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The Combined Association of Psychosocial Stress and Chronic Hypertension with Preeclampsia

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Abstract

OBJECTIVE—This study aims to evaluate perceived lifetime stress (LS), perceived stress during pregnancy (PS), chronic hypertension (CH) and their joint association with preeclampsia risk.

STUDY DESIGN—This study includes 4,314 women who delivered a singleton live birth at the Boston Medical Center from October 1998 through February 2008. CH is defined as hypertension diagnosed before pregnancy. Information regarding LS and SP was collected by questionnaire. Preeclampsia was diagnosed by clinical criteria.

RESULTS—LS, SP and CH were each associated with an increased risk of preeclampsia (OR(95%CI)=2.1(1.6–2.8) for LS; 1.7(1.3–2.1) for SP; 11.1(8.1–15.4) for CH). Compared with normotensive pregnancy with low LS, both normotensive pregnancy with high LS (2.1(1.5–2.9)) and pregnancy with CH and low LS (10.6(7.5–15.1)) showed an increased risk of preeclampsia, while pregnancy with high LS and CH yielded the highest risk of preeclampsia (21.3(10.3–44.3)). The joint association of SP and CH on preeclampsia was very similar to that of the joint association of LS and CH.

CONCLUSIONS—This finding indicates that high psychosocial stress and CH can act in combination to increase the risk of preeclampsia up to 20-fold. This finding underscores the importance of efforts to prevent, screen and manage CH, along with reducing psychosocial stress, particularly among women with CH.

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Conflicts of interests
The authors have declared that no conflicting interests exist.

Keywords

Psychosocial stress; chronic hypertension; combined effect; preeclampsia

Introduction

Preeclampsia occurs in 5–7% of pregnancies, and is a major cause of maternal and fetal mortality and morbidity in both developed and developing countries. Onset early in pregnancy is associated with a poorer prognosis. For the fetus, preeclampsia may result in growth retardation, preterm birth, hypoxia, and death. For the mother, it may induce placental abruption with possible disseminated intravascular coagulation, end organ damage as a result of accelerated hypertension, stroke, and death[1]. Women who have preeclampsia as a multipara, as a recurrent event, or who develop it in the second trimester have been found to be at higher risk for hypertension and diabetes later in life[2]. Worldwide, 10–15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy, mainly preeclampsia/eclampsia (PE/E)[3]. In Canada, PE/E was one of the leading causes of maternal death in 1997–2000, accounting directly for 21% of maternal deaths[4].

Previous studies have found that women with certain conditions, including nulliparity, a family or self-history of preeclampsia, increased body mass index (BMI), multiple pregnancies, increased age, chronic hypertension, diabetes mellitus, renal and connective tissue diseases, work-related psychosocial strain during pregnancy, poor social status, diabetes mellitus, coagulation abnormalities, and dyslipidemia are at increased risk for preeclampsia[2,5]. Of note, chronic hypertension is a well-known risk factor for preeclampsia. Its prevalence in pregnant women varies from 1% to 5%; and the rates are higher in older, obese, or black women[6]. It is estimated that 25% of women with preexisting hypertension will have PE/E during pregnancy[7]. In Thailand, pregnant women with chronic hypertension had a 19.5-fold (95%CI=2.4–155.7) increased risk of preeclampsia, compared with those without chronic hypertension[5]. Previously, our study group found that chronic hypertension was associated with preeclampsia among African and White pregnant women[8]. In short, data from different studies have consistently shown that chronic hypertension is a leading cause of PE/E[5–8].

In contrast, findings to date on psychosocial stress and PE/E have been inconsistent. Some studies found depression, anxiety, and other psychopathologies during pregnancy to be risk factors for adverse fetal and neonatal outcomes including preterm delivery[9–11], fetal growth restriction[12], and low Apgar scores[13]. In addition, mothers' anxiety during pregnancy is associated with an increased risk of asthma in children[14]. Indeed, accumulating evidence indicates that psychiatric disorders during pregnancy are related to an increased risk of preeclampsia. One prospective study indicated that women with depression, anxiety, or both had a 3.1-fold increased risk for preeclampsia, compared to those without them[15]. Another recent study (by Qiu et al.) found that a positive history of maternal mood or anxiety disorder was associated with a 2.12-fold increased risk of preeclampsia[16]. Four further studies observed an association of preeclampsia/gestational hypertension with job stress in working women[17–20], and anther demonstrated that anxiety during early pregnancy increased the risk of preeclampsia more than three-fold among 652 Finnish nulliparous women (OR=3.2; 95%CI =1.4–7.4)[15]. Likewise, both depression and perceived stress during pregnancy were associated with increased rates of preeclampsia[15,21].

Data from animal studies have indicated that in 14-day pregnant rats, chronic stress leads to increased adrenal weight and lower endothelium-derived relaxing factor release; likewise, in

20-day pregnant rats, chronic stress caused higher blood pressure, increased vasomotility and proteinuria, and lower endothelium-derived relaxing factor release[22]. The animal data also implies that mental stress during pregnancy may increase the risk of hypertension-associated disorders. In contrast with these animal findings, there was no association between work stress, anxiety, depression or pregnancy-related anxiety early in pregnancy and the development of gestational hypertension or preeclampsia later in pregnancy among a cohort of 3679 pregnant women in Amsterdam[23]. Two other prospective studies did not observe an association between depression or anxiety and hypertensive complications[24,25], and moreover, these studies also did not find a significant association between maternal psychopathology and preeclampsia[23–25].

To date, no study has examined the combined association of psychosocial stress and chronic hypertension with PE/E in a U.S. urban minority population, in which both psychosocial risk factors and chronic hypertension are prevalent. The objectives of this study are to examine the individual and joint association of psychosocial stress and chronic hypertension with preeclampsia in a U.S. urban population, and to explore whether the associations differ between black and non-black women.

Materials and Methods

Study population and data collection

This study is part of an ongoing NIH-funded case-control study on preterm birth, and includes women enrolled at the Boston Medical Center (BMC) from October 1998 to February 2008. The parent study (1998 to present) is being conducted at the BMC, a large urban hospital with a predominantly minority, inner-city patient population. Case mothers were those who delivered singleton, live births occurring at <37 weeks of gestation, and controls were defined as mothers delivering at ≥37 weeks of gestation with birth weight appropriate for gestational age as defined by the National Center for Health Statistics/ Centers for Disease Control and Prevention guidelines (birth weight 2500–4000 g)[26]. Pregnancies resulting in multiple births and newborns with major birth defects were excluded, and a detailed description of the study population is available elsewhere[27]. For the present study, we collected epidemiologic data, clinical data, and maternal venous blood samples. In addition, placenta samples were sent for histopathology based on routine indications, including preterm birth. The Institutional Review Boards of BMC, the Massachusetts Department of Public Health, Children's Memorial Hospital in Chicago, and the Johns Hopkins Bloomberg School of Public Health approved the study protocol, and all participants gave written informed consent.

Definition of preeclampsia and other key variables

Preeclampsia and chronic hypertension—All of the following key outcomes were defined by physician diagnosis and confirmed by a review of prenatal care records in accordance with published clinical studies[28]. Preeclampsia was defined according to the report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy[29], as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg on at least two occasions, and proteinuria of at least 1+ by urine dipstick testing on two or more occasions, after 20 weeks of gestation. In the present study, the preeclampsia group also included women with eclampsia. Women with gestational hypertension, defined as elevated blood pressure occurring after 20 weeks of gestation without preexisting hypertension, and not associated with proteinuria or other systemic manifestations, were excluded from the analysis. Chronic hypertension was defined as persistent hypertension that is present before conception or during the first 20 weeks of gestation.

Variables of psychological stress—We examined the following variables: women's perceived amount of general life stress, perceived stress during pregnancy, major stressful life events within 1 year prior to pregnancy, major stressful life events during pregnancy, any violence witnessed during pregnancy, father of baby involved in index pregnancy, father of baby supportiveness, family and friend supportiveness, whether pregnancy was desired, annual household income, and food supply. Information about psychological stress was collected by questionnaire. Lifetime Stress (LS) and Stress during Pregnancy (PS) were defined respectively by responses to the following two questions: "*How would you characterize the amount of stress in your life in general?*" and "*How would you characterize the amount of stress in your life during pregnancy?*" Three options for these questions were provided: "*Not stressful*", "*Average stressful*" and "*Very stressful*". For the analyses, "*Not stressful*" and "*Average stressful*" were considered to be low stress; "*Very stressful*" was regarded as high stress.

Statistical Analysis

All analyses were conducted using SAS software (version 8.0; SAS Institute Inc., Cary, NC). First, the sociodemographic and clinical variables were described, stratified by non-preeclampsia and preeclampsia. The continuous and categorical variables were analyzed by *t* test and χ^2 test, respectively. Second, the distributions of variables related to psychological stress were presented, stratified by the non-preeclampsia and preeclampsia groups. Third, the separate association of life stress, pregnancy stress, and either life or pregnancy stress combined with chronic hypertension relative to the risk of preeclampsia was analyzed before and after the adjustment of covariates using logistic regression models. Finally, the adjusted joint effect of life stress, pregnancy stress, and chronic hypertension on the risk of preeclampsia were evaluated for entire study samples as well as ethnic subgroups (black and non-black mothers), using logistic regression models.

In the logistic regression models, the following covariates were included: maternal ethnicity, maternal active and passive smoking during pregnancy, maternal age, pre-pregnancy BMI, parity, drug use and alcohol use.

Results

Altogether, 4314 mothers were included in the final analysis, including 3890 mothers without preeclampsia and 424 mothers with preeclampsia. The prevalence of preeclampsia was 9.9% in the study population. Table 1 shows the demographic and clinical characteristics of the study sample. As compared to those without preeclampsia, mothers with preeclampsia were older, had higher pre-pregnancy BMI, and had delivered babies with lower gestational age and/or lower birthweight (all $P < 0.001$). Mothers with preeclampsia were more likely to be black and primiparous, and have a lower prevalence of active smoking and chronic hypertension (all $P < 0.01$). The prevalence of passive smoking, illicit drug use and alcohol drinking during pregnancy were similar between the two groups (all $P > 0.05$).

Table 2 presents the distribution of stress-related variables in the two groups. Women with preeclampsia had higher perceived levels of general stress in their lives, and also higher perceived stress during pregnancy. They also had higher job-related stress during the first and second trimester compared to those without preeclampsia, and experienced more major stressful events within 1 year prior to pregnancy. The distributions of the other stress variables were similar in the two groups.

The association of chronic hypertension, life stress, pregnancy stress, and either general life stress or pregnancy stress with the risk of preeclampsia were evaluated for the entire study

population (Table 3). After adjusting for potential confounding variables, the risk of preeclampsia was increased by life stress (OR (95%CI) = 2.2 (1.6–2.9), P=6.0×10^{-6}), stress during pregnancy (1.62 (1.3–2.1), P=1.8×10^{-4}), and chronic hypertension (10.6 (7.7–14.6), P=4.9×10^{-46}). Additionally, having either general life stress or pregnancy stress also increased the risk of preeclampsia (OR (95%CI) = 1.6(1.3–2.1); P =1.5×10^{-4}). Meanwhile, in the sub-analyses based on maternal ethnicity (Supplement Table 2), the strength of the association between chronic hypertension, life stress, pregnancy stress and either general life stress or pregnancy stress with the risk of preeclampsia among black mothers and non-black mothers was highly similar to those in the entire study sample.

Tables 4a and 4b present the joint association between stress and chronic hypertension in the entire study population, and in black and non-black subgroups. Mothers with both chronic hypertension and high stress had a high risk of preeclampsia. Normotensive mothers with high life stress, and chronic hypertensive mothers with either low or high life stress, had an increased risk of preeclampsia as compared with normotensive mothers with low life stress. Notably, the combination of high life stress and chronic hypertension yielded the highest risk of preeclampsia (OR (95%CI) = 21.3 (10.3–44.3); P = 2.3×10^{-16}). Hypertensive mothers with both life stress and pregnancy stress also had a markedly high increased risk of preeclampsia with an (OR=21.5, 95% CI = 9.6 – 47.8). The joint effect of stress during pregnancy, having either general life stress or pregnancy stress with chronic hypertension on preeclampsia was very similar (Table 4). The mothers with chronic hypertension and high stress during pregnancy had a 17.4-fold (95% CI = 9.5 – 31.8) increased risk of preeclampsia, compared with normotensive mothers with low stress during pregnancy. Additionally, the joint effects of psychological stress and chronic hypertension on preeclampsia were also observed among black mothers and non-black mothers, respectively, except for the association of chronic hypertension and stress during pregnancy on preeclampsia among black mothers (Supplement Table 3).

Discussion

This study found that perceived general lifetime stress, stress during pregnancy, and chronic hypertension were associated with an increased risk of preeclampsia. A critical finding was that chronic hypertension, in combination with high stress before or during pregnancy, was associated with a dramatically increased risk of preeclampsia. Compared with normotensive women with low life stress and low stress during pregnancy, the adjusted odds ratio (OR) of hypertensive mothers with high life stress or high stress during pregnancy reached to 21.3 and 17.4, respectively. Furthermore, in the sub-analyses of black mothers and non-black mothers, the joint association of CH and perceived stress on the risk of preeclampsia was basically consistent with that from the entire study sample.

Chronic hypertension is a relatively common and increasingly prevalent comorbidity in pregnancy. Recent U.S. data have shown that the age-adjusted prevalence of all-cause chronic hypertension increased significantly throughout the seven 2-year intervals, from 1.01% in 1995–1996 to 1.76% in 2007–2008[30]. Our results revealed that chronic hypertension is associated with an elevated risk of preeclampsia (OR = 10.9, 95% CI = 7.7–14.6), a finding that is consistent with the results of other investigators[5,31]. Whereas the ORs of chronic hypertension relative to the development of preeclampsia from different studies have varied from 2.21 to 19.5 [5,30,31], all human epidemiological studies have consistently shown that chronic hypertension increases the risk of preeclampsia [5,30,31]. Moreover, separate analyses of black and non-black mothers showed results similar to those from the entire study population, which indicates that the association of chronic hypertension with preeclampsia was very stable. As well, the clinical data indicated that controlling blood pressure can decrease the risk of preeclampsia among pregnant women with chronic

hypertension. It also showed that chronic hypertension was associated with an increased risk of preeclampsia.

Thus far, our understanding of whether psychological stress is related to an increased risk for preeclampsia is controversial. It has been hypothesized that preeclampsia is, in part, a stress-related disease, and epidemiologic studies have shown that the relative risk for preeclampsia increases in relation to the number of stressful situations experienced[32]. Our findings suggest that psychological stress, in general or during pregnancy, is moderately associated with an increased risk of preeclampsia -- findings that are similar to previous studies[15,16,31]. For example, a prospective cohort study found that anxiety in early pregnancy was associated with a 3.2-fold increased risk for subsequent preeclampsia among mothers in the Helsinki metropolitan area[15]. Another study found a positive history of maternal mood or anxiety disorder was associated with a 2.12-fold increased risk of preeclampsia[16]. Stressful work or home environments were also found to be associated with an increased risk of preeclampsia[31], and pregnant women with worsening or severe preeclampsia/severe gestational hypertension were found to have higher psychological stress than those with mild preeclampsia/mild gestational hypertension[33]. Conversely, in a study conducted in Amsterdam, there was no significant association between work stress, anxiety, depression or early pregnancy-related anxiety and the development of gestational hypertension or preeclampsia later in pregnancy[23]. Similarly, two other prospective studies did not find an association between depression or anxiety and hypertensive complications of pregnancy[24,25]. A further case-control study conducted in Canada also found no association between job stress and preeclampsia[34].

Known neuropsychoimmunological mechanisms may begin to account for a causal relationship between stress and preeclampsia. Psychological stress activates the hypothalamus–pituitary–adrenal (HPA) axis, which in turn increases blood levels of corticosteroids and catecholamines, hormones that are produced in the adrenal glands in the case of psychological or physiological stress. Stress also activates the sympathetic nervous system and has been found to influence immune system function[35,36]. In accordance with these findings, increased blood levels of corticotrophin-releasing hormone and increased sympathetic activity have been observed in women with preeclampsia[37].

Our most compelling finding was that the combination of stress and chronic hypertension is associated with a 20-fold increase in the risk of preeclampsia. The hypertensive mother with either high general life stress and pregnancy stress, or the combination of both, had up to a 39.7-fold (95% CI = 8.5 – 184.4) increased risk of preeclampsia. Importantly, the findings from the entire study sample were confirmed by analyses performed on individual ethnic sub-groups.

This is the first study to examine the combined effects of psychological stress and chronic hypertension on the incidence of preeclampsia. With this stated, there is mounting evidence that chronic hypertension and psychological stress are associated individually with an increased risk of preeclampsia -- almost all previous studies suggest that chronic hypertension is positively related to the risk of preeclampsia. There are plausible mechanisms by which the synergistic influences of psychological stress and chronic hypertension could contribute to the development of preeclampsia. For example, psychological stress can lead to sympathetic over-activity in the hypothalamic-pituitary-adrenal (HPA) axis, and the resulting increase in sympathetic activity may contribute to vasoconstriction -- the key abnormality in preeclampsia. Understanding the effects of stress during human pregnancy is complicated by the development of the placenta as a significant endocrine organ that may be highly "stress-sensitive"[38,39]. All HPA-axis peptides increase during human gestation, but the dramatic elevations of placental corticotropin-releasing

hormone (CRH) in maternal plasma during pregnancy reach levels observed only in the hypothalamic portal system during physiological stress[40]. Stress is also indicated in the pathogenesis of chronic hypertension[41].

Pregnant black women have a greater risk of preeclampsia and chronic hypertension, particularly Americans of West African origin[42]. The high prevalence of chronic hypertension in blacks can be partly explained by the individual social and racial status of living in the U.S.; such psychosocial stress may evoke neuroendocrine responses favoring an increase in arterial pressure[43]. Moreover, depression and anxiety during pregnancy could prove harmful through the altered excretion of vasoactive hormones or other neuroendocrine transmitters[44–47], which in turn may increase the risk for hypertension.

Relative to the sympathetic nervous system, Schobel et al.[48] observed a greater increase in activity in pregnant women with preeclampsia than in normotensive pregnant and non-pregnant women. Because sympathetic nervous system activity has been found to revert to normal in some pregnant women with preeclampsia, it has been hypothesized that preeclampsia is a state of increased sympathetic activity. As well, stress can have its effects on individuals via an increase in sympathetic vasoconstrictor activity. For example, women experiencing high levels of stress during pregnancy have increased circulating levels of proinflammatory cytokines relative to women who do not report high levels of prenatal stress[49]. This is a potentially critical observation, since increased levels of pro-inflammatory cytokines and decreased amounts of anti-inflammatory cytokines have been associated with the occurrence of preeclampsia[50]. Moreover, an increase in pro-inflammatory cytokines is associated with the general occurrence of hypertension in humans[51]. Hence, psychological stress combined with chronic hypertension via the inflammatory cytokine pathway may also drive the occurrence of preeclampsia during pregnancy. Our study reveals a synergistic effect between perceived stress and chronic hypertension, resulting in a strongly increased risk of preeclampsia. This key data can be harnessed to inform clinical practice. Currently, prevention of preeclampsia focuses primarily on lowering blood pressure, and does not generally address the reduction of psychological stress. We suggest that efforts to control stress during pregnancy could decrease the risk of preeclampsia.

Our study has the following limitations. First, levels of general life stress and pregnancy stress were recalled by the mothers in our study after delivery and could be subject to recall bias. Second, both the duration and period of psychological stress may have different effects on preeclampsia; however, information about duration and period of psychological stress was not obtained in this study, thus hampers further exploration into the effects of psychological stress on preeclampsia. Third, other psychological disorders (e.g., neurosis), which were not identified in our study, might distort the joint association of psychological stress and chronic hypertension with preeclampsia. Fourth, while each type of psychological stress was determined by only a single question in the questionnaire, it is possible that this may better reflect stress than more comprehensive measures of stress load (e.g. life event scales). Moreover, it is possible that a single question may make interpretation of the results more distinct than a conglomerate of combined items and questions. Our question on stress has been used in several previous studies and found to be related to indicated increased risk for dementia[52], hypertension [53], cancer[54] and psychosomatic diseases[55].

In summary, we studied an urban, predominantly minority, population, and found that high perceived stress and chronic hypertension interact synergistically to increase the risk of preeclampsia up to 40-fold. Given the high prevalence of these risk factors in the general population, we propose that a substantial reduction in the incidence of preeclampsia might be gained through effective control of maternal stress and hypertension, both pre-pregnancy and throughout the gestational period. While further research to validate the efficacy of such

interventions is needed, this research holds great promise and tremendous potential to yield substantial human and economic benefits.

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Table 1

Study Population Characteristics.

Variable	No Preeclampsia	Preeclampsia	*P*
N	3890	424	
Maternal age, in years (Mean ± SD)	27.8±6.4	29.3±6.9	<0.001
Pre-pregnancy BMI, kg/m^2 (Mean ± SD)	25.6±6.0	28.2±7.1	<0.001
Gestational age, in weeks (Mean ± SD)	38.2±3.2	35.3±3.7	<0.001
Birth weight, in grams (Mean ± SD)	3015.9±743.9	2332.3±898.4	<0.001
Maternal Age Distribution, n(%)			
<19 years	453(11.6)	41(9.7)	<0.001
20~ years	2027(52.1)	178(42.0)	
30~ years	820(21.1)	109(25.7)	
>=35 years	590(15.2)	96(22.6)	
Highest Education Completed n(%) n(%)			
Primary School	245(6.4)	28(6.7)	0.022
Middle School	1020(26.5)	83(19.9)	
High School	1317(34.2)	168(40.3)	
Some College	861(22.4)	88(21.1)	
College Degree or Above	403(10.5)	50(12.0)	
Marital Status, n(%)			
Married	2549(65.7)	270(63.8)	0.447
Unmarried	1332(34.3)	153(36.2)	
Maternal Ethnicity, n(%)			
Black	1998(51.4)	259(61.1)	0.002
White	444(11.4)	39(9.2)	
Hispanic	968(24.9)	84(19.8)	
Other	480(12.3)	42(9.9)	
Parity, n(%)			
0	1559(40.1)	204(48.1)	0.001
>=1	2331(59.9)	220(51.9)	
Maternal smoking, n(%)			
Never	3061(78.7)	361(85.1)	<0.001
Intermittent	264(6.8)	34(8.0)	
Persistent	565(14.5)	29(6.8)	
Passive Smoking, n(%)			
No	2961(76.1)	337(79.5)	0.121
Yes	929(23.9)	87(20.5)	
Maternal Illicit Drug Use, n(%)			
No	3356(86.3)	379(89.4)	0.074
Yes	534(13.7)	45(10.6)	
Maternal Alcohol Use, n(%)			

Variable		No Preeclampsia	Preeclampsia	*P*
	No	3736(96.0)	415(97.9)	0.060
	Yes	154(4.0)	9(2.1)	
Preterm Birth, n(%)				
	No	2964(76.2)	167(39.4)	<0.001
	Yes	926(23.8)	257(60.6)	
Low Birth Weight Delivery, n(%)				
	No	2506(64.4)	208(49.1)	<0.001
	Yes	1384(35.6)	216(50.9)	
Chronic Hypertension, n(%)				
	No	3787(97.4)	318(75.0)	<0.001
	Yes	103(2.6)	106(25.0)	

Table 2

Stress-Related Variables in the Study Population

Variable	Level	No Preeclampsia n(%)	Preeclampsia n(%)	*P*
N		3890	424	
Life stress$^{\psi}$	Low	3460(88.9)	345(81.4)	<0.001
	High	430(11.1)	79(18.6)	
Pregnancy stress$^{\Theta}$	Low	3126(80.4)	310(73.1)	<0.001
	High	764(19.6)	114(26.9)	
Job stress during 1st and 2nd trimester	Low	3074(79.0)	308(72.6)	0.002
	High	816(21.0)	116(27.4)	
Job stress during 3rd trimester	Low	3357(86.3)	359(84.7)	0.357
	High	533(13.7)	65(15.3)	
Event within 1 year*	No	3381(86.9)	349(82.3)	0.009
	Yes	509(13.1)	75(17.7)	
Event during pregnancy$^{\#}$	No	3026(77.8)	325(76.7)	0.593
	Yes	864(22.2)	99(23.3)	
Violence$^{\&}$	No	3695(95.0)	410(96.7)	0.119
	Yes	195(5.0)	14(3.3)	
Father involved¶	Low	976(25.1)	101(23.8)	0.566
	High	2914(74.9)	323(76.2)	
Father supportive§	Low	967(24.9)	96(22.6)	0.314
	High	2923(75.1)	328(77.4)	
Family supportive$^{£}$	Low	349(9.0)	27(6.4)	0.071
	High	3541(91.0)	397(93.6)	
Planned pregnancy$^{\Delta}$	Yes	2059(52.9)	227(53.5)	0.812
	No	1831(47.1)	197(46.5)	
Annual household income	<$15k	1216(43.9)	132(42.0)	0.308
	$15~ k	726(26.2)	75(23.9)	
	>=$30k	831(30.0)	107(34.1)	
Food supply	Sufficient	3557(91.4)	386(91.0)	0.779
	Insufficient	333(8.6)	38(9.0)	

$^{\psi}$Amount of stress in mother's life in general

$^{\Theta}$Amount of stress in mother's life during pregnancy

*Major stressful events within 1 year prior to pregnancy

$^{\#}$Major stressful events during pregnancy

$^{\&}$Any violence witnessed during pregnancy

¶Father of baby involved in index pregnancy

§father of baby support

$^{£}$Family and friends support

[Δ] Mother wanted to become pregnant at this time

Table 3

The Adjusted* Associations of Chronic Hypertension, Life Stress, Pregnancy Stress and any one of Life and Pregnancy Stress with the Risk of Preeclampsia Among the Whole Sample.

Variable	Preeclampsia n(%)	No Preeclampsia n(%)	OR(95%CI)	*P*
Life stress				
Low	345(9.1)	3460(90.9)	1.0	--
High	79(15.5)	430(84.5)	2.1(1.5–2.8)	1.6×10^{-6}
Pregnancy stress				
Low	310(9)	3126(91)	1.0	--
High	114(13)	764(87)	1.6(1.3–2.1)	1.8×10^{-4}
Either life or pregnancy stress				
Low	301(8.9)	3063(91.1)	1.0	--
High	123(12.9)	827(87.1)	1.6(1.3–2.1)	1.5×10^{-4}
Chronic hypertension				
No	318(7.7)	3787(92.3)	1.0	--
Yes	106(50.7)	103(49.3)	10.9(7.7–14.6)	4.9×10^{-46}

*Covariates included maternal ethnicity, maternal active and passive smoking during pregnancy, maternal age, pre-pregnancy BMI, parity, drug use and alcohol use. Additionally, chronic hypertension was included as a covariate when the associations of life stress, pregnancy stress and either one with preeclampsia were analyzed; life stress and pregnancy stress were included as covariates when the associations of chronic hypertension with preeclampsia were analyzed.

Table 4

The Joint* Associations of Life Stress vs. Chronic Hypertension and Stress During Pregnancy vs. Chronic Hypertension with the Risk of Preeclampsia Among all Mothers.

Variable		Preeclampsia n(%)	No Preeclampsia n(%)	OR(95%CI)	*P*
Hypertension	**Life stress**				
No	Low	262(7.2)	3370(92.8)	1.0	--
	High	56(11.8)	417(88.2)	2.1(1.5–2.9)	7.4×10^{-6}
Yes	Low	83(48.0)	90(52.0)	10.6(7.5–15.1)	1.4×10^{-39}
	High	23(63.9)	13(36.1)	21.3(10.3–44.3)	2.3×10^{-16}
Hypertension	**Stress during pregnancy**				
No	Low	235(7.2)	3044(92.8)	1.0	--
	High	83(10.0)	743(90.0)	1.6(1.2–2.1)	5.3×10^{-4}
Yes	Low	75(47.8)	82(52.2)	10.6(7.4–15.4)	1.9×10^{-36}
	High	31(59.6)	21(40.4)	17.4(9.5–31.8)	1.8×10^{-20}
Hypertension	**Any one of life and pregnancy stress**				
No	Low	230(7.2)	2983(92.8)	1.0	--
	High	88(9.9)	804(90.1)	1.6(1.2–2.1)	5.7×10^{-4}
Yes	Low	71(47.0)	80(53.0)	10.4 (7.165–15.1)	1.3×10^{-34}
	High	35(60.3)	23(39.7)	17.7(10.0–31.5)	1.2×10^{-22}
Hypertension	**Both life and pregnancy stress**				
No	Low	230(7.2)	2983(92.8)	1.0	.--
	High	51(12.5)	356(87.5)	2.3(1.6–3.2)	2.3×10^{-6}
Yes	Low	71(47.0)	80(53.0)	10.3(7.1–15.0)	6.5×10^{-34}
	High	19(63.3)	11(36.7)	21.5(9.6–47.8)	5.9×10^{-14}

*Covariates included maternal ethnicity, maternal active and passive smoking during pregnancy, maternal age, pre-pregnancy BMI, parity, drug use and alcohol use.