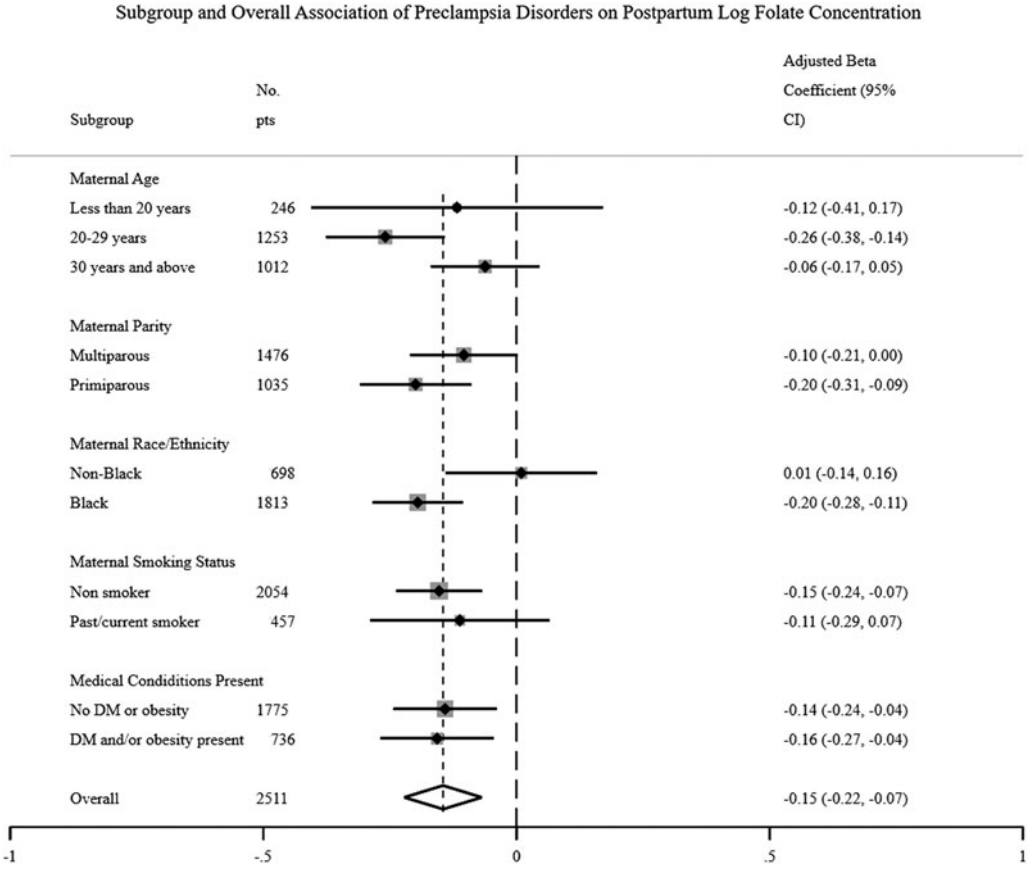

FIG. 2. Forest plots on the association of pre-eclampsia status with postpartum folate levels, stratified key maternal characteristics (age, parity, race/ethnicity, smoking status, and medical conditions.

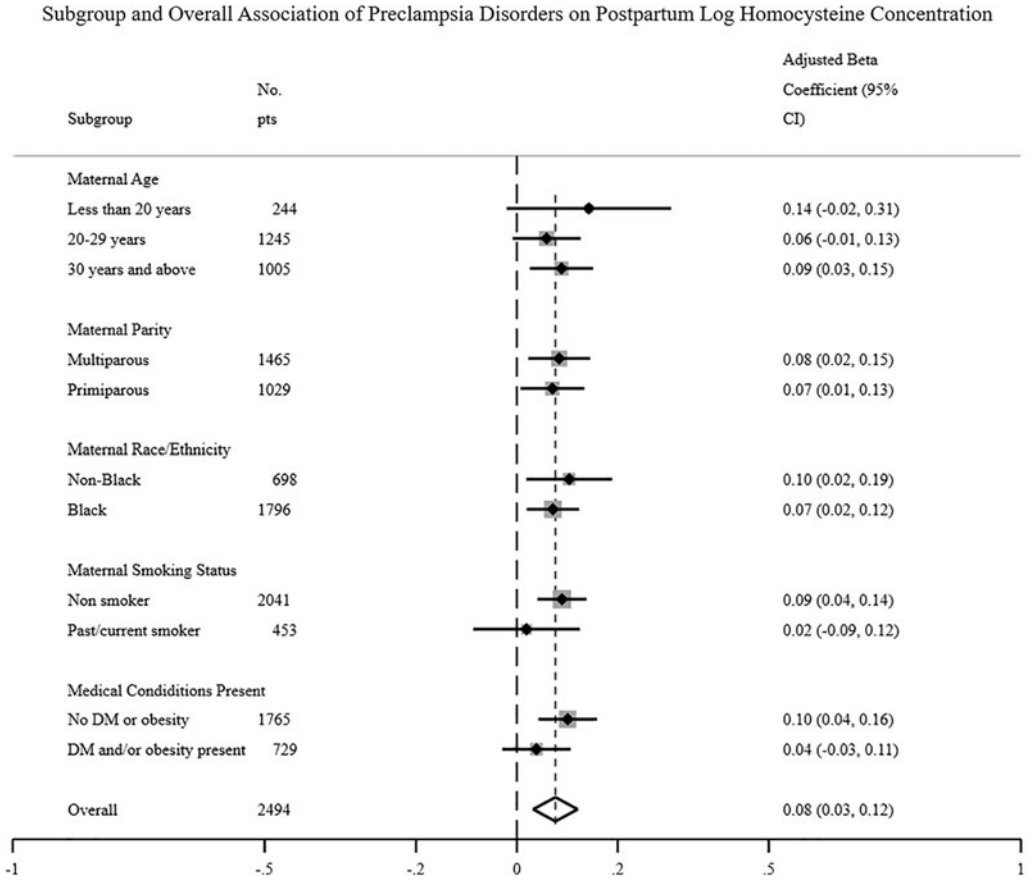

FIG. 3. Forest plots on the association of pre-eclampsia status with postpartum homocysteine levels, stratified by key maternal characteristics (age, parity, race/ethnicity, smoking status, and medical conditions.

Finally, given the racial/ethnic differences highlighted by this study, it appears that additional attention needs to be given to minority populations, including non-Hispanic Black and Hispanic women.

Other subgroups of interest may potentially include older nulliparous women as well as those with existing cardiometabolic conditions. Attention to these high-risk groups will help reduce long-standing health disparities in maternal perinatal morbidity and mortality and women's health in the United States. Our study results may be also relevant to low-resource settings globally, where there are high rates of hypertensive disorders and a lack of a formal micronutrient fortification program.[23] In such settings, there may be an even greater need to improve micronutrient levels to potentially mitigate adverse pregnancy outcomes and associated consequences.[24]

This study has some limitations. We recognize that a single plasma maternal B vitamins measurement postpartum cannot be used to differentiate between a transitory decrease in dietary intake and chronic deficiency/excess states. However, in populations that have stable sources of micronutrients, such as in the United States where there is mandatory folic acid fortification, plasma concentrations are unlikely to fluctuate dramatically. In addition, the small sample size of women with gestational hypertension did not allow for more rigorous analysis and our observational study design did not permit inferences of causality. Finally, although we have adjusted major known confounders in the analyses, unmeasured or unknown confounding may still be an issue. Owing to these limitations, our findings serve as hypothesis generating rather than as conclusive. Additional prospective studies are needed to confirm our findings.

Conclusion

In summary, our study found that in this predominantly urban low-income multiethnic U.S. population, pre-eclampsia disorders were significantly associated with lower plasma folate and higher homocysteine concentrations postpartum, particularly among non-Hispanic Black women. Our study findings, if further confirmed, may have implications for postpartum and interpregnancy care, including attention to maternal micronutrient status to prevent hypertensive disorders in pregnancy and reduce its associated consequences in subsequent pregnancies and lifespan.

Authors' Contributions

B.O., S.A., and X.W. designed research; B.O. performed statistical analyses; G.W. and X.H. performed laboratory assays; B.O. wrote the article; and all other coauthors have participated in data interpretation and presentation, critical review, and revision of the article. X.W. is the PI of the Boston Birth Cohort and had primary responsibility for final content.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Figure S1

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