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Incidence and determinants of hypertensive disorders of pregnancy in the US: hospitalization discharge rate for preeclampsia, eclampsia, and gestational hypertensions, 2016-2018.

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INCIDENCE AND DETERMINANTS OF HYPERTENSIVE DISORDERS OF PREGNANCY IN THE US: HOSPITALIZATION DISCHARGE RATE FOR PREECLAMPSIA, ECLAMPSIA, AND GESTATIONAL HYPERTENSIONS, 2016-2018

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ABSTRACT

INCIDENCE AND DETERMINANTS OF
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Background: Hypertension remains one of the most prevalent medical issues in pregnancy. It contributes considerably to maternal and fetal morbidity and mortality, making it one of the most significant public health problems. Although various epidemiological studies have been conducted over the past decades to assess the disease incidence and key risk factors associated with hypertensive disorders of pregnancy, current incidence rates and trends are lacking. This is a novel and significant study because there are no current population-based incidence estimates of hypertensive disorders of pregnancy and their subtypes and very few studies with the power to explore a wide range of risk factors.

Objective: The purpose of this dissertation is to provide the most current national trend incidence rates of gestational hypertension, preeclampsia, and eclampsia in the United

States from 2016 to 2018, as well as to investigate the associated risk factors in women with hypertensive disorders of pregnancy.

Design: Serial cross-sectional secondary analysis

Setting: The Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP), which was drawn from all 48 States participating in HCUP, covering more than 97% of the U.S. population. The NIS represents a stratified sample of approximately 20% of discharges from community hospitals in the United States, excluding rehabilitation and long-term acute care hospitals.

Participants: 11,097,776 deliveries of US women aged 15–45 years between 2016 and 2018.

Methods: The descriptive patient and hospital characteristics of the study cohort, which included all women who had one or more live or stillbirths between 2016 and 2018, were given in counts and percentages. The incidence of gestational hypertension, preeclampsia, and eclampsia was reported in crude rates per 1000 delivery hospitalizations. The risks of gestational hypertension, preeclampsia, and eclampsia among US pregnant women aged 15–45 years were assessed using univariate and multivariable regression models that were adjusted for previously known covariates.

Primary outcome measures: Gestational hypertension, preeclampsia, and eclampsia.

Results: The incidence rate of hypertensive disorders of pregnancy is 54.6 per 1,000 deliveries for gestational hypertension, 48.9 per 1,000 deliveries for preeclampsia, and 0.8 per 1,000 deliveries for eclampsia. During the three-year study period, preeclampsia and gestational hypertension rates continued to rise while eclampsia rates declined. The

incidence rate of gestational hypertension increased by 13.2% per year and that of preeclampsia by 9.0% per year, while the incidence rate of eclampsia decreased by 16.3% per year on average. Hospitalizations with gestational hypertension disorder were associated with higher risk among younger age groups (age 15–19), and older age groups (age 40–45) compared to 30-34 years-old, white race, women living in the south, the poorest area, women delivered in urban teaching hospitals, women with private insurance, and women with preexisting conditions including gestational diabetes and non-gestational diabetes, obesity, anemia, and hypothyroidism. The risk ratio of gestational hypertension was significantly lower in women with a history of smoking, thrombophilia, and renal disease, after adjusting for other covariates. On the other hand, preeclampsia was linked to a higher risk in younger and older age groups, Black race, women residing in the south and poorest areas, those who gave birth in teaching hospitals in urban areas, and those who had preexisting conditions like gestational diabetes and non-gestational diabetes, multiple pregnancy, obesity, systemic lupus erythematosus, antiphospholipid syndrome, anemia, hypothyroidism, and renal disease. The risk ratio of preeclampsia was significantly lower in women with a history of smoking and thrombophilia. Further, eclampsia was more likely to occur in younger age groups (<25), women of the Black race, Southern women, women who gave birth in rural hospitals, and women with preexisting conditions such as multiple pregnancy, anemia, and renal disease.

Conclusion: This work provides, to the best of the author's knowledge, the most recent large-scale population-based studies that have estimated the incidence of the main types of hypertensive disorders in pregnancy and investigated the risk factors associated with

those conditions on a larger scale. The risk of gestational hypertension, preeclampsia, and eclampsia increased among US women from 1979 to 2018. Additional efforts are needed to monitor and revise trends, as well as construct a risk-based model that could aid in early detection.

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INTRODUCTION

Background

Hypertensive disorders of pregnancy remain a major public health concern around the world. These diseases represent a set of clinical conditions that affect pregnant women and are associated with high blood pressure (hypertension), abnormally high levels of protein in their urine (proteinuria), and other neurological or significant end-organ dysfunction. This multisystem progressive disorder is associated with significant maternal and fetal morbidity and mortality [1]. Preeclampsia and eclampsia are also associated with later-life cardiovascular complications among women and their offspring. In the United States (US), hypertensive disorders of pregnancy contribute to about 6.3 percent of all pregnancy-related deaths and represent the seventh leading cause of maternal mortality [2]. Updated national trends are lacking, and the rise in incidence is concerning [3-6].

Definitions and Classification

Classification and diagnostic criteria for hypertensive disorders of pregnancy have varied in the past, which has led to some confusion both clinically and in term of research efforts to comprehend and prevent this disorder. Currently, definitions and diagnostic criteria are generally similar worldwide, and the major hypertensive disorders that occur in pregnancy have been classified into four major clinical categories:

(1) preeclampsia/eclampsia/HELLP syndrome; (2) gestational hypertension; (3) chronic hypertension; and (4) preeclampsia superimposed upon chronic hypertension (Table 1). Precise definitions and accurate diagnosis for each of these entities are often difficult and a major challenge in the study of hypertensive disorders of pregnancy.

Preeclampsia and eclampsia

Preeclampsia is defined as a new onset of high blood pressure (≥140/90 mm Hg systolic/diastolic) after 20 weeks of gestation in a previously normotensive woman and proteinuria (≥300 mg protein in a 24-hour maternal urine collection or 1+ protein on a urine dipstick) or new-onset hypertension with significant end-organ dysfunction (with or without proteinuria).

In 2013, The American College of Obstetricians and Gynecologists (ACOG) updated the diagnostic criteria (Table 1) and removed proteinuria as an essential criterion to diagnose preeclampsia. Additionally, they eliminated some features that were characteristic of severe preeclampsia, such as oliguria, fetal growth restriction, and large proteinuria (5 g/24 hours) [7].

Eclampsia refers to the occurrence of a generalized seizure in a woman with preeclampsia that cannot be attributed to other causes. HELLP syndrome is a subtype of preeclampsia presenting with hemolysis, elevated liver enzymes, and low platelets.

Chronic (preexisting) hypertension

Chronic hypertension is hypertension (≥140/90 mm Hg systolic/diastolic) present before pregnancy or before 20 weeks of gestation. De novo hypertension at any time during pregnancy that persists for at least 12 weeks post-delivery is also considered chronic hypertension.

Gestational hypertension

Gestational hypertension is defined as hypertension that develops after 20 weeks of gestation without proteinuria or other end-organ dysfunction related to preeclampsia.

Preeclampsia superimposed upon chronic hypertension

Preeclampsia superimposed upon chronic hypertension occurs when a woman with chronic hypertension experiences new features of preeclampsia syndrome, such as a sudden increase in blood pressure that was previously well-controlled, new onset of proteinuria or a sudden increase in proteinuria, and/or new end-organ dysfunction after 20 weeks of gestation and characterized by worsening or resistant hypertension.

Classification of Hypertensive Disorders of Pregnancy		
Disorder	**Diagnostic criteria**	**Onset**
Gestational hypertension	BP ≥ 140/90 mm Hg*	> 20 weeks
Preeclampsia	+ proteinuria† or + end-organ dysfunction¶	> 20 weeks
Eclampsia	preeclampsia + seizure	> 20 weeks
Chronic hypertension	BP ≥ 140/90 mm Hg	< 20 weeks
Preeclampsia superimposed upon chronic hypertension	Chronic hypertension + preeclampsia	> 20 weeks

* Systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥ 90 mmHg on at least 2 occasions, 4 hours apart.

† ≥ 0.3 g/24-hour urine specimen or protein/creatinine ratio ≥ 0.3 in a random urine specimen or dipstick > 1+.

¶ New onset of 1 or more of the following: platelet count <100,000/microL, serum creatinine >1.1 mg/dL, liver transaminases x2 the upper limit of the normal concentrations, pulmonary edema, new-onset and persistent headache, or visual symptoms (e.g., blurred vision or flashing lights).

Epidemiology and Etiology

Global burden

Assessing the epidemiology of hypertensive disorders of pregnancy is difficult due to the lack of consistency of the definitions, changes in definitions over time, and diagnostic challenges. Variation in incidence of hypertensive disorders of pregnancy by geography, age, ethnicity, and over time can be speculated due to differences in maternal characteristics (maternal age distribution, proportion of nulliparous pregnant, distribution of risk factors), a lack of standardization of the diagnostic criteria worldwide, and differences in early risk assessment and prevention programs both across and within countries [8, 9].

Worldwide, the incidence of hypertensive disorders of pregnancy varies by country; it has been estimated to occur in between 5.2 and 8.2 percent of pregnancies every year [10]. A systemic review estimated that 4.6 percent and 1.4 percent of deliveries were complicated by preeclampsia and eclampsia, respectively [11], whereas gestational hypertension develops in 1.8 to 4.4 percent of all pregnancies [10]. In low- and middle-income countries, 10 to 15 percent of direct maternal deaths are thought to be related to preeclampsia and eclampsia [12]. Sub-Saharan Africa is the most affected region, with 16 percent of maternal deaths in this region attributable to hypertensive disorders of pregnancy [13], and preeclampsia and eclampsia are among the top five leading causes of maternal and fetal morbidity and mortality [14, 15].

Nationwide

In the US, the prevalence of hypertensive disorders of pregnancy increased from 2.8 percent in 1989 to 8.2 percent in 2020, with a 3.6 percent average annual percentage

change. Chronic hypertension complicates 1 to 2 percent of deliveries, with a positive average annual percentage change of 4.1 percent. On the contrary, the incidence of eclampsia has been decreasing with an average annual percentage change of -2.5 percent and complicates about 0.3 to 0.6 percent of all U.S. pregnancies [5, 16]. Gestational hypertension is more common among nulliparous women (6–17 percent) and affects 2–4 percent of multiparous pregnant women [17-19]. The incidence of preeclampsia in the United States was approximately 5 percent in 2014, a 21 percent increase from 2005 [20]. Although there has been a decline in maternal mortality related to hypertensive disorders and in the trend of eclampsia over the last two decades, prior studies indicated that the rise in the secular trend in the incidence of chronic hypertension, gestational hypertension, and preeclampsia in the United States is mainly because of increases in the incidence of pre-pregnancy weight, diabetes, and maternal age [6].

Pathophysiology and Potential Biological Mechanisms

It should be emphasized that the exact cause of preeclampsia is still unknown. It is referred to as the "disease of hypotheses". In general, hypertensive disorders in the majority of cases (between 90 percent and 95 percent) have been classified as primary hypertension (formerly called "essential" hypertension), referring to those with no clear single cause for their raised blood pressure. In the remainder, 5 percent to 10 percent of cases are classified as secondary hypertension due to a secondary underlying cause such as renal disease, adrenal disease, or medicine side effects.

It has been postulated that the primary factors that contribute to the raised blood pressure in hypertensive patients are most likely the result of a combination of several genetic and environmental factors that have an interrelated effect on the renin-angiotensin

system and the sympathetic nervous system. Obesity, insulin-resistance, physical inactivity, advancing age, Black race, family history, salt intake, and excessive alcohol consumption are some of the risk factors that have been linked to an increased risk of hypertension. These risk factors are also linked to hypertensive disorders in pregnancy. The similarities in risk factor patterns between gestational hypertension and preeclampsia may also indicate common underlying mechanisms. However, gestational hypertension and preeclampsia are associated with other additional risk factors linked to pregnancy, the fetus, and the male partner. Although the risk factors are similar between gestational hypertension and preeclampsia, epidemiological studies showed differences in the magnitude of the association between these two disorders [21].

Preeclampsia, which normally presents in the third trimester and remits after delivery or pregnancy termination, even occurs in ectopic (extrauterine) and molar pregnancy, suggesting that the placenta has an essential role in the pathogenic process. Abnormalities in spiral arteriole remodeling of placental vasculature early in pregnancy, which can lead to inadequate blood flow and oxygen supply to the fetus. This abnormal placental development may be triggered by an interaction between the invading trophoblasts and uterine Natural Killer cells, which suggests a potential immunologic mechanism. Moreover, maternal and fetal genetic factors may suggest disease susceptibility. Placental hypoperfusion, hypoxia, and ischemia are believed to result in a subsequent release of antiangiogenic peptides into maternal circulation, which leads to widespread maternal vascular inflammation, endothelial dysfunction, or damage to the lining of blood vessels, which contributes to the development of high blood pressure and other manifestations of preeclampsia [22-25]. However, the cause of defective placental

implantation is unknown, and it is thought to be caused by two interconnected stages: abnormal placentation and an abnormal maternal inflammatory response (Figure 1). The relationship between the two stages of this preeclampsia etiological concept has been extensively researched and debated in recent years.

Abnormal Development of The Placenta

It is widely believed that the failure of maternal uterine spiral arteries to develop, which support the growing placenta, is the primary cause of preeclampsia. In normal pregnancies, remodeling of the spiral arteries is most likely initiated by the end of the first trimester and finished by 18 to 20 weeks of gestation, when the cytotrophoblast cells of the placenta migrate and infiltrate the decidua and part of the myometrium.

As compared to preeclampsia, the cytotrophoblast that infiltrates the decidual segment of the spiral arteries has shallow invasion and fails to infiltrate the myometrial region [22, 26]. These abnormalities in placentation and the development of uteroplacental circulation are believed to occur in the early stages before the clinical manifestations of preeclampsia arise. As a result, the placenta does not develop the wide, convoluted vascular channels that are typical of a healthy placenta; instead, the vessels remain narrow, leading to hypoperfusion and/or oxidative stress. As pregnancy progresses, hypoperfusion becomes more evident and leads to hypoxia and ischemia, which are critical components in the pathogenesis of preeclampsia and are believed to be responsible for the release of endothelial factors that lead to systemic endothelial dysfunction, resulting in the preeclamptic phenotype [22, 24, 27-30].

Endothelial Factors

Ischemic placentas are believed to release a variety of endothelial-related factors (such as antiangiogenic proteins [sFlt-1 and endoglin] and inflammatory cytokines) into the mother's bloodstream that alter the function of the mother's endothelial cells and result in the typical systemic signs and symptoms of preeclampsia. sFlt-1, which is a soluble fms-like tyrosine kinase-1 protein secreted by a diseased placenta and circulated in the maternal bloodstream.

sFlt-1 has antiangiogenic properties that bind to angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and inhibit their growth effects on blood vessels. Since sFlt-1 circulates into mother’s blood stream and can reach distant tissue, it causes generalized endothelial dysfunction. It is a key mediator of the maternal signs and symptoms of preeclampsia [27-30]. Yet another potential mediator is soluble endoglin; however, it is unclear how exactly endoglin and sFlt-1 are connected [31-34]. Preeclampsia's various clinical manifestations can be explained as a clinical reaction to widespread endothelial dysfunction.

The presence of preexisting vascular disease, which is common in women with comorbidities known to be associated with vascular disease, such as autoimmune diseases, diabetes, hypertension, and chronic renal diseases, increases the risk of developing preeclampsia. These conditions are likely to have preexisting endothelial damage [35], which may also explain why preeclamptic women have an increased risk of developing cardiovascular disease in the future [36, 37].

Inflammation cascade and cytokines

Poor placental perfusion causes placental hypoxia, which can increase the release of inflammatory signals into the mother's blood and increase the risk of preeclampsia [38]. Additionally, by further releasing cytokines, the activation of maternal neutrophils as they go through the placenta might provide an effective route for the transmission of oxidative stress from the placenta to the maternal circulation. Leukocytes in the uterine veins are significantly more activated in preeclampsia compared to the peripheral circulation [39] and the decidua and placenta, which are frequently found in acute atherosclerosis sites [40].

In response to hypoxia, the human placenta can directly make tumor necrosis factor-alpha, which in theory could induce endothelial dysfunction by interfering with or competing with maternal free fatty acids, especially unsaturated FFAs [40]. TNFa and other cytokines, such as IL-6, IL-1a, and IL-1b, have been released from tissues from preeclamptic pregnancies, although studies to date have not revealed a substantial change [41]. This brings into question the placenta's role in releasing inflammatory cytokines directly.

Immunologic Factors

The observation that previous exposure to paternal and fetal antigens appears to protect against preeclampsia as well as maternal-paternal immune dysfunction has led to the emphasis on immunologic factors as a potential contribution to placental abnormalities [42-44]. Women with preeclampsia have also been shown to have changes

in their circulating immunity, such as a relative lack of regulatory T cells and an increase in agonistic autoantibodies that target the angiotensin-1 receptor [45].

Genetic Factors

Despite the fact that the majority of preeclampsia cases are sporadic, the clustering of cases within families clearly shows that the disease's susceptibility is influenced by a hereditary component. Numerous epidemiological studies have suggested that preeclampsia has a genetic basis, including:

- Women with a family history of preeclampsia have about triple the risk of developing preeclampsia, according to two cohort studies [46, 47]. In primigravid women, a family history of preeclampsia is associated with a two- to fivefold increased risk of preeclampsia compared to those without this history [48-50].
- Women with a history of preeclampsia in a previous pregnancy had a sevenfold higher risk of having preeclampsia [51].
- Preeclampsia is more likely to develop in men and women who were the offspring of preeclampsia-complicated pregnancies than in people without such a history [50, 52].
- A woman who becomes pregnant by a man who has previously fathered a pregnancy complicated by preeclampsia has a higher risk of developing the disorder [53].

Numerous gene studies have identified several candidate genes as being linked to preeclampsia; however, other studies have found no link between the candidate genes and the disease's susceptibility. [54]. In summary, both maternal and fetal genes from either

the mother or father may play a role in triggering abnormal placentation and subsequent preeclampsia. More specifically, two genetic loci (Flt-1 and sFlt-1) that are carried on chromosome 13 appeared to be associated with preeclampsia and likely responsible for producing the circulating anti-endothelial factors [55]. Additionally, these women have significantly higher levels of the circulating sFlt-1/PIGF ratio, which is a more reliable index of the circulating angiogenic state and a better predictor of preeclampsia risk even before clinical signs [56].

Risk Factors

Numerous epidemiological studies have identified a number of risk factors that increase the likelihood of developing preeclampsia.

Preeclampsia is thought of as a condition of first pregnancies. In a systematic review study, the risk of preeclampsia nearly tripled among nulliparous women compared to other cohorts (RR = 2.91, 1.28 to 6.61) [51]. Although it is yet unknown why a nulliparous condition predisposes to preeclampsia, immunological hypotheses have been proposed. Nulliparous women have a higher circulating sFlt-1 level and sFlt-1/PIGF ratio compared to multiparous women. This maternal immune maladaptation to fetal or parental antigens may indirectly lead to poor blood flow to the uterus and placenta, which may contribute to the development of preeclampsia [57, 58]. The protective advantages of multiparity, however, are no longer present when a woman changes partners [59].

A prolonged interval between pregnancies or a paternal factor, such as men who were born from or fathered a preeclamptic pregnancy, may explain the increased risk of preeclampsia with a change in paternity or having a new partner [52, 53, 60].

Maternal age extremes can raise the risk of preeclampsia. Young maternal age was associated with a significant risk for both preeclampsia and eclampsia. According to a study using national US data, women under the age of 15 had a 2.8-fold higher risk of preeclampsia compared to women between the ages of 30 and 34, and those under the age of 20 had a 1.8-fold increased risk compared to women aged 20 and older. The risk declined with age until the age of 35, when it began to rise significantly [61]. Women aged 35 and above had a relative risk of 1.2 (95% confidence interval: 1.1–1.3), while women aged 40 and above had a relative risk of 1.5 (95% confidence interval: 1.2.1–1.2.0) [62].

Multifetal pregnancies have significantly higher risks than singleton pregnancies (RR 2.9, 95% CI 2.6–3.1) [62]. In five cohort studies, women with twin pregnancies nearly quadrupled their risk of preeclampsia (2.9, 95% CI: 2.0–4.2) [21, 63-66], and a triplet pregnancy nearly triples the risk of preeclampsia compared to a twin pregnancy, according to one study (2.8, 1.25–6.4) [67].

Women with a past history of preeclampsia have sevenfold the risk of developing preeclampsia in a subsequent pregnancy compared with patients without this history (RR 7.2, 95% CI: 5.9–8.8) [51], and the risk is nearly tripled for pregnant women who have a family history of preeclampsia (2.9, 95% CI: 1.7–4.9) [51].

Alcohol consumption and the risk of hypertensive disorders during pregnancy have been significantly linked, according to a cross-sectional study of Chinese individuals [68]. Participants with alcohol consumption had a 1.75-times higher risk of hypertensive disorders of pregnancy compared to those with no history of alcohol intake [68]. On the contrary, a prospective study among the U.S. population found that those

who regularly used alcohol had a 0.55-times lower risk of preeclampsia than those who did not [69].

Other risk factors include preexisting hypertension (RR 5.1, 95% CI: 4.0–6.5) [62], pre-gestational diabetes (RR 3.7, 95% CI: 3.1–4.3) [62], renal disease (RR 1.8, 95% CI: 1.5–2.1) [62], pre-pregnancy overweight or obesity (BMI > 25 [RR 2.1, 95% CI: 2.0–2.2] and > 30 [RR 2.8, 95% CI: 2.6–3.1]) [62], and autoimmune diseases, such as systemic lupus erythematosus (RR 1.8, 95% CI: 1.5–2.1) and antiphospholipid syndrome (RR 2.8, 95% CI: 1.8–4.3) [62].

Smoking, prolonged sperm exposure with the same partner, a history of spontaneous or induced abortion, and partner change without a preeclampsia history are protective factors that have been found to be associated with a lower risk of preeclampsia [70-73].

Risk Factors of Hypertensive Disorders of Pregnancy
Modifiable risk factors
• Obesity/overweight
• Anemia
• Multifetal pregnancy (in infertility treatment)
• Smoking
• Alcohol intake
• Low socioeconomic status
• New male partner, change partner, limited sperm exposure
• Extremes of maternal age (<20 and ≥ 35)
Nonmodifiable risk factors
• Nulliparity
• Multifetal gestation
• Past medical history
• Family history

• Preexisting medical conditions
○ Chronic hypertension
○ Renal disease
○ Non-gestational diabetes
○ Gestational diabetes
○ Autoimmune diseases
▪ Antiphospholipid syndrome
▪ Thrombophilia
▪ Systemic lupus erythematosus
Protective factors
• Smoking
• Long-term sperm exposure with the same partner
• History of abortion (spontaneous or induced)
• Partner change with no history of preeclampsia

Study Rationale

Several epidemiological studies have investigated the incidence of hypertension diseases of pregnancy and their subtypes, as described in the previous section; however, the exact incidence of hypertensive disorders of pregnancy and preeclampsia remains largely undetermined. In previous studies, the measurement of risk factors such as maternal age, parity, race or ethnicity, socioeconomic status, and other factors associated with these disorders was controversial. Providing a large, well-powered population-based data set can contribute to our understanding of the disease's etiology, clinical diagnosis, ACOG recommendations and guidelines, and public health prevention efforts.

Objectives

To provide the most recent national trend incidence rates of gestational hypertension, preeclampsia, and eclampsia in the United States from 2016 to 2018, as

well as to examine the relationship between maternal sociodemographic and clinical risk factors and the three major subtypes of hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, and eclampsia).

Specific Aims

1) To estimate the incidence and trends in rates among major types of hypertensive disorders in pregnancy in women aged 15–45 in the United States between 2016 and 2018, overall and stratified by patient and hospital characteristics, using the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project.

   Hypothesis 1.1: The overall trends in the annual incidence of gestational hypertension and preeclampsia will increase over time, while eclampsia will decrease.

2) Identifying clinical and public health-relevant maternal risk factors that are associated with major types of hypertensive disorders in pregnancy: gestational hypertension, preeclampsia, and eclampsia.

   Hypothesis 2.1: There is a positive association between gestational hypertension and women who are younger than 20 years or older than 35 years, who are Black or Hispanic, who delivered in the South or Midwest, who are residing in the poorest areas, and who have preexisting conditions such as diabetes, obesity, multiple pregnancy, anemia, autoimmune disease, and renal disease.

   Hypothesis 2.2: There is a positive association between preeclampsia and women who are younger than 20 years or older than 35 years, who are Black or Hispanic,

who delivered in the South or Midwest, who are residing in the poorest areas, and who have preexisting conditions such as diabetes, obesity, multiple pregnancy, anemia, autoimmune disease, and renal disease.

Hypothesis 2.3: There is a positive association between eclampsia and women who are younger than 20 years or older than 35 years, who are Black or Hispanic, who delivered in the South or Midwest, who are residing in the poorest areas, and who have preexisting conditions such as diabetes, obesity, multiple pregnancy, anemia, autoimmune disease, and renal disease.

Literature Review

Several reviews attempted to investigate national trends in incidence rates of hypertension disorders in pregnancy as well as the associations of various factors with major types of hypertensive disorders in pregnancy. Two prior studies utilized the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample. However, they were out-of-date because the most recent study was published in 2014, and none of these studies used the most recent disease's definition and classification (the new ICD-10-CM diagnosis codes). There are a limited number of studies that use clinical risk factors as predictors to aid in early disease detection and intervention.

Ananth and colleagues [4] made one of the earliest attempts to estimate incidence. They conducted a population-based retrospective study utilizing the 1980–2010 National Hospital Discharge Survey (NHDS) datasets, assembled by the CDC. These data represent hospital discharges in 50 states, including the District of Columbia, that resulted

in childbirth. A weighted total of 120 million women were admitted to a hospital for delivery during this study period. All pregnant women aged 18 to 23 who gave birth were included (n = 6,504). The study excluded women who were more than 46 years of age, women born before 1940 or during 1994 or later, had chronic hypertension, chronic hypertension with superimposed PE, and/or gestational hypertension. The study objective was to assess the associations of maternal age, obesity (BMI > 30), smoking, trends in incidence, and cohort curves with preeclampsia.

The Ananth study estimated that the prevalence rate of preeclampsia was 3.4%. The study showed a strong association between maternal age and developing preeclampsia, with both extremes of maternal age They showed a progressive increase in prevalence rates of severe preeclampsia in the US. The study also showed that the declines in smoking prevalence in the US were associated with increases in the period effect for both mild and severe preeclampsia. On the other hand, increases in the prevalence of obesity in the US are temporally associated with increases in the cohort effect among severe preeclampsia patients, according to statistics. The study argues that changes in the diagnostic criteria for preeclampsia may also have influenced these trends and associations.

One of the strengths of this study was the use of a large population-based cohort (120 million births) to estimate temporal changes in the incidence rates of mild and severe preeclampsia in the US. Case ascertainment to identify the diagnosis of preeclampsia is considered excellent using the NHDS data, with the sensitivity and specificity of the hospital discharge records versus chart abstraction of prenatal, medical,

and obstetrical records estimated in some studies to be 88% and 95%, respectively [74]. Ananth and colleagues accounted for period, age, and cohort effects in relation to temporal changes in rates of mild and severe preeclampsia. The analyses showed significant period effects for the temporal trend in preeclampsia up to the 1990s. However, since the early 2000s, maternal age and maternal birth cohort effects (time of mother's birth) appear to be mainly responsible for the temporal increase. Women born in the 1970s were at an increased risk for mild preeclampsia, while women born in more recent periods showed an increased risk of severe preeclampsia, suggesting a birth cohort effect.

There were some limitations to this study. First, geographic variation was not considered in this study. Although the incidence of preeclampsia varies in the US, with states in the south showing higher rates than other regions, and despite the fact that hospitals in the NHDS dataset were classified into the four geographic regions of the US, this study did not take into account the regional disparity. Second, the possibility of women being pregnant more than once over the study period could affect sample size and confound any attempted association between parity and outcomes. Furthermore, some confounding factors, such as some maternal sociodemographic and behavioral factors, were not considered that might affect the findings. Some demographic factors are available in NHDS data, such as age, sex, race, hospital region, and insurance type. However, this study did not account for these factors due to either missing data when restricted to a subgroup analysis or poorly recorded factors such as race or ethnicity. Some risk factors are either unavailable (such as parity, body mass index, or smoking) or

poorly recorded (such as a significant proportion of births missing information on race or ethnicity in the survey).

Wallis et al. [6] utilized the NHDS datasets and described secular trends in the incidence rates of gestational hypertension, preeclampsia, and eclampsia in the US between 1987 and 2004. These data include hospitals in all 50 states with at least 40,000 or more discharges annually. The sampled discharge records were weighted, and approximately 4 million hospitalizations for delivery were reported in 2004. The study includes all hospital admissions for which a delivery of one or more live or stillborn babies occurred between 1987 and 2004. The crude and age-adjusted annual incidence rates were calculated per 1,000 deliveries over the 18-year study period, and the study showed a significant increase in the trend of gestational hypertension and preeclampsia. The age-adjusted rate of gestational hypertension rose by 186% (from 10.7% to 30.6%) and that of preeclampsia by 25% (from 23.6% to 29.4%) over the 18-year study period. On the other hand, the eclampsia rate decreased by 22%. Rate ratios were calculated to estimate the risk of preeclampsia, eclampsia, and gestational hypertension associated with maternal age and the geographic region of the sampled hospitals. The authors found that the youngest women (age <20) and women from the south of the US were at significantly greater risk for all three outcomes.

This population-based study is the only one to report the national incidence rates of gestational hypertension, preeclampsia, and eclampsia during an 18-year period ending in 2004 in the US. The acknowledged strengths of the NHDS multi-tiered sampling method and the higher sensitivity and specificity of hospital discharge records reported

compared to birth certificate records and surveys in identifying cases allow this analysis to be more accurate and reliable in comparing the national rate and comparing these rates to other countries.

There were a few limitations that constrained the conclusion of this study. First, the NHDS data were restricted to using ICD-9-CM diagnosis codes to identify cases; some studies have reported a positive predictive value (PPV) of 74.4% for all preeclampsia, with the potential for underestimating deliveries and the possibility of counting a single mother more than once. Another concern related to NHDS data was the high percentage of missing information on some of the variables, such as maternal race/ethnicity and marital status; the most important is the fact that the variables for maternal race were so poor that the authors could not report on differences. In addition, other established risk factors for hypertensive disorders of pregnancy, such as prepregnancy BMI, reproductive history, parity, family history of preeclampsia, income level, and health behaviors factors such as smoking history and alcohol use history, were not collected by the NHDS data and thus not considered in this study, which might influence the findings' ability to draw conclusions. Lastly, the small sample size of rare outcomes, such as eclampsia, using NHDS data did not allow the authors to detect important changes and associations in the occurrence of these rarer outcomes.

Kuklina and colleagues [75] performed a cross-sectional study in 2009 based on the 1998–2006 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project (HCUP). This study examined national trends in the rates of hypertensive disorders in pregnancy and compared the rates of severe obstetric complications for

delivery hospitalizations with and without hypertensive disorders. After excluding non-delivery pregnancy outcomes, such as hydatidiform moles, ectopic pregnancy, abortion, and missing information, the study utilized 36,537,061 delivery discharges between 1998 and 2006 from US hospitals.

Logistic regression and population-attributable fractions were used to assess the impact of hypertensive disorders in pregnancy on the rate of severe obstetric complications. The study used the following covariates in the model: acute renal failure, adult respiratory distress syndrome, puerperal cerebrovascular disorder, disseminated intravascular coagulation syndrome, pulmonary edema, ventilation, and mortality. The study reported that the prevalence of hypertensive disorders rose from 67 in 1998 to 81 per 1,000 deliveries in 2006, whereas the prevalence of hospitalizations with severe preeclampsia and/or eclampsia increased from 9 to 12 per 1,000 deliveries (*p*-value for linear trend <0.001). The odds of having severe obstetric complications ranged from 3.3 (95% CI 2.6–4.2) to 34.8 (95% CI 30.4–39.9) for women with severe preeclampsia and/or eclampsia compared to pregnant women without any hypertensive disorders. While among pregnant women with gestational hypertension and those without any hypertensive disorders, the odds of having severe obstetric complications ranged from 1.4 (95% CI 1.1–1.9) to 2.2 (95% CI 1.7–2.9). In general, hospitalizations with hypertensive disorders in pregnancy were associated with 57% of women with acute renal failure, 27% of those with disseminated intravascular coagulation syndrome, and 30% or more with ventilation, pulmonary edema, puerperal cerebrovascular disorders, and respiratory distress syndrome.

One of the strengths of HCUP is that it has a large, multicenter, nationwide database, which increases the generalizability of the study. Furthermore, the very large sample size of this study allowed the authors to estimate the national trend of hypertensive disorders of pregnancy among subgroups of pregnant women and perform a secondary analysis to detect any associations among these subgroups and the several covariates. The representativeness and strong methodology of NIS data collection make HCUP a practical and reliable data source for studying temporal trends in hypertensive disorders in pregnancy in the US.

The potential limitations of this study that result from using discharge-level data from HCUP include the fact that NIS data do not account for multiple delivery hospitalizations of the same patient over time. In addition, the identification of hypertensive disorders in pregnancy cases and severe obstetric complications is based solely on ICD-9-CM codes, which vary in their accuracy as some studies showed high to moderate specificity but low sensitivity in ICD-9-CM diagnoses. Finally, there are some gaps in information, such as deliveries that occur outside hospitals, which are estimated to be less than 1% of the population, and information regarding race/ethnicity.

Using the HCUP-NIS data, Fingar et al. [20] also conducted a population-based study. This statistical brief analyzed data from delivery discharges between 2005 and 2014 from US hospitals (n = 3,796,490). Patient and hospital characteristics such as age, race/ethnicity, expected payer, community income, residence's location, hospital region, length of stay, and cost per stay are used to describe the trend and rate of

preeclampsia/eclampsia. All delivery hospitalizations and cases were identified using diagnosis-related groups (DRGs) and the ICD-9-CM diagnosis codes.

The study estimated the incidence of delivery hospitalizations involving preeclampsia/eclampsia in 2014 at about 5%, a 21% increase from 2005. Compared with other deliveries, a higher percentage of those with preeclampsia/eclampsia were among women who were the youngest, the oldest, Black, and from the poorest areas and the South, and the length of stay was 70% higher.

The use of HCUP data increases the generalizability of the findings. The large size of the NIS data allows the study to estimate the rates for specific subgroups of patients. In addition, NIS data are standardized across years and weighted to estimate approximate national rates.

The limitations of this study were similar to those of others that used HCUP discharge data. The data did not account for more than one delivery hospitalization for the same patient. Moreover, the identification of all delivery hospitalizations and hypertensive disorders in pregnancy cases is based only on ICD-9-CM codes. Some studies indicated high to moderate specificity but low sensitivity for case identification using the ICD-9-CM codes. Lastly, there was a lack of some information, such as race/ethnicity in some states and the number of deliveries that occur outside hospitals, which is estimated to be less than 1%.

A hospital-based study conducted by Paré et al [76] aimed to validate several clinical risk factors described earlier for preeclampsia, specifically risk factors such as

advanced maternal age, obesity, multiple gestations, smoking, and chronic hypertension, using a large, multicenter, prospective cohort. Women were recruited from the obstetric population at three large urban academic centers, two in Boston and one in Philadelphia, from October 2006 to August 2008. The study examined the association between certain clinical risk factors such as maternal age, BMI, smoking, chronic hypertension, pregestational diabetes, multiple gestations, African American race, history of prior preeclampsia, nulliparity, and assisted reproductive techniques. Women were selected for the study if they were 16 years of age or older, presented for prenatal care before 15 weeks of gestation, and carried three or fewer fetuses.

The results of this study showed that among the 2637 women included in this analysis, 9% were diagnosed with preeclampsia. In the adjusted analysis, the adjusted odds ratios (aOR) among women with chronic hypertension were 2.7 (95% confidence interval 1.8–4.1), gestational diabetes aOR was 3.9 (2.1–7.3), multiple gestation aOR was 3.0 (1.7–5.0), African American race aOR was 1.9 (1.4–2.7), prior preeclampsia aOR was 3.6 (2.3–5.7), nulliparity aOR was 1.73 (1.3–2.4), assisted reproductive techniques aOR was 1.7 (1.1–2.7,) and being overweight aOR was for body mass index [BMI, kg/m2] greater than 25–30: 1.7 (1.1–2.4) or obese (BMI greater than 30–35: aOR was 2.3 (1.5–3.6); aOR for BMI greater than 35–40: 3.6 (2.1–6.0); aOR for BMI greater than 40: 6.0 (3.6–10.2) were associated with preeclampsia. However, the results of this study showed that advanced maternal age was not associated with preeclampsia. Similar associations were found for severe preeclampsia. The study also reflects a dose-response effect in the relationship between BMI and both preeclampsia and severe preeclampsia. The most

significant risk factor for both preeclampsia and severe preeclampsia was being overweight or obese, with an attributable risk percent of 65% and 64%, respectively.

One of the study's strengths is the use of a large multicenter prospective cohort to estimate the temporal increase in the incidence of preeclampsia in a prospective cohort study design. Women were recruited from three different large urban regions, two in Boston and one in Philadelphia, which makes the study's results generalizable to the North American population. An additional strength was the ascertainment of cases through a trained staff and a comprehensive process of data entry, which was reviewed independently by a study monitor.

The study has some limitations related to any observational study. First, the possibility of unmeasured confounding exists, where some confounding factors were not considered and could influence the relationship between the risk factors and preeclampsia. Second, the small number of women who developed early preeclampsia could limit the power to detect significant associations between risk factors for preeclampsia requiring delivery before 34 weeks of gestation. Lastly, the study uses the ACOG definitions from 2002 and not the revised definitions introduced in 2013.

Last of all, a cross-sectional study conducted by Direkvand-Moghadam et al. [77] was published in 2012 to assess the predictive factors for preeclampsia among Iranian women in Ilam, a mid-sized Kurdish city located in the north of Iran. The data were collected during face-to-face interviews with all pregnant women referred to the hospital from May 2010 to September 2010. A total of 610 pregnant women were included during the 5 months of the study period, exclusive of women presenting for abortion. Risk

factors such as level of education or history of preeclampsia, history of hypertension, and history of infertility were evaluated for associations with preeclampsia.

This study revealed that the prevalence of preeclampsia was 9.5% (95% CI: 7.4–11.6%). After using a multivariate logistic regression model, the study indicated that three predictors proved to be suitable independent predictor variables for preeclampsia. The odds ratios for having preeclampsia were increased for women with a history of preeclampsia (OR = 5.5, 95% CI: 2.5–12.1), a history of hypertension (OR = 2.3, 95% CI: 1.03–4.4), and a history of infertility (OR = 3.1, 95% CI: 1.3–5.8). The study used area under the Receiver Operating Characteristic (ROC) curves to predict the efficacy of the model for the prediction of the outcome, with 67% predictive ability and a p-value <0.01. (ROC curves are usually for sensitivity, specificity, and predictive ability.) There was no statistically significant association between BMI, maternal age, education level, occupation, type of pregnancy, type of previous delivery, or contraceptive method and preeclampsia. Some of these results agree with the results of some studies but contrast with others, indicating that the difference could be related to the characteristics of each population and the hospital they attend.

Direkvand-Moghadam and colleagues attempted to determine the predicative factors for preeclampsia among Iranian women using demographic (age, education, and occupation), anthropometric (weight and height), medical, and obstetric variables. Data collected from May 2010 to September 2010 during a face-to-face interview and examination from hospital records in Ilam city, west of Iran. These predictors used in regression analysis could help predict an early diagnosis of preeclampsia and hence allow for early intervention.

The study had several limitations. First, the regression analysis did not account for such possible covariates as the demographic and socioeconomic characteristics of the participants. Possibility of bias such as selection bias due to a hospital-based study, measurement bias and recall bias during data collection, and lastly, the possibility of an external validity issue due to the population sample study based on Iranian women in a certain geographic region.

METHODS

Study Design and Data Source

This dissertation describes a hospital-based, cross-sectional analysis of national trends in hypertensive disorders of pregnancy among women aged 15 to 45 years in the United States from 2016 to 2018. It reflects on overall and stratified findings associated with the major types of hypertensive disorders in pregnancy (preeclampsia, eclampsia, and gestational hypertension). The Healthcare Cost and Utilization Project (HCUP) and the Nationwide Inpatient Sample (NIS) databases were used in this research study. The HCUP is a collection of healthcare datasets and services developed by a Federal-State-Industry collaboration and administered by the Agency for Healthcare Research and Quality (AHRQ) of the United States Department of Health and Human Services. The HCUP databases combine the data collection efforts of state data agencies, hospital associations, private data organizations, and the federal government to form a national information resource for encounter-level healthcare data. HCUP has the largest collection of longitudinal hospital care data in the United States, including inpatient, emergency department, and ambulatory surgery, with all-payer, encounter-level data commencing in 1988. These databases enable studies on a wide range of health policy topics, including health service cost and quality, medical practice patterns, access to healthcare programs, and treatment outcomes at the national, state, and local market levels [78].

NIS data includes over seven million annual inpatient stays and discharges. This large sample size is optimal for developing national estimates and corresponds to a stratified sample of 20% of discharges from community hospitals in the United States, excluding rehabilitation and long-term acute care hospitals. The NIS sampling frame has expanded from 8 states in 1988 to 22 states in 1998, 46 states in 2011, and 48 states and the District of Columbia in 2018, representing 97 percent of the U.S. population. The NIS survey applies sampling techniques that ensure national representation and provides sampling weights to enable national rate calculations [79].

The Nationwide Inpatient Sample contains diagnostic and procedure codes for primary and secondary diagnoses, as well as patient and hospital characteristics. Patient-level characteristics, such as age, gender, race/ethnicity, household income for ZIP Code, patient residence, insurance type, total charge, and length of stay, were then derived from the research population cohort. These variables aid in describing the socioeconomic status and burden of health care utilization, as well as the risk factors for the outcome. Hospital location (urban or rural), hospital region (Northeast, South, Midwest, and West), and teaching status were among the hospital-level characteristics.

Study Population, Eligibility, and Exclusion Criteria

The study population included all women discharged from NIS during 2016 and 2018 who had one or more live or stillborn infants. This analysis includes all women who had deliveries while they were hospitalized. Delivery hospitalization was identified using a combination of both *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis codes and Diagnosis-Related Groups (DRGs) pertained to delivery (Z37x, DRG: 370–375, except 769 and 770) among women aged

15–45 years. The study excludes pregnant women under the age of 15 and those beyond the age of 45 due to the small frequency of pregnancies among this age group.

Primary Outcomes and Case Ascertainment

Our primary outcomes are gestational hypertension, preeclampsia, and eclampsia crude and adjusted rates per 1000 delivery hospitalizations. Hypertensive disorders in pregnancy were classified based on ICD-10-CM diagnosis codes to identify gestational hypertension (ICD-10-CM O13x), preeclampsia (ICD-10-CM O14x), and eclampsia (ICD-10-CM O15x), as well as other preexisting conditions (see appendix).

Potential Covariates

Secondary covariates that may affect the relationship between our outcome and the independent variables, including effect modifiers, were examined. In the initial data analysis, the following demographic and clinical variables were investigated based on evidence from the literature review and theories: maternal age groups, maternal race/ethnicity, insurance type, community income level, hospital type and region, and preexisting conditions such as gestational diabetes, non-gestational diabetes, multiple gestation, obesity or overweight, antiphospholipid syndrome, systemic lupus erythematosus, thrombophilia, anemia, hypothyroidism, renal disease, alcohol-related disorder, and nicotine dependence. All the preexisting condition variables were obtained using the ICD-10-CM diagnosis codes (Appendix). This study could not examine other covariates such as parity, family history of preeclampsia, partner change, and education level due to the limitations of these databases.

Statistical Analysis

Descriptive statistics are presented as weighted frequency and percentage for women aged 15 to 45 with live or still births between 2016 and 2018 in the United States, stratified by patient and hospital characteristics. The crude incidence rates for gestational hypertension, preeclampsia, and eclampsia were calculated as weighted cases per 1,000 delivery hospitalizations. All significant variables ($p<0.2$) in the univariate model were included in the multivariable logistic regression with hierarchical backward elimination, which was used to determine the magnitude of association between gestational hypertension, preeclampsia, and eclampsia and other covariates while controlling for confounding variables. Potential confounding and interaction were assessed for the selected covariates. The p-value of the Wald Chi-Square of univariate logistic regression was utilized to identify potential confounding variables or effect modifiers. If independent variables achieved bivariate significance at p.05, the independent variable was first evaluated to determine whether it was an effect modifier. A significant interaction term with a p-value of 0.05 was added to the multivariate model using the backward elimination method. To test model multicollinearity, the %collin macro for SAS's PROC LOGISTIC procedure was used [80]. Collinearity is indicated by condition indexes (CIs) more than 30 and related variance decomposition proportions (VDPs) greater than 0.5 [81]. When there was collinearity, interactions were removed from the model. Multicollinearity was caused by the interaction terms. As a result, the interaction terms were eliminated from the final model, and the best-fitting model is determined using backward elimination and the Hosmer-Lemeshow goodness-of-fit test. The Hosmer-Lemeshow test is used to measure how well the model fits. A non-significant test

(P >.05) implies a satisfactory fit in a chi-square goodness of fit test. The adjusted rate ratio and their 95% confidence intervals (CIs) were calculated to evaluate the associations between each risk factor and the incidence of gestational hypertension, preeclampsia, and eclampsia.

All analyses were performed using SAS software (Version 9.4; SAS Institute Inc., Cary, NC, USA). SAS survey procedures were used to weight the data and produce national estimates that accounted for the complex survey design and sample weights in accordance with the HCUP analysis recommendations. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Study Population Demographics

Patient and hospital characteristics of the study sample are reported in Table 1. We identified 11,097,776 live or still births in the U.S. to women aged 15 to 45 years from 2016 to 2018—approximately 3.7 million births per year. Most births were among White women (50.1%), living in the South (39%), from Urban teaching hospitals (68.6%), and women who resided in the poorest areas (28% in income quartile 1). In addition, approximately half of women had private insurance (51.3%) or Medicaid (43.2%). Five percent of the sample were women younger than 20 years; 19.9% were aged between 20 and 24 years; 29.1% were aged between 25 and 29 years; 28.4% were aged between 30 and 34 years; 14.4% were aged between 35 and 39 years; and 3.1% were aged between 40 and 45 years. The majority of deliveries had anemia (14.4%), obesity/overweight (8.9%), gestational diabetes (7.5%), nicotine dependence (4.4%), hypothyroidism (3.4%), and less than 2% had other coexisting conditions.

Overall Rates and Trends

The crude incidence rates (per 1,000 deliveries) were 54.6 for gestational hypertension, 48.9 for preeclampsia, and 0.8 for eclampsia for the 3-year study period. The trend in rates continues to increase for preeclampsia and gestational hypertension and decrease for eclampsia over the 3-year study period (Table 2).

Gestational Hypertension Incidence Rates

The crude incidence rate (per 1,000 deliveries) of gestational hypertension increased by 13.2% per year (from 48.1 per 1,000 deliveries in 2016 to 61.6 per 1,000 deliveries in 2018). Overall, deliveries with gestational hypertension were more likely than all other deliveries to be among women in the oldest age group (63.5 among women aged 40 to 45 years) and the youngest (57.9 among women aged 15 to 20 years) and to be among Black women (64.5). In addition, gestational hypertension was more common among women who resided in the 3rd quartile of median household income of residents in the patient's ZIP Code (56.2), had private insurance type (59.2), and those who delivered in urban teaching hospitals (57.0) and in the South (59.1). Furthermore, the crude incidence rates of gestational hypertension were higher among women with coexisting conditions: women with obesity or overweight (109.3), non-gestational diabetes (84.7), multiple gestations (75.9), gestational diabetes (74.8), hypothyroidism (67.7), alcohol-related disorders (67.0), renal disease (66.5), anemia (62.8), systemic lupus erythematosus (61.3), antiphospholipid syndrome (58.7), and nicotine dependence (56.1). However, this study showed that women with thrombophilia had a slightly lower crude incidence rate of gestational hypertension (54.3) than all other deliveries (Table 3A).

Preeclampsia Incidence Rates

In 2016, 169,445 delivery hospitalizations had a diagnosis of preeclampsia, representing 45.1 cases per 1,000 total deliveries, which increased to 179,240 (48.8) and 192,915 (53.6) in 2017 and 2018, respectively (average percent change = 9.0% per year).

The crude incidence rate (per 1,000 deliveries) of preeclampsia was higher among women in the youngest age group (67.5 among women aged 15 to 20 years), among Black women (65.2), those who delivered in the South (51.4), delivered in urban teaching hospitals (53.2), had Medicaid insurance (51.0), and women who resided in the poorest areas (54.6 in income quartile 1).

In addition, the preeclampsia crude incidence rate was higher among women with coexisting medical conditions such as gestational diabetes (74.0), non-gestational diabetes (146.5), multiple gestations (146.8), obesity/overweight (95.8), systemic lupus erythematosus (88.9), antiphospholipid syndrome (96.5), anemia (68.6), hypothyroidism (64.6), renal disease (232.7), alcohol-related disorders (64.2), and nicotine dependence (46.1). Still, women with thrombophilia had a slightly lower crude incidence rate of preeclampsia (48.6) than all other deliveries (Table 3B).

Eclampsia Incidence Rates

The crude incidence rate of eclampsia decreased from 1.0 per 1,000 deliveries in 2016 to 0.7 per 1,000 deliveries in 2018 (average percent change = 16.3% per year). A higher crude incidence rate of eclampsia was observed among women in the youngest age group (2.1 among women aged 15 to 20 years), among Black women (1.5), those who delivered in the South (1.0), had Medicaid insurance (1.1), and women who resided in the poorest areas (1.1), with the exception of eclampsia being more common among those who delivered in rural hospitals (1.0).

Additionally, eclampsia was more common among women with coexisting medical conditions such as renal disease (15.7), systemic lupus erythematosus (3.4), antiphospholipid antibodies (2.5), multiple gestations (2.4), non-gestational diabetes (2.0), alcohol-related disorders (1.7), obesity/overweight (1.3), and anemia (1.3). The crude rate of eclampsia was slightly higher or there was no change in rate among women with gestational diabetes (0.9), nicotine dependence (0.9), hypothyroidism (0.8), and thrombophilia (0.7) (Table 3C). In 2016, all of the listed coexisting conditions were more common among deliveries with eclampsia than among other deliveries. However, in 2017, women with thrombophilia, nicotine dependence, hypothyroidism, and alcohol-related disorders had lower crude rates of eclampsia. In 2018, women with gestational diabetes had lower rates compared to the overall crude rate (Table 3C).

Rate Ratios

Table 4 presents the ratios of the unadjusted and adjusted models for the three hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, and eclampsia) in the 3-year study period.

Gestational Hypertension Rate Ratios

The unadjusted rate ratio (RR) comparing the incidence of gestational hypertension to the reference group (Table 4A) was highest among the oldest age group (aged 40–45 years) (RR = 1.21, 95% CI, 1.17–1.25) compared to women aged 30–34 years. In addition, the unadjusted rate ratio was 1.10 (95% CI, 1.07–1.13) for women aged 15-20 years, 1.04 (95% CI, 1.02-1.06) for women aged 20–24 years and women aged 35–39 years, and 1.02 (95% CI, 1.01–1.04) for women aged 25–29 years, compared

to women aged 30–34 years over the study period. After adjusting for other covariates, the risk of gestational hypertension was significantly highest among the youngest age group (aRR = 1.24, 95% CI: 1.21–1.28), 1.12 (95% CI: 1.10–1.14) among women aged 20–24 years, and 1.11 (95% CI: 1.07–1.14) for women aged 40–45 years compared to women aged 30–34 years.

Moreover, the unadjusted rate ratio of gestational hypertension was higher among Black women (RR = 1.05; 95% CI, 1.04–1.07) compared to White women. However, after adjusting for other covariates, the risk of gestational hypertension was significantly lower among Black women (aRR = 0.93, 95% CI = 0.91-0.95), among Hispanics (aRR = 0.67, 95% CI = 0.66-0.69), and among other minorities (aRR = 0.66, 95% CI = 0.65-0.68), compared to White women. Furthermore, the risk of gestational hypertension was significantly higher among women who delivered in the South (RR = 1.17, 95% CI: 1.15–1.15; aRR = 1.24, 95% CI: 1.22-1.27) and in the Midwest regions (RR = 1.15, 95% CI: 1.13–1.17; aRR = 1.17, 95% CI: 1.14–1.19), and among women who delivered in the West (aRR = 1.05, 95% CI, 1.03–1.07), compared to women who delivered in the Northeast.

Additionally, women who delivered in urban teaching hospitals are at higher risk of gestational hypertension compared to women who delivered in rural areas (RR = 1.13, 95% CI: 1.11–1.15, and aRR = 1.10, 95% CI: 1.08–1.13), as well as women who resided in the wealthiest area, which has an 11–12% lower risk of gestational hypertension compared to the poorest areas (RR = 0.89, 95% CI: 0.86-0.92, and aRR = 0.88, 95% CI, 0.87–0.90). The unadjusted rate ratio of gestational hypertension was higher among

women who had self-pay, Medicaid, and other types of insurance compared to private insurance, and after adjusting for other covariates, the rate ratio was lower only among women who had self-pay insurance compared to private insurance (aRR = 0.81, 95% CI, 0.75-0.88).

Lastly, the unadjusted rate ratio of gestational hypertension was significantly higher among women with certain coexisting conditions such as obesity/overweight (RR = 2.36, 95% CI: 2.33-2.40), gestational diabetes (RR = 1.45, 95% CI: 1.42-1.48), non-gestational diabetes (RR = 1.61, 95% CI: 1.54-1.68), anemia (RR = 1.19, 95% CI: 1.17-1.21), and hypothyroidism (RR = 1.27, 95% CI, 1.23-1.31). However, the unadjusted rate ratio of gestational hypertension was lower among women with alcohol-related disorders (RR = 0.79, 95% CI = 0.66-0.94) and nicotine dependence (RR = 0.97, 95% CI = 0.94-0.99). After adjusting for other covariates, women with multiple gestations were not at significant increase risk of gestational hypertension, and the risk of gestational hypertension was lower among women with thrombophilia (RR = 0.84, 95% CI = 0.76-0.92), renal diseases (RR = 0.72, 95% CI = 0.63-0.81), and nicotine dependence (RR = 0.95, 95% CI = 0.92-0.98) (Table 4A).

Preeclampsia Rate Ratios

The incidence rate ratios of preeclampsia were highest among the youngest age group (RR = 1.58, 95% CI: 1.54–1.62, and aRR = 1.65, 95% CI: 1.60–1.69 for women aged 15-20 years vs. 30–34 years). The other age groups rate ratios were higher as well compared to women aged 30-34 years for women aged 20–24 years (RR=1.22, 95% CI, 1.20–1.24 and aRR=1.27, 95% CI, 1.25–1.29), 25–29 years (RR=1.03, 95% CI, 1.01–

1.05 and aRR=1.07, 95% CI, 1.05–1.09), 35–39 years (RR=1.17, 95% CI, 1.15–1.28), and 40–45 years (RR=1.56, 95% CI, 1.51–1.22 and aRR=1.19, 95% CI, 1.15–1.24).

In addition, the rate ratio of preeclampsia was higher among Black women (RR = 1.46, 95% CI: 1.44–1.49, and aRR = 1.12, 95% CI: 1.10–1.14) and Hispanic women (RR = 1.12, 95% CI: 1.11–1.14, and aRR = 1.05, 95% CI: 1.03–1.07) compared to White women, and lower among other races (RR = 0.92, 95% CI: 0.90-0.94, and aRR = 0.87–0.91).

Furthermore, the risk of preeclampsia was significantly higher among women who delivered in the South (RR = 1.09, 95% CI: 1.15–1.15, and aRR = 1.25, 95% CI: 1.22-1.27), in the Midwest regions (RR = 1.15, 95% CI: 1.13–1.17, and aRR = 1.17, 95% CI: 1.14–1.19), and among women who delivered in the West (aRR = 1.05, 95% CI, 1.03–1.07), compared to women who delivered in the Northeast. The rate ratio of preeclampsia was higher among women who delivered in urban teaching hospitals compared to women who delivered in rural hospitals (RR = 1.37, 95% CI: 1.34–1.40; aRR = 1.08, 95% CI: 1.06–1.11). Women who resided in the wealthiest area (income quartile 4) had significantly lower rate ratios of preeclampsia compared to women who resided in the poorest areas (RR = 0.77, 95% CI, 0.76-0.78, and a RR = 0.82, 95% CI, 0.80-0.84), and lower rates among women who had self-pay (RR = 0.84, 95% CI, 0.79-0.90), Medicaid (RR = 0.62, 95% CI, 0.58-0.67), and other types of insurance (RR = 0.74, 95% CI, 0.69-0.80) compared to private insurance.

Coexisting conditions were more common among deliveries with preeclampsia than other deliveries. Such as, gestational diabetes (RR=1.63, 95% CI, 1.59-1.66 and

aRR=1.38, 95% CI, 1.35-1.41), non-gestational diabetes (RR=3.41, 95% CI, 3.30-1.3.54 and aRR=1.85, 95% CI, 1.78-1.92), multiple gestations (RR=3.47, 95% CI, 3.37-3.57 and aRR=1.98, 95% CI, 1.92-2.04), obesity/overweight (RR=2.28, 95% CI, 2.25-2.32 and aRR=1.61, 95% CI, 1.58-1.64), systemic lupus erythematosus (RR=1.95, 95% CI, 1.72-2.20 and aRR=1.18, 95% CI, 1.04-1.35), antiphospholipid syndrome (RR=2.08, 95% CI, 1.76-2.45 and aRR=1.33, 95% CI, 1.12-1.59), anemia (RR=1.54, 95% CI, 1.52-1.57 and aRR=1.12, 95% CI, 1.10-1.13), hypothyroidism (RR=1.36, 95% CI, 1.32-1.40 and aRR=1.13, 95% CI, 1.10-1.17), and renal disease (RR=5.93, 95% CI, 5.52-6.38 and aRR=2.29, 95% CI, 2.12-2.48). Whereas the risk of preeclampsia was lower among women with nicotine dependence (RR = 0.94, 95% CI = 0.91-0.97, and aRR = 0.89, 95% CI = 0.86–92) and thrombophilia (aRR = 0.85, 95% CI = 0.76–94) (Table 4B).

Eclampsia Rate Ratios

The incidence rate ratios of eclampsia were significantly higher among the youngest age groups: women aged 15-20 years (RR=3.32, 95% CI, 2.83-3.89 and aRR=2.50, 95% CI, 2.11-2.95) and women aged 20-24 years (RR=1.61, 95% CI, 1.41-1.84 and aRR=1.37, 95% CI, 1.19-1.57) compared to women aged 30-34 years, in both unadjusted and adjusted models. In addition, the adjusted rate ratio of gestational hypertension was higher among Black women (RR = 2.15, 95% CI: 1.92-2.41, and aRR = 1.42, 95% CI: 1.25-1.60) compared to White women, and among women who delivered in the South (RR and aRR = 1.31, 95% CI: 1.14–1.51) compared to women who delivered in the Northeast.

Further, the incidence rate ratios of eclampsia were significantly lower among women who delivered in an urban teaching hospital compared to women who delivered in rural areas (aRR = 0.71, 95% CI = 0.58–0.74) and among women who resided in the wealthiest area (income quartile 3; RR = 0.65, 95% CI = 0.58–0.74, aRR = 0.84, 95% CI = 0.74-0.96, and income quartile 4; RR = 0.46, 95% CI, 0.40-0.53, aRR = 0.64, 95% 0.55-0.75) compared to women who reside in the poorest areas. The rate ratio of eclampsia was not significantly different among those paid by private insurance, Medicaid, self-pay, or other types of insurance.

Last, the adjusted rate ratios of eclampsia were significantly higher among women with coexisting conditions such as multiple gestations (RR = 2.93, 95% CI: 2.38–3.50, and aRR = 1.60, 95% CI: 1.30–1.98), anemia (RR = 1.78, 95% CI: 1.60–1.98, and aRR = 1.14, 95% CI: 1.02-1.27), and renal disease (RR = 19.93, 95% CI, 15.59–25.48, and aRR = 7.20, 95% CI, 5.56–9.33). Other medical coexisting conditions were not significant when adjusted for other covariates such as non-gestational diabetes (RR = 2.44, 95% CI, 1.85–3.20), obesity/overweight (RR = 1.62, 95% CI, 1.42-1.85), systemic lupus erythematosus (RR = 3.88, 95% CI, 2.08–7.24), and antiphospholipid syndrome (RR = 2.94, 95% CI, 1.10–7.85) (Table 4C).

DISCUSSION

Overview

This analysis of 11,097,776 deliveries of all women who had one or more live or stillbirths in the United States between 2016 and 2018 provides the most recent population-level estimate of the incidence rate of the major hypertensive disorders of pregnancy: gestational hypertension, preeclampsia, and eclampsia. Between 2016 and 2018, the national rate of gestational hypertension and preeclampsia increased, while the rate of eclampsia declined significantly, according to the study. This finding is consistent with previous reports that indicate a similar trend of increasing gestational hypertension and preeclampsia and decreasing eclampsia rates [6, 75, 82]. These findings extend this research effort to update the rates of hypertensive disorders of pregnancy to a current timeframe using the nationally representative HCUP database, especially after adjusting for all covariates and the post-ICD-10 and ACOG updates eras, during which there was a significant change in the definition criteria for these disorders.

Summary of Findings

Gestational hypertension

The incidence of gestational hypertension increased from 48.1 per 1,000 women delivering in 2016 to 55.2 per 1,000 deliveries in 2017 to 61.6 per 1,000 deliveries in 2018. The trend pattern was also consistent by patient and hospital characteristics in all

three consecutive years, such as the rates being highest in the youngest and oldest age groups, Black women living in the South, women delivered in urban teaching hospitals, women with private insurance, and women with preexisting conditions including gestational diabetes and preexisting diabetes, multifetal pregnancies, obesity, anemia, hypothyroidism, and renal diseases. The incidence of gestational hypertension is lower in women with a history of smoking and drinking alcohol, but neither income nor autoimmune disease are significant risk factors. Adjusting for other covariates had no effect on these findings, except that multifetal pregnancies were no longer a significant risk factor, teens became the highest risk group over age 40, and women with thrombophilia and renal illness had a lower risk of gestational hypertension.

Preeclampsia

The incidence of preeclampsia increased from 45.1 per 1,000 women delivering in 2016 to 48.8 per 1,000 deliveries in 2017 to 53.6 per 1,000 deliveries in 2018. The upward trend was also paralleled by patient and hospital characteristics in each of the three consecutive years, with rates being the greatest in the oldest and youngest age groups (with adolescents higher than the older age group), among Black women living in the South, women delivered in urban teaching hospitals, women with Medicaid insurance, and women with preexisting conditions including gestational diabetes and preexisting diabetes, multifetal pregnancies, obesity, systemic lupus erythematosus, antiphospholipid syndrome, anemia, hypothyroidism, renal diseases, and women with alcohol dependence. Preeclampsia is less common in women with a smoking history. Adjusting for other covariates had no influence on the results above, with the exception

that insurance type and alcoholism were no longer significant risk factors, and women with thrombophilia had a significantly lower risk of developing preeclampsia.

Contrary to the risk factors for gestational hypertension, women with low income, Medicaid rather than private insurance, and autoimmune disease (systemic lupus erythematosus and antiphospholipid antibodies) are significant risk factors for preeclampsia.

Eclampsia

Eclampsia incidence declined from 1.0 per 1000 women giving birth in 2016 to 0.8 per 1000 in 2017 to 0.7 per 1000 in 2018. In each of the three subsequent years, there was no consistency in trend rates by patient and hospital characteristics. Crude rates were highest among teens and older age groups, Black and Hispanic women, women living in the South, women delivered in rural hospitals, women living in the poorest areas, and women with preexisting conditions such as diabetes, multifetal pregnancies, obesity, systemic lupus erythematosus, antiphospholipid antibodies, anemia, and renal diseases. Adjusting for other covariates had no effect on the above-mentioned results, with the exception that the oldest age group and Hispanics were no longer significant risk factors, and only women with multifetal pregnancies, anemia, and renal disorders were at a higher risk for eclampsia.

Comparison and contrast with other literature

Several prior studies indicated that women with advanced maternal age (> 35 years old) exhibited a higher risk of hypertensive disorders of pregnancy than younger women [81], whereas the risk for adolescents (< 20 years old) is more debatable [51, 82]. After adjusting for other covariates, our study suggests that the younger age group was

the most prominent risk factor compared to the older age group. Advanced maternal age was the second most significant risk age group for developing gestational hypertension and preeclampsia, but not for eclampsia, even after controlling for other covariates, such as preexisting conditions that predispose them to developing eclampsia.

For the race factor, previous studies showed that Black race was a significant risk factor for gestational hypertension, preeclampsia, and eclampsia [76, 83]. Our research revealed that Black women were at higher risk of gestational hypertension with an unadjusted rate ratio. However, contrary to previous reports, when adjusting for other covariates were taken into account, Black, Hispanic, and other race/ethnicity women had a considerably lower risk of gestational hypertension than White women. Significant covariates to consider when evaluating the association between race and gestational hypertension include maternal age groups, insurance type, community income level, hospital type and region, and preexisting conditions such as gestational diabetes, non-gestational diabetes, multiple gestation, obesity or overweight, thrombophilia, anemia, hypothyroidism, renal disease, and nicotine dependence. In contrast, White women had a much lower risk of preeclampsia than did Black and Hispanic women, while the risk of eclampsia was only higher among Black women than among White women.

Overall, women who delivered in the South were more likely to experience hypertensive diseases during pregnancy, such as gestational hypertension, preeclampsia, and eclampsia. The Midwest had the next-highest region, and the Northeast had the lowest. However, the rate of gestational hypertension increased more among births in the Northeast, where it increased by 35%, as opposed to the Midwest, South, and West, where it increased by 31%, 23%, and 29%, respectively. Preeclampsia rates increased in

the Northeast and Midwest by 21%, the South by 15%, and the West by 23%. In addition, hypertensive disorders of pregnancy were more prevalent among women who resided in the poorest areas (income quartile 1) after adjusting for other potential covariates. This finding is consistent with previous years and prior studies. This result is consistent with findings from earlier research. There was no correlation between hypertensive disorders of pregnancy and the type of insurance women had, except that women with private insurance had a higher risk of developing gestational hypertension.

Urban-Teaching hospitals have a higher incidence of gestational hypertension and preeclampsia, whereas rural hospitals have the highest incidence of eclampsia. There were no previous reports comparing hospital types among these three major types of hypertensive disorders of pregnancy; however, the overall findings were consistent with higher incidence rates in rural regions [84].

Preexisting conditions were more prevalent in pregnancies with gestational hypertension, preeclampsia, and eclampsia than in pregnancies without these conditions. Our findings are also consistent with those of previous research [10, 51]. However, those with thrombophilia had a reduced risk of developing gestational hypertension and preeclampsia.

Clinical and Public Health Implication

To prevent hypertensive disorders in pregnancy and enhance future health, it is essential to address the risk factors associated with these disorders throughout the lifespan. Early detection, timely diagnosis, and treatment of these disorders are critical in order to prevent serious consequences and premature death. The term prevention has

three different implications: primary, secondary, and tertiary. The phrase ‘primary prevention’ refers to preventing the occurrence of a disease. Secondary prevention refers to stopping the progression of the illness before it manifests clinically. Tertiary prevention is, more or less, synonymous with treatment because it refers to preventing complications brought on by the illness process.

Primary prevention

For primary prevention, the clinical recommendations for decreasing issues associated with hypertensive disorders in pregnancy emphasize prompt identification [85]. Recommendations for identifying and monitoring pregnant women at high risk include continuous blood pressure monitoring involving self-monitoring. Using various risk factors may help in early prediction, and for women with a high risk of hypertensive disorders in pregnancy, long-term follow-up is important for those women. This study confirms some identifiable risk factors, such as extremes of maternal age, race, geographic region, low-income families, and some comorbid conditions. The differences among hypertensive disorders in pregnancy subtypes in these risk factors may indicate underlying etiology mechanisms behind each subtype and may aid in further investigation and future research. In this study, some risk factors, such as anemia and obesity, were prevalent in all three subtypes, while others were unique to each subtype.

Studies recommend using a risk factor checklist for preeclampsia during prenatal visits. Age, parity, family history of preeclampsia, past history of preeclampsia, multifetal pregnancy, duration between pregnancies, comorbidities (diabetes, preexisting hypertension, renal disease, autoimmune disease), BMI, blood pressure level, and proteinuria are among the 10 risk factors suggested by Duckitt et al. [51]. Umesawa et al.

also recommend adding anemia and urinary tract infections [10]. We suggest adding hypothyroidism and thrombophilia disorders to the list of preexisting medical conditions above.

Secondary prevention

The key to secondary prevention is preventing the progression of hypertensive disorders in pregnancy by avoiding the more severe maternal consequences of the disease through prompt management. For women with a history of hypertensive disorders in pregnancy, early prediction using multiple risk factor indicators, prevention via appropriate interventions, and long-term follow-up are critical. To successfully implement secondary prevention, it is necessary to understand pathophysiological mechanisms, accessibility to early detection tools, and ways of intervention and correction of pathophysiological abnormalities.

Tertiary prevention

Major complications as well as mortality due to hypertensive disorders in pregnancy are preventable with effective implementation of plans to detect and monitor those with hypertensive disorders in pregnancy [85] and quality improvement efforts to enhance timely intervention and raise maternal awareness of warning signs [86]. Proper prenatal care and on-time delivery are critical in the tertiary prevention of pregnancy-induced hypertension, preeclampsia, and eclampsia. In this analysis, the significant risk factors detected for eclampsia were women who were younger than 25 years, Black, from the South and the poorest areas, and had anemia or a multifetal pregnancy.

Racial and regional disparities

There were racial, ethnic, and regional disparities in the incidence of gestational hypertension, preeclampsia, and eclampsia throughout the course of the three-year period. Blacks have a higher risk among the three major types of hypertensive disorders in pregnancy; however, after adjusting for other covariates, gestational hypertension was higher among Whites than other racial groups. This is probably due to disparities in genetic factors, lifestyles, and social and healthcare settings. The large population-based data allowed us to perform secondary analyses for a small race group; hence, in our analysis and after controlling for a wide range of covariates, it became evident that White women have a greater risk for gestational hypertension than for preeclampsia and eclampsia.

To address disparities in maternal health and inform policy and clinical practice, studies must include sufficient numbers of participants from all racial groups, notably Black women. The necessity of controlling for all feasible potential covariates to obtain accurate estimates is further highlighted by the use of accurate diagnosis codes after 2015 with ICD-10-CM in identifying gestational hypertension and other diseases. This may contribute to excluding Black women with essential hypertension.

Maternal age

This study revealed that younger adolescents are at greater risk than women of advanced maternal age, that there is no difference with each year of maternal age progress between 25 and 45 years, and that younger women aged 20 to 25 years are at greater risk than those aged 35 to 40 years. The trend for gestational hypertension is

higher in women younger than 25 years than those older than 35 years, and eclampsia risk is only significantly elevated in women younger than 25. This may be explained by the hypothesis that younger women had limited exposure to sperm, making them more susceptible to gestational hypertension than preeclampsia and eclampsia. Although maternal age is a nonmodifiable risk factor, teen pregnancy can be avoided by women at high risk, such as those with a strong family history or other associated factors. Policymakers and program administrators have to establish pregnancy prevention programs that take into account risk factors for teenage pregnancy at the individual, school, community, and national levels. Furthermore, health policy initiatives at the state and national levels should prioritize ensuring that females receive reliable healthcare from childhood through puberty and adulthood.

Obesity and anemia

In this study, obesity is the most significant risk factor for developing pregnancy-induced hypertensive disorders, including gestational hypertension, preeclampsia, and eclampsia. The findings of this research are consistent with most studies, in which overweight and obesity raise the risk of preeclampsia by two- to threefold [62]. Insulin resistance is associated with obesity. Although the precise mechanisms by which obesity and insulin resistance are linked to a higher risk of hypertensive disorders in pregnancy remain unknown, some theories attribute this to the rise in cytokine-mediated oxidative stress, dyslipidemia, and the direct impact of hyperinsulinemia and insulin resistance on maternal hemodynamic circulation and blood pressure. Moreover, the incidence of

hypertensive disorders in pregnancy is likely to increase as a result of the global rise in the prevalence of obesity.

While a cross-sectional study found that women with anemia had a 4-fold higher incidence of preeclampsia than non-anemic women [87], the association of preeclampsia and eclampsia with anemia is more controversial [88]. A systematic review of four studies concluded that daily oral intake of iron during pregnancy failed to decrease the incidence of preeclampsia [89]. In our analysis, anemia was the only significant risk factor associated with all three major types of hypertensive disorders in pregnancy after adjusting for other covariates.

Anemia and obesity are the most modifiable risk factors to prevent three types of hypertensive disorders in pregnancy, and policy should target lifestyle and early detection of these comorbidity conditions. The prevention or management of these two conditions could result in a substantial reduction in hypertensive disorders in pregnancy. Improving monitoring of these two conditions, particularly in women at high risk of hypertensive disorders in pregnancy, modifying lifestyle behaviors, and providing health education could be vital initiatives in reducing the consequences of these disorders and, consequently, the morbidity and mortality associated with hypertensive disorders in pregnancy.

Community-level income and socio-economic status (SES)

In this study, gestational hypertension, preeclampsia, and eclampsia were more common in women who lived in the poorest communities (income quartile 1). The median household income for the patient's ZIP Code is used in the HCUP database to

calculate the community-level income, which is then divided into quartiles. Community-level income is regarded as a valuable indicator of the socioeconomic status (SES) of the hospitalized women [89], as women's social and physical environments have a number of income-related effects on them [90]. The sample proportion of hospitalizations for each income quartile of the three health outcomes was large enough to have a small standard error, resulting in more accurate estimates. While we control for health insurance coverage for pregnant women with deliveries, the community-income level of women remains a significant indicator in this analysis for disparities in health care access and quality and suggests that additional efforts may be required to increase access and quality of care for low-income women.

Smoking and thrombophilia

In this study, women with nicotine dependence tended to protect against preeclampsia. In univariate analyses, we also found that alcohol intake is protective. The apparent protective effect of alcohol may be due to smoking, as it was not found to be statistically significant in multivariate models. This was also confirmed in previous studies. Although smoking and alcohol use may provide some protection against hypertensive disorders in pregnancy, the well-established hazards to the fetus exceed the minor benefit. In addition, according to some studies, the neonatal mortality rate due to preeclampsia was higher among infants born to smokers than to nonsmokers.

The association between thrombophilia and hypertensive disorders of pregnancy, including preeclampsia, eclampsia, and HELP syndrome, has been thoroughly investigated, with contradictory results and conclusions. According to most studies, women with thrombophilia are more likely to develop severe preeclampsia and have an

increased risk of preeclampsia recurrence [91, 92]. In this study, we observed a negative association between primary thrombophilia and the three major types of hypertensive disorders in pregnancy. Primary thrombophilia coded using the new ICD-10-CM diagnosis coding may play a role in having a specific diagnosis for this disorder, excluding other specified coagulation defects. Researchers should be aware of the various coagulopathy types, and further studies are needed to determine the association between different types of thrombophilia and specific classes of hypertensive disorders in pregnancy, such as disease severity and complication.

Strengths and Limitations

The use of a large, multicenter, nationwide database from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) is a significant strength of this analysis, as it increases the generalizability of the study findings. This large sample of approximately 3.5 million births per year, which is about 97% of the U.S. population, and pregnant women hospitalized between 2016 and 2018 enable robust analyses of subgroups of pregnant women as well as the ability to perform a secondary analysis to detect any associations between these subgroups and several covariates. NIS data are standardized across years and weighted to estimate approximate national rates, making them the most practical and reliable source of data for tracking temporal trends in hypertensive disorders in pregnancy in the United States.

This study has limitations. First, NIS data did not account for a patient's hospitalization for more than one delivery. Second, identification of hypertensive disorders in pregnancy and preexisting conditions based solely on the *International Classification of Disease, 10th Revision, Clinical Modification* (ICD-10-CM codes). The

validity of ICD-10-CM case definitions varies by subtype of hypertensive disorder. Overall, the validity of the ICD-10 codes used to identify health-related diagnoses had a high positive predictive value, negative predictive value, specificity (> 90percent), and sensitivity (> 80 percent). Sensitivity was high (>80 percent) for gestational hypertension but moderate for preeclampsia (58.3 percent) and eclampsia (66.6 percent) [93]. These results suggested the potential for underestimation rather than overestimate. With the large sample size, it been postulated that the impact of such would be diminished.

The 2013 The American College of Obstetricians and Gynecologists (ACOG)'s revisions to the diagnostic criteria, particularly the removal of proteinuria as an essential criterion for diagnosing preeclampsia, may cause uncertainty among some physicians when diagnosing preeclampsia and could result in misclassification bias when determining disease incidence. However, the effect of such a modification would be minimized due to the large sample size.

Lastly, there was missing information regarding race in a few states (which represent about 5 percent for the years 2016-2018) and the anticipated number of births that occurred outside of hospitals (less than 1 percent). Less than 2 percent of stays were missing data on community income, and less than 1 percent of stays were missing data on expected payer and location of residence. Therefore, some caution should be used in interpreting the results concerning these variables.

CONCLUSION

Due to the lack of recent large-scale population-based studies that estimate the current rates of the major types of hypertensive disorders in pregnancy, a current study that includes a nationwide multicenter study with a diverse population was conducted to understand the magnitude of disease occurrence and the temporal trends in hospitalizations.

Our current understanding of the relationships between the major types of hypertensive disorders in pregnancy is based on studies conducted prior to 2013, before the 2013 revisions to the diagnostic criteria for preeclampsia and severe preeclampsia by the American College of Obstetricians and Gynecologists. Thus, an update is required for the national trends of these disorders, stratified by age, gender, and race/ethnicity across the U.S. states.

Finally, it is important to identify the risk factors associated with the main types of hypertensive disorders in pregnancy among women in the United States who have never had high blood pressure. Assessing the public health burden of these disorders, creating a risk-based model based on maternal and hospital characteristics, educating women about the risk and its negative consequences, and developing effective preventive measures and improved management for these disorders are essential.

TABLES

Table 1. Descriptive statistics, by patient and hospital characteristics, for women aged 15 to 45 years with live or still births between 2016 and 2018, United States

	Deliveries			
	2016	**2017**	**2018**	**2016-2018**
Characteristics	n (%)	n (%)	n (%)	n (%)
Overall	3,753,271	3,675,061	3,599,739	11,097,776
Age (years)				
15-20	206,635 (5.5)	190,635 (5.2)	174,930 (4.9)	576,019 (5.2)
20-24	768,954 (20.5)	729,094 (19.8)	694,140 (19.3)	2,205,498 (19.9)
25-29	1,092,084 (29.1)	1,073,979 (29.2)	1,044,945 (29.0)	3,229,442 (29.1)
30-34	1,054,199 (28.1)	1,041,374 (28.3)	1,032,800 (28.7)	3,146,443 (28.4)
35-39	520,995 (13.9)	527,310 (14.3)	538,820 (15.0)	1,599,419 (14.4)
40-45	110,405 (2.9)	112,670 (3.1)	114,105 (3.2)	340,955 (3.1)
Race				
White	1,873,003 (49.9)	1,825,758 (49.7)	1,832,529 (50.9)	5,562,104 (50.1)
Black	519,325 (13.8)	529,730 (14.4)	513,795 (14.3)	1,576,415 (14.2)
Hispanic	730,354 (19.5)	725,654 (19.7)	729,240 (20.3)	2,200,993 (19.8)
Others	630,590 (16.8)	593,919 (16.2)	524,175 (14.6)	1,758,263 (15.8)
Region				
Northeast	597,715 (15.9)	587,625 (16.0)	567,529 (15.8)	1,762,044 (15.9)
Midwest	788,745 (21.0)	779,693 (21.2)	762,645 (21.2)	2,344,523 (21.1)
South	1,455,883 (38.8)	1,426,155 (38.8)	1,415,991 (39.3)	4,327,324 (39.0)
West	910,928 (24.3)	881,588 (24.0)	853,573 (23.7)	2,663,884 (24.0)
Hospital type				
Rural	351,324 (9.4)	344,508 (9.4)	326,608 (9.1)	1,027,325 (9.3)
Urban nonteaching	950,368 (25.3)	796,579 (21.7)	698,722 (19.4)	2,461,504 (22.2)
Urban teaching	2,451,579 (65.3)	2,533,974 (69.0)	2,574,409 (71.5)	7,608,947 (68.6)
Income Quartile				
Quartile 1 (lowest)	1,061,474 (28.6)	1,021,709 (28.1)	971,230 (27.2)	3,077,668 (28.0)
Quartile 2	908,769 (24.5)	935,309 (25.7)	931,575 (26.1)	2,793,643 (25.4)
Quartile 3	926,779 (24.9)	888,644 (24.4)	880,515 (24.7)	2,711,588 (24.7)
Quartile 4 (highest)	818,154 (22.0)	795,299 (21.8)	783,535 (22.0)	2,408,973 (21.9)
Insurance				
Medicaid	1,621,798 (43.2)	1,600,333 (43.5)	1,539,515 (42.8)	4,796,331 (43.2)
Private	1,923,083 (51.2)	1,879,638 (51.1)	1,864,754 (51.8)	5,696,445 (51.3)
Self-pay	94,040 (2.5)	94,020 (2.6)	97,575 (2.7)	289,630 (2.6)
Other	114,350 (3.0)	101,070 (2.8)	97,895 (2.7)	315,370 (2.8)
Coexisting condition				
Gestational diabetes	267,905 (7.1)	279,595 (7.6)	287,500 (8.0)	835,884 (7.5)
Non-gestational diabetes	40,980 (1.1)	41,850 (1.1)	43,805 (1.2)	127,890 (1.2)
Multiple gestation	66,975 (1.8)	66,575 (1.8)	63,380 (1.8)	197,415 (1.8)
Obesity/overweight	278,185 (7.4)	331,015 (9.0)	365,670 (10.2)	982,154 (8.9)
Systemic lupus erythematosus	4,520 (0.1)	4,610 (0.1)	5,335 (0.1)	14,680 (0.1)
Antiphospholipid syndrome	2,430 (0.1)	2,535 (0.1)	2,875 (0.1)	7,925 (0.1)
Thrombophilia	12,940 (0.3)	13,285 (0.4)	13,535 (0.4)	40,045 (0.4)
Anemia	466,725 (12.4)	542,394 (14.8)	571,475 (15.9)	1,597,924 (14.4)
Hypothyroidism	121,025 (3.2)	124,665 (3.4)	129,170 (3.6)	376,865 (3.4)
Renal disease	5,795 (0.2)	6,410 (0.2)	6,665 (0.2)	20,070 (0.2)
Alcohol related disorders	3,295 (0.1)	2,520 (0.1)	2,940 (0.1)	8,950 (0.1)
Nicotine dependence	157,930 (4.2)	163,075 (4.4)	163,715 (4.5)	490,105 (4.4)

Table 2 Incidence rates* and weighted number of cases of gestational hypertension, preeclampsia, and eclampsia from 2016 to 2018, United States

	Year			
Characteristics	**2016**	**2017**	**2018**	**Total 2016-2018**
Gestational hypertension	180,685 (48.1)	202,680 (55.2)	221,835 (61.6)	605,795 (54.6)
Preeclampsia	169,445 (45.1)	179,240 (48.8)	192,915 (53.6)	542,435 (48.9)
Eclampsia	3,880 (1.0)	2,870 (0.8)	2,475 (0.7)	9,340 (0.8)

* Crude rate = cases per 1,000 deliveries.

Table 3.1 Incidence rates* and weighted number of cases of gestational hypertension by patients and hospital characteristics, 2016 to 2018, United States

	Gestational hypertension			
Characteristics	**2016**	**2017**	**2018**	**2016-2018**
Overall	180,685 (48.1)	202,680 (55.2)	221,835 (61.6)	605,795 (54.6)
Age (years)				
15-20	10,830 (52.4)	10,835 (56.8)	11,650 (66.6)	33,350 (57.9)
20-24	36,580 (47.6)	40,465 (55.5)	44,160 (63.6)	121,285 (55.0)
25-29	52,505 (48.1)	58,350 (54.3)	63,880 (61.1)	174,890 (54.2)
30-34	49,060 (46.5)	56,460 (54.2)	60,905 (59.0)	166,600 (52.9)
35-39	25,525 (49.0)	29,305 (55.6)	33,085 (61.4)	88,020 (55.0)
40-45	6,185 (56.0)	7,265 (64.5)	8,155 (71.5)	21,650 (63.5)
Race				
White	101,435 (54.2)	113,580 (62.2)	126,295 (68.9)	341,570 (61.4)
Black	29,755 (57.3)	34,845 (65.8)	36,850 (71.7)	101,610 (64.5)
Hispanic	26,405 (36.2)	30,125 (41.5)	34,680 (47.6)	91,310 (41.5)
Others	23,090 (36.6)	24,130 (40.6)	24,010 (45.8)	71,305 (40.6)
Region				
Northeast	26,215 (43.9)	29,975 (51.0)	33,580 (59.2)	89,850 (51.0)
Midwest	40,000 (50.7)	45,380 (58.2)	50,875 (66.7)	136,365 (58.2)
South	77,595 (53.3)	85,435 (59.9)	92,650 (65.4)	255,945 (59.1)
West	36,875 (40.5)	41,890 (47.5)	44,730 (52.4)	123,635 (46.4)
Hospital type				
Rural	15,715 (44.7)	18,010 (52.3)	18,430 (56.4)	52,195 (50.8)
Urban nonteaching	41,480 (43.6)	40,040 (50.3)	38,060 (54.5)	119,665 (48.6)
Urban teaching	123,490 (50.4)	144,630 (57.1)	165,345 (64.2)	433,935 (57.0)
Income Quartile				
Quartile 1 (lowest)	52,610 (49.6)	57,515 (56.3)	62,075 (63.9)	172,415 (56.0)
Quartile 2	44,585 (49.1)	51,990 (55.6)	57,830 (62.1)	154,550 (55.3)
Quartile 3	45,530 (49.1)	50,255 (56.6)	56,380 (64.0)	152,300 (56.2)
Quartile 4 (highest)	36,255 (44.3)	41,255 (51.9)	43,910 (56.0)	121,515 (50.4)
Insurance				
Medicaid	71,450 (44.1)	81,000 (50.6)	88,575 (57.5)	241,310 (50.3)
Private	101,080 (52.6)	113,005 (60.1)	123,120 (66.0)	337,460 (59.2)
Self-pay	2,755 (29.3)	3,350 (35.6)	4,235 (43.4)	10,365 (35.8)
Other	5,400 (47.2)	5,325 (52.7)	5,905 (60.3)	16,660 (52.8)
Coexisting condition				
Gestational diabetes	18,670 (69.7)	21,195 (75.8)	22,620 (78.7)	62,530 (74.8)
Non-gestational diabetes	3,120 (76.1)	3,505 (83.8)	4,195 (95.8)	10,835 (84.7)
Multiple gestation	4,700 (70.2)	5,205 (78.2)	5,070 (80.0)	14,975 (75.9)
Obesity/overweight	27,990 (100.6)	36,430 (110.1)	42,815 (117.1)	107,380 (109.3)
Systemic lupus erythematosus	265 (58.6)	270 (58.6)	360 (67.5)	900 (61.3)
Antiphospholipid syndrome	125 (51.4)	160 (63.1)	180 (62.6)	465 (58.7)
Thrombophilia	610 (47.1)	725 (54.6)	835 (61.7)	2,175 (54.3)
Anemia	25,770 (55.2)	33,750 (62.2)	40,595 (71.0)	100,305 (62.8)
Hypothyroidism	7,375 (60.9)	8,690 (69.7)	9,415 (72.9)	25,510 (67.7)
Renal disease	360 (62.1)	445 (69.4)	530 (79.5)	1,335 (66.5)
Alcohol related disorders	140 (42.5)	205 (81.3)	255 (86.7)	600 (67.0)
Nicotine dependence	7,590 (48.1)	9,370 (57.5)	10,495 (64.1)	27,505 (56.1)

* Crude rate = cases per 1,000 deliveries.

Table 3.2 Incidence rates* and weighted number of cases of preeclampsia by patients and hospital characteristics from 2016 to 2018, United States

	Preeclampsia			
Characteristics	**2016**	**2017**	**2018**	**2016-2018**
Overall	169,445 (45.1)	179,240 (48.8)	192,915 (53.6)	542,435 (48.9)
Age (years)				
15-20	12,710 (61.5)	13,055 (68.5)	13,085 (74.8)	38,895 (67.5)
20-24	37,025 (48.1)	38,505 (52.8)	41,090 (59.2)	116,755 (52.9)
25-29	45,095 (41.3)	48,180 (44.9)	51,985 (49.7)	145,475 (45.0)
30-34	42,710 (40.5)	45,415 (43.6)	49,110 (47.6)	137,455 (43.7)
35-39	24,845 (47.7)	26,555 (50.4)	29,510 (54.8)	81,095 (50.7)
40-45	7,060 (63.9)	7,530 (66.8)	8,135 (71.3)	22,760 (66.8)
Race				
White	78,650 (42.0)	83,235 (45.6)	91,230 (49.8)	253,395 (45.6)
Black	31,275 (60.2)	34,630 (65.4)	36,635 (71.3)	102,810 (65.2)
Hispanic	34,445 (47.2)	36,695 (50.6)	40,820 (56.0)	112,080 (50.9)
Others	25,075 (39.8)	24,680 (41.6)	24,230 (46.2)	74,150 (42.2)
Region				
Northeast	25,610 (42.8)	28,355 (48.3)	29,310 (51.6)	83,420 (47.3)
Midwest	34,590 (43.9)	37,240 (47.8)	40,385 (53.0)	112,360 (47.9)
South	70,630 (48.5)	72,785 (51.0)	78,840 (55.7)	222,605 (51.4)
West	38,615 (42.4)	40,860 (46.3)	44,380 (52.0)	124,050 (46.6)
Hospital type				
Rural	12,890 (36.7)	13,745 (39.9)	13,745 (42.1)	40,420 (39.3)
Urban nonteaching	34,805 (36.6)	31,645 (39.7)	30,745 (44.0)	97,295 (39.5)
Urban teaching	121,750 (49.7)	133,850 (52.8)	148,425 (57.7)	404,720 (53.2)
Income Quartile				
Quartile 1 (lowest)	53,700 (50.6)	55,990 (54.8)	57,930 (59.6)	167,905 (54.6)
Quartile 2	41,715 (45.9)	45,635 (48.8)	50,545 (54.3)	138,085 (49.4)
Quartile 3	40,320 (43.5)	42,135 (47.4)	46,215 (52.5)	128,855 (47.5)
Quartile 4 (highest)	31,910 (39.0)	33,850 (42.6)	36,450 (46.5)	102,370 (42.5)
Insurance				
Medicaid	75,535 (46.6)	81,395 (50.9)	87,090 (56.6)	244,465 (51.0)
Private	85,680 (44.6)	89,870 (47.8)	96,735 (51.9)	272,620 (47.9)
Self-pay	3,515 (37.4)	3,260 (34.7)	4,255 (43.6)	11,080 (38.3)
Other	4,715 (41.2)	4,715 (46.7)	4,835 (49.4)	14,270 (45.2)
Coexisting condition				
Gestational diabetes	19,145 (71.5)	20,905 (74.8)	21,750 (75.7)	61,835 (74.0)
Non-gestational diabetes	5,850 (142.8)	5,960 (142.4)	6,915 (157.9)	18,740 (146.5)
Multiple gestation	9,575 (143.0)	9,985 (150.0)	9,415 (148.5)	28,980 (146.8)
Obesity/overweight	25,950 (93.3)	31,900 (96.4)	36,120 (98.8)	94,115 (95.8)
Systemic lupus erythematosus	395 (87.4)	430 (93.3)	475 (89.0)	1,305 (88.9)
Antiphospholipid syndrome	190 (78.2)	260 (102.6)	310 (107.8)	765 (96.5)
Thrombophilia	720 (55.6)	635 (47.8)	585 (43.2)	1,945 (48.6)
Anemia	29,745 (63.7)	37,295 (68.8)	42,245 (73.9)	109,580 (68.6)
Hypothyroidism	7,470 (61.7)	7,935 (63.7)	8,900 (68.9)	24,350 (64.6)
Renal disease	1,345 (232.1)	1,535 (239.5)	1,790 (268.6)	4,725 (235.4)
Alcohol related disorders	170 (51.6)	150 (59.5)	250 (85.0)	575 (64.2)
Nicotine dependence	6,345 (40.2)	7,670 (47.0)	8,540 (52.2)	22,615 (46.1)

* Crude rate = cases per 1,000 deliveries.

Table 3.3 Incidence rates* and weighted number of cases of eclampsia by patients and hospital characteristics from 2016 to 2018, United States

	Eclampsia			
Characteristics	**2016**	**2017**	**2018**	**All**
Overall	3,880 (1.0)	2,870 (0.8)	2,475 (0.7)	9,340 (0.8)
Age (years)				
15-20	410 (2.0)	480 (2.5)	335 (1.9)	1,230 (2.1)
20-24	905 (1.2)	745 (1.0)	635 (0.9)	2,295 (1.0)
25-29	1,070 (1.0)	650 (0.6)	580 (0.6)	2,315 (0.7)
30-34	905 (0.9)	585 (0.6)	490 (0.5)	2,015 (0.6)
35-39	480 (0.9)	305 (0.6)	325 (0.6)	1,145 (0.7)
40-45	110 (1.0)	105 (0.9)	110 (1.0)	340 (1.0)
Race				
White	1,680 (0.9)	1,110 (0.6)	1,070 (0.6)	3,890 (0.7)
Black	925 (1.8)	760 (1.4)	605 (1.2)	2,345 (1.5)
Hispanic	725 (1.0)	565 (0.8)	520 (0.7)	1,820 (0.8)
Others	550 (0.9)	435 (0.7)	280 (0.5)	1,285 (0.7)
Region				
Northeast	600 (1.0)	350 (0.6)	370 (0.7)	1,325 (0.8)
Midwest	800 (1.0)	525 (0.7)	485 (0.6)	1,840 (0.8)
South	1,665 (1.1)	1,390 (1.0)	1,115 (0.8)	4,235 (1.0)
West	815 (0.9)	605 (0.7)	505 (0.6)	1,940 (0.7)
Hospital type				
Rural	325 (0.9)	345 (1.0)	315 (1.0)	995 (1.0)
Urban nonteaching	930 (1.0)	580 (0.7)	490 (0.7)	2,015 (0.8)
Urban teaching	2,625 (1.1)	1,945 (0.8)	1,670 (0.6)	6,330 (0.8)
Income Quartile				
Quartile 1 (lowest)	1,435 (1.4)	1,080 (1.1)	850 (0.9)	3,430 (1.1)
Quartile 2	1,005 (1.1)	790 (0.8)	745 (0.8)	2,565 (0.9)
Quartile 3	855 (0.9)	555 (0.6)	560 (0.6)	1,985 (0.7)
Quartile 4 (highest)	545 (0.7)	400 (0.5)	295 (0.4)	1,250 (0.5)
Insurance				
Medicaid	2,060 (1.3)	1,665 (1.0)	1,395 (0.9)	5,190 (1.1)
Private	1,640 (0.9)	1,050 (0.6)	925 (0.5)	3,650 (0.6)
Self-pay	85 (0.9)	70 (0.7)	85 (0.9)	250 (0.9)
Other	95 (0.8)	85 (0.8)	70 (0.7)	250 (0.8)
Coexisting condition				
Gestational diabetes	295 (1.1)	275 (1.0)	170 (0.6)	740 (0.9)
Non-gestational diabetes	130 (3.2)	55 (1.3)	65 (1.5)	260 (2.0)
Multiple gestation	210 (3.1)	170 (2.6)	95 (1.5)	475 (2.4)
Obesity/overweight	475 (1.7)	395 (1.2)	365 (1.0)	1,255 (1.3)
Systemic lupus erythematosus	20 (4.4)	15 (3.3)	15 (2.8)	50 (3.4)
Antiphospholipid syndrome	10 (4.1)	5 (2.0)	5 (1.7)	20 (2.5)
Thrombophilia	20 (1.5)	10 (0.8)	0 (0.0)	30 (0.7)
Anemia	765 (1.6)	690 (1.3)	630 (1.1)	2,130 (1.3)
Hypothyroidism	130 (1.1)	80 (0.6)	95 (0.7)	310 (0.8)
Renal disease	75 (12.9)	95 (14.8)	130 (19.5)	315 (15.7)
Alcohol related disorders	10 (3.0)	0 (0.0)	5 (1.7)	15 (1.7)
Nicotine dependence	205 (1.3)	130 (0.8)	115 (0.7)	455 (0.9)

* Crude rate = cases per 1,000 deliveries.

Table 4.1 Incidence rates and rate ratios for gestational hypertension by patients and hospital characteristics, 2016 to 2018, United States

Covariates	Gestational hypertension		
	Rate (2016-2018)	Univariate RR (95% CI)	Multivariate RR* (95% CI)
Age (years)			
15-20	57.9	**1.10 (1.07-1.13)**	**1.24 (1.21-1.28)**
20-24	55.0	**1.04 (1.02-1.06)**	**1.12 (1.10-1.14)**
25-29	54.2	**1.02 (1.01-1.04)**	**1.06 (1.04-1.08)**
30-34	53.0	1.00 (referent)	1.00 (referent)
35-39	55.2	**1.04 (1.02-1.06)**	1.01 (0.99-1.03)
40-45	**63.5**	**1.21 (1.17-1.25)**	**1.11 (1.07-1.14)**
Race			
White	61.5	1.00 (referent)	1.00 (referent)
Black	**64.4**	**1.05 (1.04-1.07)**	**0.93 (0.91-0.95)**
Hispanic	41.5	**0.66 (0.65-0.67)**	**0.67 (0.66-0.69)**
Others	40.6	**0.65 (0.64-0.66)**	**0.66 (0.65-0.68)**
Region			
Northeast	0.0	1.00 (referent)	1.00 (referent)
Midwest	58.2	**1.15 (1.13-1.17)**	**1.17 (1.14-1.19)**
South	**59.2**	**1.17 (1.15-1.19)**	**1.24 (1.22-1.27)**
West	46.4	**0.90 (0.89-0.92)**	**1.05 (1.03-1.07)**
Hospital type			
Rural	50.9	1.00 (referent)	1.00 (referent)
Urban nonteaching	48.7	**0.96 (0.93-0.98)**	0.99 (0.96-1.01)
Urban teaching	**57.1**	**1.13 (1.11-1.15)**	**1.10 (1.08-1.13)**
Income Quartile			
Quartile 1 (lowest)	56.1	1.00 (referent)	1.00 (referent)
Quartile 2	55.3	0.99 (0.97-1.00)	**0.98 (0.97-1.00)**
Quartile 3	**56.2**	1.00 (0.99-1.02)	0.99 (0.97-1.00)
Quartile 4 (highest)	50.5	**0.89 (0.88-0.91)**	**0.88 (0.87-0.90)**
Insurance			
Medicaid	50.3	**0.84 (0.83-0.85)**	0.95 (0.89-1.01)
Private	59.2	1.00 (referent)	1.00 (referent)
Self-pay	35.8	**0.59 (0.56-0.62)**	**0.81 (0.75-0.88)**
Other	52.8	**0.89 (0.86-0.92)**	1.03 (0.95-1.10)
Coexisting condition			
Gestational diabetes	74.9	**1.45 (1.42-1.48)**	**1.30 (1.28-1.33)**
Non-gestational diabetes	84.4	**1.61 (1.54-1.68)**	**1.09 (1.05-1.15)**
Multiple gestation	75.7	**1.43 (1.38-1.48)**	1.03 (0.99-1.07)
Obesity/overweight	109.2	**2.36 (2.33-2.40)**	**2.05 (2.02-2.08)**
Systemic lupus erythematosus	61.0	1.12 (0.97-1.30)	
Antiphospholipid syndrome	60.0	1.11 (0.90-1.36)	
Thrombophilia	54.2	1.01 (0.92-1.11)	**0.84 (0.76-0.92)**
Anemia	62.8	**1.19 (1.17-1.21)**	**1.04 (1.02-1.05)**
Hypothyroidism	67.7	**1.27 (1.23-1.31)**	**1.10 (1.06-1.13)**
Renal disease	64.8	**1.20 (1.06-1.36)**	**0.72 (0.63-0.81)**
Alcohol related disorders	68.6	**0.79 (0.66-0.94)**	1.20 (1.00-1.45)
Nicotine dependence	56.1	**0.97 (0.94-0.99)**	**0.95 (0.92-0.98)**

* Adjusted for maternal age group, maternal race/ethnicity, hospital region, hospital type, income, payer, gestational and non-gestation diabetes, multiple gestation, obesity/overweight, thrombophilia, anemia, hypothyroidism, renal disease, alcohol related disorders, and nicotine dependence; Bold font indicates statistical significance $P < 0.05$.

Table 4.2 Incidence rates and rate ratios for preeclampsia by patients and hospital characteristics, 2016 to 2018, United States

Characteristics	Preeclampsia		
	Rate (2016-2018)	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age (years)			
15-20	**67.5**	**1.58 (1.54-1.62)**	**1.65 (1.60-1.69)**
20-24	52.9	**1.22 (1.20-1.24)**	**1.27 (1.25-1.29)**
25-29	45.1	**1.03 (1.01-1.05)**	**1.07 (1.05-1.09)**
30-34	43.8	1.00 (referent)	1.00 (referent)
35-39	50.9	**1.17 (1.15-1.19)**	**1.06 (1.04-1.08)**
40-45	66.9	**1.56 (1.51-1.62)**	**1.19 (1.15-1.24)**
Race			
White	45.6	1.00 (referent)	1.00 (referent)
Black	**65.3**	**1.46 (1.44-1.49)**	**1.12 (1.10-1.14)**
Hispanic	51.0	**1.12 (1.11-1.14)**	**1.05 (1.03-1.07)**
Others	42.2	**0.92 (0.90-0.94)**	**0.89 (0.87-0.91)**
Region			
Northeast	47.4	1.00 (referent)	1.00 (referent)
Midwest	48.0	1.01 (0.99-1.03)	**1.18 (1.16-1.21)**
South	**51.5**	**1.09 (1.07-1.11)**	**1.25 (1.22-1.27)**
West	46.6	0.98 (0.96-1.00)	**1.16 (1.14-1.19)**
Hospital type			
Rural	39.5	1.00 (referent)	1.00 (referent)
Urban nonteaching	39.6	1.00 (0.98-1.03)	**0.91 (0.89-0.94)**
Urban teaching	**53.3**	**1.37 (1.34-1.40)**	**1.08 (1.06-1.11)**
Income Quartile			
Quartile 1 (lowest)	**54.6**	1.00 (referent)	1.00 (referent)
Quartile 2	49.6	**0.90 (0.89-0.92)**	**0.96 (0.94-0.97)**
Quartile 3	47.6	**0.86 (0.85-0.88)**	**0.92 (0.90-0.93)**
Quartile 4 (highest)	42.5	**0.77 (0.76-0.78)**	**0.82 (0.80-0.84)**
Insurance			
Medicaid	51.0	**0.84 (0.79-0.90)**	1.04 (0.97-1.11)
Private	47.9	1.00 (referent)	1.00 (referent)
Self-pay	38.3	**0.62 (0.58-0.67)**	0.99 (0.91-1.07)
Other	45.2	**0.74 (0.69-0.80)**	1.07 (0.99-1.15)
Coexisting condition			
Gestational diabetes	74.1	**1.63 (1.59-1.66)**	**1.38 (1.35-1.41)**
Non-gestational diabetes	146.3	**3.41 (3.30-3.54)**	**1.85 (1.78-1.92)**
Multiple gestation	146.5	**3.47 (3.37-3.57)**	**1.98 (1.92-2.04)**
Obesity/overweight	95.8	**2.28 (2.25-2.32)**	**1.61 (1.58-1.64)**
Systemic lupus erythematosus	90.9	**1.95 (1.72-2.20)**	**1.18 (1.04-1.35)**
Antiphospholipid syndrome	96.5	**2.08 (1.76-2.45)**	**1.33 (1.12-1.59)**
Thrombophilia	48.9	1.00 (0.90-1.11)	**0.85 (0.76-0.94)**
Anemia	68.7	**1.54 (1.52-1.57)**	**1.12 (1.10-1.13)**
Hypothyroidism	64.7	**1.36 (1.32-1.40)**	**1.13 (1.10-1.17)**
Renal disease	232.7	**5.93 (5.52-6.38)**	**2.29 (2.12-2.48)**
Alcohol related disorders	63.1	**1.31 (1.09-1.58)**	
Nicotine dependence	46.3	**0.94 (0.91-0.97)**	**0.89 (0.86-0.92)**

* Adjusted for maternal age group, maternal race/ethnicity, hospital region, hospital type, income, payer, gestational and non-gestation diabetes, multiple gestation, obesity/overweight, systemic lupus erythematosus, antiphospholipid syndrome, thrombophilia, anemia, hypothyroidism, renal disease, and nicotine dependence; Bold font indicates statistical significance $P < 0.05$.

Table 4.3 Incidence rates and rate ratios for eclampsia, by patients and hospital characteristics, 2016 to 2018, United States

Characteristics	Eclampsia		
	Rate (2016-2018)	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age (years)			
15-20	2.1	**3.32 (2.83-3.89)**	**2.50 (2.11-2.95)**
20-24	1.0	**1.61 (1.41-1.84)**	**1.37 (1.19-1.57)**
25-29	0.7	1.12 (0.98-1.27)	1.04 (0.91-1.20)
30-34	0.6	1.00 (referent)	1.00 (referent)
35-39	0.7	1.13 (0.96-1.33)	1.05 (0.90-1.24)
40-45	1.0	**1.55 (1.20-2.00)**	1.20 (0.93-1.55)
Race			
White	0.7	1.00 (referent)	1.00 (referent)
Black	1.5	**2.15 (1.92-2.41)**	**1.42 (1.25-1.60)**
Hispanic	0.8	**1.18 (1.05-1.34)**	0.99 (0.86-1.13)
Others	0.7	1.05 (0.91-1.21)	1.05 (0.91-1.22)
Region			
Northeast	0.8	1.00 (referent)	1.00 (referent)
Midwest	0.8	1.05 (0.90-1.23)	1.12 (0.95-1.31)
South	1.0	**1.31 (1.14-1.51)**	**1.31 (1.14-1.51)**
West	0.7	0.97 (0.83-1.14)	1.14 (0.97-1.34)
Hospital type			
Rural	1.0	1.00 (referent)	1.00 (referent)
Urban nonteaching	0.8	0.85 (0.72-1.01)	0.85 (0.71-1.01)
Urban teaching	0.8	0.87 (0.75-1.01)	**0.71 (0.61-0.83)**
Income Quartile			
Quartile 1 (lowest)	1.1	1.00 (referent)	1.00 (referent)
Quartile 2	0.9	0.81 (0.72-0.91)	0.95 (0.85-1.07)
Quartile 3	0.7	**0.65 (0.58-0.74)**	**0.84 (0.74-0.96)**
Quartile 4 (highest)	0.5	**0.46 (0.40-0.53)**	**0.64 (0.55-0.75)**
Insurance			
Medicaid	1.1	0.85 (0.55-1.31)	1.06 (0.69-1.64)
Private	0.6	1.00 (referent)	1.00 (referent)
Self-pay	0.9	0.68 (0.41-1.13)	1.16 (0.69-1.96)
Other	0.8	0.62 (0.37-1.03)	0.98 (0.59-1.64)
Coexisting condition			
Gestational diabetes	0.9	1.06 (0.90-1.25)	
Non-gestational diabetes	2.0	**2.44 (1.85-3.20)**	
Multiple gestation	2.4	**2.93 (2.38-3.60)**	**1.60 (1.30-1.98)**
Obesity/overweight	1.3	**1.62 (1.42-1.85)**	
Systemic lupus erythematosus	3.3	**3.88 (2.08-7.24)**	1.71 (0.90-3.23)
Antiphospholipid syndrome	2.5	**2.94 (1.10-7.85)**	
Thrombophilia	0.7	0.88 (0.39-1.96)	
Anemia	1.3	**1.78 (1.60-1.98)**	**1.14 (1.02-1.27)**
Hypothyroidism	0.8	0.96 (0.75-1.24)	
Renal disease	16.0	**19.93 (15.59-25.48)**	**7.20 (5.56-9.33)**
Alcohol related disorders	1.6	1.94 (0.62-6.01)	
Nicotine dependence	0.9	1.09 (0.89-1.35)	

* Adjusted for maternal age group, maternal race/ethnicity, hospital region, hospital type, income, payer, multiple gestation, systemic lupus erythematosus, anemia, and renal disease; Bold font indicates statistical significance $P < 0.05$.

FIGURES

Figure 1 Potential biological mechanisms and risk factors related to hypertensive disorders of pregnancy

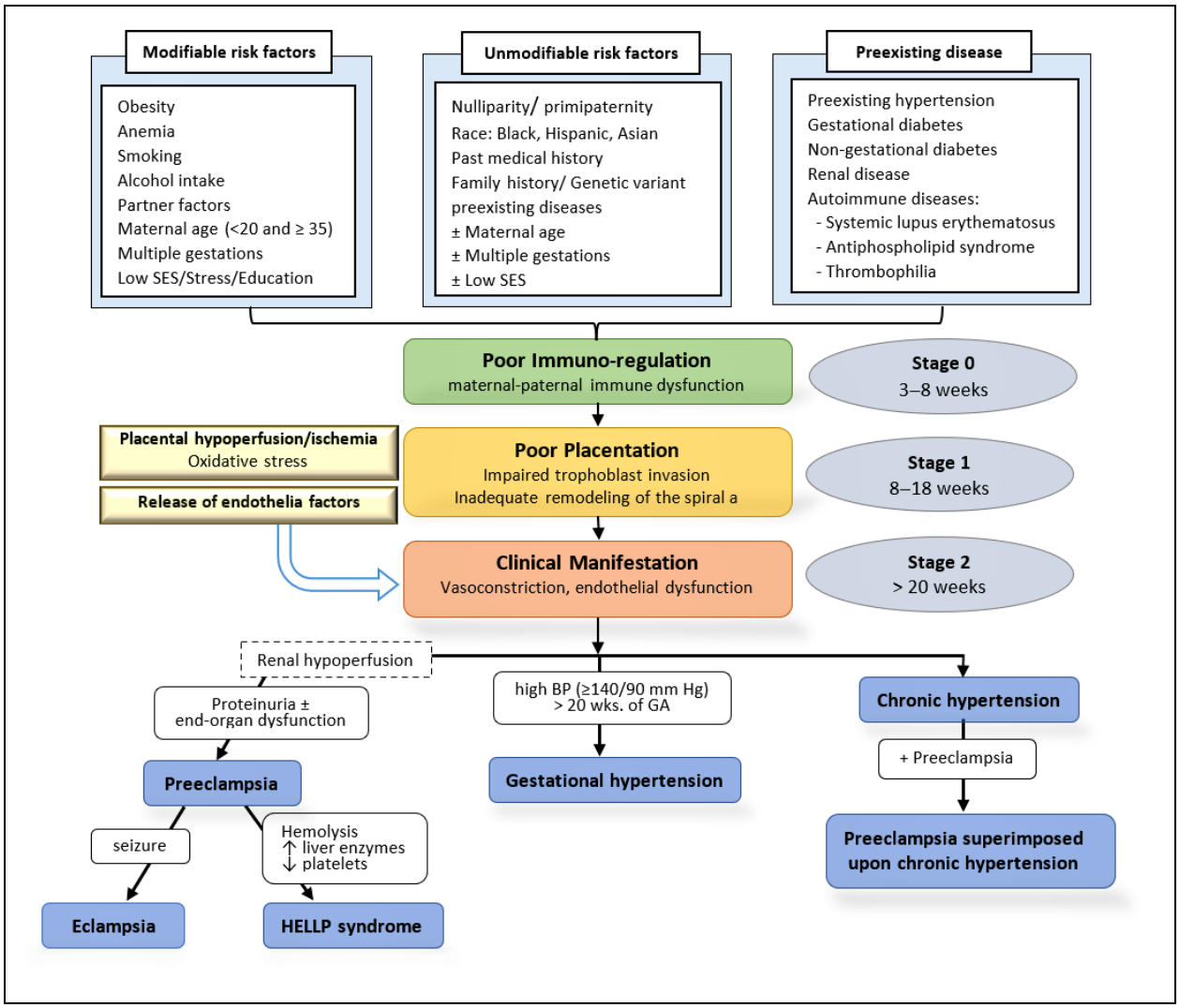


Figure 2 Incidence rates of gestational hypertension, preeclampsia, and eclampsia, from 2016 to 2018, United States

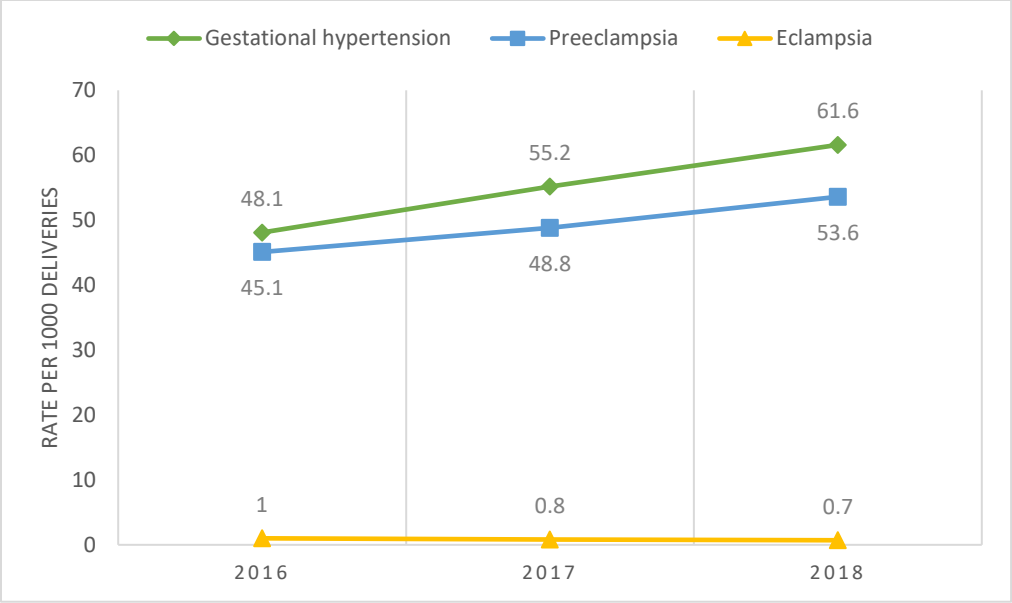


Figure 3.1 Incidence rates of gestational hypertension, by patients and hospital characteristics, 2016 to 2018, United States

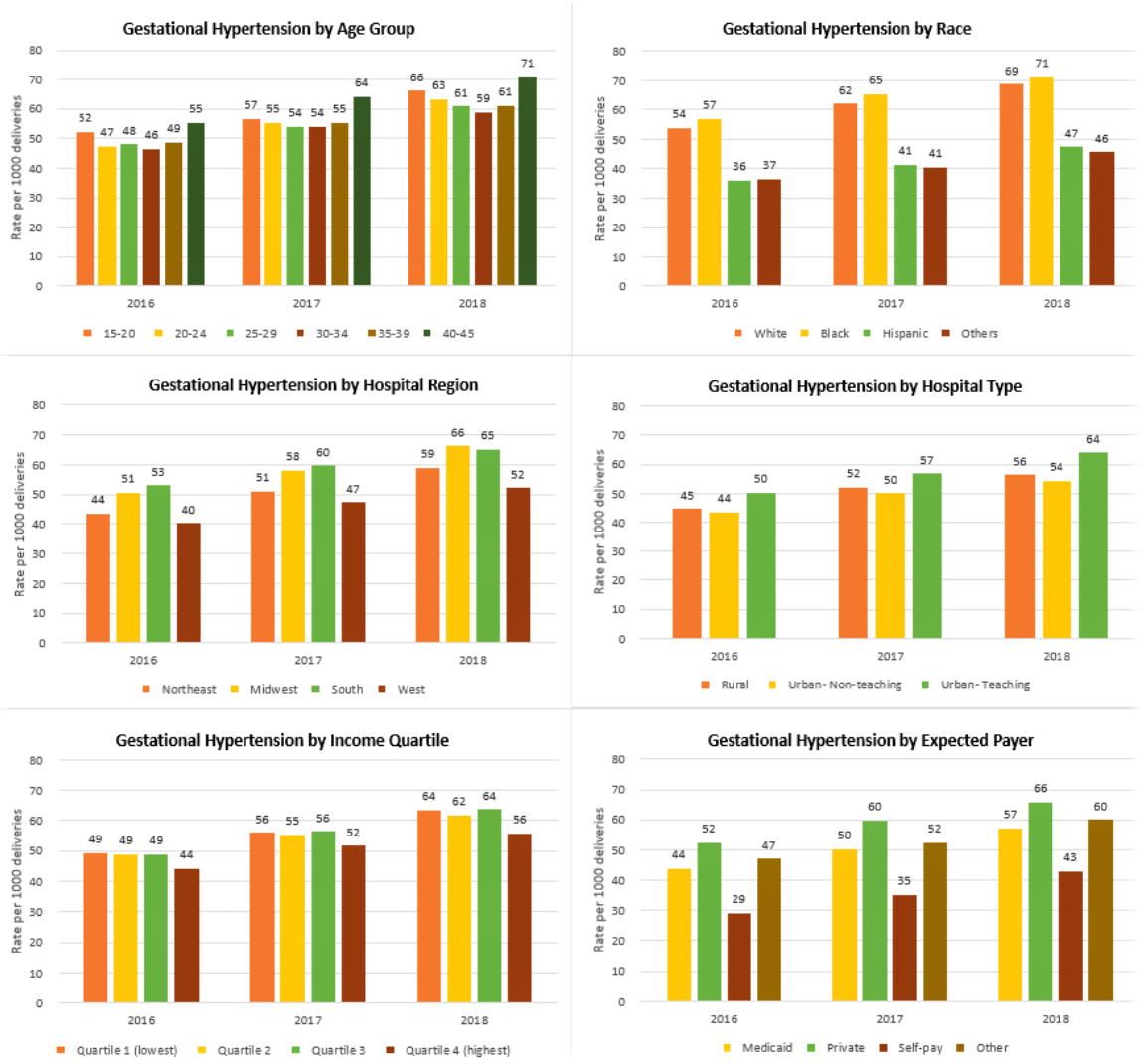


Figure 3.2 Incidence rates of preeclampsia, by patients and hospital characteristics, from 2016 to 2018, United States

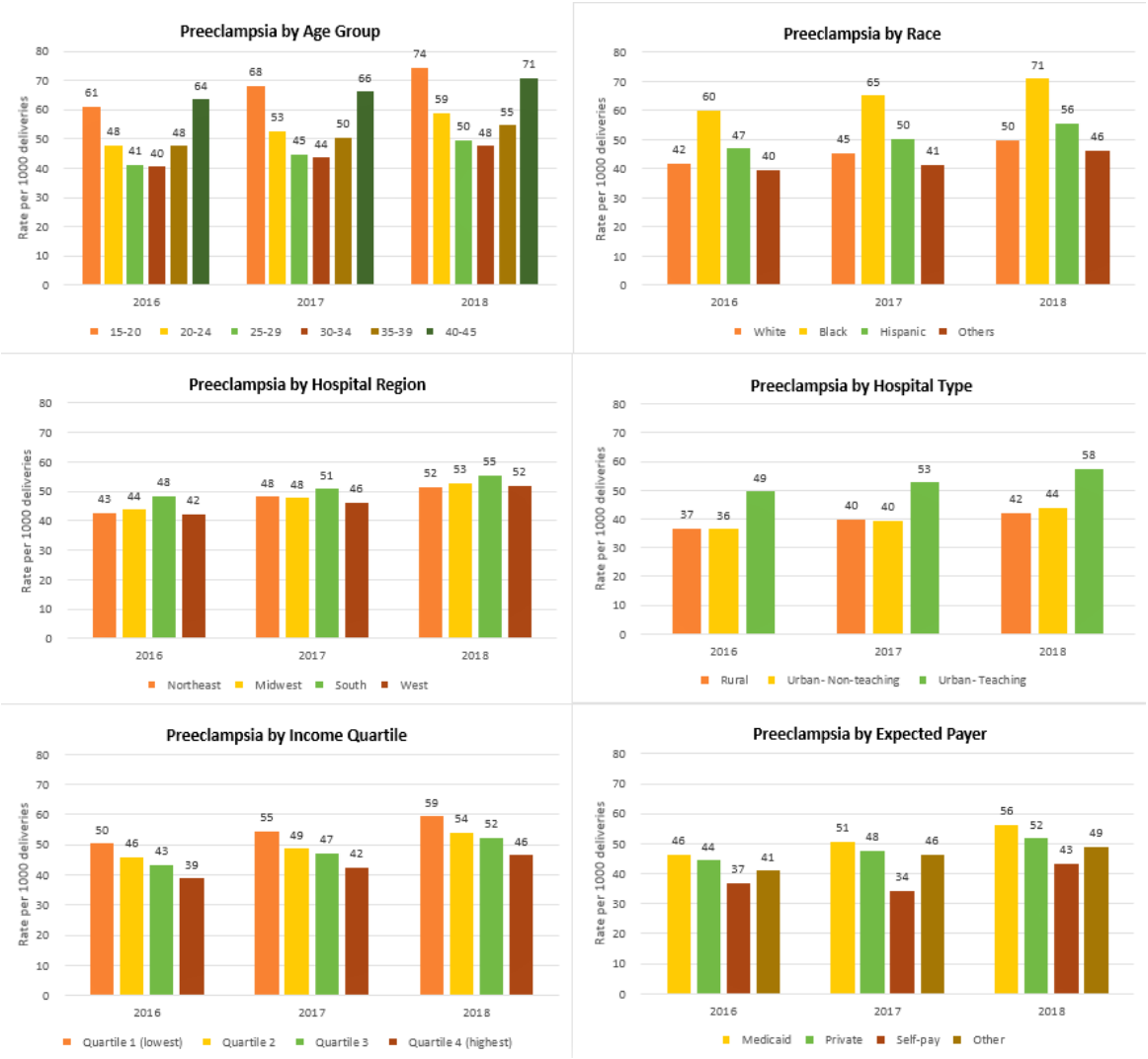
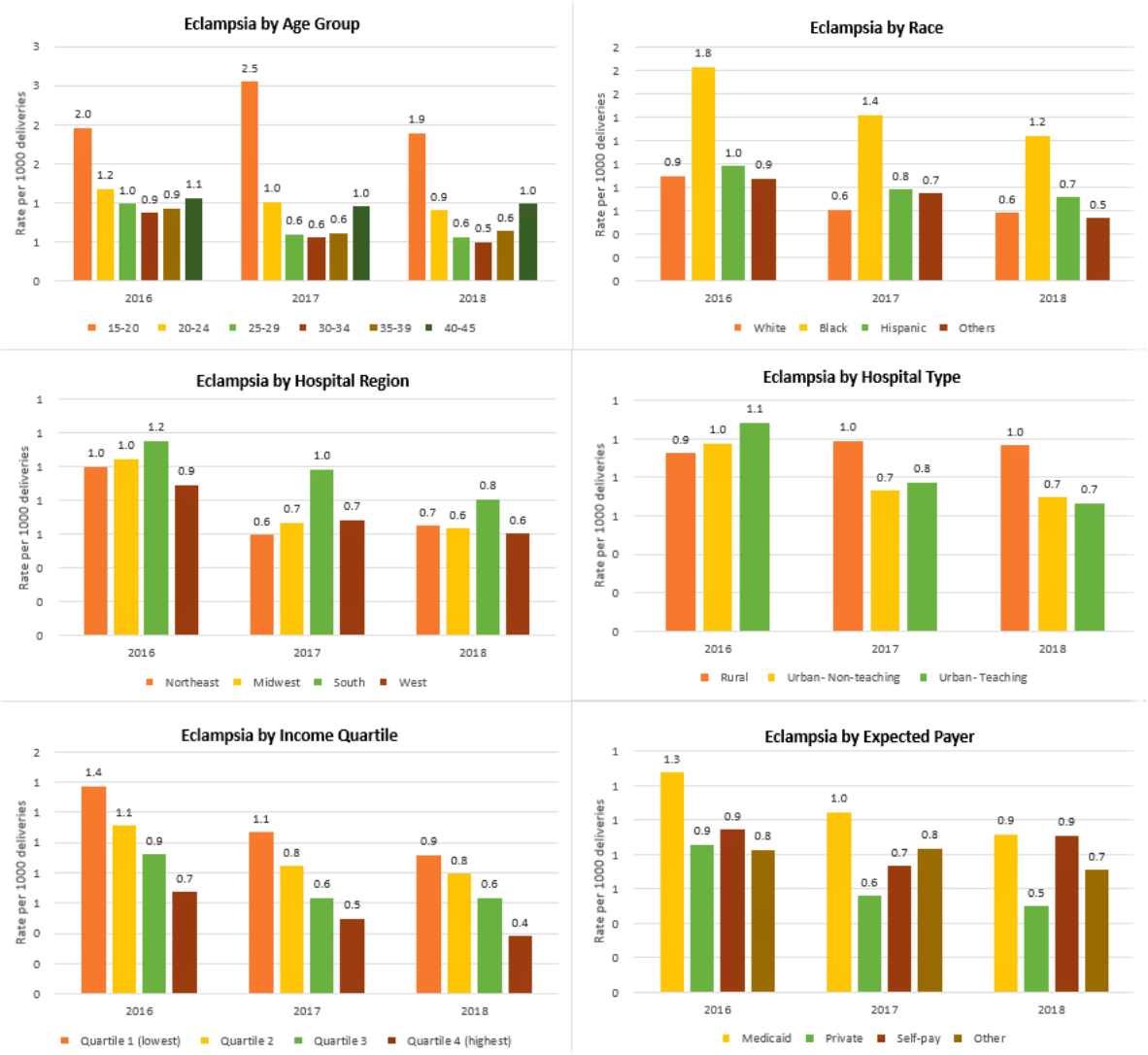


Figure 3.3 Incidence rates of eclampsia, by patients and hospital characteristics, from 2016 to 2018, United States



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APPENDIX A - Summary of The Literature Review

Study, Year	Study Design	Study Population	Data Source	Outcome, Covariate	Inclusion/ Exclusion Criteria	Key Findings	Limitations
Ananth et al (2013)	Cross-sectional hospital-based study	Women admitted to the US hospitals for delivery between 1980 – 2010, aged 18-23 y (n=6504)	National hospital discharge survey datasets, (1980-2010), USA	Outcome: mild and severe PE Covariates Maternal age Obesity (BMI>30) Smoking	Exclusion: Age ≥46 years. Women born before 1940 or during 1994 or later. Women with chronic HTN, chronic HTN with superimposed PE, and gestational HTN.	Prevalence rates of PE was 3.4%. Rates of severe PE have been increasing in the US and age-period-cohort effects all contribute to these trends. Although, increase in secular trend of obesity and declining smoking prevalence rates may drive these trends, changes in the diagnostic criteria of PE may have also contributed to these trends.	Geographic variation in the prevalence of PE was not considered in this study. Confounding by SES and behavioral factors was not considered and may have influenced the findings. The possibility of women being pregnant >1 over the study period was not considered. Some factors were poorly recorded, e.g., race/ethnicity
Wallis et al (2008)	Cross-sectional hospital-based study	Women admitted to the US hospitals for delivery between 1987 – 2004	National hospital discharge survey datasets, (1987-2004), USA	Outcome: PE, eclampsia, & GH Covariates Maternal age Geographic region	Inclusion: All hospital admissions for which a delivery of one or more live or stillborn occurred between 1987 and 2004.	A significant increase in the trend of GH and PE, the age-adjusted rate of GH rose by 186% (from 10.7% to 30.6%) and by 25% (from 23.6% to 29.4%) for PE over the 18-years study period. Eclampsia rate decreased by 22%. The study indicated that the youngest women (age < 20 years) and women from the south of the US were at significantly greater risk for all three outcomes.	Limitation related to NHDS data such as using solely ICD-9-CM odes to identify cases (PPV 74.4%), potential for underestimating of deliveries, the possibility of counting a single mother more than once, missing information on some of established covariates associated with PE, & limited sample size for eclampsia.
Kuklina et al (2009)	Cross-sectional hospital-based study	US women with delivery discharges between 1998-2006 in US hospitals (n=36,537,061)	Nationwide Inpatient Sample HCUP, (1998–2006)	Outcome: Severe obstetric complications, PE Covariates: ARF Pulmonary edema ARDS PCD DICS Ventilation Mortality	Exclusion: Non-delivery pregnancy outcomes, e.g., hydatidiform mole, ectopic pregnancy, abortion, and missing information. Historical condition or a "ruled out" condition (short LOS).	Prevalence of HDP increased from 67.2 in 1998 to 81.4 per 1000 deliveries in 2006. Prevalence of hospitalizations with severe PE ± eclampsia increased from 9.4 to 12.4 per 1,000 deliveries. The risk of severe obstetric complications among pregnant with severe PE ± eclampsia was 34.8 compared to 3.3 for hospitalized pregnant women without any hypertensive disorders, and 2.2 for GH compared to 1.4 for women without any HDP. Overall, hospitalizations with HDP were associated with 57% of hospitalizations with ARF, 27% with DICS, 30% ventilation, pulmonary edema, PCD, & ARDS.	Discharge-level data does not account for multiple delivery hospitalizations of the same women for one year. Limitation related to identification of HDP cases and severe complications based on ICD-9-CM codes, which vary in their accuracy; some studies showed high to moderate specificity but low sensitivity. Absence of information such as deliveries that occur outside hospitals (estimated <1%) and race.
Fingar et al (2017)	Cross-sectional hospital-	US women with	Nationwide Inpatient	Age, race, expected payer,	All delivery hospitalizations using the	Delivery hospitalization rate for PE/eclampsia in 2014 about 5%, a 21%	NIS data did not account for a patient's hospitalization for

	based study	delivery discharges between 2005–2014 in US hospitals (n=3,796,490)	Sample HCUP, (2005–2014)	community income, residence' s location, hospital region, LOS, cost per stay)	DRG and ICD-9-CM diagnosis codes	increase from 2005. Compared with other deliveries, a higher percentage of those with PE/eclampsia were among women who were the youngest, the oldest, black, and from the poorest areas and the South, and LOS were 70% higher.	more than one delivery. Limitation related to identification of HDP cases and based on ICD-9-CM codes, with high to moderate specificity but low sensitivity. Missing information regarding deliveries outside hospitals (<1%) and race (<5%).
Paré et al (2014)	Prospective cohort study	Women were recruited from the obstetric population at 3 large urban academic centers, 2 in Boston and 1 in Philadelphia, October 2006 to August 2008	The BIRTH (BIomarkers Related To HTN in pregnancy) study designed to prospectively collect serum for biomarkers and clinical information to assess in predicting or diagnosing PE	Outcome: PE Covariates: Maternal age, Smoking, Chronic HTN, Pregestational DM Multiple gestation AA race Prior PE Nulliparity Assisted reproductive techniques BMI	Women were eligible for the birth study if they were ≥ 16 years, presented for prenatal care before 15 weeks of gestation, and carried three or fewer fetuses	Among the 2637 women; 9% had PE Risk Factor aOR Risk Factor aOR Chronic hypertension 2.7 ART 1.7 Gestational diabetes 3.9 BMI 25-30 1.7 Multiple gestation 3.0 BMI 30-35 2.3 AA race 1.9 BMI 34-40 3.6 Prior preeclampsia 3.6 BMI >40 6 **Advanced maternal age** was not significant RF. - Similar associations were found for severe PE. - A dose–response effect was observed in the relationship between BMI and both PE and severe PE. - The most significant risk factor for both PE and severe PE were **being overweight or obese** with an attributable risk percent of 65% and 64%, respectively.	The possibility of unmeasured confounding factors that could influence the relationship between the various risk factors and PE. The small number of women developed early PE limiting the power to detect significant associations.
Direkvand-Moghadam et al (2012)	Cross-sectional hospital-based study	All the pregnant women that were referred to the hospital in Iran, from May 2010 to September 2010 (n=610)	Data collected by a face-to-face interview	Outcome: PE Covariates: Education History of PE, HTN, or infertility	Include all pregnant women referred to the hospital of Ilam in the west of Iran during the 5 months study period, except case with abortion.	Prevalence of PE was 9.5%. Three predictors (history of PE, HTN, and infertility) were significant predictor for PE with an increased ORs.	The study did not account for the possible confounder such as the SES characteristics of participants. Possibility of selection bias due to hospital-based study, measurement bias and recall bias during data collection, and external validity issue as the population sample study focused on Iranian women in certain geographic area

*HTN: hypertension; GH: gestational hypertension; PE: preeclampsia; SES: socioeconomic status; LOS" lengths of stay; HCUP: Healthcare Cost and Utilization Project; ARF: acute renal failure; ARDS: adult respiratory distress syndrome; PCD; puerperal cerebrovascular disorder; DICS; disseminated intravascular coagulation syndrome; BMI: body mass index; DM: diabetes; OR: odds ratio; AA: African American; ART: assisted reproductive techniques.

APPENDIX B – ICD 10 and DRG codes

Table A. Codes defining delivery hospitalizations.

ICD-10-CM code	**Description**
Z37x	Outcome of delivery
O80	Encounter for full-term uncomplicated delivery
O82	Encounter for cesarean delivery without indication
DRG* codes	**Description**
765	Cesarean section with complicating conditions/major complicating conditions
766	Cesarean section without complicating conditions/major complicating conditions
767	Vaginal delivery with sterilization and/or dilation and curettage
768	Vaginal delivery with operating room procedure except for sterilization and/or dilation and curettage
774	Vaginal delivery with complicating diagnoses
775	Vaginal delivery without complicating diagnoses

Table B. ICD-10-CM diagnosis codes defining gestational hypertension, preeclampsia, and eclampsia.

ICD-10-CM code	**Description**
O13x	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14x	Preeclampsia
O15x	Eclampsia

Table C. ICD-10-CM diagnosis codes defining preexisting conditions.

ICD-10-CM code	**Description**	**Condition**
D50x-D53x	Nutritional anemias	Anemia
D55x-D59x	Hemolytic anemias	
D60x-D64x	Aplastic and other anemias and other bone marrow failure syndromes	
O24.4x	Abnormal glucose tolerance	Gestational diabetes
O24.0x	Pre-existing type 1 diabetes mellitus, in pregnancy, childbirth and the puerperium	Pregestational diabetes
O24.1x	Pre-existing type 2 diabetes mellitus, in pregnancy, childbirth and the puerperium	
O24.3x	Unspecified pre-existing diabetes mellitus in pregnancy, childbirth and the puerperium	

O24.8x	Other pre-existing diabetes mellitus in pregnancy, childbirth, and the puerperium	
O24.9x	Unspecified diabetes mellitus in pregnancy, childbirth and the puerperium	
O30x	Multiple gestation	Multiple gestations
Z372	Twins, both liveborn"	
Z373	Twins, one liveborn and one stillborn"	
Z374	Twins, both stillborn"	
Z3750	Multiple births, unspecified, all liveborn"	
Z3751	Triplets, all liveborn"	
Z3752	Quadruplets, all liveborn"	
Z3753	Quintuplets, all liveborn"	
Z3754	Sextuplets, all liveborn"	
Z3759	Other multiple births, all liveborn"	
Z3760	Multiple births, unspecified, some liveborn"	
Z3761	Triplets, some liveborn"	
Z3762	Quadruplets, some liveborn"	
Z3763	Quintuplets, some liveborn"	
Z3764	Sextuplets, some liveborn"	
Z3769	Other multiple births, some liveborn"	
Z377	Other multiple births, all stillborn"	
E66x	Overweight and obesity	Obesity
E02	Subclinical iodine-deficiency hypothyroidism	Hypothyroidism
E03x	Other hypothyroidism	
M32x	Systemic lupus erythematosus	SLE
D68.61	Antiphospholipid syndrome	Antiphospholipid syndrome
D68.5x	Thrombophilia	Thrombophilia
N00x-N08x	Glomerular diseases	Renal disease
N10x-N16x	Renal tubulo-interstitial diseases	
N17x-N19x	Acute kidney failure and chronic kidney disease	
F10x	Alcohol related disorders	Alcohol related disorders
F17x	Nicotine dependence	Nicotine dependence

CURRICULUM VITAE

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EDUCATION

University of Louisville / School of Public Health and Information Sciences — Louisville, KY
Doctor of Philosophy (PhD) / Epidemiology — 2017 – 2023

University of Louisville / School of Public Health and Information Sciences — Louisville, KY
Master of Public Health (MPH) / Biostatistics Concentration — 2014 – 2016

University of Baghdad, College of Medicine — Baghdad, Iraq
Doctor of Medicine (MD) — 1997 – 2004

WORK EXPERIENCE

Norton Healthcare / Norton Children's Research Institute, affiliated with University of Louisville School of Medicine / CAHRDS — Louisville, KY
Biostatistician, *Sarah Deans, RN, BSN, CCRC* — 2021 – present
Work with clinical investigators on different health research areas to help in optimize research design, data management, plan and implement multiple statistical analysis, interpreting the results and draw conclusion.

University of Louisville / Pediatric department - CAHRDS — Louisville, KY
Biostatistician II, *Deborah W Davis, PhD* — 2017 – 2021
Work with clinicians and biomedical investigators on different health study areas from initial developing objectives, help in optimize research design, data management, plan and perform statistical analysis, to interpreting the results and finalizing a report.

University of Louisville — Louisville, KY
Biostatistician Volunteer, *Arnold Schecter, MD, MPH* — 2015 – 2017
Worked on data analysis "Biomonitoring of Organohalogen Compounds and Metals in Vietnamese Female Electronic Waste Recyclers". My role as biostatistician includes data management, study design and perform statistical analysis, interpreting the results and writing method and result section in the manuscripts and the posters of each project.

University of Louisville / Cardiothoracic Surgery — Louisville, KY
Research Assistant, *Jaimin Trivedi, MD, MPH* — 2016
Worked on a project involving HCUP DATA to evaluate outcomes patients undergoing re operative coronary revascularization, data management and implementing statistical analysis and interpreting the results.

Various Health Clinics — Louisville, KY
Clinical Intern — 2009 – 2016
Exposed to a wide variety of pediatrics and adult outpatient and urgent care cases. Observed and participate

in taking history and physical examinations along side with attending physician. Participate in patients counseling. Discussed differential diagnoses, management plan and follow up with the attending physician and participated in scientific discussion.

The Specialty Hospital Amman, Jordan
Pediatric Resident 2006 – 2008
Provided and managed direct patient care, including history, physical examinations, evaluations, assessments, diagnoses, treatment and follow up in all pediatric departments. Performed and participated in several clinical procedures.

Ministry of Health / Iraqi's Hospitals Babylon, Iraq
Physician Resident 2004 – 2005
Equivalent to the United Kingdom Foundation Training (FY). Residency rotations in internal medicine, psychiatry, surgery, obstetrics and gynecology, pediatrics, and other specialties. Duties included clinical evaluation of patients on admission, performing history and physical exams, ordering required diagnostic tests, interpretation of lab results, performing bedside procedures, assisting in surgeries, documentation of clinical notes, participating in daily rounds and structured educational activities, managing patients on inpatient and outpatient settings, and planning and follow-up of patient management.

Ministry of Health / Martyr Sadr Hospital Baghdad, Iraq
Area of Need Primary Care Physician 2004
Provided primary care for disadvantaged population in Baghdad suburban area.

FUNDED RESEARCH

NICHD (IDeA State Grant); *Sullivan/Watson (Co-PI's*) 01/2019 – present
IDeA State Network Grant: The Kentucky Pediatric Clinical Trials Rural/Urban Partnership
The goal of this grant is to provide medically underserved/rural populations access to state-of-the-art clinical trials, applying findings from relevant pediatric cohort studies to children in IDeA states, and building pediatric research capacity at a national level; and providing professional development to train the next generation of clinician scientists.

Merck MCO (Medicaid Match); *Wattles (PI)* 12/2020 – present
The impact of a provider feedback intervention on inappropriate antibiotic prescribing in Kentucky children. The primary objective is to evaluate the impact of provider feedback on inappropriate antibiotic prescribing in Kentucky children. The secondary objective is to assess the feasibility of collaboration between antimicrobial stewardship clinicians and Medicaid to design and distribute provider feedback reports.

KY State Partnership (Medicaid); *Davis (PI)* 07/2016 – 06/2022
Safeguarding Medication Use and Improving Care Delivery for Children Receiving Kentucky Medicaid. The purpose of this project is to plan interventions to reduce the prescribing of various classes of medication and improve health care quality for children receiving Kentucky Medicaid.

Merck COVID; *Wattles (PI)* 12/2020 – 06/2022
Changes in Pediatric Outpatient Antibiotic Prescribing Practices Through the COVID-19 Pandemic and Associated Telehealth Visits: A Historical Control Study. Objectives are to (1) Describe pediatric outpatient visits and antibiotic prescribing during the COVID-19 pandemic and a corresponding time period in 2019; (2) Compare the quality of pediatric antibiotic prescribing in telehealth visits to in-person visits; and (3) Generate factors associated with inappropriate prescribing in telehealth visits and targets to guide future interventions.

America Diabetes Association; *Watson (PI)* 2018 – 2019
Impact of Distance to Pediatric Diabetes Center on Outcomes in Youth with Type 1 Diabetes. Funding Agency: JAEB Center for Health Research.

Kentucky Medicaid; *Eastep (PI)* 01/2018 – 12/2018
Trends in Prescription Opioid Patterns Among Children Enrolled in Kentucky Medicaid: A Review From 2012 to 2016. Funding Agency: AMA.
FOCUS / GILEAD; *Espinosa (PI)* 03/2018 – 06/2019
Hepatitis C in adults: screening and linkage to care.

PUBLICATIONS / PRESENTATIONS

Peer Reviewed Journals

Wattles BA, Feygin Y, **Jawad KS**, … Smith MJ. Use of the Child Opportunity Index to Examine Racial Variations in Outpatient Antibiotic Prescribing to Children. J Pediatr. 2023 Jun 19:113572. doi: 10.1016/j.jpeds.2023.113572. Epub ahead of print. PMID: 37343705.

Van Hersh, A., **Jawad, K**., Feygin, Y., Johnsrude, C., Dasgupta, S., Significance of electrocardiogram abnormalities in children presenting to the emergency department with acute COVID-19 infection. The American Journal of Emergency Medicine, 2023. 71: p. 195-199.

Le, J., **Jawad, K**., Feygin, Y., Lohr, W.D., Creel, L., Jones, V.F., Schultz, K.V., Stevenson, M.D., Kong, M., Davis, D.W. (2022). Examination of U.S. national rates of emergency department visits and hospitalizations for depression and suicidal behaviors after the release of the 13 Reasons Why Netflix series by demographic characteristics, Journal of Affective Disorders, 311, 508–514. https://doi.org/10.1016/j.jad.2022.05.116.

Davis, D.W., **Jawad, K.,** Lohr, W.D., Trace, M., Le, J., Feygin, Y., and Jones, V.F. (Accepted). First-line Behavioral Health Treatment Prior to Stimulant or Alpha-2 Agonist Use for Preschoolers on Kentucky Medicaid in 2017 (Journal of Attention Disorders, Accepted December 3, 2022).

Wattles, B, Feygin, Y., **Jawad, K.,** Stevenson, M.D., Vidwan, N.K., Blatt, D.B, Davis, D.W., Creel, L., Porter, J., Jones. V.F., and Smith, M.J. (Submitted). Use of the Child Opportunity Index to Examine Racial Variations in Outpatient Antibiotic Prescribing to Children (Journal of Pediatrics, Submitted December 2022)

Fallat ME, Treager C, Humphrey S, **Jawad K**, et al. A Novel Approach to Assessment of US Pediatric Trauma System Development. *JAMA Surg*. Published online September 21, 2022. doi:10.1001/jamasurg.2022.4303

Wattles BA, Vidwan NK, Feygin Y, **Jawad KS**, Creel LM, Smith MJ. Antibiotic prescribing to Kentucky Medicaid children, 2012-2017: Prescribing is higher in rural areas. J Rural Health. 2022 Mar;38(2):427-432. doi: 10.1111/jrh.12584. Epub 2021 May 12. PMID: 33978987.

Robert Clemons, Maiying Kong, **Kahir Jawad**, Yana Feygin & Kerry Caperell (2022) The Impact of Converting a Power Plant from Coal to Natural Gas on Pediatric Acute Asthma, Journal of Asthma, DOI: 10.1080/02770903.2021.2022159

Wattles, B., **Jawad, K.**, Feygin, Y., Kong, M., Vidwan, N., Stevenson, M., & Smith, M. (2021). Inappropriate outpatient antibiotic use in children insured by Kentucky Medicaid. Infection Control & Hospital Epidemiology, 1-7. doi:10.1017/ice.2021.177

Davis DW, **Jawad K**, Feygin Y, Creel L, Kong M, Sun J, Lohr WD, Williams PG, Le J, Jones VF, Trace M, Pasquenza N. Disparities in ADHD Diagnosis and Treatment by Race/Ethnicity in Youth Receiving Kentucky Medicaid in 2017. Ethn Dis. 2021 Jan 21;31(1):67-76. doi: 10.18865/ed.31.1.67. PMID: 33519157; PMCID: PMC7843039.

Wattles BA, **Jawad KS**, Feygin Y, et al. 1333. A Cross-Sectional Analysis of Inappropriate Outpatient Antibiotic Use in Children Insured by Kentucky Medicaid. Open Forum Infect Dis. 2020;7(Suppl 1):S678. Published 2020 Dec 31. doi:10.1093/ofid/ofaa439.1515.

Montgomery EL, **Jawad KS**, Eubanks S, Wintergerst KA, Rush HM, Watson S, 920-P: Continuous Glucose Monitor Utilization and Adherence in Children with Type 1 Diabetes. Diabetes, 2020. 69(Supplement 1): p. 920-P.

Davis DW, Feygin Y, Creel L, Kong M, **Jawad K**, Sun J, Blum NJ, Lohr WD, Williams PG, Le J, Jones VF, Pasquenza N. Epidemiology of Treatment for Preschoolers on Kentucky Medicaid Diagnosed with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2020 Sep;30(7):448-455. doi: 10.1089/cap.2020.0015. Epub 2020 Jun 30. PMID: 32614247.

Davis DW, Feygin Y, Creel L, Williams PG, Lohr WD, Jones VF, Le J, Pasquenza N, Ghosal S, **Jawad K**, Yan X, Liu G, McKinley S. Longitudinal Trends in the Diagnosis of Attention-Deficit/Hyperactivity Disorder and Stimulant Use in Preschool Children on Medicaid. J Pediatr. 2019;207:185-191.e1. doi:10.1016/j.jpeds.2018.10.062

Watson, S., **Jawad, K. S.**, Rodriguez, M. A., & Wintergerst, K. A. (2019, June 1). 1372-P: Impact of Distance to Pediatric Diabetes Center on Outcomes in Youth with Type 1 Diabetes. Diabetes 2019 Jun; 68(Supplement 1): https://doi.org/10.2337/db19-1372-P.

Conference Presentation

Davis, D.W., **Jawad, K.**, Feygin, Y., Stevenson, M., Wattles, B., Porter, J., and Jones, V.F. Measuring the impact of neighborhood disadvantage on child health outcomes: All tools are not equal. Poster presentation at the annual conference for the Society for Research in Child Development, March 23-25, 2023, Salt Lake City, UT.

Van Hersh A, **Jawad K**, Feygin Y, Johnsrude C, Dasgupta S. Electrocardiogram Abnormalities in Patients with Acute covid-19 Infection: What Is Its Significance? Poster presented at: American Academy of Pediatrics (AAP) Annual Meeting; October 2022; Anaheim, CA. https://www.eventscribe.net/2022/AAPexperience/searchbyposterbucket.asp?f=PosterSessionName&pfp=PosterSessionName

Porter J, **Jawad K**, Davis D, Jones V, Feygin Y. Parents' Perceptions of Medical Provider Encounters and Access to Care by Race/ethnicity from the National Survey of Children's Health. Poster presented at: American Academy of Pediatrics (AAP) Annual Meeting; October 2022; Anaheim, CA. https://www.eventscribe.net/2022/AAPexperience/searchbyposterbucket.asp?f=PosterSessionName&pfp=PosterSessionName

Jawad K, Feygin Y, .., Davis D. Disparities in Rates of ADHD Diagnosis and Treatment by Race/Ethnicity in Youth Receiving Kentucky Medicaid in 2017.Poster presented at: Academy Health Annual Meeting; June 2019; Washington, DC. https://academyhealth.confex.com/academyhealth/2019arm/meetingapp.cgi/Session/21684

Burton, C., Furlong-Dillard, J., **Jawad, K.**, Feygin, Y., Berkenbosch, J., Tzanetos, D., (Sept 2019). A Descriptive Analysis of Viscoelastic Testing in Pediatric Ecmo Patients Using The Pediatric Ecmo Outcomes Registry. 30th Annual ELSO Conference

Myers, J., **Jawad, K.**, Feygin, Y., Creel, L., Espinosa, C., Kong, M., Duncan, S. (May 2017). Social Inequality's Impact on the Rate of Neonatal Abstinence Syndrome among Low-Income Children. Poster presented at: Pediatric Academic Societies Meeting; Toronto, Canada.

Woods, A., **Jawad, K.**, Myers, J., Creel, L., Woods, C. (May 2017). Characteristics of Orbital Cellulitis Hospitalizations in Children, United States, 2003 – 2012. Poster presented at: Pediatric Academic Societies Meeting; Toronto, Canada.

Schecter, A., Kincaid, J., Quynh, H.T.,…, **Jawad, K.**, Rashid, S., Birnbaum, L.. (August, 2016). Exposures and Health Issues of Vietnamese Female Electronic Waste Recycling Workers. Poster presented at: Dioxin 2016 Annual Meeting; Florence, ITA.

Schecter, A., Quynh, H.T., Kincaid, J., **Jawad, K.**,…, Birnbaum L. (March, 2016). Biomonitoring of Organohalogen Compound and Metals in Vietnamese Female Electronic Waste Recyclers. Poster presented at: 2016 Society of Toxicology Annual Meeting; New Orleans, LA, USA.