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Risk factors differ between recurrent and incident preeclampsia: a hospital-based cohort study

Nansi S. Boghossian, PhD, MPH^{1,2}, Edwina Yeung, PhD¹, Pauline Mendola, PhD¹, Stefanie N. Hinkle, PhD¹, S. Katherine Laughon, MD, MS¹, Cuilin Zhang, MD, PhD¹, and Paul S. Albert, PhD³

¹Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda MD

²Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC

³Biostatistics and Bioinformatics Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda MD

Abstract

Purpose—Examine whether risk factors, including prepregnancy body mass index (BMI), differ between recurrent and incident preeclampsia.

Methods—Data included electronic medical records of nulliparas (n=26,613) delivering 2 times in Utah (2002–2010). Modified Poisson regression models were used to examine: 1) adjusted relative risks (RR) of preeclampsia and 95% confidence intervals (CI) associated with prepregnancy BMI; 2) maternal risk factor differences between incident and recurrent preeclampsia among primiparous women.

Results—In the 1st pregnancy, compared to normal weight women [BMI:18.5–24.9], preeclampsia risks for overweight [BMI:25–29.9], obese class I [BMI:30–34.9], and obese class II/III [BMI: 35] women were 1.82 (95% CI=1.60–2.06), 2.10 (95% CI=1.76–2.50), and 2.84

Address correspondence to: Edwina Yeung, PhD, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda MD, 6100 Executive Blvd Room 7B03, Bethesda, MD 20892. yeungedw@mail.nih.gov. Phone #(301)435-6921. Fax # (301) 402-2084.

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(95% CI=2.32–3.47), respectively while 2nd pregnancy incident preeclampsia risks were 1.66 (95% CI=1.27–2.16), 2.31 (95% CI=1.67–3.20), and 4.29 (95% CI=3.16–5.82), respectively. Recurrent preeclampsia risks associated with BMI were highest among obese class I women (RR=1.60; 95% CI=1.06–2.42) without increasing in a dose-response manner. Non-white women had higher recurrence risk than white women (RR=1.70; 95% CI=1.16–2.50) while 2nd pregnancy incident preeclampsia risk did not differ by race.

Conclusion—Prepregnancy BMI appeared to have stronger associations with risk of incident preeclampsia either in the 1st or 2nd pregnancy, than with recurrence risk. Non-white women had higher recurrence risk.

Keywords

preeclampsia; recurrent; incident; obesity; body mass index

INTRODUCTION

Preeclampsia, defined as new onset hypertension and proteinuria after 20 weeks of gestation, complicates 5–8% of all pregnancies in the United States and contributes significantly to maternal and neonatal morbidity and mortality (1–4). Although preeclampsia pathogenesis remains elusive, maternal prepregnancy body mass index (BMI) has been identified as an important independent risk factor for preeclampsia development (5–6). In a recent meta-analysis of nulliparous women and multiparas, overweight or obese women (BMI ≥ 25 kg/m²) had approximately 2–4 fold increased preeclampsia risk compared to normal weight women (BMI 20–24.9 kg/m²) (7). Women with preeclampsia in a previous pregnancy also have increased recurrence risk in subsequent pregnancies (8–11). While prepregnancy BMI is an established risk factor for incident preeclampsia, less is known about this relationship in recurrent preeclampsia.

Apart from prepregnancy BMI, other factors may differ by whether preeclampsia is incident or recurrent among primiparous women (9,10,12–14). However, studies evaluating how these factors differ are limited. We used data from the National Institute of Child Health and Human Development (NICHD) Consecutive Pregnancies Study which captured data from women with ≥ 2 consecutive pregnancies to: 1) assess the association between prepregnancy BMI and incident preeclampsia in the 1st pregnancy, incident preeclampsia in the 2nd pregnancy, and recurrent preeclampsia after adjusting for confounders; and 2) examine the association between demographic and clinical factors (in addition to prepregnancy BMI) and preeclampsia risk in the 2nd pregnancy, both incident and recurrent.

METHODS

Study Population

The NICHD Consecutive Pregnancies Study is a longitudinal retrospective study of women with ≥ 2 consecutive pregnancies delivered during 2002–2010 at 20 hospitals in Utah (15). Data sources included both electronic medical records (EMRs) and International Classification of Diseases, 9th revision (ICD-9) discharge codes. Hospitals extracted detailed information from the EMRs for each delivery on maternal demographics, obstetric and

medical history, as well as neonatal outcomes. ICD-9 discharge codes from maternal and newborn discharge summaries were linked to each delivery. The dataset included 114,679 pregnancies (livebirths or stillbirths ≥ 20 weeks' gestation) from 51,086 women who gave birth at least twice and up to 6 times during the study period. All study sites obtained approval from their individual institutional review boards.

As multifetal pregnancies increase preeclampsia risk (11), we limited this study to women ($n=49,868$) who delivered *singletons* in their first 2 pregnancies during the study period. We excluded 202 women with data inconsistencies such as women on hypertensive medications or with hypertension recorded as the reason for labor induction without having any hypertensive disorder diagnosis resulting in 49,666 women with 99,332 singleton deliveries.

Since nulliparous women have a higher preeclampsia risk than multiparous women (11) and to control for absence of past medical history among parous women in the dataset, in the primary analysis we restricted our sample to nulliparous women at study entry who had their first 2 singleton pregnancies observed during the study period ($n=26,963$). Due to a small number, women with eclampsia ($n=20$) were combined with the preeclampsia group. Women with superimposed preeclampsia or chronic hypertension during either pregnancy were excluded ($n=350$) resulting in 26,613 women for the primary analysis (Supplemental Table S1). We also conducted secondary analysis including the singleton pregnancies irrespective of parity at study entry and similarly excluding women with superimposed preeclampsia or chronic hypertension resulting in 48,941 women with 109,837 singleton deliveries.

Study variables

During the study period, preeclampsia defined as blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic occurring ≥ 20 weeks' gestation among previously normotensive women plus proteinuria, urinary excretion ≥ 0.3 g protein in 24-h urine specimen, was widely adopted in US clinical practice (16). Hypertensive disorders were ascertained from both EMRs and ICD-9 discharge codes. Women were categorized as having the condition during pregnancy if a diagnosis was coded in either source (Supplemental Table S2 lists ICD-9 codes). Once diagnosed with a chronic condition, women were considered to have the condition during all subsequent pregnancies. In instances where the two sources disagreed (e.g. preeclampsia vs. gestational hypertension), ICD-9 codes took precedence over the EMRs. In the primary analysis (nulliparous women with their first two singleton pregnancies during the study period), 266 (14.5%) pregnancies had a preeclampsia diagnosis in only one source (263 in the medical record and 3 in the ICD-9 discharge codes), and 34 (1.9%) pregnancies had discrepant diagnoses between the two sources.

For incident preeclampsia in the 1st pregnancy, all demographic and clinical factors were drawn from the 1st pregnancy. When examining preeclampsia risk in the 2nd pregnancy, demographic and clinical factors were drawn from the 2nd pregnancy while obstetric characteristics including small for gestational age (SGA) birth (< 5 th percentile of sex specific birthweight for gestational age) (17), and early preterm birth (< 34 weeks' gestation) were drawn from the 1st (previous) pregnancy. Interpregnancy interval was defined as time elapsed between the woman's 1st delivery date and her 2nd pregnancy last menstrual period

date (18), and prepregnancy weight difference, weight difference between the first two births, was examined as: lost >2 kg, maintained within 2 kg, and gained >2 kg (19).

Statistical Analysis

Poisson regression models with robust variance estimation (20) examined the unadjusted and adjusted associations between prepregnancy BMI (categorical variable) accounting for confounders and risk of: 1) preeclampsia in the 1st pregnancy, 2) preeclampsia in the 2nd pregnancy without prior preeclampsia, and 3) recurrent preeclampsia. Confounding variables (noted in table footnotes) were included based on previous literature. Additionally, we examined the unadjusted association between preeclampsia risk (incident in the 1st or 2nd pregnancy or recurrent) and a continuous prepregnancy BMI using generalized additive models where cross validation was used to choose the smoothing degree in the cubic spline function. These models make no assumptions about the shape of the association between the exposure of interest and the outcome other than to assume additive effects of the adjustment variable.

To examine the significance of other factors (in addition to BMI) on 2nd pregnancy incidence and recurrence risk, we used longitudinal transition models (modified Poisson regression with an interaction between preeclampsia occurrence in the 1st pregnancy and each of the risk factors of interest to distinguish incident and recurrent preeclampsia risk). In these models, we tested for a significant multiplicative interaction between 1st pregnancy preeclampsia and each risk factor. A significant interaction denotes that for the examined factor, the risk associated with preeclampsia in the 2nd pregnancy differs based on having a prior pregnancy with preeclampsia (i.e. differs between incident versus recurrent preeclampsia).

In secondary analysis utilizing the whole dataset irrespective of parity at study entry, we examined if there were changes in the risk estimates. Analyses were conducted using SAS (version 9.3; SAS Institute, Cary, NC) with a p-value <0.05 considered for statistical significance for main effects and interactions. R (version 3.0.1) was used to fit the generalized additive models and to plot the risk estimates.

RESULTS

A total of 23,913 women were normotensive in their 1st pregnancy and nearly all remained normotensive in their 2nd pregnancy (n=23,301, 97.4%). Preeclampsia/eclampsia in the 1st pregnancy occurred among 5.0% of women. A total of 11.6% (155/1,336) of women experienced preeclampsia/eclampsia *recurrence* while 1.3% (341/25,451) experienced *incident* preeclampsia/eclampsia in their 2nd pregnancy. There were no differences in maternal age and marital status between the examined groups (Table 1). Women with preeclampsia in either pregnancy were more likely to have a higher prepregnancy BMI and preterm birth <34 weeks in their 1st pregnancy compared to women with preeclampsia during their first two pregnancies.

Incident preeclampsia risk whether in the 1st or 2nd pregnancy increased continuously with BMI (Figure 1). Recurrent preeclampsia risk also increased in a dose response manner up to

a BMI of about 31 kg/m². Although the risk slightly decreased or leveled off with increasing BMI thereafter, only 14 women with recurrent preeclampsia had a BMI >35 kg/m² which limits our ability to make definitive conclusions for higher BMI. Worth noting is that the absolute risk of preeclampsia is highest in the recurrent preeclampsia group at every BMI level up to about 37 kg/m².

Risk estimates by BMI categories reflected the strong dose-response relationship between prepregnancy BMI and incident preeclampsia in the 1st or 2nd pregnancy (Table 2). For example, compared to normal weight women, incident preeclampsia risk was 1.7–1.8 fold higher among overweight women and 2.1–2.3 fold higher among class I obese women. Among class II/III obese women however, incident preeclampsia risk in the 2nd pregnancy (RR=4.29; 95% CI=3.16–5.82) was more pronounced than incident risk in the 1st pregnancy (RR=2.84; 95% CI=2.32–3.47). This dose-response relationship was not as apparent among women with recurrent preeclampsia. For instance, among overweight women recurrence risk was 1.47 (95% CI=1.04–2.09) similar to the observed 1.60 (95% CI=1.06–2.42) risk estimate among class I obese women and there was no significantly increased risk among class II/III obese women compared to normal weight women.

The differences observed in the associations between BMI and incident preeclampsia risk in the 2nd pregnancy and recurrent preeclampsia risk, were further substantiated by our test for interaction between preeclampsia in the 1st pregnancy and BMI (Table 3). While 2nd pregnancy incident preeclampsia risk increased from 0.42 (95% CI=0.17–1.03) for underweight women to 2.97 (95% CI=2.10–4.20) for obese class II/III women, this increase was not observed among women with recurrent preeclampsia. Race/ethnicity also differed in its associations between incident and recurrent preeclampsia (Table 3). Non-white women had an increased recurrence risk (RR=1.70; 95% CI=1.16–2.50) compared to Non-Hispanic white women, while no association was observed when preeclampsia was incident in the 2nd pregnancy. Preterm birth <34 weeks in the first pregnancy increased both recurrent (RR=1.96; 95% CI=1.34–2.88) and 2nd pregnancy incident preeclampsia risk (RR=3.29; 95% CI=1.99–5.45). Longer inter-pregnancy interval (≥ 24 months) compared to 18–23 month interval was only associated with an increased incident preeclampsia risk (RR=1.63; 95% CI=1.18–2.25). The other examined risk factors including maternal age, marital status, insurance type, smoking, alcohol, diabetes, other maternal chronic conditions, and 1st pregnancy SGA were not significantly associated with either 2nd pregnancy incident preeclampsia or recurrent preeclampsia.

As BMI was the strongest risk factor for preeclampsia, weight change between the two pregnancies was of interest. In analyses adjusting for 2nd prepregnancy BMI, no significant associations were identified for either incident or recurrent preeclampsia with a 2 kg weight change (Table 3) or a 4.5 kg weight change (equivalent to a 2 unit BMI change for an overweight woman of average height) (data not shown). In a different model adjusting for prepregnancy BMI at 1st pregnancy rather than in the 2nd pregnancy (as most previous studies have done), we noted an increase in only incident and not recurrent preeclampsia risk among women who gained >2 BMI units between pregnancies (RR=1.44; 95% CI=1.13–1.83) (data not shown).

When we examined the whole dataset of singleton pairs irrespective of parity at study entry, there were no meaningful qualitative changes in the associations between prepregnancy BMI and incident or recurrent preeclampsia risk (Supplemental Table S3). While the impact of prepregnancy BMI, preterm birth in the previous pregnancy, and interpregnancy interval on the risk of incident preeclampsia in the 2nd pregnancy and recurrent preeclampsia using the whole dataset was similar to what we reported using the nulliparous dataset, we observed other significant factors (Supplemental Table S4).

DISCUSSION

In this large longitudinal dataset of women with at least two consecutive pregnancies, we show that prepregnancy BMI was more strongly associated with incident preeclampsia risk, whether incident in the 1st pregnancy or 2nd pregnancy than with recurrent preeclampsia risk. Our findings build on previous studies that have shown the importance of prepregnancy BMI on incident preeclampsia risk (7). We expand on these findings by examining the association between prepregnancy BMI, using both a continuous and a categorical measure, and risk of incident and recurrent preeclampsia among primiparous women.

To our knowledge, studies examining incident preeclampsia risk among nulliparous women in association with a continuous prepregnancy BMI measure are limited. Bodnar et al., found that preeclampsia risk increases steeply from BMI values of 15 to 30, plateaus between BMI values of 30 to 35, and finally declines beyond a BMI of 35 (5). The authors however, noted that the sample size of women with a BMI ≥ 30 was limited, constituting only 15% of the overall sample (obese $n=178$) (5). We did not observe the decline in incident preeclampsia risk at higher BMI levels, whether incident in the 1st or 2nd pregnancy, but we demonstrate a continuous increase in risk even within the conventional BMI groupings. The plateau and declining effects in preeclampsia risk among obese women however, were observed when we examined recurrent preeclampsia risk. While we hypothesize that the plateauing might be a ceiling effect where very high BMI levels no longer have additional impact due to the high underlying risk among women with a previous preeclampsia history, a limited sample size precludes a definitive conclusion. Women with a BMI ≥ 30 constituted 25% of the sample of those with recurrent preeclampsia (obese $n=325$) while those with a BMI ≥ 35 constituted 12% of the sample ($n=150$).

Our reported estimates of preeclampsia recurrence (11.6%) and preeclampsia incidence in the 2nd pregnancy (1.3%) are fairly similar to what has been previously published (approximately 15% and 0.5%–1.8%, respectively) (13,14,21,22). While recurrence estimates have been examined previously in several studies, data assessing prepregnancy BMI impact on the risk of incident and recurrent preeclampsia among primiparous women are very limited. In an Icelandic study of women with preeclampsia in their 1st pregnancy ($n=151$), being overweight (BMI ≥ 25 kg/m²) was not associated with preeclampsia recurrence (OR=1.34; 95% CI=0.40–4.46) (23). In another population based study using maternally-linked birth certificate data in Missouri, prepregnancy BMI had a more pronounced impact on 2nd pregnancy incident preeclampsia risk than recurrence. Compared to normal weight women, incident preeclampsia risk in the 2nd pregnancy increased from 2.1 (95% CI=1.8–2.4) among overweight women to 4.5 (95% CI=3.9–5.3) among class II/III

obese women while recurrent preeclampsia risk only increased from 1.3 (95% CI=1.1–1.5) among overweight women to 1.8 (95% CI=1.5–2.2) among obese class II/III women (13). While we similarly noted the pronounced increase in incident preeclampsia risk in the 2nd pregnancy with increasing prepregnancy BMI, we did not observe this increased risk with recurrent preeclampsia. Differences in data sources, sample size, and study populations might explain the observed discrepancies.

How obesity impacts preeclampsia risk is not well understood but several features characterize both conditions including oxidative stress, circulating markers of inflammation, dyslipidemia, hyperinsulinemia, insulin resistance, and impaired vascular function (24–26). As biomarkers become delineated (27), more will be understood about the association.

Our findings indicate that after accounting for 1st prepregnancy BMI, women who gained >2 BMI units between pregnancies had increased incident preeclampsia risk in the 2nd pregnancy. Similarly, in a nationwide Swedish study, women who gained >3 BMI units had increased preeclampsia risk (OR=1.8; 95% CI=1.5–2.1) compared to those whose BMI remained relatively unchanged (i.e. ± 1 unit) between pregnancies (28). Our null findings for weight change as a risk factor for recurrent preeclampsia risk are in contrast to another study which found that women who increased their BMI by >2 units between pregnancies increased their recurrence risk (RR=1.3; 95% CI=1.2–1.4) compared to those who remained relatively unchanged (i.e. ± 2 units) (9).

Other than prepregnancy BMI, very few factors differed between 2nd pregnancy incident and recurrent preeclampsia. Non-white women (12%) had increased recurrent but not incident preeclampsia risk. Given the sample size, we cannot make firm conclusions about recurrence risk among non-White women. However, Hispanics who predominantly comprise this group (76%) have been previously shown to have a higher preeclampsia risk than non-Hispanic Caucasian women (29). And while some evidence also suggests that black women have a higher preeclampsia risk, (30,31) we were limited in examining this further given the low number of black women in our study (n=110).

The impact of prior preterm birth on subsequent preeclampsia risk was similar whether preeclampsia was incident or recurrent. It is well established that preeclampsia recurrence risk is higher with an earlier gestational age at delivery in the prior pregnancy complicated by preeclampsia (13,32). Recurrence risk estimates increased from approximately 13% when gestational age at 1st birth was ≥ 37 weeks to 39% when gestational age was ≤ 28 weeks (13). Preterm birth as a risk factor for future preeclampsia among women without prior preeclampsia is postulated to be due to the two conditions sharing a common pathway or that these women were destined to develop preeclampsia but their preterm delivery occurred prior to its clinical manifestation (13).

Strengths of our study include its large size and diagnostic data availability from EMRs and ICD9 discharge codes. As our study design requires women to have ≥ 2 pregnancies to be in the dataset, we are only able to provide risk estimates for 1st pregnancy incident preeclampsia based on those who successfully achieved a subsequent pregnancy within the study period. We lacked data on preeclampsia severity. We also did not have data on

paternity and were unable to examine the association between change in paternity and preeclampsia risk. Whether partner change or longer interpregnancy interval confounds or modifies the paternal effect on preeclampsia risk is debated (22,33). In our study population however, we expect that the majority of the women are in stable relationships. Married women constituted 89% of our sample compared to the 41.5% national estimate (34). As Caucasians comprised the majority of our study population (87%), we were unable to examine whether the impact of prepregnancy BMI on preeclampsia risk differed by race/ethnicity. A previous study has reported a significant interaction between BMI and race/ethnicity; lean black women had higher preeclampsia risk than lean white women while this trend reversed at high BMI values (6). Finally, the lack of associations between smoking and alcohol and preeclampsia risk in our study might have been due to the low prevalence of gestational smoking (2.9%) and alcohol drinking (1.6%).

In conclusion, we show that prepregnancy BMI is more strongly related to incident than recurrent preeclampsia while women of non-white race may have a higher recurrence risk. Further studies are needed to confirm our findings and to explore the different underlying mechanisms that differ between incident versus recurrent preeclampsia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
EMR	electronic medical record
ICD9	International Classification of Diseases ninth revision
SGA	small for gestational age

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Figure 1.

Unadjusted association between prepregnancy body mass index (BMI, kg/m^2) of the index pregnancy and the risk of incident preeclampsia in the 1st pregnancy (solid black line), incident preeclampsia in the 2nd pregnancy (solid grey line), and recurrent preeclampsia (dotted grey line) using generalized additive models with a spline smoother.

For incident preeclampsia in the 1st pregnancy, prepregnancy BMI of the 1st pregnancy was used.

For incident preeclampsia in the 2nd pregnancy and recurrent preeclampsia, prepregnancy BMI of the 2nd pregnancy was used.

Maternal characteristics of the 2nd pregnancy and obstetric outcomes of the 1st pregnancy by preeclampsia status among nulliparous women in the NICHD Consecutive Pregnancy Study, 2002–2010

Table 1

	No preeclampsia in 1 st or 2 nd pregnancy ^c N=24,980	Preeclampsia in 1 st pregnancy only ^d N=1,137	Preeclampsia in 2 nd pregnancy only ^e N=341	Recurrent preeclampsia N=155
Maternal characteristics of the 2nd pregnancy/Obstetric outcomes of the 1st pregnancy				
Maternal age (y) ^a	26.2 (4.1)	26.3 (4.3)	26.5 (4.1)	26.2 (4.7)
Non-Hispanic White ^b	21802 (87)	1007 (89)	298 (88)	125 (81)
Married	22278 (89)	1010 (89)	299 (88)	138 (89)
Private insurance	18187 (73)	833 (73)	238 (70)	100 (65)
Alcohol during pregnancy	405 (2)	9 (1)	8 (2)	3 (2)
Smoke during pregnancy	710 (3)	32 (3)	12 (4)	6 (4)
Interpregnancy interval (months)				
0–5	1423 (6)	68 (6)	24 (7)	18 (12)
6–11	4602 (18)	196 (17)	49 (14)	24 (16)
12–17	6583 (26)	304 (27)	88 (26)	31 (20)
18–23	5477 (22)	238 (21)	55 (16)	31 (20)
24	6895 (28)	331 (29)	125 (37)	51 (33)
1 st & 2 nd prepregnancy weight difference (kg)				
<–2 kg	4876 (20)	235 (21)	51 (15)	31 (21)
–2 to 2 kg	8571 (35)	325 (29)	86 (26)	42 (28)
>2 kg	10813 (45)	543 (49)	195 (59)	77 (51)
Pre-pregnancy BMI (kg/m ²) ^a	24.5 (5)	26.9 (6)	27.9 (7)	27.3 (6)
Pre-pregnancy BMI (kg/m ²)				
Underweight [<18.5]	1378 (6)	25 (2)	5 (1)	1 (1)
Normal [18.5–24.9]	14435 (59)	514 (46)	139 (41)	55 (36)
Overweight [25.0–29.9]	5361 (22)	302 (27)	88 (26)	53 (35)
Obese class I [30.0–34.9]	2138 (9)	147 (13)	49 (14)	28 (19)
Obese class II & III [>35.0]	1321 (5)	136 (12)	58 (17)	14 (9)

Maternal characteristics of the 2 nd pregnancy/Obstetric outcomes of the 1 st pregnancy	No preeclampsia in 1 st or 2 nd pregnancy ^c N=24,980				Preeclampsia in 1 st pregnancy only ^d N=1,137		Preeclampsia in 2 nd pregnancy only ^e N=341		Recurrent preeclampsia N=155	
Gestational weight gain (kg) ^d	13.4 (6)				13.8 (6)		13.9 (7)		14.3 (7)	
Thyroid disease	1253 (5)				68 (6)		17 (5)		9 (6)	
Asthma	2078 (8)				105 (9)		24 (7)		15 (10)	
Depression	2496 (10)				141 (12)		38 (11)		20 (13)	
Gestational diabetes	683 (3)				58 (5)		11 (3)		15 (10)	
Preexisting diabetes	152 (1)				10 (1)		3 (1)		2 (1)	
Antihypertensive medication	15 (0)				3 (0)		25 (7)		19 (12)	
Induction of labor	9157 (37)				437 (38)		235 (69)		72 (46)	
Cesarean delivery	4408 (18)				369 (32)		92 (27)		76 (49)	
Cesarean for failing to progress	518 (2)				37 (3)		8 (2)		11 (7)	
SGA in 1 st pregnancy	1017 (4)				92 (8)		19 (6)		8 (5)	
Preterm <34 week in 1 st pregnancy	393 (2)				80 (7)		15 (4)		25 (16)	

Abbreviations: BMI: body mass index; SGA: small for gestational age.

Data were missing for: race/ethnicity: 30; married: 2; alcohol: 67; smoke: 18; prepregnancy weight difference: 768; prepregnancy BMI: 366; gestational weight gain: 397; gestational diabetes/preexisting diabetes: 13; cesarean delivery: 1; SGA in previous pregnancy: 26.

All figures are N (%) unless otherwise stated.

^a Mean (SD).

^b Non-whites included: non-Hispanic Black (n=110, 0.4%); Hispanic (n=2554, 10%); Asian/Pacific Islander (n=592, 2%); Other race (n=95, 0.4%).

^c Includes normotensive women and women with gestational hypertension during the 1st and/or 2nd pregnancy.

^d Includes women with preeclampsia/eclampsia in their 1st pregnancy who were either normotensive or had gestational hypertension in their 2nd pregnancy.

^e Includes women with preeclampsia/eclampsia in their 2nd pregnancy who were either normotensive or had gestational hypertension in their 1st pregnancy.

Table 2

Association between prepregnancy body mass index categories and the risk of preeclampsia among nulliparous women at study entry in the NICHD Consecutive Pregnancy Study, 2002–2010

Body mass index kg/m ²	Incident preeclampsia in 1 st pregnancy ^a N=26,613		Incident preeclampsia in 2 nd pregnancy ^b N=25,321		Recurrent preeclampsia ^c N=1,292	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Underweight [<18.5]	0.54 (0.39, 0.76)	0.54 (0.38, 0.76)	0.38 (0.16, 0.92)	0.38 (0.15, 0.92)	0.40 (0.06, 2.76)	0.38 (0.05, 2.72)
Normal [18.5–24.9]	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Overweight [25.0–29.9]	1.82 (1.61, 2.07)	1.82 (1.60, 2.06)	1.69 (1.30, 2.21)	1.66 (1.27, 2.16)	1.54 (1.08, 2.20)	1.47 (1.04, 2.09)
Obese I [30.0–34.9]	2.09 (1.76, 2.49)	2.10 (1.76, 2.50)	2.35 (1.70, 3.24)	2.31 (1.67, 3.20)	1.66 (1.09, 2.53)	1.60 (1.06, 2.42)
Obese II & III [>35.0]	2.85 (2.34, 3.49)	2.84 (2.32, 3.47)	4.41 (3.26, 5.96)	4.29 (3.16, 5.82)	0.97 (0.55, 1.69)	0.91 (0.52, 1.61)

RRs and CIs from a modified Poisson regression model. Models adjusted for maternal race/ethnicity (non-Hispanic white, other), age (<29 , 30–34, 35years), marital status (married, not married), insurance (public, private), and smoking status (yes, no).

^a Association examined with prepregnancy BMI of the 1st pregnancy. Final sample size after excluding missing values: unadjusted model N=26,160 (1,270 preeclampsia cases), adjusted model N=26,095 (1,268 preeclampsia cases). BMI distribution: underweight n=1635, normal n=16763, overweight n=5093, class I n=1762, class II/III n=907.

^b Association examined with prepregnancy BMI of the 2nd pregnancy. Final sample size after excluding missing values: unadjusted model N=24,972 (339 preeclampsia cases), adjusted model N=24,926 (338 preeclampsia cases). BMI distribution: underweight n=1383, normal n=14574, overweight n=5449, class I n=2187, class II/III n=1379.

^c Association examined with prepregnancy BMI of the 2nd pregnancy. Final sample size after excluding missing values: unadjusted model N=1,275 (151 preeclampsia cases), adjusted model N=1,273 (151 preeclampsia cases). BMI distribution: underweight n=26, normal n=569, overweight n=355, class I n=175, class II/III n=150.

Table 3

Adjusted risk of recurrent and incident preeclampsia in the 2nd pregnancy according to maternal characteristics of the 2nd pregnancy and neonatal outcomes of the 1st pregnancy among nulliparous women at study entry in the NICHD Consecutive Pregnancy Study, 2002–2010

Maternal characteristics of the 2 nd pregnancy/Obstetric outcomes of the 1 st pregnancy	Recurrent Preeclampsia			Incident Preeclampsia in the 2 nd pregnancy		
	Unadjusted		Adjusted	Unadjusted		Adjusted
	RR	95% CI	RR	95% CI	RR	95% CI
Maternal age, years						
13–29	1.00	Referent	1.00	Referent	1.00	Referent
30–34	0.89	0.56, 1.40	0.82	0.51, 1.32	1.31	0.99, 1.73
35	1.46	0.83, 2.57	1.47	0.83, 2.61	1.12	0.67, 1.88
Race/ethnicity						
White	1.00	Referent	1.00	Referent	1.00	Referent
Other	1.72	1.20, 2.47	1.70	1.16, 2.50	1.07	0.77, 1.47
Marital status						
Married	1.00	Referent	1.00	Referent	1.00	Referent
Non-married	0.98	0.61, 1.57	0.69	0.40, 1.17	1.20	0.87, 1.65
Insurance						
Private	1.00	Referent	1.00	Referent	1.00	Referent
Public	1.43	1.05, 1.94	1.30	0.94, 1.80	1.21	0.97, 1.52
SGA in 1 st pregnancy ^c						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.65	0.33, 1.29	0.69	0.36, 1.30	1.35	0.85, 2.14
Prem <34 weeks in 1 st pregnancy						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	2.17	1.49, 3.17	1.96	1.34, 2.88	3.15	1.88, 5.26
Interpregnancy interval, months						
0–5	1.82	1.07, 3.08	1.33	0.76, 2.34	1.71	1.06, 2.74
6–11	0.95	0.58, 1.57	0.87	0.53, 1.44	1.06	0.72, 1.55
12–17	0.83	0.50, 1.29	0.75	0.46, 1.20	1.33	0.95, 1.86
18–23	1.00	Referent	1.00	Referent	1.00	Referent

Maternal characteristics of the 2 nd pregnancy/Obstetric outcomes of the 1 st pregnancy	Recurrent Preeclampsia				Incident Preeclampsia in the 2 nd pregnancy			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
24	1.16	0.76, 1.76	1.12	0.73, 1.72	1.74	1.27, 2.38	1.63	1.18, 2.25
Prepregnancy body mass index								
Underweight [<18.5]	0.40	0.06, 2.76	0.40	0.06, 2.85	0.40	0.17, 0.98	0.42	0.17, 1.03
Normal weight [18.5–24.9]	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Overweight [25.0–29.9]	1.55	1.09, 2.20	1.40	0.99, 1.98	1.53	1.17, 2.00	1.43	1.07, 1.89
Obese Class I [30.0–34.9]	1.66	1.09, 2.53	1.47	0.94, 2.28	1.96	1.41, 2.72	1.76	1.23, 2.53
Obese Class II & III [>35.0]	0.97	0.55, 1.69	0.92	0.51, 1.66	3.32	2.43, 4.55	2.97	2.10, 4.20
1st & 2nd pregnancy weight difference kg								
<-2 kg	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
-2 to 2 kg	0.98	0.63, 1.52	1.03	0.67, 1.58	0.97	0.69, 1.37	0.98	0.70, 1.39
>2 kg	1.07	0.72, 1.58	0.92	0.63, 1.36	1.60	1.18, 2.18	1.19	0.87, 1.64
Smoking during pregnancy								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.33	0.63, 2.81	1.43	0.63, 3.23	1.34	0.76, 2.36	1.19	0.67, 2.12
Alcohol during pregnancy								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	2.10	0.78, 5.66	1.50	0.52, 4.33	1.45	0.72, 2.90	1.25	0.64, 2.45
Gestational diabetes in 1 st pregnancy								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.51	0.79, 2.88	1.36	0.69, 2.68	1.39	0.76, 2.56	1.24	0.67, 2.30
Preexisting diabetes mellitus								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	2.33	1.37, 3.95	1.73	0.92, 3.26	1.26	0.63, 2.50	0.93	0.46, 1.87
Asthma/depression/thyroid disease								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.97	0.69, 1.37	0.94	0.66, 1.34	0.71, 1.20	0.79	0.60, 1.03	

RRs and CIs from a modified Poisson regression with preeclampsia occurrence in the 1st pregnancy treated as a covariate. Model mutually adjusted for all factors in the table. Final analytic sample was 25,688 after excluding women who were missing any of the above examined factors in the model.

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p-value, only presented for the adjusted RR, represents the global significance of each of the examined predictive factor within the recurrent or incident preeclampsia group using the score test derived from generalized estimating equations.

p-value, only presented for the adjusted RR, represents the interaction of each of the examined predictive factor between recurrent and incident preeclampsia.

SGA defined as <5th percentile of sex specific birthweight for gestational age based on a Canadian reference population.