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ORIGINAL RESEARCH

Preeclampsia Across Pregnancies and Associated Risk Factors: Findings From a High-Risk US Birth Cohort

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BACKGROUND: Preeclampsia increases women's risks for maternal morbidity and future cardiovascular disease. The aim of this study was to identify opportunities for prevention by examining the association between cardiometabolic risk factors and preeclampsia across 2 pregnancies among women in a high-risk US birth cohort.

METHODS AND RESULTS: Our sample included 618 women in the Boston Birth Cohort with index and subsequent pregnancy data collected using standard protocols. We conducted log-binomial univariate regression models to examine the association between preeclampsia in the subsequent pregnancy (defined as incident or recurrent preeclampsia) and cardiometabolic risk factors (ie, obesity, hypertension, diabetes mellitus, preterm birth, low birth weight, and gestational diabetes mellitus) diagnosed before and during the index pregnancy, and between index and subsequent pregnancies. At the subsequent pregnancy, 7% (36/540) had incident preeclampsia and 42% (33/78) had recurrent preeclampsia. Compared with women without obesity, women with obesity had greater risk of incident preeclampsia (unadjusted risk ratio [RR], 2.2 [95% CI, 1.1–4.5]) and recurrent preeclampsia (unadjusted RR, 3.1 [95% CI, 1.5–6.7]). Preindex pregnancy chronic hypertension and diabetes mellitus were associated with incident, but not recurrent, preeclampsia (hypertension unadjusted RR, 7.9 [95% CI, 4.1–15.3]; diabetes mellitus unadjusted RR, 5.2 [95% CI, 2.5–11.1]. Women with new interpregnancy hypertension versus those without had a higher risk of incident and recurrent preeclampsia (incident preeclampsia unadjusted RR, 6.1 [95% CI, 2.9–13]); recurrent preeclampsia unadjusted RR, 2.4 [95% CI, 1.5–3.9]).

CONCLUSIONS: In this diverse sample of high-risk US women, we identified modifiable and treatable risk factors, including obesity and hypertension for the prevention of preeclampsia.

Key Words: hypertension ■ obesity ■ preeclampsia/pregnancy ■ pregnancy and postpartum ■ prevention ■ women and minorities

Preeclampsia, a pregnancy-specific multisystem disorder characterized by the development of hypertension and proteinuria (or other evidence of end-organ damage) after 20 weeks of gestation, complicates approximately 2% to 8% of pregnancies in the United States.[1] Similar to broader trends in overall maternal morbidity and mortality, preeclampsia disproportionately affects underrepresented racial and ethnic groups.[2,3] Black women experience a 1.5 times higher incidence of severe preeclampsia and >3 times higher incidence of preeclampsia superimposed on chronic hypertension, compared with White women.[4] In addition, Black women experience more maternal and obstetric complications related to preeclampsia[5] and have a 2 to 3 times higher preeclampsia case fatality rate compared with White women.[6] Similarly, preeclampsia represents the leading cause of pregnancy-related death among Hispanic women, and the risk of mortality related to preeclampsia is 3 to 8 times higher among Hispanic women compared with White women.[3,7]

Although the definitive management for preeclampsia involves delivery, preeclampsia is recognized as a

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CLINICAL PERSPECTIVE

What Is New?

- In a large birth cohort in a racially and ethnically diverse population, we identified women who had 2 pregnancies (index and subsequent) and assessed the relationship between prepregnancy (versus interpregnancy) cardiometabolic risk factors and preeclampsia.
- Preindex pregnancy obesity, diabetes mellitus, and chronic hypertension were independently and jointly associated with the risk of incident preeclampsia at a subsequent pregnancy.
- Preindex pregnancy overweight and obesity and a new diagnosis of interpregnancy hypertension were associated with recurrent preeclampsia (in both index and subsequent pregnancies).

What Are the Clinical Implications?

- A life course perspective considers reproductive health in the development of chronic disease and adverse pregnancy outcomes; obesity and chronic hypertension are modifiable risk factors that impact incident and recurrent preeclampsia risk.
- Behavioral interventions to reduce prepregnancy and interpregnancy overweight or obesity are important to address preeclampsia risk and may also reduce risk of postpartum development of other obesity-related cardiometabolic diseases.
- There is a need to develop effective behavioral interventions for low income and historically marginalized communities who face structural and interpersonal barriers to weight loss to enhance long-term sustainability of behavior change and wellness.

Nonstandard Abbreviations and Acronyms

DM	diabetes mellitus
GDM	gestational diabetes mellitus

risk factor for future diagnoses of chronic hypertension[8,9] and other significant cardiovascular outcomes such as stroke, coronary artery disease, and heart failure.[10–14] Preeclampsia itself is an independent risk factor for the development of early cardiovascular disease.[15,16] Importantly, preventable prepregnancy cardiometabolic risk factors are also significant risk factors for the development of preeclampsia. For example, women with prepregnancy chronic hypertension have a 5-fold greater risk of superimposed preeclampsia, and chronic diabetes mellitus (DM) is associated with a 3- to 4-fold greater risk of preeclampsia. In terms of pregnancy-related factors, having a history of preeclampsia in a prior pregnancy is the strongest risk factor for preeclampsia development (unadjusted risk ratio [RR] 8.4 [95% CI, 7.1–9.9]).[17,18]

In trying to understand associations between cardiometabolic risk factors and preeclampsia risk, most previous studies have focused on the role of prepregnancy body mass index (BMI) or interpregnancy weight change on preeclampsia risk and included predominantly White populations.[19] Few longitudinal studies have broadly assessed multiple cardiometabolic health conditions (chronic DM, chronic hypertension, gestational DM [GDM], preterm birth, low-birth-weight infant) and considered the timing of diagnosis (ie, prepregnancy, during pregnancy, and between pregnancies).

A prospective birth cohort with repeat pregnancies provides a unique opportunity to (1) examine longitudinal associations between maternal health conditions and preeclampsia risk in subsequent pregnancy and (2) propose life course–informed interventions to ameliorate risk and improve future pregnancy outcomes and long-term health.[20,21] Using maternal data from the Boston Birth Cohort, a racially/ethnically diverse cohort of predominantly low-income pregnant women and infants, we identified a subsample of women who had both an index and subsequent pregnancy captured within the cohort. We had 2 study outcomes and corresponding aims. We assessed the association between prepregnancy, pregnancy, and interpregnancy cardiometabolic risk factors and the outcome of incident preeclampsia, that is, preeclampsia diagnosed only in a subsequent pregnancy compared with never having preeclampsia (Aim 1); and the outcome of recurrent preeclampsia, that is, preeclampsia diagnosed in both pregnancies compared with diagnosed only in the index pregnancy (Aim 2).

METHODS

The data used to conduct this research will be made available by the corresponding author upon reasonable request and after institutional review board review.

The institutional review boards of Boston Medical Center and the Johns Hopkins Bloomberg School of Public Health approved the study protocol, and all participants gave written informed consent.

Study Design, Setting, and Sample Selection

We analyzed maternal data from the Boston Birth Cohort. The Boston Birth Cohort is a prospective birth cohort designed with oversampling of preterm birth/low-birth-weight infants. The study took place at Boston Medical Center, which serves a low-income, predominately minority population in the inner city of Boston, Massachusetts. Details about the study design have been previously published.[22] Women were recruited into the study if they met the criteria for a case (gestational age <37 weeks or birth weight <2500 g) or control (gestational age ≥37 weeks and birth weight ≥2500 g). For every case, approximately 2 controls matched for age and ethnicity were enrolled in the study. Women were excluded from the study if they had a multiple gestation pregnancy, a pregnancy that resulted from in vitro fertilization, a preterm birth caused by trauma, or a fetus with severe birth defects. Since 1998 to the end of 2015, there have been 7890 unique mother–infant pairs enrolled in the parent study.

This study includes a subset of the Boston Birth Cohort, which consisted of 618 mothers who had 2 live births (index birth and subsequent birth), enrolled in the cohort.

Definition of Key Variables

Maternal electronic health record data and laboratory data, including maternal blood samples, were collected for all participants. In addition, all participants were interviewed 1 to 3 days after delivery using standardized questionnaires.

Primary Exposures: Prepregnancy, Pregnancy, and Interpregnancy Cardiometabolic Risk Factors

The primary exposures of interest were cardiometabolic risk factors in 1 of these 3 perinatal intervals: before the index pregnancy (preindex), diagnosed during the index pregnancy, or acquired between pregnancies (ie, not present at index pregnancy) but reported as diagnosed before the subsequent pregnancy (interpregnancy).

We assessed several chronic cardiometabolic conditions including obesity, chronic DM, and chronic hypertension. We used self-reported prepregnancy weight and height (ascertained during maternal interview) to calculate BMI (kilograms per meters squared). Validation of self-reported prepregnancy weight in this cohort has been previously described; the Pearson correlation coefficient between self-reported prepregnancy weight and electronic health record–documented weight at first prenatal appointment was 0.93.[23] We defined BMI cut points and categorized overweight as a BMI≥25 and <30 kg/m^2 and obesity as a BMI≥30 kg/m^2.[24] Chronic hypertension was defined using the electronic health record as blood pressure ≥140/90 persistently present (eg, >1 elevated blood pressure reading*)* before or up to 20 weeks of gestation. Chronic DM was defined by physician diagnosis as documented in the electronic health record.

We evaluated pregnancy complications known to be independently associated with future cardiovascular disease (GDM, preterm birth, and low-birth-weight infant).[25] GDM diagnosis was ascertained via the electronic health record. Preterm birth was defined as delivery at gestational age <37 weeks. Gestational age was defined by an algorithm based on 2 methods: time since the first day of the last menstrual cycle and confirmed by early ultrasound as previously described.[22] Low birth weight was defined as infant birth weight <2500 g at delivery.

Definition of Main Outcomes: Incident or Recurrent Preeclampsia

Preeclampsia was defined using standard clinical criteria with data abstracted from the electronic health record.[1] These criteria were: blood pressure >140/90 on 2 separate occasions, and evidence of at least 1+ proteinuria in urine after 20 weeks gestation.[1] In this study, eclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome were included in the diagnosis of preeclampsia.[26] Gestational hypertension was not included in the definition because of >10% missingness of this variable. Women with gestational hypertension were classified as not having preeclampsia.

We defined the subsequent pregnancy outcomes based on the preeclampsia status at the index and subsequent pregnancies: "never preeclampsia," no preeclampsia at either the index or subsequent pregnancy; "incident preeclampsia," no preeclampsia at the index pregnancy, preeclampsia at the subsequent pregnancy; "nonrecurrent preeclampsia," preeclampsia at the index pregnancy, no preeclampsia at the subsequent pregnancy; or "recurrent preeclampsia," preeclampsia at both the index and subsequent pregnancy.

Other Covariates

We calculated the time interval between pregnancies, the interpregnancy BMI change, and the interpregnancy percent weight change. Maternal age at delivery and parity were obtained from the electronic health record. Maternal race/ethnicity, education level, income level, marital status, smoking history, alcohol use history, lifetime stress, and stress during the index pregnancy were obtained from the study questionnaire and maternal interview.

Statistical Analysis

We performed χ^2 and *t* tests to describe differences between groups based on preeclampsia status at subsequent pregnancy. For the main analysis, we created unadjusted log-binomial models to estimate RRs to evaluate the association between each of the cardiometabolic risk factors and risk of incident and recurrent preeclampsia. For Aim 1, which focused on the outcome of incident preeclampsia, the reference group was no preeclampsia. For Aim 2, which focused on the outcome of recurrent preeclampsia, the reference group was nonrecurrent preeclampsia. All models were unadjusted because of small cell sizes.

Because parity is an important consideration in assessing preeclampsia risk (eg, nulliparous women have higher risk of preeclampsia[17]) and because not all women enrolled in the study had consecutive live births, nor were they all nulliparous, we performed a sensitivity analysis restricted to nulliparous women with a parity difference of 1 (indicating a consecutive pregnancy). We also examined the combined effect of obesity and chronic hypertension, as well as obesity and DM, as additional sensitivity analysis.

We used simple imputation (using means to replace continuous variables and highest frequency categories to replace categorical variables) for missing variables if the missingness was <5% and assumed to be missing at random. This technique approximates multiple imputation for variables missing <5%.

All analyses were conducted using Stata version 15 (StataCorp, College Station, TX).

RESULTS

Of the 7890 women in the parent study, 618 women had an index and subsequent pregnancy captured (Figure 1). Among the 540 without preeclampsia at the index pregnancy, 36 (7%) women had incident preeclampsia at the subsequent pregnancy. Among the 78 women with preeclampsia in the index pregnancy, 33 (42%) had recurrent preeclampsia at the subsequent pregnancy.

Table 1 shows the baseline characteristics by preeclampsia status at the index and subsequent pregnancy. The racial/ethnic distribution was similar across groups. Women from racial/ethnic minorities were the majority across all diagnoses, with non-Hispanic Black women representing 61% of the sample, followed by Hispanic women (23%), White women (8%), and women from other racial and ethnic groups (7%).

Compared with women with never preeclampsia, women with incident preeclampsia were older at both their index (aged 29.4 years; SD, 5.2 years versus aged 26.2 years; SD, 5.7 years) and subsequent pregnancies. They were also less likely to be nulliparous at the index pregnancy (33% versus 54%). Women with incident preeclampsia (versus never preeclampsia) had a higher mean BMI before the index pregnancy (29.6 kg/m^2; SD, 9.9 kg/m^2 versus 25.7 kg/m^2; SD, 6.3 kg/m^2), as well as before the subsequent pregnancy (31.8 kg/m^2; SD, 6.8 kg/m^2 versus 27.2 kg/m^2; SD, 6.4 kg/m^2).

Compared with women with nonrecurrent preeclampsia, women with recurrent preeclampsia had a higher mean BMI before both their index (29.5 kg/m^2; SD, 7.1 kg/m^2) versus (25.0 kg/m^2; SD, 5.3 kg/m^2) and subsequent (30.0 kg/m^2; SD, 6.4 kg/m^2 versus 27.1 kg/m^2; SD, 4.7 kg/m^2) pregnancies.

Table 2 compares prepregnancy, pregnancy, and interpregnancy cardiometabolic risk factors for women by preeclampsia status at index and subsequent pregnancy. We assessed the Aim 1 outcome of incident preeclampsia. Compared with women with never preeclampsia, women with incident preeclampsia had higher proportions of all measured preindex and interpregnancy cardiometabolic risk factors. There were no differences in the during index pregnancy risk factors between women with never versus incident preeclampsia. However, the proportion of women with new interpregnancy hypertension was significantly higher among women with incident preeclampsia compared with never preeclampsia (24% versus 4%). Women with incident preeclampsia also had a higher proportion of preterm birth and low-birth-weight infants in their subsequent pregnancies (64% and 67%, respectively) compared with women with never preeclampsia (25% and 23%, respectively).

We assessed the Aim 2 outcome of recurrent preeclampsia. Compared with women with nonrecurrent preeclampsia, women with recurrent preeclampsia had higher proportions of obesity before index pregnancy (30% versus 13%). There were no other significant differences between any of the preindex or during index pregnancy risk factors. However, women with recurrent preeclampsia (versus nonrecurrent preeclampsia) had a higher proportion of new interpregnancy chronic hypertension (40% versus 8%). In their subsequent pregnancy, women with recurrent preeclampsia had a higher proportion of preterm birth and low-birth-weight infants (63% and 48%, respectively) compared with women with nonrecurrent preeclampsia (29% and 24%, respectively).

Risk of Incident and Recurrent Preeclampsia Using Regression Models

Figure 2 shows the results of log binomial regression assessing the unadjusted relative risk of incident preeclampsia (Figure 2A) and recurrent preeclampsia (Figure 2B) associated with preindex pregnancy, during pregnancy, and interpregnancy cardiometabolic risk factors.

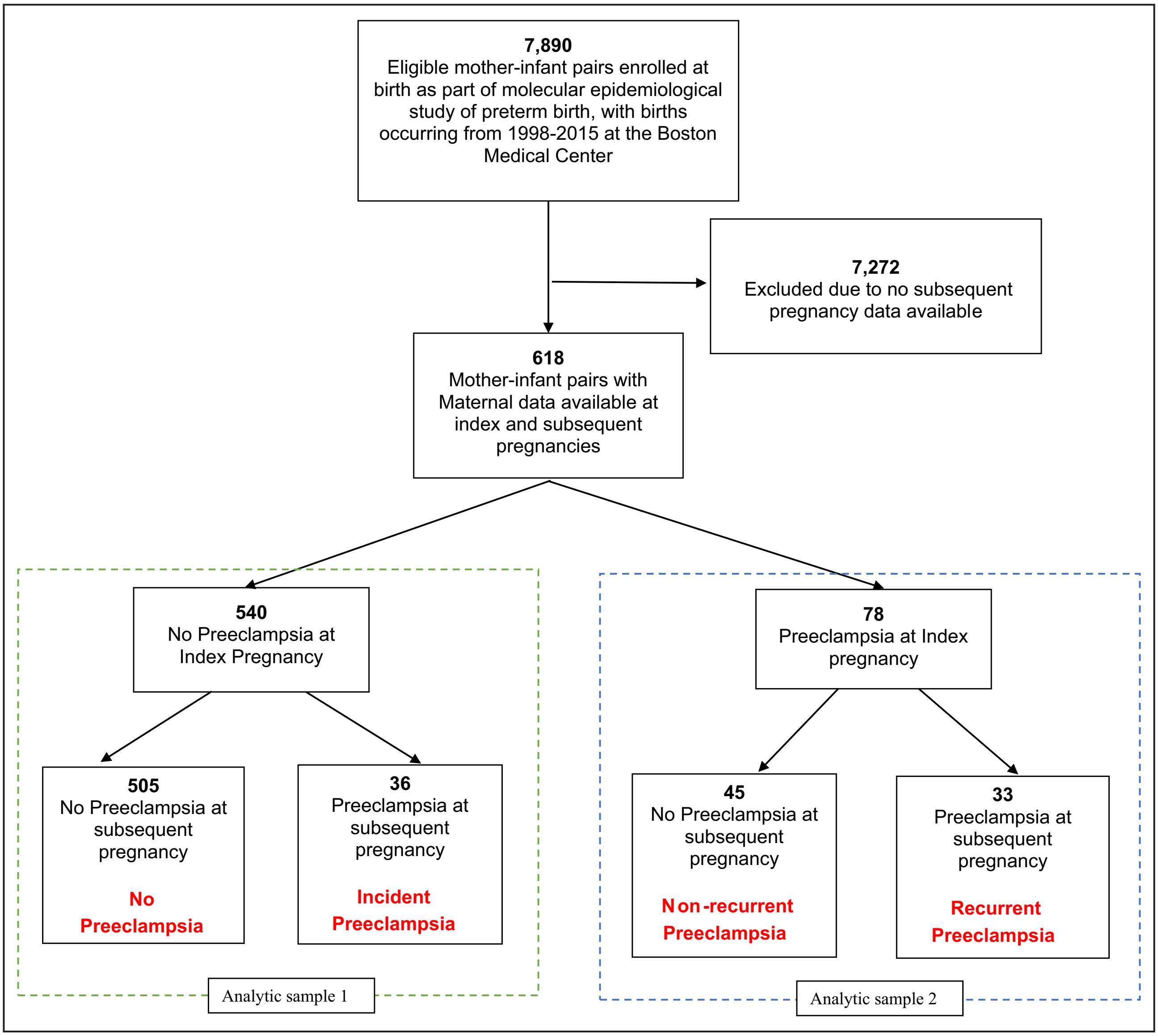

Figure 1. Flowchart of sample included in the analysis.

Outcome of Incident Preeclampsia (Study Aim 1)

Compared with women with a normal preindex pregnancy BMI, women with preindex pregnancy obesity had a 2-fold greater risk of incident preeclampsia (unadjusted RR, 2.2 [95% CI, 1.1–4.5]). Women with preindex pregnancy chronic hypertension and chronic DM were more likely to have incident preeclampsia compared with women without these risk factors (chronic hypertension unadjusted RR, 7.9 [95% CI, 4.1–15.3]; DM unadjusted RR, 5.2 [95% CI, 2.5–11.1]).

Additionally, we performed a sensitivity analysis to evaluate the individual and combined association of obesity and hypertension, and obesity and DM for incident preeclampsia. Women with chronic hypertension alone, obesity alone, and both hypertension and obesity had higher risk for incident preeclampsia, compared with those who had none of these risk factors (obesity unadjusted RR, 1.9 [95% CI, 0.87–4.2], chronic hypertension unadjusted RR, 8.9 [95% CI, 3.4–23.1], both hypertension and obesity unadjusted RR, 9.2 [95% CI, 4.0–21.4]). Similarly, the risk of recurrent preeclampsia was higher with obesity alone, chronic DM alone, and both compared with none (obesity unadjusted RR, 1.8 [95% CI, 0.85–4.0], chronic DM unadjusted RR, 3.9 [95% CI, 1.1–14.5], both unadjusted RR, 7.9 [95% CI, 3.3–18.6]).

There was no statistically significant association between cardiometabolic risk factors (GDM, preterm birth, and low birth weight) during the index pregnancy and incident preeclampsia.

Women with new interpregnancy hypertension (versus those without) were 6 times more likely to

Table 1. Sociodemographic and Clinical Characteristics by Preeclampsia Status at Index Pregnancy

	No Preeclampsia at Index Pregnancy				Preeclampsia at Index Pregnancy			
	Overall, N=540	No Preeclampsia, n=504	Incident Preeclampsia, n=36	*P* Value	Overall, N=78	Nonrecurrent Preeclampsia, n=45	Recurrent Preeclampsia, n=33	*P* Value
Sociodemographic characteristics								
Race/ethnicity								
Non-Hispanic Black	329 (61)	302 (60)	27 (75)	0.17	51 (65)	29 (64)	22 (67)	0.38
Hispanic	128 (24)	124 (25)	4 (11)		15 (19)	7 (16)	8 (24)	
Other	36 (7)	35 (7)	1 (3)		7 (10)	6 (13)	1 (3)	
Non-Hispanic White	47 (9)	43 (9)	4 (11)		5 (6)	3 (7)	2 (6)	
Maternal age, y, at index	26.3±5.7	26.2±5.7	29.4±5.2	<0.01	26.4±6.0	26.0±6.2	27.0±5.8	0.47
Maternal age, y, at subsequent	30.1±5.9	29.9±5.8	33.6±5.7	<0.01	30.1±6.0	29.8±6.2	30.5±5.7	0.59
Married vs not married, at index	173 (32)	157 (31)	16 (44)	0.10	32 (41)	19 (42)	13 (39)	0.80
Baseline education, at index								
No school or elementary	23 (4)	21 (4)	2 (6)	0.65	5 (6)	4 (9)	1 (3)	0.40
Some secondary school	151 (28)	143 (28)	8 (22)		20 (26)	12 (27)	8 (24)	
High school graduate/GED	183 (34)	170 (34)	13 (36)		25 (32)	11 (24)	14 (42)	
Some college	110 (20)	100 (20)	10 (28)		17 (22)	10 (22)	7 (21)	
College and above	73 (14)	70 (14)	3 (8)		11 (14)	8 (18)	3 (9)	
Annual income, at index								
<$30 000	248 (46)	230 (46)	18 (50)	0.30	30 (38)	18 (40)	12 (36)	0.46
≥$30 000	57 (11)	51 (10)	6 (17)		14 (18)	6 (13)	8 (24)	
Unknown	235 (44)	223 (44)	12 (33)		34 (44)	21 (47)	13 (39)	
Health behavior/social factors								
ETOH during pregnancy, index	46 (9)	44 (9)	2 (6)	0.51	4 (5)	3 (7)	1 (3)	0.47
Smoking during pregnancy, index	101 (19)	93 (18)	8 (22)	0.58	7 (9)	4 (9)	3 (9)	0.98

(Continued)

Table 1. Continued

	No Preeclampsia at Index Pregnancy				Preeclampsia at Index Pregnancy			
	Overall, N=540	No Preeclampsia, n=504	Incident Preeclampsia, n=36	*P* Value	Overall, N=78	Nonrecurrent Preeclampsia, n=45	Recurrent Preeclampsia, n=33	*P* Value
Smoking before either pregnancy								
Never smoked before index or subsequent	405 (78)	378 (78)	27 (77)	0.30	63 (81)	39 (87)	24 (73)	0.12
Started smoking before subsequent	24 (5)	23 (5)	1 (3)		9 (12)	3 (7)	6 (18)	
Quit smoking before subsequent	24 (5)	24 (5)	0 (0)		2 (3)	0 (0)	2 (6)	
Continue smoking before index and subsequent	65 (13)	58 (12)	7 (20)		4 (5)	3 (7)	1 (3)	
Stress during pregnancy, index, very vs not/average	103 (19)	93 (18)	10 (28)	0.17	15 (19)	8 (18)	7 (21)	0.70
Clinical factors								
Parity, at index								
0	283 (52)	271 (54)	12 (33)	0.02	54 (69)	33 (73)	21 (64)	0.46
1	142 (26)	132 (26)	10 (28)		14 (18)	6 (13)	8 (24)	
>1	115 (21)	101 (20)	14 (39)		10 (13)	6 (13)	4 (12)	
Parity, at subsequent*								
1	255 (47)	247 (49)	8 (22)	<0.01	48 (62)	30 (67)	18 (55)	0.28
>1	285 (53)	257 (51)	28 (78)		30 (38)	15 (33)	15 (45)	
BMI, kg/m^2, at index	25.9±6.7	25.7±6.3	29.6±9.9	<0.01	26.9±6.5	25.0±5.4	29. 5±7.1	0.003
BMI, kg/m^2, at subsequent	27.5±6.8	27.2±6.4	31.8±6.8	<0.01	28.3±5.6	27.1±4.7	30.0±6.4	0.02

Data are presented as number (percent) or mean±SD. BMI indicates body mass index; ETOH, ethyl alcohol; and GED, general education development.

*Not all index and subsequent pregnancies were consecutive in this sample. The subsequent pregnancy was not the consecutive pregnancy for 8 (10%) women in the preeclampsia at index pregnancy group and 78 (14%) women in the no preeclampsia at index group. We determined this by calculating the difference between parity at subsequent pregnancy and parity at index pregnancy. Parity difference = 1 represented consecutive index and subsequent pregnancies; parity difference >1 represented nonconsecutive index and subsequent pregnancies.

Table 2. Prepregnancy Chronic Disease, Pregnancy Complications at Index, Subsequent Pregnancies, and Interpregnancy Changes

	No Preeclampsia at Index Pregnancy				Preeclampsia at Index Pregnancy			
	Overall, N=540	No Preeclampsia, n=504	Incident Preeclampsia, n=36	*P* Value	Overall, N=78	Nonrecurrent Preeclampsia, n=45	Recurrent Preeclampsia, n=33	*P* Value
Cardiometabolic risk factors, prepregnancy								
Obesity, at index								
Normal, BMI <25	280 (52)	264 (52)	16 (44)	0.04	35 (45)	28 (62)	7 (21)	<0.01
Overweight, BMI 25–29.9	164 (30)	156 (31)	8 (22)		27 (35)	11 (24)	16 (49)	
Obese, BMI >30	96 (18)	84 (17)	12 (33)		16 (21)	6 (13)	10 (30)	
Obesity, at subsequent								
Normal, BMI <25	211 (39)	201 (40)	10 (28)	0.19	24 (31)	18 (40)	6 (18)	0.05
Overweight, BMI 25–29.9	184 (34)	172 (34)	12 (33)		27 (35)	16 (36)	11 (33)	
Obese, BMI >30	145 (27)	131 (26)	14 (39)		27 (35)	11 (24)	16 (48)	
Chronic hypertension, at index	16 (3)	9 (2)	7 (19)	<0.01	8 (10)	5 (11)	3 (9)	
Chronic hypertension, at subsequent	37 (7)	24 (5)	13 (36)	<0.01	18 (23)	4 (9)	14 (42)	<0.01
Chronic diabetes mellitus, at index	20 (4)	14 (3)	6 (17)	<0.01	4 (5)	1 (2)	3 (9)	0.17
Chronic diabetes mellitus, at subsequent	30 (6)	22 (4)	8 (22)	<0.01	4 (5)	2 (4)	2 (6)	0.75
Cardiometabolic risk factors, during pregnancy								
Caesarean delivery, at index	146 (27)	130 (26)	16 (44)	0.02	39 (50)	23 (51)	16 (48)	0.82
Caesarean delivery, at subsequent	199 (37)	178 (35)	21 (58)	<0.01	43 (55)	24 (53)	19 (58)	0.71
Gestational diabetes mellitus, at index	28 (5)	27 (5)	1 (3)	0.50	5 (6)	4 (9)	1 (3)	0.30
Gestational diabetes mellitus, at subsequent	41 (8)	36 (7)	5 (14)	0.14	8 (10)	5 (11)	3 (9)	0.77
Preeclampsia severity, at index								
Mild	NA	NA	NA	NA	34 (44)	22 (49)	12 (36)	0.27
Severe	NA	NA	NA		44 (56)	23 (51)	21 (64)	
Preeclampsia severity, at subsequent								
None	506 (94)	504 (100)	0 (0)	<0.01	45 (58)	45 (100)	0 (0)	<0.01
Mild	15 (3)	0 (0)	15 (42)		12 (15)	0 (0)	12 (36)	
Severe	19 (4)	0 (0)	21 (58)		21 (27)	0 (0)	21 (64)	

(*Continued*)

Table 2. Continued

	No Preeclampsia at Index Pregnancy				Preeclampsia at Index Pregnancy			
	Overall, N=540	No Preeclampsia, n=504	Incident Preeclampsia, n=36	*P* Value	Overall, N=78	Nonrecurrent Preeclampsia, n=45	Recurrent Preeclampsia, n=33	*P* Value
Preterm birth, at index, <37 wk	142 (26)	131 (26)	11 (31)	0.55	50 (64)	27 (60)	23 (70)	0.38
Preterm birth, at subsequent	151 (28)	128 (25)	23 (64)	<0.1	34 (44)	13 (29)	21 (63)	<0.01
Low birth weight at index, <2500 g	139 (26)	127 (25)	12 (33)	0.28	50 (64)	30 (67)	20 (61)	0.58
Low birth weight at subsequent	138 (26)	114 (23)	24 (67)	<0.01	27 (35)	11 (24)	16 (48)	0.03
Cardiometabolic risk factors, interpregnancy*								
New interpregnancy obesity								
New interpregnancy overweight, normal BMI at index	86 (31)	81 (31)	5(31)	0.41	10 (29)	9 (32)	1 (14)	0.59
New interpregnancy obese/morbid obese, normal BMI at index	15 (5)	13 (5)	2(13)		3 (9)	2 (7)	1 (14)	
New interpregnancy obese/morbid obese, overweight BMI at index	52 (32)	50 (32)	2(25)	0.76	10 (37)	4 (36)	6 (38)	0.96
BMI change between pregnancies, subsequent-index	1.6±4.7	1.6±4.5	2.1±6.7	0.49	1.4±4.0	2.1±3.3	0.58±4.7	0.11
Interpregnancy percent weight change, kg, mean change	7.5±20.5	7.4±20.7	9.7±18.3		8.5±16.5	11.5±16.5	4.4±16	0.06
Interpregnancy percent weight change by								
Obesity status at index, mean weight change, %								
Normal, BMI <25	10.1±14.2	9.9±14.2	12.2±13.7	0.54	13.5±17.3	14.5±18.5	9.7±11.7	0.52
Overweight, BMI 25–29.9	7.8±28.8	7.7±29.2	9.6±22.1	0.86	8.6±15.1	8.8±10.7	8.5±17.9	0.95
Obese, BMI >30	−0.35±17.2	−1.3±16.4	6.5±22.0	0.14	−2.9±11.4	2.0±11.1	−5.8±11.0	0.19
New interpregnancy chronic hypertension	25 (5)	18 (4)	7 (24)	<0.01	15 (21)	3 (8)	12 (40)	<0.01
New interpregnancy chronic diabetes mellitus	16 (3)	14 (3)	2 (7)	0.24	3 (4)	1 (2)	2 (7)	0.35
Interpregnancy interval, y	3.8±2.4	3.7±2.3	4.2±3.3	0.27	3.7±2.1	3.9±2.0	3.6±2.3	0.62

Data are presented as number (percent) or mean±SD. BMI Indicates body mass index.
* New interpregnancy diagnosis refers to women who did not have the condition at index pregnancy and where at risk of developing the condition at subsequent pregnancy (hence the variation in denominators for each condition).

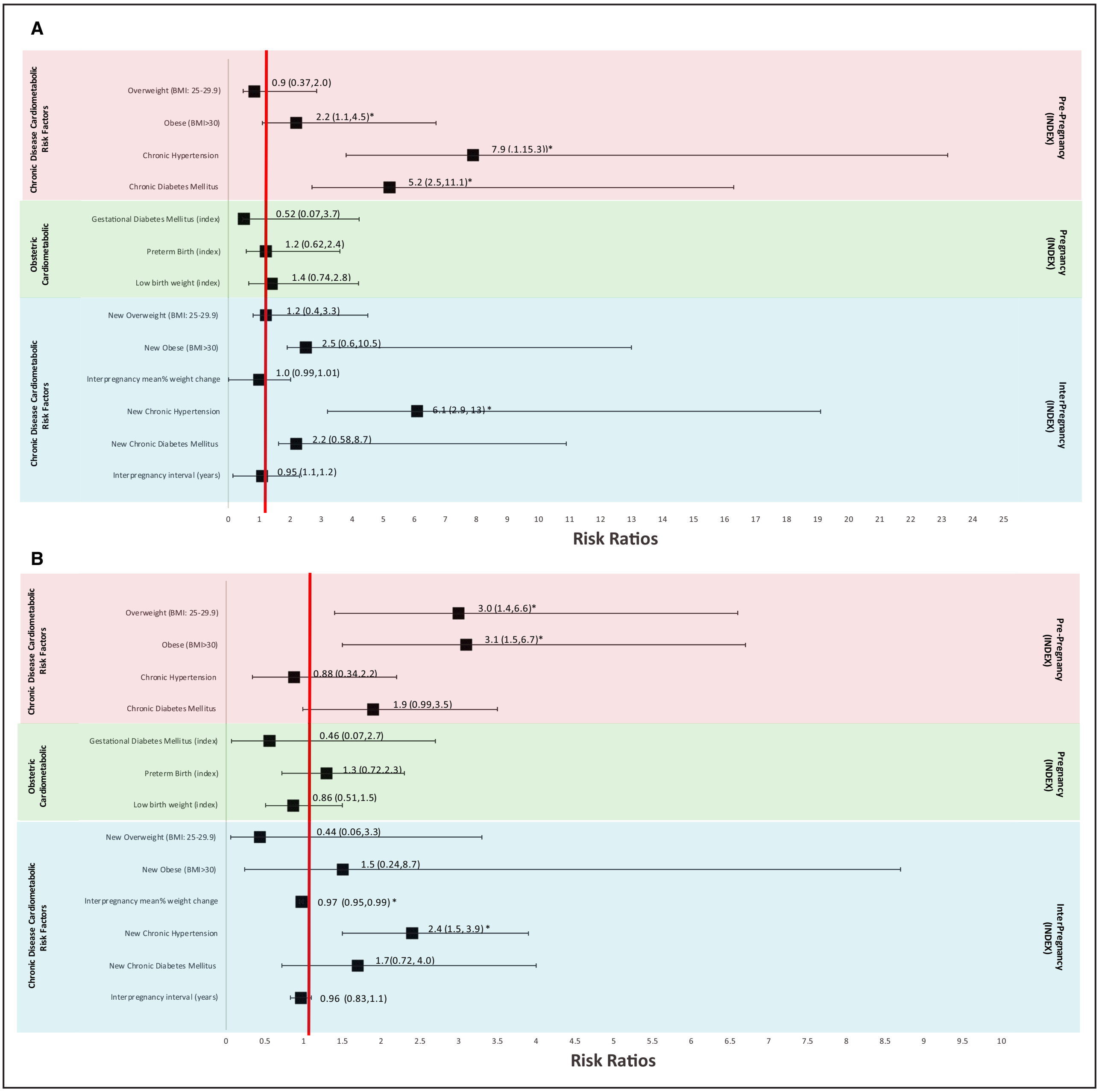

Figure 2. Risk ratios and 95% CIs for incident preeclampsia (A) and recurrent preeclampsia (B) by prepregnancy, pregnancy, and interpregnancy cardiometabolic risk factors.
Asterisk denotes statistical significance at a *p* value <.05. BMI indicates body mass index.

have incident preeclampsia (unadjusted RR, 6.1 [95% CI, 2.9–13]). Neither interpregnancy obesity nor chronic DM were significantly associated with incident preeclampsia. Women with incident preeclampsia gained more weight in between pregnancies than those with never preeclampsia (2.1-unit BMI increase versus 1.6-unit BMI increase, respectively), and this trend was apparent regardless of index pregnancy obesity categories (ie, normal weight, overweight, and obese). Neither interpregnancy percent weight change nor interpregnancy interval was significantly associated with incident preeclampsia.

Outcome of Recurrent Preeclampsia (Study Aim 2)

Compared with women with a normal preindex pregnancy BMI, women with preindex pregnancy overweight or obesity were 3 times more likely to have recurrent preeclampsia (overweight unadjusted RR, 3.0 [95% CI, 1.4–6.6]; obese unadjusted RR, 3.1 [95% CI, 1.5–6.7]). The other preindex pregnancy cardiometabolic risk factors were not associated with recurrent preeclampsia, and tests to evaluate the individual and combined association between chronic hypertension and obesity, and between chronic DM and obesity, did not meet statistical significance. We conducted a sensitivity analysis showing the ratios of hypertension in each BMI category (Table S1). However, because of small cell sizes with 2 strata we could not draw meaningful conclusions.

There was no statistically significant association between the during index pregnancy cardiometabolic risk factors (GDM, preterm birth, and low birth weight) and recurrent preeclampsia.

Women with interpregnancy hypertension had a 2-fold greater risk of recurrent preeclampsia, compared with women without hypertension (unadjusted RR, 2.4 [95% CI, 1.5–3.9]). Interpregnancy obesity and DM were not significantly associated with recurrent preeclampsia. Women with recurrent preeclampsia had less weight gain between pregnancies than those with nonrecurrent preeclampsia (4.4-unit BMI increase versus 11.5-unit BMI increase), and this trend was apparent regardless of index pregnancy obesity category (ie, normal weight, overweight, and obese). Neither interpregnancy weight change nor interpregnancy interval was associated with a statistically significant risk of recurrent preeclampsia. In a sensitivity analysis restricting our sample to nulliparous women with a parity difference of 1 (reflecting consecutive pregnancies), the inferences did not change.

DISCUSSION

In this racially and ethnically diverse cohort of women with both index and subsequent pregnancy data captured, we found strong associations between preindex pregnancy and new interpregnancy cardiometabolic risk factors and both incident (Aim 1) and recurrent (Aim 2) preeclampsia in the subsequent pregnancy. For study Aim 1, preindex pregnancy obesity, DM and chronic hypertension independently and jointly influenced the risk of incident preeclampsia at a subsequent pregnancy. Importantly, a new interpregnancy diagnosis of hypertension was associated with a 6-fold greater risk of incident preeclampsia. We also showed that the combined effect of obesity with other cardiometabolic risk factors (chronic hypertension and DM) was associated with higher risk of incident preeclampsia. For study Aim 2, a diagnosis of overweight and obesity before the index pregnancy, as well as interpregnancy hypertension, were associated with recurrent preeclampsia. There was no statistically significant combined effect of obesity with other cardiometabolic risk factors and risk of recurrent preeclampsia. Pregnancy risk factors, including preterm birth, having a low-birth-weight infant, and GDM, were not associated with incident or recurrent preeclampsia in a subsequent pregnancy. Interpregnancy risk factors, such as interpregnancy interval and interpregnancy weight change, were also not associated with incident or recurrent preeclampsia in a subsequent pregnancy.

Similar to other recent studies, we found strong associations between preexisting prepregnancy cardiometabolic risk factors including obesity, hypertension, and DM, and both incident and recurrent preeclampsia.[27–29] In addition, we were able to evaluate the timing of risk-factor acquisition (preindex pregnancy versus interpregnancy) and by doing so offered a life course perspective that considered reproductive health in the longitudinal development of chronic disease and adverse pregnancy outcomes. We also stratified our analysis by preeclampsia status at index pregnancy, which helped define a high-risk group of women with recurrent preeclampsia.

In Aim 1, we focused on incident preeclampsia and showed that preindex pregnancy obesity, DM, and chronic hypertension, as well as new interpregnancy hypertension, were all associated with incident preeclampsia. Although several other studies have assessed obstetric risk factors associated with incident preeclampsia in a subsequent pregnancy, few have focused on prepregnancy cardiometabolic risk factors. Catov et al evaluated the population attributable risk of preexisting conditions on preeclampsia among 70 924 women in a Danish cohort study and found similar importance of cardiometabolic risk factors.[27] The investigators found that among multiparous women, having at least 1 identified risk factor (ie, prior preeclampsia, definite hypertension, obesity, or DM) was associated with over half of all cases of preeclampsia (52.2% [95% CI, 46.4–57.9]). Prior preeclampsia (26%) followed by obesity (11%) and overweight (8%) contributed most, whereas DM (0.2%) and hypertension (1.3%) contributed negligible amounts. When history of prior preeclampsia was removed from the model, cardiometabolic risk factors accounted for nearly 30% of all preeclampsia case (29.6% [95% CI, 24.2–35.4]).

In Aim 2 we focused on the outcome of recurrent preeclampsia. Our main finding was that preindex pregnancy overweight and obesity were strongly associated with recurrent preeclampsia, as well as a new diagnosis of interpregnancy hypertension, although to a lesser extent. Other studies have examined the outcome of recurrent preeclampsia. In a population-based cohort study of 103 860 mostly White women in Missouri with 2 or more deliveries, Mostello et al assessed risk factors associated with recurrent preeclampsia.[30] Similar to our findings, the investigators found that women with preindex pregnancy overweight and obesity had higher risk of recurrent preeclampsia (14% and 19.3%, respectively) compared with women with normal weight (11.2%). In a large hospital-based study of 26 613 nulliparous women, Boghossian and colleagues also found that prepregnancy obesity was associated with recurrent preeclampsia (though to a lesser extent and without the dose response that was seen with incident preeclampsia).[19] In this study, the risk of recurrent preeclampsia was highest among women with obese class I (obese class I women RR, 1.60 [95% CI, 1.06–2.42]). Neither studies considered independent associations of other cardiometabolic risk factors such as chronic hypertension or chronic DM.

Our null findings related to the pregnancy-associated cardiometabolic risk factors and preeclampsia risk are inconsistent with prior research.[31,32] For example, in a retrospective, population-based, nested case-control study, Wainstock et al evaluated risk factors for incident preeclampsia in a subsequent pregnancy among 40 673 Israeli women.[32] The investigators reported significant independent associations between low-birth-weight infant, preterm birth, GDM, and incident preeclampsia. They also found the odds of incident preeclampsia increased with 2 or more pregnancy complications versus 1 or none. It is likely that we were underpowered to detect the influence of these pregnancy complications, and larger studies in diverse, higher-risk populations such as ours are needed to understand how index pregnancy complications may also contribute to preeclampsia risk in subsequent pregnancies.

In terms of interpregnancy interval, we did not find an association with either incident or recurrent preeclampsia. However, prior literature shows that extreme interpregnancy intervals (either too short [eg, <6 months] or too long [eg, >5–10 years]) are associated with adverse outcomes such as placental abruption in women with a history of cesarean section, GDM, and preterm birth.[33] Accordingly, the American College of Obstetrics and Gynecology and the Society of Maternal Fetal Medicine recommend avoiding pregnancy intervals <6 to 18 months and >5 to 10 years.[34]

Our study did not show a statistically significant association between interpregnancy weight change and recurrent preeclampsia. When these results were stratified by obesity class, the 16 obese women who developed recurrent preeclampsia paradoxically had lost more weight (−5.8% loss of body weight) than the 11 obese women with nonrecurrent preeclampsia (+2.1% gain of body weight) (shown in Table 2). The weight loss of 5% to 6% of their body weight is consistent with current recommendations that recommend a weight-loss target of 5% to 10% body weight to reduce metabolic abnormalities and adverse pregnancy outcomes such as preeclampsia.[35–37] These findings may be explained by the fact that women with recurrent preeclampsia had a higher preindex pregnancy BMI than women with nonrecurrent preeclampsia and so may be more inclined to attempt to lose weight. Notably, in a cross-sectional study assessing the prepregnancy lifestyle and weight behaviors of 223 pregnant women, Lang and colleagues found that 77% of obese women compared with 38% overweight and 16% of normal weight women reported trying to lose weight before pregnancy.[38] However in our small sample, this weight loss did not impact their risk of recurrent preeclampsia, possibly because of the complexity of risk factors for preeclampsia. Importantly, because of the small sample size, this analysis was only exploratory, and we are unable to draw conclusions about the effect of interpregnancy weight change on future preeclampsia incidence.

In women without preeclampsia at index pregnancy, we see perhaps more expected findings related to interpregnancy weight change. Women with a lower BMI at the subsequent pregnancy and no preeclampsia had greater interpregnancy weight loss compared with women with incident preeclampsia.

Our results suggest the need to further evaluate the role of intensive and targeted interpregnancy weight loss strategies in high-risk groups of women, such as women with prepregnancy obesity and women with a history of prior preeclampsia. Our findings also suggest that regardless of women's preeclampsia history, postpartum weight reduction may improve subsequent pregnancy outcomes.

Clinical Implications

We identified important clinical implications and targets for future intervention and screening. First, obesity that impacts preeclampsia risk both directly and indirectly through its association with other cardiometabolic risk factors for preeclampsia such as prepregnancy chronic hypertension and DM, is a high-yield target for intervention. Prepregnancy obesity is an important risk factor for both incident and recurrent preeclampsia; thus, prepregnancy and interpregnancy weight loss may reduce the risk of preeclampsia among women with obesity. We did not show a statistically significant effect of interpregnancy weight change and preeclampsia in subsequent pregnancy, because we did not have an adequate sample size to address this question. Thus, this question remains to be determined by future larger studies. A recently published meta-analysis of 12 observational studies, representing 415 605 women, showed that interpregnancy weight loss reduced risk of hypertensive disorders of pregnancy, including preeclampsia (10% risk reduction for gestational hypertension and 7% risk reduction for preeclampsia).[39]

Behavioral interventions aimed at prepregnancy and interpregnancy weight reduction among women with overweight or obesity may be an important component of risk reduction and may also reduce risk of other obesity-related cardiometabolic risk factors, which are also risk factors for preeclampsia, such as chronic hypertension and chronic DM. However behavioral interventions targeting obesity may be challenging to deliver and sustain, and innovative multilevel approaches are needed that include community-informed adaptation of evidence–based lifestyle interventions,[40,41] community health worker or peer-supported interventions,[42,43] and electronic health technologies with culturally relevant messaging for diverse populations.[44] Escalation beyond behavioral interventions (eg, antiobesity medication or surgical options) should also be considered among women with a BMI>27 and cardiometabolic risk factors who fail to improve with behavioral interventions alone.[45] However, women who pursue these options before pregnancy need an adequate contraceptive plan in place, because antiobesity medication and surgical weight loss therapy are contraindicated during pregnancy.

Second, related to hypertension, there is an opportunity for behavioral interventions for prevention and enhanced screening around the time of pregnancy for high-risk groups. For women without a history of preeclampsia, interpregnancy lifestyle interventions to target the risk factors for chronic hypertension development (eg, obesity and chronic DM) could potentially reduce the risk of these diseases as well as incident preeclampsia in a subsequent pregnancy.[46] This may be especially important among women with multiple prepregnancy or pregnancy-acquired cardiometabolic risk factors.[47,48] Women with a history of preeclampsia in a prior pregnancy represent a group at a uniquely high risk for postpartum or new interpregnancy hypertension development, as well as future cardiovascular disease.[15,49] In a large Danish cohort of 482 972 women without preexisting hypertension, Behrens and colleagues showed compelling evidence that the risk of hypertension following a hypertensive disorder of pregnancy is highest in the early postpartum period (within the first year).[49] These findings, along with numerous others studies,[9,50,51] consistently show increased risk of early cardiovascular disease following a hypertensive disorder of pregnancy. Together, they highlight the role for postpartum and ongoing screening for hypertension and other cardiovascular disease risk factors in women with a history of preeclampsia.[16,52,53]

Related to the combined effect of obesity and other cardiometabolic risk factors, we found a statistically significant combined effect in risk for incident, but not recurrent, preeclampsia. The lack of statistically significant risk for recurrent preeclampsia associated with the combined effect of obesity and other cardiometabolic risk factors may be attributable to small sample size. Larger studies are needed to evaluate the impact of multiple cardiometabolic risk factors on risk of recurrent preeclampsia. Regardless, the strong evidence supporting associations between obesity and other cardiometabolic risk factors, including preeclampsia, further underscores the potential impact of weight loss among women of childbearing age who are obese.[45,54]

Limitations

There are several limitations of this study. First, we sought to identify women who had 2 pregnancies captured in the Boston Birth Cohort, which limited the sample size and our ability to conduct robust multivariate analysis and fully control for confounding. Second, our sample represents a high-risk group of women, the prevalence of incident preeclampsia was 7%, and recurrent preeclampsia was 42%. These rates are 2- to 4-fold higher than rates reported in larger studies.[19,30,55,56] These differences likely reflect both the higher overall risk of the women included in our study, because the parent study recruited women with low birth weight and preterm birth infants, as well as the higher proportion of women with comorbid conditions. The characteristics of our study sample may limit external validity but highlight the importance of cardiometabolic risk factors and preeclampsia outcomes among an increasingly diverse and chronic disease-laden US population. Third, prepregnancy weight is self-reported in this study, which is subject to recall bias. Also, multiple studies have shown that women are more likely to underreport their weight and overreport their height leading to lower reported BMIs.[57,58] If this was the case, our results would be potentially biased toward the null. However, given the previous validation of prepregnancy weight against documented electronic health record weight with high Pearson correlation coefficient (0.93),[23] we believed the use of self-reported prepregnancy weight was acceptable and would not meaningfully change the inferences. Finally, although the duplicate enrollment of the 618 women occurred by chance, there is the possibility of selection bias at the stage when subjects were selected into this study. To assess for this, we compared the study population to the parent study population (Table S2). The 2 groups were not significantly different in terms of the proportion of women with obesity and chronic hypertension; however, there were other notable differences at index pregnancy such as the parent study participants were older, had a lower proportion of Black women, lower proportion of nulliparous women, and higher proportion of pregnancies complicated by GDM, preterm birth, and low-birth-weight infant, all of which are associated with an increased the risk of preeclampsia, which in turn is associated with preterm delivery and low-birth-weight infants.

CONCLUSIONS

Providers who care for women of childbearing age and manage chronic disease should take into account a history of pregnancy complications such as preeclampsia, and consider pursuing programs focused on prevention and management of cardiometabolic risk factors in the prepregnancy and interpregnancy periods. Such strategies have the potential to improve future pregnancy outcomes and long-term health. The challenge of how best to do this among underserved populations, such as those with low socioeconomic status and those who are from racially and ethnically underrepresented groups is not insignificant and will require multilevel, multimodal approaches. To advance a maternal health research agenda aimed at achieving health equity, future research should involve longitudinal and life course–informed study designs, as well as test patient-centered interventions responsive to social and structural determinants of health.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Sociodemographic Characteristics at INDEX Pregnancy (parent study participants vs. analytic sample participants)

	Overall	Study Sample	Excluded Sample	p-value
N (column %)	7890	618 (counted twice)	7272	
Race				**<0.001**
Non-Hispanic Black	4,012 (51)	380 (62)	3,632 (50)	
Hispanic	2,281 (29)	143 (23)	2,138 (30)	
White	948 (12)	52 (8)	896 (12)	
Other	649 (8)	43 (7)	606 (8)	
Maternal age (years); mean (±SD)	28.0±6.5	26.3± 5.8	28.2±6.5	**<0.001**
Parity at index				**<0.001**
0	3,662 (46)	337 (55)	3,325 (46)	
1	2,201 (28)	156 (25)	2,045 (28)	
>1	2,027 (26)	125 (20)	1,902 (26)	
Delivery Type				0.63
Vaginal	5,282(67)	431 (70)	4,851 (67)	
Caesarean	2,519 (32)	185 (30)	2,334 (32)	
Unknown	89 (1.1)	2 (0.32)	87 (1.2)	
BMI (kilograms); mean (±SD)	26±5.7	26±6.6	26±5.9	0.20
Obesity				0.82
Normal (BMI<25)	3,932 (50)	315 (51)	3,617 (50)	
Overweight (BMI:25-29.9)	2,489 (32)	190 (31)	2,299 (32)	
Obese (BMI>30)	1,469 (19)	113 (18)	1,356 (19)	
Chronic Hypertension				0.46
No	7,447 (94)	589 (95)	6,858 (94)	
Yes	386 (5)	24 (4)	362 (5)	
Unknown	57 (0.7)	5 (0.8)	57 (0.7)	
Pre-gestational Diabetes Mellitus				**<0.001**
No	7,129 (90)	591 (96)	6,538 (90)	
Yes	761 (10)	27 (4)	734 (10)	
Gestational Diabetes Mellitus				**<0.001**
No	6,832 (87)	582 (94)	6,250(86)	
Yes	1,058 (13)	36 (6)	1,022 (14)	
Preeclampsia Severity				**0.023**
None	7,125 (90)	541 (88)	6,584 (90)	
Mild	290 (4)	34 (6)	256 (4)	
Severe	475 (6)	43 (7)	432 (6)	
Low birth weight infant Index				
>2500g	5,834 (74)	429 (69)	5405 (74)	**<0.001**
<2500g	2056 (26)	189 (31)	1867 (26)	
Preterm birth Index pregnancy				**0.016**
>37 weeks	5,767 (73)	426 (70)	5,341 (73)	
<37 weeks	2,123 (27)	192 (31)	1,931 (27)	

BMI=body mass index; SD=standard deviation

Table S2. Sociodemographic Characteristics at INDEX Pregnancy (parent study participants vs. analytic sample participants)

	Overall	Study Sample	Excluded Sample	p-value
N (column %)	7890	618 (counted twice)	7272	
Race				**<0.001**
Non-Hispanic Black	4,012 (51)	380 (62)	3,632 (50)	
Hispanic	2,281 (29)	143 (23)	2,138 (30)	
White	948 (12)	52 (8)	896 (12)	
Other	649 (8)	43 (7)	606 (8)	
Maternal age (years); mean (±SD)	28.0±6.5	26.3± 5.8	28.2±6.5	**<0.001**
Parity at index				**<0.001**
0	3,662 (46)	337 (55)	3,325 (46)	
1	2,201 (28)	156 (25)	2,045 (28)	
>1	2,027 (26)	125 (20)	1,902 (26)	
Delivery Type				0.63
Vaginal	5,282(67)	431 (70)	4,851 (67)	
Caesarean	2,519 (32)	185 (30)	2,334 (32)	
Unknown	89 (1.1)	2 (0.32)	87 (1.2)	
BMI (kilograms); mean (±SD)	26±5.7	26±6.6	26±5.9	0.20
Obesity				0.82
Normal (BMI<25)	3,932 (50)	315 (51)	3,617 (50)	
Overweight (BMI:25-29.9)	2,489 (32)	190 (31)	2,299 (32)	
Obese (BMI>30)	1,469 (19)	113 (18)	1,356 (19)	
Chronic Hypertension				0.46
No	7,447 (94)	589 (95)	6,858 (94)	
Yes	386 (5)	24 (4)	362 (5)	
Unknown	57 (0.7)	5 (0.8)	57 (0.7)	
Pre-gestational Diabetes Mellitus				**<0.001**
No	7,129 (90)	591 (96)	6,538 (90)	
Yes	761 (10)	27 (4)	734 (10)	
Gestational Diabetes Mellitus				**<0.001**
No	6,832 (87)	582 (94)	6,250(86)	
Yes	1,058 (13)	36 (6)	1,022 (14)	
Preeclampsia Severity				**0.023**
None	7,125 (90)	541 (88)	6,584 (90)	
Mild	290 (4)	34 (6)	256 (4)	
Severe	475 (6)	43 (7)	432 (6)	
Low birth weight infant Index				
>2500g	5,834 (74)	429 (69)	5405 (74)	**<0.001**
<2500g	2056 (26)	189 (31)	1867 (26)	
Preterm birth Index pregnancy				**0.016**
>37 weeks	5,767 (73)	426 (70)	5,341 (73)	
<37 weeks	2,123 (27)	192 (31)	1,931 (27)	

BMI= body mass index; SD= standard deviation