A review of the risk factors of pre-eclampsia and examination of the association of racism and discrimination in disparities of hypertensive disorders of pregnancy using multi-state PRAMS data

By

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official position of the Centers for Disease Control and Prevention. While I mention women and mothers often in this thesis, I acknowledge that genders other than those who identify as women may be affected by what is discussed.

Table of Contents

List of Tables

List of Illustrations

CHAPTER 1: PRE-ECLAMPSIA: A REVIEW OF RISK FACTORS AND CURRENT APPROACHES TO SCREENING IN ALL SETTINGS

A portion of Chapter 1 has been published as a review article.

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1.1 Abstract

Most of maternal deaths are preventable, and one-quarter of maternal deaths are due to pre-eclampsia and eclampsia. Prenatal screening is essential for detecting and managing pre-eclampsia. However, pre-eclampsia screening is solely based on maternal risk factors and has low (<5% in the U.S.) detection rates. This review looks at pre-eclampsia from engineering, public health, and medical points of view. First, pre-eclampsia is defined clinically, and the biological basis of established risk factors are described. The multiple theories behind pre-eclampsia etiology should serve as the scientific basis behind established risk factors for pre-eclampsia; however, African American race does not have sufficient evidence as a risk factor. We then briefly describe predictive statistical models that have been created to improve screening detection rates, which use a combination of biophysical and biochemical biomarkers, as well as aspects of patient medical history as inputs. Lastly, technologies that aid in advancing pre-eclampsia screening worldwide are explored.

The review concludes with suggestions for more robust pre-eclampsia research, including diversifying study sites, improving biomarker analytical tools, and for researchers to consider studying patients before they become pregnant to improve pre-eclampsia detection rates. Additionally, researchers must acknowledge the systemic racism involved in using race as a risk factor and include qualitative measures in study designs to capture the effects of racism on patients.

1.2 Lay summary

Pre-eclampsia is a pregnancy-specific hypertensive disorder that can affect almost every organ system and complicates 2-8% of pregnancies globally. Here, we focus on the biological basis of the risk factors that have been identified for the condition. African American race currently does not have sufficient evidence as a risk factor and has been

poorly studied. Current clinical methods poorly predict a patient's likelihood of developing pre-eclampsia, thus researchers have made statistical models that are briefly described in this review. Then, low-cost technologies that aid in advancing pre-eclampsia screening, and the review ends with suggestions for research direction to improve pre-eclampsia screening in all settings.

Overall, we suggest that the future of pre-eclampsia screening should aim to identify those at risk before they become pregnant. We also suggest that the clinical standard of assessing patient risk solely on patient characteristics needs to be reevaluated, that study locations of pre-eclampsia research need to be expanded beyond a few high-income countries, and that low-cost technologies should be developed to increase access to prenatal screening.

1.3 Introduction

Pre-eclampsia is a pregnancy-specific hypertensive disorder that can affect almost every organ system [1]. The condition complicates 2-8% of pregnancies globally [2]. New-onset of hypertension after 20 weeks of gestation and/or protein present in the urine (proteinuria) are markers of the condition. Additionally, pre-eclampsia is diagnosed by fetal growth restriction and if proteinuria is absent: new-onset dysfunction with the liver, brain, kidneys, red blood cells, and platelets [2]–[4]. One serious manifestation of pre-eclampsia is HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) and is associated with increased rates of maternal morbidity and mortality [2], [4]. Another manifestation of hypertensive disorders of pregnancy is eclampsia, which is convulsions not due to any other conditions such as epilepsy. Pre-eclampsia does not necessarily lead directly to eclampsia, as studies have shown that some patients have seizures without prior documentation of the diagnosis of hypertension or proteinuria [2]. Symptoms of pre-

eclampsia will cease (in most cases) after delivery which, the only “cure” for the condition [5].

Prenatal visits are vital to saving lives [6], and the high rates of maternal mortality worldwide would be partially preventable if access to timely care was available, especially for adverse pregnancy outcomes such as hypertensive disorders [7], [8]. Hypertensive disorders in pregnancy, such as pre-eclampsia, are a leading cause of maternal mortality [5], [7] and evaluation of patient risk factors are the sole clinically-accepted method of screening for the risk of pre-eclampsia development [2], [4]. However, this method has been shown to have low detection rates for those who actually develop the condition [9], [10]. The future of prenatal care will likely involve adoption of a mixture of virtual and in-person consultations [11], with the frequency based on patient risk [12], [13]. In order to properly allocate time and resources to this imminent change, it is necessary to review the biological basis of risk factors as related to updated theories of pre-eclampsia etiology and to identify opportunities for low-cost and/or at-home technologies for prenatal management. Additionally, since there is no treatment for pre-eclampsia besides delivery [5], it is important to consider focusing research efforts to aspire to evaluate patient risk before they become pregnant.

This review begins by clinically defining pre-eclampsia and discussing the treatment and management of the condition. Then, the molecular pathophysiology of placentation and the maternal immune response during this process is explained. An updated two-stage model of the etiology of pre-eclampsia is detailed, along with the biological basis of the risk factors that have been identified for the condition in different regions. Biomarkers of pre-eclampsia are highly debated, and here the most recent statistical models, circulating biochemical factors, and biophysical markers are discussed. Then, low-cost technologies developed for pre-eclampsia screening are highlighted to show that more

rigorous prenatal screening has the potential to occur in low-resource settings. The review ends with suggestions for more robust pre-eclampsia research to improve pre-eclampsia screening in all settings and to consider a focus on preconception risk analyses.

1.4 Clinical identification and classification of pre-eclampsia

Hypertension is defined as systolic blood pressure more than 140mmHg or diastolic blood pressure of 90mmHg. Proteinuria, which not all individuals present with, is a sign of multi-organ involvement and is defined by 300mg/dL of protein or more in a 24-hour urine collection or a protein-to-creatine ratio of 0.30 or more [2]. Additionally, pre-eclampsia is diagnosed by fetal growth restriction and if proteinuria is absent: new-onset dysfunction with the liver, brain, kidneys, red blood cells, and platelets [2]–[4]. The condition had previously been defined as mild or severe, in which mild pre-eclampsia was new-onset hypertension with proteinuria and severe pre-eclampsia was mild pre-eclampsia with an adverse feature (higher blood pressure of 160-170/ 100-110mmHg, higher proteinuria of 3g/day, and/or headache) [14]. However, it is recommended that pre-eclampsia not be distinguished into mild versus severe, as the condition can become severe in any case [4]. Instead, the condition is described as pre-eclampsia with and without severe features, as of 2019 [2]. Pre-eclampsia with severe features indicates a worsening of the multi-organ symptoms and/or nonresponse to medication [2].

For research and scientific publications' purposes, Dadelszen, Magee, and Roberts (2003) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) suggest that researchers should account for gestational age when classifying pre-eclampsia by distinguishing between early-onset versus late-onset pre-eclampsia [4], [14], [15]. Early-onset preeclampsia is usually defined as the development of pre-eclampsia before 34 weeks of gestation, and late-onset is the development of the condition at or after 34 weeks of gestation. The authors stated this distinction was important to make because

it has been shown that there are differences in the pathophysiology, maternal morbidity and mortality, and risk of future disease between the two onset points [14], [16]. Early-onset preeclampsia is considered a fetal disorder that is associated with placental dysfunction, reduction in placental volume, intrauterine growth restriction (IUGR), multiorgan dysfunction, perinatal death, and adverse maternal and neonatal outcomes, and abnormal uterine Doppler evaluation. Late-onset pre-eclampsia is considered a maternal disorder and is associated with normal and/or more favorable outcomes than early-onset pre-eclampsia [17]. In this review, the terms early-onset and late-onset will be used.

One serious manifestation of pre-eclampsia is HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) and is associated with increased rates of maternal morbidity and mortality [2], [4]. Another manifestation of hypertensive disorders of pregnancy is eclampsia, which is convulsions not due to any other conditions such as epilepsy. Pre-eclampsia does not necessarily lead directly to eclampsia, as studies have shown that some patients have seizures without prior documentation of the diagnosis of hypertension or proteinuria [2]. Symptoms of pre-eclampsia will cease (in most cases) after delivery which, the only “cure” for the condition [5].

After developing pre-eclampsia during pregnancy, the risk for pre-eclampsia in subsequent pregnancies is increased [18], and in the long-term cardiovascular-related morbidity, renal disease, metabolic syndrome, and neurological issues risk increases [1], [18]–[21]. It appears that the increased risk of these conditions is dependent upon severity of pre-eclampsia during pregnancy, prevalence of recurrent pre-eclampsia [22], and gestation age at onset [19]. In addition to an increased risk, onset of cardiovascular diseases occurs prematurely at a younger age [18]. It is not yet clear if pre-eclampsia and

other adverse pregnancy outcomes causes these morbidities or if they merely “uncover” them [21], [23].

1.4.1 Treatment and management options for pre-eclampsia

Generally, to manage pre-eclampsia, patients will be monitored either through self-monitoring or through in-clinic monitoring when presenting with severe features. Additionally, patients will be subject to increased blood pressure monitoring, ultrasonography for fetal growth and placental blood flow, laboratory tests for pre-eclampsia, and other tests deemed necessary by the physician [2]. Aspirin has been studied as a potential treatment option to reduce symptoms of severe preeclampsia and has been shown to be effective when given in low doses before 16 weeks gestation to patients that are at high to moderate risk [2]–[4]. These treatment suggestions are for ideal situations, and for lower resource settings, it is suggested that patients be referred to centers for appropriate care [4].

1.5 Molecular physiology of early placental development

The underlying pathophysiology of pre-eclampsia has not been fully established. However, the general themes of the multiple theories center around abnormal placentation and the maternal inflammatory response. Before delving into the specific theories, it is important to describe the placentation process and the general maternal inflammatory response.

1.5.1 Blastocyst implantation, trophoblast invasion, placental blood flow

Once an oocyte is fertilized by a sperm, a zygote is formed (Figure 1). The zygote will undergo a series of cell divisions until it becomes a blastocyst within 5 days post-fertilization. The blastocyst contains two main cell types: the inner cell mass, which will produce the embryo, and the trophectoderm, which will form trophoblasts. Trophoblasts will become the placenta, and the inner cell mass will differentiate into the ectoderm,

endoderm, and mesoderm to eventually become the fetus. Six or seven days after fertilization, the blastocyst will implant into the endometrium, the innermost lining of the uterus. Implantation occurs in three phases, with the first being apposition – the initial contact of the blastocyst with the decidua, a modified endometrium of pregnancy. Decidualization of the endometrium begins shortly after ovulation [24] and is regulated by estrogen, progesterone, androgens, and, if fertilization occurs, factors secreted by the implanting blastocyst. In addition, the decidua produces factors that modulate immune and vascular cell functions within the maternal-fetal microenvironment. Apposition is controlled by hormonal signaling between the decidua and the trophectoderm [25].

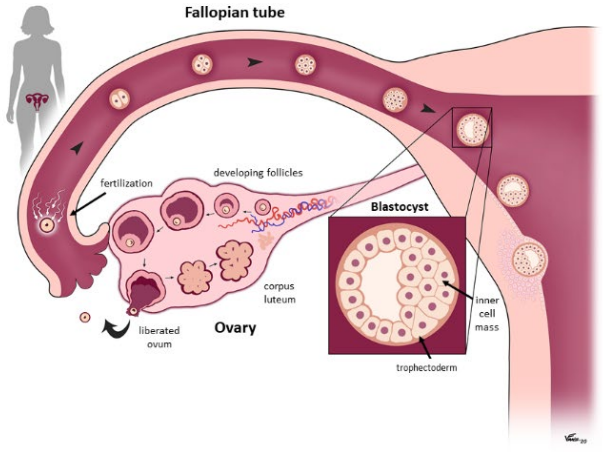

Figure 1: Blastocyst formation. *The cycle of follicle development is depicted which leads to a liberated ovum. The remaining cells of the follicle become the corpus luteum. For pregnancy to occur the ovum is fertilized in the fallopian tube and the zygote is formed, which undergoes a series of cell divisions to become the blastocyst. The blastocyst contains the trophectoderm, which will become the placenta, and the inner cell mass, which will eventually become the fetus.*

The second phase of implantation is adhesion, which is increased physical contact between the decidua and the blastocyst. For successful adhesion, the endometrium must be primed with estrogen and progesterone by the corpus luteum (Figure 1), the transient

endocrine organ that contains cells remaining of the follicle after an oocyte is released from it during ovulation [25]. During its growth phase, the corpus luteum doubles in size quickly (8-10 days in mammals) due to tissue growth and rapid angiogenesis [26]. Inflammatory cells and angiogenic molecules such as leukocytes, neutrophils, eosinophils, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and hypoxia-inducible factor (HIF) promote angiogenesis in the corpus luteum [27]. If fertilization does not occur, the corpus luteum will undergo apoptosis. On a cellular level, integrins called cellular adhesion molecules mediate adhesion between the blastocyst and the decidua. This receptivity of the decidua is limited to days 20-24 of the menstrual cycle, as after day 24, the cell-cell interaction proteins become antiadhesive [25].

Trophoblast invasion is the last phase of implantation (Figure 2). Primitive trophoblast cells originate from the trophectoderm of the blastocyst and initiate invasion into the surface of the endometrium. These primitive trophoblast cells, cytotrophoblasts and syncytiotrophoblasts, differentiate into villous and extravillous trophoblasts after implantation. Villous trophoblasts form chorionic villi which transport oxygen, nutrients, and other molecules between the mother and developing fetus. The villi consist of a core of cytotrophoblast and an outer layer of syncytiotrophoblast that is directly in contact with maternal blood flow [28]. Anchoring villi, specifically provide mechanical stability to the placenta at the maternal-fetal interface. Extravillous trophoblasts, which are preceded by cytotrophoblasts, penetrate the maternal vasculature (spiral arteries), decidua, and myometrium and are highly invasive in the first trimester. This invasion occurs in hypoxic conditions, and invasive trophoblasts secrete proteolytic enzymes that digest the extracellular matrix in the decidua [25], [28]. Extravillous trophoblasts are further classified into interstitial extravillous trophoblasts, which invade the decidua and surround spiral

arteries, and endovascular extravillous trophoblasts, which invade and transform the spiral arteries (Figure 3) [25].

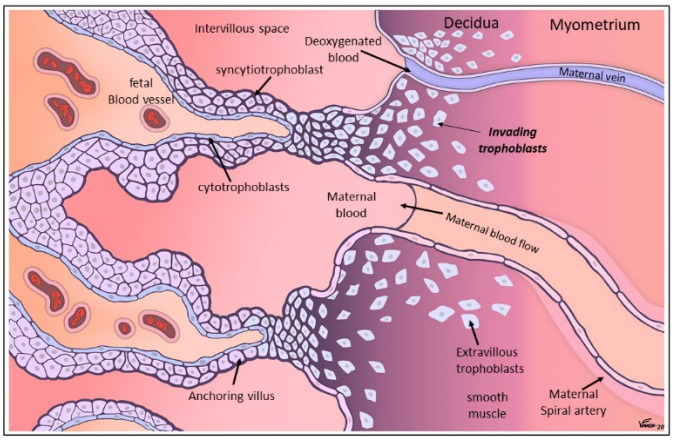

Figure 2: Trophoblast invasion during early implantation. *At the placental-maternal interface cytotrophoblasts and syncytiotrophoblasts (left) from the developing placenta invade the decidual and myometrial layers of the uterus (right). Cytotrophoblasts differentiate into extravillous trophoblasts which invade the vasculature, spiral arteries, and myometrium. Anchoring villi transport oxygen, nutrients, and other molecules from the mother to the developing fetus and contain a core of cytotrophoblasts and an outer layer of syncytiotrophoblasts. Blood flows from the spiral arteries into the intervillous space, where nutrient exchange is facilitated by villi. Deoxygenated blood will flow through maternal veins.*

Human chorionic gonadotropin (hCG), the hormone used to test for pregnancy clinically, is produced by the syncytiotrophoblast and is responsible for maintaining the corpus luteum. The corpus luteum produces progesterone to support placental development until around the 10th week of gestation when the placenta has taken over, termed the luteal-placental shift [29]. Relaxin, another important hormone, is secreted by the corpus luteum and has recently emerged as important for promoting renal vasodilation and reducing systemic vascular resistance in pregnancy. Thus, during normal pregnancy blood circulation is a low pressure and low resistance system [30], [31].

The spiral arteries, which are found in the uterus, are extensively remodeled during placental development. They are modified by two types of extravillous trophoblasts that first form cellular plugs, possibly to manage forceful blood flow into the intervillous space to protect the embryo [32]. Then, the extravillous trophoblasts destroy vascular endothelium, causing fibrinoid material to replace smooth muscle and connective tissue of the vessels (the spiral arteries later regenerate endothelium). During normal pregnancy, the luminal diameters of the spiral arteries increase 5-10-fold (Figure 3). This is necessary to reduce the velocity of uterine blood flowing into the intervillous space, to not damage the placental villi, and increase time for oxygen extraction. Smooth muscle and the capacity contract due to certain signals are lost in the decidua and inner third of the myometrium as well [33]. Blood flow to the placenta is critical for fetal growth and transport of gases such as oxygen and nutrients like glucose. Approximately 1 month after conception maternal blood flows into the intervillous space, bathes the villi and drains through decidual veins; thus, blood flow must be controlled such that the villi are not damaged. The syncytiotrophoblast-lined villi increase the surface area for nutrient absorption [34].

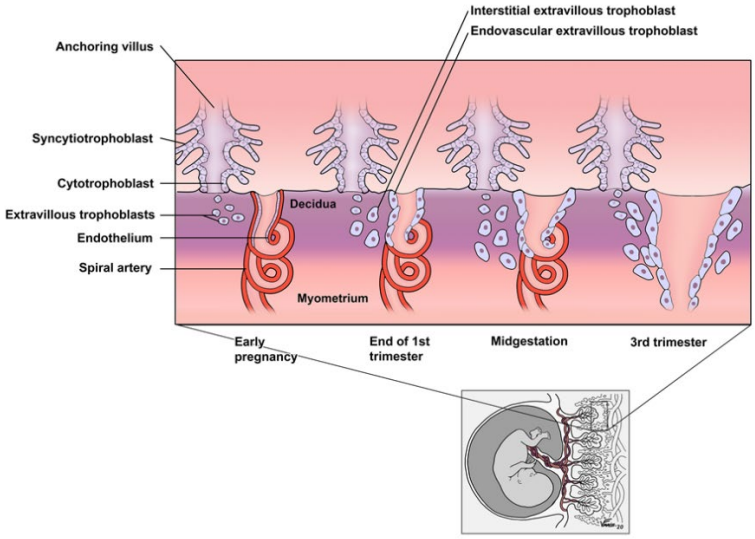

Figure 3: Spiral artery dilation throughout pregnancy. *Throughout pregnancy the diameter of the spiral arteries will increase 5-10-fold to allow for low-resistance blood flow to not damage the villi. Anchoring villi stabilize the mechanical integrity of the placenta and have an outer layer of syncytiotrophoblasts with an inner layer of cytotrophoblasts. Extravillous trophoblast invade the spiral arteries and have more specific classifications of interstitial extravillous trophoblasts, which invade the decidua, and endovascular extravillous trophoblasts which invade the spiral arteries.*

1.5.2 The uterine immune response during pregnancy, an overview

Fetal development requires the formation of a semi-allogenic object, the fetus, inside of the uterus. Therefore, the maternal immune system must be closely regulated to prevent immune rejection of fetus-derived cells, specifically trophoblast cells. Trophoblast cells are the only fetus-derived cells that are in direct contact with maternal blood and tissues. Fetal syncytiotrophoblast cells synthesize and secrete factors that regulate the immune response of maternal cells at both the implantation site and systemically. Class I human leukocyte antigens (HLA) are expressed by extravillous cytotrophoblasts, specifically HLA-C, HLA-E, HLA-F, and HLA-G. HLA-G is only expressed in humans, specifically by extravillous cytotrophoblasts in contact with maternal tissues. HLA-G plays a role in protecting extravillous cytotrophoblasts from immune rejection by modulating

decidual natural killer cells and is involved in permitting the maternal-fetal antigen mismatch [25].

In the decidua, decidual natural killer cells (dNK), are the predominant population of leukocytes present throughout the first trimester; by term, not many remain. In the first trimester, the dNK cells lie close to the extravillous trophoblasts and help to regulate invasion. Their infiltration is increased by progesterone, interluekin-15 (IL-15), and decidual prolactin; however, dNK cells are not cytotoxic towards fetal trophoblasts due to the cues of decidual macrophages [25]. dNK cells, along with macrophages, influence placental development through the provision of growth factors, immune regulation, and facilitating uterine vasculature changes to support trophoblast invasion [35].

The adaptive immune response is also important to pregnancy tolerance via T regulatory (Tregs) and effector T cells (Teff). Tregs limit excessive inflammation, establish tissue homeostasis after injury, and suppress Teff reactions to self or non-self antigens. In pregnancy, Tregs also have vaso-regulatory functions that are relevant to pregnancy establishment. Treg presence increases in early pregnancy and remains elevated through mid-gestation and decline prior to birth [35].

1.6 The two-stage model of pre-eclampsia etiology

To better explain and understand the pathophysiology of pre-eclampsia, theoretical models of the condition's causes have been developed. In 1991, a two-stage model of pre-eclampsia was introduced by C.W.G. Redman. The first stage described the theorized origin of pre-eclampsia, poor placentation caused by inadequate spiral artery remodeling early in pregnancy [36]. This manifests in abnormal dilation of the terminal portions of the vessels and maintenance of smooth muscle in the vessel wall. Inadequate spiral artery modification has been shown to occur in other conditions such as intrauterine growth restriction, recurrent pregnancy loss, and a proportion of preterm births and "normal"

pregnancies [33]. The second stage, and what is unique to pre-eclampsia compared to the aforementioned conditions, was the clinical presentation of symptoms affecting multiple organ systems [33], [36]. This groundbreaking model has been further refined by many others as pre-eclampsia has been more extensively studied, culminating in the two-stage model proposed in 2019 by Anne Catherine Staff [37]. In this model, both placental and maternal factors contribute to both stages of the disease. Here, like the 1991 model, Stage 1 represents placental dysfunction, and Stage 2 represents the maternal clinical presentation of symptoms. However in Staff's model, there are three ways in which placental dysfunction for Stage 1 could be caused: the first is via poor placentation (an "extrinsic cause"), the second is via normal placentation, but the placental capacity is exceeded closer to term (an "intrinsic cause"), and the third is via other factors like aging and/or senescent placentas. Stage 1 then leads to Stage 2, which is the maternal clinical presentation of symptoms.

Staff hypothesizes that early-onset pre-eclampsia may be due to the extrinsic cause and late-onset pre-eclampsia results from the intrinsic cause. This revised model incorporates patient risk factors that may affect progression to Stage 1 and the transition from Stage 1 to Stage 2. Staff theorizes that dysfunctional immune tolerization of the semi-allogenic trophoblasts lead to the "extrinsic cause" of poor placentation, and that syncytiotrophoblast stress, i.e. maternal endothelial activation, cause the transition from Stage 1 to Stage 2. The theoretical "intrinsic cause" of pre-eclampsia is less supported than the "extrinsic cause", but describes the placenta entering into a state of stress due to the placental capacity being exceeded [37].

1.7 The biological basis of risk factors for pre-eclampsia

Multiple risk factors for developing pre-eclampsia have been identified and are listed in **Table 1**. These risk factors are used clinically to prescribe aspirin for patients deemed

high risk, as an attempt to allay systemic symptoms in advance of their development. The risk factors listed were identified by obstetricians and gynecologists in Australia and New Zealand, the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), the American College of Obstetricians and Gynecologists (ACOG) in the United States of America (USA) [38], and by a World Health Organization (WHO) secondary analysis in low-and middle-income countries (LMICs) [8]. This section will review the biological mechanisms that provide evidence of the relevance of these risk factors to pre-eclampsia.

Table 1: Summary of the biological basis of risk factors for pre-eclampsia. *USA: United States of America, AUS: Australia, NZ: New Zealand, UK: United Kingdom, LMICs: Low- and Middle-Income countries, All: USA, AUS, NZ, UK, AND LMICs.*

Category	Risk Factor	Location	Scientific basis
Pregnancy-related	*Previous pregnancy with pre-eclampsia* [22], [39], [40]	USA, AUS, NZ, and UK	Presence of risk factors, genetics, and/or increased cardiovascular disease risk
	Multifetal gestation [41] [37]	USA, AUS, NZ, and UK	Reduced placental capacity
	Age "extremes" [42]–[46]	USA, AUS, NZ,UK, and LMICs	Oxidative stress, lower mitochondrial energy production, decreased androgen levels, placental senescence
	History of small-for-gestational age or adverse outcome [47]	USA, AUS, NZ, and UK	High association with pre-eclampsia due to impaired placentation
Lack of seminal fluid exposure	*Nulliparity* [48], [49]	USA, AUS, NZ, and UK	Lack of immune priming
	Inter-pregnancy interval > 10 years [48], [49]	USA, AUS, NZ, and UK	

Immunologic mismatch and absence of relaxin	*Assisted Reproductive Technology* [48], [50]–[54]	USA, AUS, NZ, and UK	Lack of immune priming, absence of corpus luteum, HLA mismatching
Pre-existing maternal health conditions	*Thrombophilia* [55]	USA	Increased placental vascular clotting risk
	Autoimmune disease [55]–[57]	AUS, NZ, and UK	Dysregulation of immune cells and placental injury
	Systemic lupus erythematosus [55]–[57]	USA	Increased flare ups, difficulty distinguishing symptoms, and placental injury
	BMI > 30kg/m^2 (USA) or BMI > 35kg/m^2 (all others) [33], [32], [58], [59]	All	Inflammation, risk of hypertension For metabolic syndrome – atherosclerotic plaques, which contain lipids that arises similarly in PE/preterm births
	Chronic kidney disease [60], [61]	USA, AUS, NZ, and UK	Issues with hormone regulation, and with kidney disease more likely to have hypertension and proteinuria
	Chronic hypertension [62]	All	Can be amplified during pregnancy
	Diabetes mellitus [63]	USA, AUS, NZ, and UK	Blood vessel and kidney damage
	Anemia [8], [64]	LMICs	Iron deficiency
Genetic	*Family history of pre-eclampsia* [65]–[69]	USA	Genetic predisposition and heritability, epigenetics
Sociodemographic characteristics	*African American race or low socioeconomic status* [5], [40], [78]–[85], [70]–[77]	USA, AUS, NZ, and UK	To be determined

1.7.1 Pregnancy-related risk factors

1.7.1.1 Previous pregnancy with pre-eclampsia

It is not immediately clear why a previous pregnancy with pre-eclampsia is a risk factor for recurrence of pre-eclampsia in a subsequent pregnancy. This could be due to genetics (which will be discussed later), the presence of other risk factors such as obesity, or hypertensive pregnancy being a predictor of cardiovascular disease later in life [22], [39], [40].

1.7.1.2 Multifetal gestation

Multifetal gestation requires a larger placenta, which ties into the “intrinsic cause” of the updated two-stage model of pre-eclampsia etiology [37]. The larger placenta may be larger than the uterus’ capacity, compressing the villi and leading to late-onset pre-eclampsia [41].

1.7.1.3 History of small-for-gestational-age or adverse outcome

Small-for-gestational age (SGA) infants are those that are born at a weight less than the tenth percentile for gestational age. This could be due to growth restriction (IUGR) or other causes. IUGR and SGA are often used interchangeably, but differ in stage of that IUGR is referring to a fetus that is growth-restricted, and SGA is referring to an infant that has a lower than expected birth weight [86]. If caused by IUGR, SGA could occur due to abnormal placentation or infection. In non-pre-eclamptic pregnancies, those with SGA have similar biomarkers and maternal symptoms to that of pre-eclamptic pregnancies [47].

1.7.1.4 Age extremes: Advanced patient age and adolescent pregnancy

Advanced patient age is a well-known risk factor for adverse pregnancy outcomes [46], [87], with multiple theories as to why. These theories include decreased androgen levels, lower mitochondrial energy production and cytoplasmic quality, oxidative stress, and placental senescence [42], [43]. When tied together with the theorized etiology of pre-

eclampsia, all these theories could lead to issues with placentation. The WHO lists *adolescent* pregnancy as a risk factor [5], and this could be a due to social factors such as partner abuse or socioeconomic status. Additionally, patients at this age may be physically immature for reasons like less menstrual cycles and/or hormone fluctuations [44], [45].

1.7.2 Lack *of* seminal fluid exposure: Nulliparity and long inter-pregnancy intervals

A well-established risk factor is a nulliparity, which refers to women who have never given birth, has not been well studied mechanistically [88]. It could be a risk factor possibly due to a lack of immune priming of the uterine environment, which has been discussed previously. The lack of immune priming and/or loss of short term T cell memory also may play a role in why a long inter-pregnancy interval is a risk factor [48], [49].

1.7.3 Immunologic mismatch and absence of relaxin: Pregnancy via assisted reproductive technologies

Assisted reproductive technologies (ART) are the variety of methods developed to treat male and female fertility. Pregnancies achieved via ART are associated with a higher risk of pregnancy-related hypertensive conditions [50], [89]–[91]. This could be explained also by a lack of seminal fluid exposure in the uterus depending upon the method of ART, such as that which involves artificial insemination with donor sperm [48]. Additionally, in some methods of ART like *in vitro* fertilization (IVF) a corpus luteum is not always present thus the vasodilatory hormone relaxin is not produced, or supplemented, leading to increased risk of vascular dysfunction [54]. The age of patients that undergo ART is increasing [92], which also increases risk of adverse pregnancy outcomes [46], [87]. For pregnancies achieved with oocyte donations, it has been hypothesized that an

immunological reaction occurs in the recipients, leading to abnormal placentation [51]. Additionally, both HLA Class I (expressed on trophoblasts) and Class II (which are expressed by B lymphocytes, monocytes, macrophages, dendritic cells, and activated T lymphocytes [93]) mismatching between oocyte donor and recipient has been shown to increase the risk of pre-eclampsia development [51]–[53]. The number of pregnancies is a consideration when discussing ART and adverse pregnancy outcomes, but many studies have shown that singleton pregnancies are at high risk of these outcomes as well [94]. There are many theories related to why patients undergoing ART are at a higher risk of developing pre-eclampsia, but the ability to have more control over immunologic mismatching provides opportunities to allay this risk.

1.7.4 Pre-existing patient health conditions

Pre-existing patient health conditions that are considered risk factors are thrombophilias, autoimmune disease, obesity or being overweight, chronic kidney disease, diabetes mellitus, and/or chronic hypertension.

1.7.4.1 Thrombophilias

Thrombophilias are inherited or acquired conditions that predispose an individual to thrombosis (blood clots) that could eventually block vasculature. Placental vascular lesions, specifically from cell types such as the syncytiotrophoblast, are present in all pregnancies, and the increased thrombotic risk of those with thrombophilias makes them at a higher risk for placental infarction. Therefore the high rate of placental lesions in thrombophilias is associated with pre-eclampsia and other conditions like miscarriage, intrauterine growth restriction (IUGR), and stillbirth [55].

1.7.4.2 Autoimmune disease: antiphospholipid syndrome and systemic lupus erythematosus

The UK, New Zealand, and Australia more generally list autoimmune disease as a risk factor, but are most often referring to the antiphospholipid syndrome (APS) and/or systemic lupus erythematosus (SLE) [3]. APS is an autoimmune condition that is an acquired thrombophilia, which spans into two pre-eclampsia risk factors: thrombophilias and autoimmune diseases. In pregnancy, the APS is associated with placental vascular thrombosis, decidual vasculopathy, intervillous fibrin deposition, and placental infarction. These placental pathologies may result in miscarriage, IUGR, stillbirth, and early severe pre-eclampsia [55].

SLE is an autoimmune disease that can be associated with APS, In SLE, autoantibodies are produced to ubiquitously expressed nuclear, cell, and tissue antigens. Due to the toxicity of some medications treating SLE, they are often stopped during pregnancy, leading to a higher chance of a flare-up. However, more recently, there are more medications that have been deemed acceptable for pregnancy. In addition to increased flare-ups, some symptoms and laboratory tests of flare-ups are the same as those of pre-eclampsia, delaying the management of pre-eclampsia [56]. Like APS, the placental injury seems to increase in pregnancies with SLE, likely due to hypercoagulability, hypertension, and immune-mediated vessel damage [56], [57].

1.7.4.3 Obesity

Body mass index (BMI), which is used as an indicator of obesity, is a risk factor for pre-eclampsia that has different cutoffs in different settings. In the USA a BMI greater than 30kg/m^2 is considered a risk factor while in Australia, New Zealand, the UK , and LMICs, a BMI greater than 35kg/m^2 is the cutoff to be considered a risk factor for pre-eclampsia. Obesity is considered a low-grade chronic inflammatory disease that is linked to metabolic

disorders such as type 2 diabetes and insulin resistance [58]. Thus, early pregnancy modifications can become dysregulated due to pre-existing metabolic regulation problems. This could be due to multiple reasons, including increased insulin resistance and/or increased adipose tissue presence could cause increased low-density lipoprotein toxicity [59]. Increased insulin resistance affects placental growth and gene expression [59], and lipoprotein toxicity can affect endothelial cells [32].

1.7.4.4 Chronic kidney disease

Blood vessels and blood flow undergo large changes during pregnancy, which also occur in the kidneys. Both the fetus and placenta are in demand of an expanded cardiovascular system. Those who have pre-existing chronic kidney disease are at a higher risk of developing pre-eclampsia because they are less able to make the necessary renal adaptions for pregnancy [61].

1.7.4.5 Chronic hypertension

Maintenance of the cardiovascular system is very important in pre-eclampsia. Preexisting cardiovascular risk factors, especially chronic hypertension, can be amplified in pregnancy and lead to pre-eclampsia due to the increase in metabolic and vascular stress on the body [62].

After developing pre-eclampsia during pregnancy, the risk for pre-eclampsia in subsequent pregnancies is increased [18], and in the long-term cardiovascular-related morbidity, renal disease, metabolic syndrome, and neurological issues risk increases [1], [18]–[21]. It appears that the increased risk of these conditions is dependent upon severity of pre-eclampsia during pregnancy, prevalence of recurrent pre-eclampsia [22], and gestation age at onset [19]. In addition to an increased risk, onset of cardiovascular diseases occurs prematurely at a younger age [18]. It is not yet clear if pre-eclampsia and

other adverse pregnancy outcomes causes these morbidities or if they merely “uncover” them [21], [23].

1.7.4.6 Diabetes mellitus

Pre-existing diabetes mellitus is associated with conditions like obesity and cardiovascular stress but also can cause kidney and blood vessel damage. These conditions are closely related to worse pregnancy outcomes [95], such as pre-eclampsia and IUGR [63].

1.7.4.7 Anemia

Anemia, a risk factor in LMICs, is not well-established but could lead to pre-eclampsia due to iron deficiency, which is vital for maintaining pregnancy [8], [64].

1.7.5 Genetic predisposition and heritability

1.7.5.1 Family history of pre-eclampsia

There has been evidence that preeclampsia could be heritable since the early 1960s, due to evidence of pre-eclampsia in family lineages, specifically mothers and daughters [65], [66]. It has been suggested that there are both maternal and fetal contributions to the heritability [65], [67], [69]. Epigenetic modifications have been implicated in the defective invasion characteristic of trophoblasts in pre-eclampsia [68], [96].

1.7.5.2 Sociodemographic characteristics: racism, not race

Socioeconomic status is a well-established social determinant of health [70], [71], and in low-resource settings, eclampsia is a significant cause of maternal death [2]. This is largely due to inadequate access to care [5]. In addition to socioeconomic status, African American race is a sociodemographic risk factor for pre-eclampsia. African American women are three times as likely to die from pre-eclampsia than White women [97]. However, though widely thought, socioeconomic status differences, which are closely tied with a poorer health status, do not fully explain this difference [72]–[74]. On the

contrary, studies have found that African American patients are not protected by higher socioeconomic status [73], [75].

In a recent review of pre-eclampsia in African American pregnant women it was concluded that generally more research is needed to understand why African American patients are at a higher risk of developing pre-eclampsia [72]. Often when examining disparities in pre-eclampsia incidence researchers conclude that due to higher prevalence of the risk factors listed in Table 1, African Americans are a more likely to develop pre-eclampsia. This has led several studies to more closely investigated this concept. African American (and Hispanic) patients with this pre-existing systemic lupus erythematosus are more likely to have poorer outcomes unrelated to pregnancy such as chronic renal failure. Thus if they do become pregnant their pregnancy-related outcomes are also more likely to be worse [76], [77], making causality difficult to establish. For patients with pre-existing chronic hypertension in the UK, it was found that those of “Black ethnicity” were at a higher risk of developing pre-eclampsia during pregnancy [78]. However, there is conflicting data on that conclusion when comparing studies that have pursued a similar research question [78], [79].

African American and Asian patients with a previous history of pre-eclampsia were found to be more likely to have recurrent pre-eclampsia compared to White patients; however, this study did not collect other demographic information besides race/ethnicity [40]. Of patients in California, USA with gestational diabetes mellitus, African American patients were more likely to develop pre-eclampsia when compared to White, Hispanic, and Asian patients [81]. In New York, USA, Non-Hispanic Black, Hispanic, and South Asian patients, with pre-existing diabetes mellitus were at a higher risk of developing pre-eclampsia when compared to Non-Hispanic White patients when unadjusted and adjusted for educational attainment and other maternal characteristics [82]. A few genes related to

kidney disease and thrombophilia have been shown to be mutated in African American pre-eclamptic pregnancies, but more evidence is needed [72]. These gene-based studies need to be more generalized; in one study pregnant African Americans were compared to non-pregnant African Americans, and no other races/ethnicities were included in that study [83]. In another, the sample size is relatively small, ~140 people of patients that have a pre-existing mutation of a gene that predisposes people to developing thrombophilias [84]. Taken together there is little, if any, causal evidence for why African Americans are at a higher risk of developing pre-eclampsia [85].

1.8 Biomarkers for screening pre-eclampsia: A lack of consensus among clinicians and researchers

There are several other biomarkers that have been identified and reviewed for being potentially clinically relevant for pre-eclampsia [98]–[101], and therefore will not be discussed in detail here. These include markers of oxidative stress, inflammation, and angiogenesis, the renin-angiotensin-aldosterone system, endothelial dysfunction, and placental stress. Researchers have also performed genome wide association studies (GWAS), RNA expression, epigenetics, proteomics, exosomal, and metabolic studies. The molecules analyzed are from various bodily sources and span multiple biological functions such as angiogenesis, immune modulation, hormone production, cell proliferation, and more These studies have been reviewed and have not found a clear marker(s) or pathways for pre-eclampsia [68], [102]. Though, in African American patients, there a few genes mutations with have higher frequencies of mutation that have been identified. These genes are associated with an increased risk of kidney disease and thrombophilia [72], conditions which are associated with pre-eclampsia.

Predictive models have been created to determine the risk of developing preeclampsia and use logistic regression, Bayes theorem, machine learning, or other methods [103]. These models aim to predict preeclampsia early, such that the recommendation of aspirin would be made during its effective period of between 12 to 28 weeks gestation. Generally, select patient characteristics, biochemical biomarkers, and/or biophysical biomarkers as used as predictors, i.e. inputs, into the models. Biochemical biomarkers include molecules like growth factors or metabolites that circulate in the peripheral blood, while biophysical biomarkers include measurements such as mean arterial pressure (MAP) and/or uterine artery pulsatility index (UtA-PI). 70 predictive models for preeclampsia have been recently systematically reviewed by De Kat et al, and due to the vast differences of predictors chosen for each model, it is difficult to directly compare them [103]. Additionally, the studies were rarely externally validated or calibrated, and most were done retrospectively, making it difficult to determine clinical relevance. Generally, most models used BMI, UtA-PI, blood pressure, medical history, maternal race/ethnicity and maternal age as predictors. The biochemical biomarkers chosen for each model varied drastically, though [103].

Clinicians are not fully convinced of the utility of biomarkers in pre-eclampsia. At the time of ACOG's Practice Bulletin's publication in January 2019, they were not convinced of the predictability of the statistical models, and believe they should remain investigational, along with biochemical biomarkers [2]. ISSHP recommended in 2018 against the use of placental growth factor (PlGF) as rule-in or rule-out tests, which aims to distinguish pre-eclamptic and non-pre-eclamptic patients based on concentrations of those biomarkers [4]. NICE does suggest offering PlGF testing to help rule out pre-eclampsia between 20 weeks and 35 weeks gestation [3]. Due to the specificity of the

predictors for each model created, external validation is difficult to perform, limiting clinical relevance [104].

Predictive modelling has the potential to greatly improve early prediction of a patient developing pre-eclampsia later in their pregnancy. A few models have been used in trials to detect high risk patients that would be eligible for aspirin administration, hoping that more accurate early detection of these patients would reduce the incidence of pre-eclampsia [105], [106]. They have seen positive results, that incidence was reduced, thus providing some evidence that predictive models could have a future in the clinic.

1.9 Low-cost technologies to improve access to pre-eclampsia screening and diagnosis

Current accepted pre-eclampsia screening is solely based on patient characteristics, and diagnosis requires measurements taken by a clinician, for high blood pressure and/or proteinuria. Thus, access to prenatal care is essential for pre-eclampsia management, which is a large reason as to why there are more deaths in low resource settings [107]. To be most effective, the predictive models developed require sufficient medical history from medical records and for non-routine measurements such as UtA-PI and PlGF to be taken [108]. This limits their applicability to a variety of settings; thus, low-cost technologies are needed to increase access to modelling methods. More generally, since Additionally, as telehealth becomes more common practice [109], at-home testing will help to not only make health more accessible, but to further empower patients.

In low resource settings in LMICs, blood pressure is likely not measure during routine antenatal visits due to equipment cost and lack of trained personnel [110]. Researchers have created lower-cost blood pressure monitors for pregnancy, but they few have been validated for pre-eclampsia diagnosis [111], [112]. In high-income countries, blood pressure testing devices are readily available, but studies have shown that measurements

are lower when measured at home versus in the clinic [113]. The use of ultrasound is on the rise in LMICs, and some studies have mentioned uterine artery Doppler measurements [114]. Ultrasound measurements and analyses do require skilled sonographers, which could present a challenge in certain locations.

Regarding the biochemical marker that is most relevant to the competing risks approach, there are commercially available assays to measure PlGF which have been reviewed by Hurrell et al [115]. The Triage PlGF test is a single-use fluorescence immunoassay and can be used at the point-of-care with a low-cost analyzer. The Triage PlGF test has a high sensitivity and is recommended to be used for patients between 20- and 34-weeks gestation. The other assay described measures the ratio of PlGF and an anti-angiogenic protein, soluble fms-like tyrosine kinase-1 (sFlt1). Each has its own disadvantages and advantages, and the likelihood of clinical use will be clinic specific [115]. However, as previously stated these are not used clinically, and are currently only recommended by the UK to aid in diagnosis of pre-eclampsia [3].

Proteinuria, which does not occur in all patients with pre-eclampsia, is measured via quantitative methods such as immunoassays in high-resource settings, for non-urgent situations or as a confirmatory test [2], [116]. In low-resource settings and for urgent situation in high-resource settings, proteinuria is measured via a dipstick that is placed into urine. Additionally, in low-resource settings proteinuria may not be measured due to the cost of urine dipsticks [107]. These colorimetric-based urine dipstick tests are notorious for having false-positive results [2], [116], [117]. Some point-of-care diagnostics that have been developed for proteinuria include lower cost colorimetric tests, which likely will lead to similar issues as the dipstick test [111]. Others have specifically made tests for certain proteins that were found to be misfolded in severe pre-eclamptic patients [111], [118].

Low-cost technologies that could be used to provide the measurements necessary to be input into predictive models for pre-eclampsia would greatly increase access to improving detection rates for patients in a variety of settings. Low-cost tools should not only be considered for LMICs, but other settings such as at-home around the world.

1.10 Suggestions and outlook for pre-eclampsia research and screening

1.10.1 Diversification of study sites for pre-eclampsia

A quarter of maternal deaths in the Caribbean and Latin America and one tenth of maternal deaths in Africa and Asia are associated with hypertensive disorders of pregnancy [119]; yet most of the recommendations for pre-eclampsia come from the USA, UK, and Australia/New Zeeland and other high-income countries [5]. For the predictive models reviewed by De Kat et al, 76% of them were from the USA, Australia, and the UK [98]. A diversification of study sites for all aspects of pre-eclampsia screening and risk factor analysis is needed. Researchers and clinicians in LMICs should be empowered to not only screen for pre-eclampsia, but to be able to study genetic biomarkers. For example, Brazil has begun to perform country-specific and region-specific analyses on risk factors and genetic biomarkers [102], [120]. This need has also been recognized by researchers from a consortium of seven Latin American countries, the Red Iberoamericana de alteraciones Vasculares Asociadas a TRastornos del EMbarazo (RIVA-TREM). The consortium makes several suggestions such as the need for clinical guidelines for Latin America, multicenter studies, collaborations, and to seek local risk factors and biomarkers [121]. As shown in this review, some risk factors are specific to different populations, but one study did show that risk factors in 878,680 Latin American and Caribbean women were similar to those in North American and European women [122]. Similarly, many of the risk factors identified by the USA, UK, and Australia were found to be risk factors of patients in sub-Saharan Africa in a systematic review of pre-

eclampsia and eclampsia in sub-Saharan Africa [123]. While there are clear differences between regions, such as nutrition environmental threats, and access to care, most risk factors are similar. This is likely due to worldwide trends of morbidity and mortality shifting towards non-communicable diseases, which most risk factors for pre-eclampsia are classified as.

1.10.2 A need for improved biomarker analytical tools

Since pre-eclampsia's etiology is not fully elucidated, it is difficult to know if the plethora of possible biomarkers identified cause dysfunctional placentation or vice versa [124], making them hard to be accepted clinically. Therefore, future studies need to refine further the many biochemical biomarkers identified since causality cannot be established from the current plethora of information available. One contributing factor to this are issues with obtaining consistent measurements of potential biomarkers. For example, to draw conclusions on the clinical relevance of deported trophoblasts, there are discrepancies between studies due to differences in isolation and detection methods of the trophoblasts. There is a lack of antibody specificity, low concentration of deported trophoblasts in the maternal peripheral circulation, and lack of continuity with the presence of circulating deported trophoblasts [125]. More generally, when utilizing placental lysates, which are used to study placental biomarkers, analytical methods do not distinguish between which cell types express the molecules of interest. Secondly, the quantification of circulating biomarkers depends on assays such as an ELISA to capture the analyte. This may not be the case if factors are present in bound and free forms in the circulation [100]. Lastly, the classification of pre-eclampsia (e.g. preterm vs early-onset) highly varies throughout the literature, this complicates systematic reviews and drawing parallels between distinct datasets. As machine learning and other models continue to improve, it is important to consider sample origin to make accurate predictions. *In vitro* models of pre-eclampsia for

predictive purposes is an area also in need of more attention. Trophoblast cell invasion has shown to be hindered when treated with sera from human pre-eclamptic patients, indicating the potential for *in vitro* predictive models [126]–[128].

Platforms to simplify the analysis of biomolecules should be developed to ease the cost burden of performing genetic-based and protein-based studies on patient populations. Genetic analyses requires complex equipment, but also careful extraction of the nucleic acids. Point-of-care devices such as microfluidic devices and lateral flow assays should be implemented into study designs for laboratory sample analysis to expand the access of these studies. Additionally, those developing the assays should have collaborators in the location in which they hope to work, to truly understand the challenges outside of their home setting [129]. Lower cost single-cell sequencing platforms would also be beneficial for studies involving placental lysates and other sample types, to increase the granularity of biomarker data. To better validate biomarker research overall, more specific assays must be developed, and studies should aim to be prospective versus retrospective to better understand pre-eclampsia at a molecular level.

In addition to blood and placental lysates, alternative biological samples, such as follicular fluid, should be considered when performing pre-eclampsia biomarker studies, which allows for insight into the oocyte microenvironment. Follicular fluid can be obtained from *in vitro* fertilization patients, who are also at high risk for developing pre-eclampsia, and follicular fluid's RNA expression has been studied previously for understanding oocyte quality [130]. This would allow for patients to be studied before they are pregnant, which would better indicate causality in pre-eclampsia etiology theories [131].

1.10.3 Risk Factors for pre-eclampsia – a need for specificity and evidence

African Americans are thought to be at a higher risk of developing pre-eclampsia due to a higher prevalence of pre-existing conditions [132]. However, few studies show evidence of this. Studies have highlighted the importance of evaluating psychosocial factors for various outcomes in pregnancy or postpartum [133]–[136], which is where differences may truly lie between races and ethnicities, since inequities can affect all aspects of health [137]. Institutionalized racism is a fundamental cause of health inequities, yet that concept is often not considered in research articles [138]. Race is not biological; it is a social construct. Researchers should more carefully examine causalities not erroneously to indicate associations that may not exist [139].Future studies should consider stress, institutionalized racism, and quality of healthcare received when studying African American pregnancies complicated with pre-eclampsia [75].

Increasing disparities in maternal mortality between African American and White mothers was recently highlighted in an article by Amy Roeder of the Harvard T.H. Chan School of Public Health, which discussed the concept of weathering. Weathering is described as a way that health is corroded due to social disadvantage, that was first described by Arline Geronimus [140]. This could be due to stressful situations that leave one in a constant state of fight-or-flight, such as working multiple minimum wage jobs to maintain livelihood [141] and/or institutionalized racism, which affects African Americans and other minority populations regardless of socioeconomic status. Thus, these social factors impart stress on the body that may lead to adverse health outcomes earlier in life, including the risk factors of pre-eclampsia, which African Americans are at a higher risk of having [72]. Additionally, African Americans are at a higher risk of these morbidities such as obesity due to social factors like inaccessibility to healthy food options, further adding to stress [142]. Stress can also be passed down generationally, and studies have shown

that cardiovascular disease risk can be inherited due to similar stressors present in one's life [143]. Elevated levels of stress can affect the placental pathophysiology seen in pre-eclampsia [43]. Additionally, Roeder highlights the systemic racism present in healthcare, which led to near-death experiences and maternal deaths. The concept of transgenerational racism affecting the body epigenetically and peoples' telomere lengths has also been explored as a biological impact of racism [144].

People of Southeast Asian descent have also been identified as being at a higher risk for developing pre-eclampsia, but are not recognized as a risk factor by major societies of obstetricians and gynecologists [108], [145], [146]. Interestingly, the studies that were performed in the USA found that Southeast Asian people not born in the USA were at a higher risk that USA-born people of the same ethnicity. This highlights not only the importance of thorough groupings of individuals included in studies, but again the importance of psychosocial factors in pregnancy such as immigration status. The competing risk approach model did find that people of South Asian descent are at a higher risk of developing pre-eclampsia [108]. However, the authors use white race as a reference population, among other factors such as nulliparity. This demonstrates another potentially harmful aspect of race in research practice, since using one race as a reference population limits the generalizability of the research to other locations, especially in those where that race is not as prevalent.

When it comes to obesity, BMI is a highly debated metric to define the condition [147]–[149]. BMI is a Euro-centric measurement that has been shown to be inaccurate for various non-Caucasian populations such as those of recent African, Polynesian, and Asian descent [150]. Excess weight may not be what is the cause of comorbidities associated with obesity, but excess body fat [148]. However, more research is needed to understand the implications of this fat's role in morbidity. This debate has implications in

pre-eclampsia screening as well, since BMI is often a predictor included in predictive models for the condition.

1.10.4 Pre-conception analyses: an unmet need

The largest gap in terms of the focus of pre-eclampsia screening efforts is that the focus is on patients after they become pregnant, not beforehand. Even as prediction tools have improved detection rates, once a patient is pregnant, only delivery may “cure” pre-eclampsia. Previous history of pre-eclampsia has been shown to be predictive of an increased cardiovascular risk later in life, and at a younger age [1], [18]–[21], [23]. If patients were aware of their risk of developing pre-eclampsia before becoming pregnant, knowing the post-pregnancy risks as well, they would be empowered to decide if they would like to become pregnant or seek other options. Additionally, pre-conception studies could improve research around the etiology of pre-eclampsia, which remains highly theoretical. In one study by Foo et al. showed a different etiology than placental dysfunction via studying patients prospectively before and after they became pregnant [151]. This highlights the significance of studying patients pre-conception in the understanding of pre-eclampsia.

1.11 Conclusions and Outstanding Questions

Pregnancy could be considered a stress test for the body, and the stress of pre-eclampsia may accelerate the presentation of cardiovascular-related morbidities. Pre-eclampsia is a complex condition with multiple theorized causality pathways, making the condition challenging to study and define. When screening for the risk of developing pre-eclampsia to prescribe aspirin to high- risk patients, physicians use risk factors that involve patient medical history, family medical history, sexual history, and maternal demographic characteristics. Not only does this method have low detection rates, these risk factors, especially obesity and race, need to be analyzed more closely to establish a true

association. Additionally, the study locations of pre-eclampsia research need to be expanded beyond a few high-income countries to include more LMICs since hypertensive disorders of pregnancy are a worldwide cause of maternal mortality. Potential biomarker analyses need to be better regulated, and low-cost technologies have the chance to increase access to patient sample-based research for pre-eclampsia. Lastly, pre-conception prospective studies for pre-eclampsia are critical to establishing causality for the “disease of theories”. Expertise from multiple fields is vital for the advancement of pre-eclampsia screening, research, diagnosis, and management.

CHAPTER 2: THE ASSOCIATION OF RACISM AND DISCRIMINATION IN DISPARITIES OF HYPERTENSIVE DISORDERS OF PREGNANCY USING MULTI-STATE PRAMS DATA

Chapter 2 has been submitted as an original research article.

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2.1 Abstract

Background: Hypertensive disorders of pregnancy are a leading cause of maternal mortality. Racial disparities in maternal mortality in the United States are well-documented, but the role of racism and/or discrimination in affecting one's risk of developing a hypertensive disorder of pregnancy is not well-studied.

Methods: Data from 17 sites that asked questions regarding experiences with racism and/or discrimination during pregnancy via the Pregnancy Risk Assessment Monitoring System (PRAMS) Phase 8 (2016-2020) from was used. Regression models were used to estimate odds of hypertensive disorder diagnosis in pregnancy using adjusted models controlling for confounders: biological risk factors, socioeconomic factors, and experiences of racism and/or discrimination.

Results: Among participants with live births (N = 69,751), 14.9% of participants stated they were diagnosed with hypertension during pregnancy with non-Hispanic and Hispanic Black individuals having the highest rates (19.8%). 13.1% of participants experienced racism and 15.6% of participants experienced discrimination. Experiencing racism or discrimination increased one's odds of having hypertension during pregnancy by 1.14 times (CI: 1.00 - 1.31) and 1.30 times (CI: 1.02 - 1.65), respectively. When experiences with discrimination were included, non-Hispanic and Hispanic Black individuals did not have statistically significantly higher odds of having hypertension during pregnancy compared to non-Hispanic White individuals.

Conclusions: Experiences of racism and/or discrimination drive racial disparities in hypertensive disorders in pregnancy.

Public Health Implications: It is vital to eliminate racist and discriminatory practices in healthcare to reduce maternal morbidity and mortality.

2.2 Background

The United States spends twice as much on healthcare per capita than other high income countries, yet has the highest maternal mortality rate amongst those countries [152], [153] and this rate is rising [154]. Racial disparities in maternal mortality in the United States are well documented, with non-Hispanic Black patients having a maternal mortality rate twice the national average [154]. A significant contributor to maternal mortality and morbidity is hypertensive disorders of pregnancy, which complicate up to 10% of pregnancies worldwide[155]. Hypertensive disorders include the continuum of chronic hypertension, gestational hypertension, and pre-eclampsia [2].

In addition to maternal mortality, racial disparities also have been shown in the prevalence of hypertensive disorders, with Black and Hispanic women being more likely to develop hypertensive disorders of pregnancy than non-Hispanic White women [155], [156]. Literature on disparities among Hispanic women are more mixed, but non-Hispanic Black women have higher rates of hypertensive disorders than both Hispanic and non-Hispanic White women [155], [157], [158]. Some studies have found that those of South Asian descent are also at a higher risk than of developing hypertensive disorders than non-Hispanic White women [82], [108] as are Native American women [158].

Researchers have often speculated that the striking disparities among non-Hispanic Black women are due to higher rates of comorbidities including obesity, chronic hypertension, and diabetes mellitus [156], [159]. However, many studies have controlled for comorbidities and socioeconomic status and find that the disparities remain [74], [160], [161]. Race is a social construct meant to subjugate certain groups in the context of white supremacy and not a biological one, thus there has been a focus shift to social determinants of health in explaining the disparities in maternal mortality. In addition to

socioeconomic status, studies have suggested that factors like geographic location, access to prenatal care, quality of hospitals patients attend, medical gaslighting or psychosocial factors are reasons for the racial disparities in maternal mortality rate in the US [74], [161]–[163]. Psychosocial factors are particular of interest in the context of hypertension in pregnancy, since stress can impart biological changes to the body, and is associated with hypertension development [164]. Experiencing discrimination in pregnancy and beyond is a social determinant of health that has negative psychosocial and biological effects on one's health, which is the concept of allostatic load [165]. A prior meta-analysis showed an association between mental stress and gestational hypertension and pre-eclampsia [166]. However, this study lacked an in-depth analysis into race and social determinants of health. Smiith Barber and Robinson used Virginia's PRAMS data to study the influence of racial discrimination on other adverse birth outcomes. They found that non-Hispanic Black women in Virginia who experience racism and discrimination were at a higher risk of having low birth weight and preterm births, but they did not investigate impact of hypertensive disorders [167].

Many studies have been published that show racial disparities in diagnosis rates of gestational hypertension disorders, but to our knowledge, none have examined the influence of racism or discrimination on gestational hypertension diagnoses in the US. Thus, this study aims to examine the association between discrimination and hypertension in pregnancy. We hypothesized that despite the adjustment for socioeconomic factors and biological risk factors for gestational hypertension, Black and Hispanic women will be at a higher risk of having hypertension during pregnancy. Additionally, we hypothesized that those who experience racism and/or discrimination will be at a higher risk of being diagnosed with a gestational hypertensive disorder. Examining the influence of racism

and/or discrimination on gestational hypertension disorder diagnosis is important to reframe race/ethnicity being utilized as a risk factor versus a risk marker [168].

2.3 Methods

2.3.1 Data source and study population

To investigate the association between discrimination and hypertension, the Centers for Disease Control and Prevention's (CDC) surveillance project, the Pregnancy Risk Assessment Monitoring System (PRAMS) was used. PRAMS was developed in 1987 and collects population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy. Forty-seven states, New York City, Puerto Rico, and the District of Columbia participate in PRAMS. This is an extremely rich dataset that also data from birth certificates, which are documents containing health information as well as demographic information about the mother, father, and newborn. PRAMS data has been used to investigate a range of health outcomes including influenza vaccine uptake and postpartum depression [169]–[172]. The PRAMS Phase 8 dataset, which covers years 2016-2020, was used in this analysis. Each site surveys approximately 1,000 – 3,000 people who recently had a live birth per year [173]. The current study focused on variables that include birth certificate information, the CDC Core Questions, the CDC Standard Questions, and selected state-specific questions requested regarding racism and discrimination (BB1, VA76, LA66, OR77, MN70, NH84, CT71, DC69, CT70, DC65). These questions asked if the participant felt emotionally upset as a result of how they were treated based on their race, or if they experienced discrimination, harassment, or were made to feel inferior based on: race, ethnicity, culture, insurance status, weight, marital status, immigration status, age, income, sex/gender, sexual orientation, religion, substance addiction, or language spoken. Therefore, the 17 sites that were included were Connecticut (CT), District of Columbia (DC), Florida (FL), Georgia (GA), Iowa (IA),

Indianapolis (IN), Louisiana (LA), Minnesota (MN), Missouri (MO), North Carolina (NC), New Hampshire (NH), New Jersey (NJ), New York City (YC), Oregon (OR), Virginia (VA), Wisconsin (WI), Wyoming (WY). Survey weights were applied to the dataset as instructed by the CDC. Only "live" birth pregnancies were included in the current study. Those with "live" births were inferred from birth certificate information certifying that the infant was alive at the time of the birth certificate being filled out. Since the reasons for non-live births were unknown, they were excluded.

2.4 Measures and analysis

2.4.1 Independent variables

The primary predictor, mother's race and ethnicity, was taken from the birth certificate and was categorized as either Hispanic or non-Hispanic for ethnicity and Other Asian, White, Black, American Indian, Chinese, Japanese, Filipino, Hawaiian, Other (not White), Alaskan Native, and mixed race. After analyzing the frequency per category racial/ethnic groups were condensed as follows (Table 2):

Table 2: Categorization of races and ethnicities done in this study from the original PRAMS dataset. *To achieve at least 900 individuals per racial/ethnic grouping, the racial/ethnic data from the PRAMS dataset was combined as shown in the table. Non-Hispanic, White individuals were used at the reference category.*

Study Categorization	PRAMS categorization
Hispanic White	Hispanic White
Non-Hispanic & Hispanic American Indian & Hawaiian	Non-Hispanic and Hispanic Hawaiian, American Indian
Non-Hispanic & Hispanic Asian	Non-Hispanic and Hispanic Asian, Other Asian, Chinese, Japanese, and Filipino
Hispanic and Non-Hispanic Black	Non-Hispanic Black and Hispanic Black
Non-Hispanic and Hispanic Mixed Race	Non-Hispanic and Hispanic Mixed Race
Non-Hispanic and Hispanic Other Non-White	Non-Hispanic and Hispanic Non-White
Non-Hispanic White (reference)	Non-Hispanic White

2.4.2 Dependent variable

Our primary outcome was gestational hypertension which was measured using self-reported: “During your most recent pregnancy, did you have any of the following health conditions: High blood pressure (that started during this pregnancy), pre-eclampsia or eclampsia?” (Response: Yes/No)

2.4.3 Covariates and confounders

Risk factor-based covariates and confounders were selected based the literature and restricted to those factors known to be associated with hypertension during pregnancy, as well as socioeconomic factors. In the United States, risk factors for hypertension during pregnancy that are available from either the birth certificate or self-report questionnaire include nulliparity (birth certificate), multifetal gestations (birth certificate), chronic hypertension (questionnaire), pregestational diabetes (questionnaire), gestational diabetes (questionnaire), pre-pregnancy body mass index (BMI) greater than 30 (birth certificate), mother’s age greater than 35 years (birth certificate), and use of assisted reproductive technology (birth certificate) [2]. Socioeconomic status was inferred from the birth certificate variables of use of food assistance programs (i.e., if the mother uses or used Special Supplemental Nutrition Program for *Women*, *Infants*, and *Children* (WIC)) and payment method for the hospital visit.

To include racism and discrimination as confounders, the answers for various state-specific and one Standard Question were combined into a singular variable. For racism, the state-specific questions that either asked about racism or included racism as a response when asking about experiences with discrimination were combined. That is, if someone answered yes to experiencing racism to one of those questions they would be listed as “yes” in the racism variable. If they answered no, they would be listed as “no” in the racism variable; if they did not answer any of the questions they were listed as “N/A”

in the racism variable. A similar process was performed to make the discrimination variable. For this variable, discrimination included questions regarding discrimination on the basis of: age, language spoken, citizenship/immigration status, insurance status, income, sex/gender, sexual orientation, religion, pregnancy, marital status, weight, substance addiction, or other.

The distinction between confounders and covariates was established via chi-squared tests (alpha=0.05), testing the association between race/ethnicity and the variable of interest and hypertension during pregnancy and the variable of interest. All the variables were confounders, as they were significantly associated with hypertension and race/ethnicity. In addition, those who had missing data for any of the variables of interest were excluded, which was approximately 3% of the sample of 69,751 individuals for the Unadjusted Model, 8.4% for Adjusted Model 1, 34.3% for adjusted Model 2, and for Model 3 76% of the sample was excluded (Figure 4).

2.4.4 Statistical Analyses

Descriptive statistics were calculated for each adjusted model. Chi-squared tests were conducted (alpha = 0.5) to identify confounders from a candidate list. A generalized linear model with a logit function was used for the four models. A non-adjusted logistic regression model using race as the predictor and hypertension as the outcome was fit (Unadjusted Model). Adjusted logistic models including the biological risk factors and socioeconomic status confounders (Adjusted Model 1), including the biological risk factors, socioeconomic status, and racism confounders (Adjusted Model 2), and including the biological risk factors, socioeconomic status, and discrimination confounders were also fit (Adjusted Model 3). All models were adjusted by survey weights as instructed by the CDC. Missing data was omitted from all models. Odds ratios and 95% confidence intervals (CI) were calculated to examine the association between the predictors and

confounders and the outcome hypertension during pregnancy. All analyses were performed in RStudio (version 2022.02.3, Build 492) with the significance level set at alpha=0.05 *a priori*.

2.5 Results

Of the total number participants within states that fit our criteria of asking about discrimination and/or racism (N = 70,085), 69,751 participants had infants who were born alive. 67,639 participants reported their race and ethnicity. Of these, 64,699 participants responded to all the risk factor and socioeconomic status questions (Adjusted Model 1), 46,413 participants responded to the risk factor, socioeconomic, and racism questions (Adjusted Model 2), and 16,838 responded to the risk factor, socioeconomic, and discrimination questions (Adjusted Model 3) (Figure 4). Depending upon the model, between 14.8% - 15.4% of participants stated they had hypertension during pregnancy, with Non-Hispanic and Hispanic Black participants having the highest rates of hypertension during pregnancy (between 19.3%-19.6%). 13.1% of participants experienced racism (Table 4), with Non-Hispanic and Hispanic mixed race (33.8%), Non-Hispanic and Hispanic American Indian and Hawaiian (31%), and Non-Hispanic and Hispanic Black individuals (20.2%) reporting the highest rates of experiencing racism. 15.6% of participants experienced discrimination (Table 5), with Non-Hispanic and Hispanic American Indian and Hawaiian (37.3%) and Non-Hispanic and Hispanic mixed race (37.2%) individuals reporting the highest rates of experiencing discrimination.

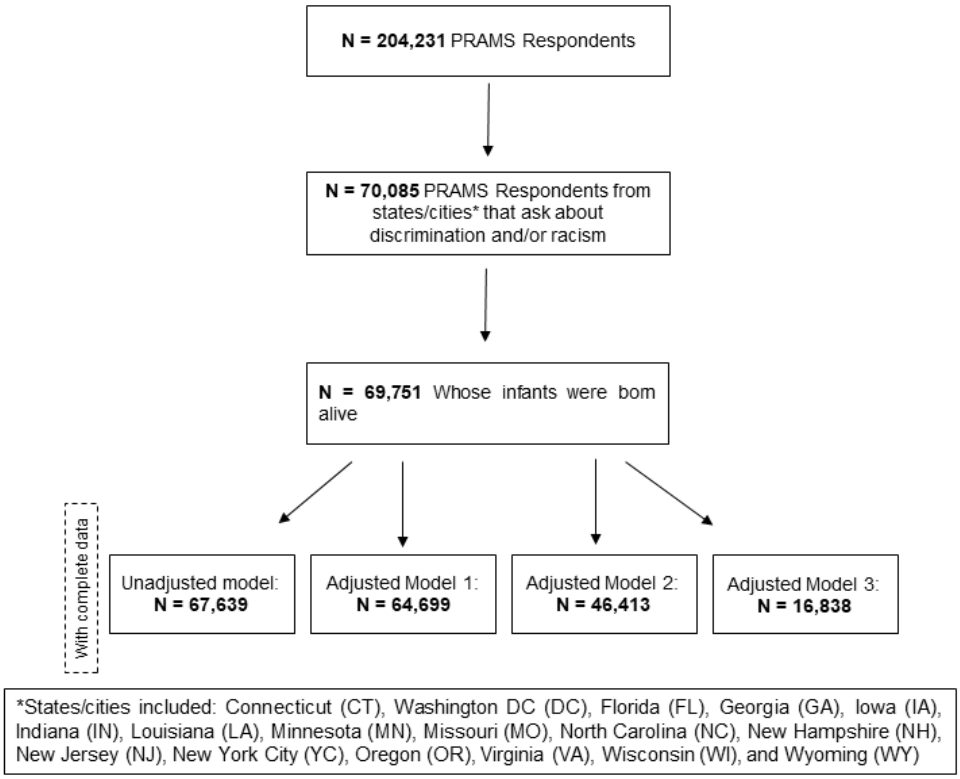

Figure 4: PRAMS respondents for each model.

The Unadjusted Model (Table *6*) showed that, on average, Hispanic White individuals had an odds 0.78 times (CI: 0.68 - 0.89), non-Hispanic and Hispanic Asian participants had an odds 0.47 times (CI: 0.40 – 0.56), and non-Hispanic and Hispanic other non-White women had an odds 0.82 times (CI: 0.71 – 0.96) that of non-Hispanic White women of having hypertension during pregnancy. Non-Hispanic and Hispanic Black women had higher odds of having hypertension during pregnancy, 1.47 times (CI: 1.35 – 1.59) that of non-Hispanic White individuals.

To include the established risk factors of gestational hypertension and socioeconomic confounders, Adjusted Model 1 was evaluated (Table 3). This model

(Table 6) showed that, on average, Non-Hispanic and Hispanic Black women had higher odds of having hypertension during pregnancy, 1.13 times (CI = 1.03 – 1.24) that of non-Hispanic White women. On average, a woman who was in a higher BMI category had an odds 1.6 times (CI = 1.53 – 1.67) that of a woman in a BMI category one level lower of having hypertension during pregnancy. Those who were diagnosed with hypertension before pregnancy had an odds 6 times (CI = 5.20 – 6.92) that of those who did not have chronic hypertension before pregnancy. Those who underwent infertility treatment had an odds 1.43 times (CI = 1.15 – 1.78) that of those who did not undergo infertility treatment of having hypertension during pregnancy. Those who had a multiples pregnancy had an odds 1.62 times (CI = 1.26 – 2.09) that of those who had a singleton pregnancy of having hypertension during pregnancy. Those who had gestational diabetes had an odds 2.06 times (CI = 1.85 – 2.29) that of those who did not have gestational diabetes of having hypertension during pregnancy.

Table 3: Adjusted Model 1 with biological risk factors and socioeconomic status confounders. *Hispanic is denoted as (H) and is denoted as Non-Hispanic (NH).*

	H White (N = 6,839)	**NH & H Am. Indian & Hawaiian (N = 1,441)**	**NH & H Asian (N = 5,773)**	**NH & H Black (N = 15,769)**	**NH & H Mixed Race (N = 3,777)**	**NH & H other, non-White (N = 4,151)**	**NH White (N = 26,949)**	**Overall (N = 64,699)**
Hypertension during pregnancy?								
Yes	819 (1.0%)	228 (15.9%)	471 (8.2%)	3,040 (19.3%)	596 (15.8%)	484 (11.7%)	3,980 (14.8%)	9,618 (14.9%)
No	6,020 (88.0%)	1,213 (84.2%)	5,302 (91.8%)	12,729 (80.7%)	3,181 (84.2%)	3,667 (88.3%)	22,969 (85.2%)	55,081 (85.1%)
Biological risk factors								
Age								
17-19	355 (5.2%)	112 (7.8%)	47 (0.8%)	888 (5.6%)	218 (5.7%)	240 (5.8%)	616 (2.3%)	2,476 (3.8%)
20-24	1,431 (20.9%)	383 (26.6%)	401 (6.9%)	3,422 (21.7%)	873 (23.4%)	825 (19.9%)	3,635 (13.5%)	10,970 (17.0%)
25-29	1,850 (27.1%)	416 (28.9%)	1,439 (24.9%)	4,707 (29.8%)	1,052 (27.9%)	1,166 (28.1%)	7,386 (27.4%)	18,016 (27.8%)
30-34	1,788 (26.1%)	336 (23.2%)	2,356 (40.8%)	3,951 (25.1%)	998 (26.4%)	1,051 (25.3%)	9,553 (35.4%)	20,033 (31.0%)
35-39	1,109 (16.2%)	154 (10.7%)	1,255 (21.7%)	2,219 (14.1%)	514 (13.6%)	669 (16.1%)	4,744 (17.6%)	10,664 (16.5%)

40+	306 (4.5%)	40 (2.8%)	275 (4.8%)	582 (3.7%)	122 (3.2%)	200 (4.8%)	1,015 (3.8%)	2,540 (3.9%)
BMI								
<18.5	132 (1.9%)	34 (2.4%)	380 (6.6%)	452 (2.9%)	101 (2.7%)	93 (2.2%)	881 (3.3%)	2,073 (3.2%)
18.5-24.9	2,520 (36.8%)	435 (30.2%)	3,373 (58.4%)	4,858 (30.8%)	1,376 (36.4%)	1,576 (38.0%)	12,949 (48.1%)	27,087 (41.9%)
25.0-29.9	2,104 (30.8%)	378 (26.2%)	1,333 (23.1%)	4,100 (26.0%)	979 (25.9%)	1,356 (32.7%)	6,592 (24.5%)	16,841 (26.0%)
30+	2,083 (30.5%)	594 (41.2%)	687 (11.9%)	6,359 (40.3%)	1,321 (35.0%)	1,126 (27.1%)	6,528 (24.2%)	18,698 (28.9%)
Hypertension before pregnancy?								
Yes	204 (4.4%)	97 (6.7%)	222 (3.8%)	1,601 (10.2%)	205 (5.4%)	188 (4.5%)	1,336 (5.0%)	3,953 (6.1%)
No	6,535 (95.6%)	1,344 (93.3%)	5,551 (96.2%)	14,168 (89.8%)	3,572 (94.6%)	3,963 (95.5%)	25,613 (95.0%)	60,749 (93.9%)
Diabetes before pregnancy?								
Yes	245 (3.6%)	77 (5.3%)	243 (4.2%)	607 (3.8%)	114 (3.0%)	162 (3.9%)	808 (3.0%)	3,953 (6.1%)
No	6,594 (96.4%)	1,365 (94.7%)	5,530 (95.8%)	15,162 (96.2%)	3,663 (97.0%)	3,989 (96.1%)	26,141 (97.0%)	62,443 (96.5%)
Infertility treatment?								
Yes	81 (1.2%)	9 (0.6%)	180 (3.1%)	113 (0.7%)	39 (1.0%)	28 (0.7%)	848 (3.1%)	1,298 (2.0%)
No	6,758 (98.8%)	1,432 (99.4%)	5,593 (96.9%)	15,656 (99.3%)	3,738 (99.0%)	4,123 (99.3%)	26,101 (96.9%)	63,401 (98.0%)
Birth Order								
1	6,773 (99.0%)	1,432 (99.4%)	5,715 (99.0%)	15,527 (98.5%)	3,737 (98.9%)	4,103 (98.8%)	26,457 (98.2%)	63,744 (98.5%)
2+	66 (1.0%)	9 (0.6%)	58 (1.0%)	242 (1.5%)	40 (1.1%)	48 (1.2%)	492 (1.8%)	955 (1.5%)
Plurality								
1	6,713 (98.2%)	1,423 (98.8%)	5,660 (98.0%)	15,294 (97.0%)	3,699 (97.9%)	4,053 (97.6%)	25,995 (96.5%)	62,837 (97.1%)
2+	126 (1.8%)	18 (1.2%)	113 (2.0%)	475 (3.0%)	78 (2.1%)	98 (2.4%)	954 (3.5%)	1,862 (2.9%)
Gestational diabetes?								
Yes	875 (12.8%)	174 (12.1%)	1,079 (18.7%)	1,490 (9.4%)	364 (10.2%)	541 (13.0%)	2,307 (8.6%)	6,850 (10.6%)
No	5,964 (87.2%)	1,267 (87.9%)	4,694 (81.3%)	14,279 (90.6%)	3,393 (89.8%)	3,610 (87.0%)	24,642 (91.4%)	57,849 (89.4%)
Socioeconomic factors								
Mother use WIC?								
Yes	3,592 (52.5%)	828 (57.5%)	1,270 (22.0%)	9,037 (57.3%)	1,604 (42.5%)	2,415 (58.2%)	5,536 (20.4%)	24,282 (37.5%)
No	3,247 (47.5%)	613 (42.5%)	4,503 (78.0%)	6,732 (42.7%)	2,173 (57.5%)	1,736 (41.8%)	21,143 (79.5%)	40,417 (62.5%)
Insurance type								
Medicaid	3,817 (55.8%)	997 (69.2%)	1,610 (27.9%)	10,892 (69.1%)	1,971 (52.2%)	2,559 (61.6%)	6,924 (25.7%)	28,770 (44.5%)
Private insurance	2,070 (30.3%)	325 (22.6%)	4,039 (70.0%)	4,326 (27.4%)	1,625 (43.0%)	996 (24.0%)	18,741 (69.5%)	32,122 (49.6%)

Self-pay	807 (11.8%)	49 (3.4%)	66 (1.1%)	266 (1.7%)	75 (2.0%)	492 (11.9%)	600 (2.2%)	2,355 (3.6%)
Government	60 (0.9%)	18 (1.2%)	32 (0.6%)	131 (0.8%)	48 (1.3%)	34 (0.8%)	349 (1.3%)	672 (1.0%)
Other	85 (1.2%)	52 (3.6%)	26 (0.5%)	154 (1.0%)	58 (1.5%)	70 (1.7%)	335 (1.2%)	780 (1.2%)

To include the established biological risk factors of gestational hypertension, socioeconomic confounders, and experiences of racism the racism-adjusted model was evaluated (Table 4). The racism-adjusted model (Table 6) showed that, on average, non-Hispanic and Hispanic Black had an odds of 1.15 times (CI = 1.03 – 1.28), and respectively, that of non-Hispanic White women of having hypertension during pregnancy. On average, an individual who was in a higher BMI category had an odds 1.58 times (CI = 1.50 – 1.66) that of an individual in a BMI category one level lower of having hypertension during pregnancy. Those who were diagnosed with hypertension before pregnancy had an odds 5.98 times (CI = 5.09 – 7.01) that of those who did not have chronic hypertension before pregnancy. Those who underwent infertility treatment had an odds 1.46 times (CI = 1.14 – 1.86) that of those who did not undergo infertility treatment of having hypertension during pregnancy. Those who had a multiples pregnancy had an odds 1.56 times (CI = 1.18 – 2.07) that of those who had a singleton pregnancy of having hypertension during pregnancy. Those who had gestational diabetes had an odds 2.11 times (CI = 1.87 – 2.36) that of those who did not have gestational diabetes of having hypertension during pregnancy. Those who experienced racism had an odds 1.14 times (CI = 1.00 – 1.31) that of those who did not experience racism of having hypertension during pregnancy.

Table 4: Adjusted Model 2 with biological risk factors, socioeconomic status confounders, and experiencing racism. *Hispanic is denoted as (H) and is denoted as Non-Hispanic (NH).*

	H White (N = 4,460)	NH & H Am. Indian & Hawaiian (N = 940)	NH & H Asian (N = 3,583)	NH & H Black (N = 12,229)	NH & H Mixed Race (N = 2,042)	NH & H other, non-White (N = 3,034)	NH White (N = 20,125)	Overall (N = 49,413)
Hypertension during pregnancy?								
Yes	536 (12.0%)	144 (15.3%)	297 (8.2%)	2,398 (19.6%)	339 (16.6%)	350 (11.5%)	3,102 (15.4%)	7,166 (15.4%)
No	3,924 (88.0%)	796 (84.7%)	3,286 (91.7%)	9,831 (80.4%)	1,703 (83.4%)	2,684 (88.5%)	17,023 (84.6%)	39,247 (84.6%)
Biological risk factors								
Age								
17-19	220 (4.9%)	76 (8.1%)	25 (0.7%)	730 (6.0%)	142 (7.0%)	175 (5.8%)	526 (2.6%)	1,894 (4.1%)
20-24	895 (20.1%)	250 (26.6%)	248 (6.9%)	2,749 (22.5%)	494 (24.2%)	604 (19.9%)	3,016 (15.0%)	8,256 (17.8%)
25-29	1,205 (27.0%)	28 (28.5%)	893 (24.9%)	3,586 (29.3%)	548 (26.8%)	857 (28.2%)	5,730 (27.4%)	13,087 (28.2%)
30-34	1,185 (26.6%)	218 (23.2%)	1,457 (40.7%)	3,028 (24.8%)	536 (26.2%)	765 (25.2%)	6,884 (34.2%)	14,073 (30.3%)
35-39	753 (16.9%)	101 (10.7%)	793 (22.1%)	1,698 (13.9%)	261 (12.8%)	492 (16.2%)	3,231 (16.1%)	7,329 (15.8%)
40+	202 (4.5%)	27 (2.9%)	167 (4.7%)	438 (3.6%)	61 (3.0%)	141 (4.6%)	738 (3.7%)	1,774 (3.8%)
BMI								
<18.5	83 (1.9%)	24 (2.6%)	253 (7.1%)	355 (2.9%)	54 (2.6%)	63 (2.1%)	696 (3.5%)	1,528 (3.3%)
18.5-24.9	1,652 (37.0%)	275 (29.3%)	2,136 (59.6%)	3,704 (30.3%)	700 (34.3%)	1,186 (39.1%)	9,450 (47.0%)	19,103 (41.2%)
25.0-29.9	1,359 (30.6%)	248 (26.4%)	804 (22.4%)	3,182 (26.0%)	532 (26.1%)	983 (32.4%)	4,972 (24.7%)	12,087 (26.0%)
30+	1,359 (30.5%)	393 (41.8%)	390 (10.9%)	4,988 (40.8%)	756 (35.0%)	802 (26.4%)	5,007 (24.9%)	13,695 (29.5%)
Hypertension before pregnancy?								
Yes	209 (4.7%)	67 (7.1%)	152 (4.2%)	1,277 (10.4%)	126 (6.2%)	140 (4.6%)	1,071 (5.3%)	3,042 (6.6%)
No	4,251 (95.3%)	873 (92.9%)	3,431 (95.8%)	10,952 (89.6%)	1,916 (93.8%)	2,894 (95.4%)	19,054 (94.7%)	43,371 (93.4%)
Diabetes before pregnancy?								
Yes	176 (3.9%)	50 (5.3%)	174 (4.9%)	496 (4.1%)	66 (3.2%)	122 (4.0%)	656 (3.3%)	1,740 (3.7%)
No	4,284 (96.1%)	890 (94.7%)	3,409 (95.1%)	11,733 (95.9%)	1,976 (96.8%)	2,912 (96.0%)	19,469 (96.7%)	44,673 (96.3%)
Infertility treatment?								
Yes	60 (1.3%)	4 (0.4%)	118 (3.3%)	84 (0.7%)	20 (1.0%)	21 (0.7%)	588 (2.9%)	895 (1.9%)
No	4,400 (98.7%)	936 (99.6%)	3,465 (96.7%)	12,145 (99.3%)	2,022 (99.0%)	3,013 (99.3%)	19,537 (97.1%)	45,518 (98.1%)
Birth order								
1	4,408 (98.8%)	932 (99.1%)	3,544 (98.9%)	12,043 (98.5%)	2,016 (98.7%)	2,992 (98.6%)	19,711 (97.9%)	45,646 (98.3%)

2+	52 (1.2%)	8 (0.9%)	39 (1.1%)	186 (1.5%)	26 (1.3%)	42 (1.4%)	414 (2.1%)	767 (1.7%)
Plurality								
1	4,364 (97.8%)	924 (98.3%)	3,505 (97.8%)	11,856 (96.9%)	1,991 (97.5%)	2,953 (97.3%)	19,335 (96.1%)	44,928 (96.8%)
2+	96 (2.2%)	16 (1.7%)	78 (2.2%)	373 (3.1%)	51 (2.5%)	81 (2.7%)	760 (3.9%)	1,485 (3.2%)
Gestational diabetes?								
Yes	558 (12.5%)	108 (11.5%)	671 (18.7%)	1,152 (9.4%)	222 (10.9%)	395 (13.0%)	1,780 (8.6%)	4,886 (10.5%)
No	3,902 (87.5%)	832 (88.5%)	2,912 (81.3%)	11,077 (90.6%)	1,820 (89.1%)	2,639 (87.0%)	18,345 (91.2%)	44,673 (89.5%)
Socioeconomic factors								
Mother use WIC?								
Yes	2,203 (49.4%)	525 (55.9%)	879 (24.5%)	7,158 (58.5%)	870 (42.6%)	1,763 (58.1%)	4,622 (23.0%)	18,020 (38.8%)
No	2,257 (50.6%)	415 (44.1%)	2,704 (75.5%)	5,071 (41.5%)	1,172 (57.4%)	1,271 (41.9%)	15,553 (77.0%)	28,393 (61.2%)
Insurance type								
Medicaid	2,478 (55.6%)	666 (70.9%)	1,072 (29.9%)	8,499 (69.5%)	1,083 (53.0%)	1,879 (61.9%)	5,669 (28.2%)	21,346 (46.0%)
Private insurance	1,402 (31.4%)	210 (22.3%)	2,430 (67.8%)	3,307 (27.0%)	851 (41.7%)	740 (24.4%)	13,438 (66.8%)	22,378 (48.2%)
Self-pay	491 (11.0%)	31 (3.3%)	44 (1.2%)	195 (1.6%)	41 (2.0%)	352 (11.6%)	451 (2.2%)	1,605 (3.5%)
Government	34 (0.8%)	12 (1.3%)	13 (0.4%)	102 (0.8%)	27 (1.3%)	20 (0.7%)	282 (1.4%)	490 (1.1%)
Other	55 (1.2%)	21 (2.2%)	24 (0.7%)	126 (1.0%)	40 (2.0%)	43 (1.4%)	285 (1.4%)	594 (1.3%)
Psychosocial factor								
Experience racism?								
Yes	747 (16.7%)	291 (31.0%)	655 (18.3%)	2,475 (20.2%)	690 (33.8%)	478 (15.8%)	757 (3.8%)	6,093 (13.1%)
No	3,713 (83.3%)	649 (69.0%)	2,928 (81.7%)	9,754 (79.8%)	1,352 (66.2%)	2,556 (84.2%)	19, 368 (96.2%)	40,320 (86.9%)

To include the established risk factors of gestational hypertension, socioeconomic confounders, and experiences of discrimination, Adjusted Model 3 was evaluated (Table 5). The discrimination-adjusted model (Table 6) showed that, on average, non-Hispanic and Hispanic Black women did not have a statistically significantly higher odds of having hypertension during pregnancy than non-Hispanic White individuals. On average, a woman who is in a higher BMI category had an odds 1.61 times (CI = 1.45 – 1.78) that of

a woman in a BMI category one level lower of having hypertension during pregnancy. Those who were diagnosed with hypertension before pregnancy had an odds 5.48 times (CI = 3.92 – 7.65) that of those who did not have chronic hypertension before pregnancy. Those who had a multiple pregnancy had an odds 2.11 times (CI = 1.10 – 4.04) that of those who had a singleton pregnancy of having hypertension during pregnancy. Those who had gestational diabetes had an odds 2.04 times (CI = 1.57 – 2.65) that of those who did not have gestational diabetes of having hypertension during pregnancy. Those who experienced discrimination had an odds 1.30 times (CI = 1.02 – 1.65) that of those who did not experience discrimination of having hypertension during pregnancy.

Table 5: Adjusted Model 3 with biological risk factors, socioeconomic status confounders, and experiencing discrimination. *Hispanic is denoted as (H) and is denoted as Non-Hispanic (NH).*

	H White (N = 1,970)	**NH & H Am. Indian & Hawaiian (N = 212)**	**NH & H Asian (N = 1,678)**	**NH & H Black (N = 3,698)**	**NH & H Mixed Race (N = 1,074)**	**NH & H other, non-White (N = 1,136)**	**NH White (N = 7,070)**	**Overall (N = 16,838)**
Hypertension during pregnancy?								
Yes	247 (12.5%)	36 (17.0%)	124 (7.4%)	821 (19.5%)	162 (15.1%)	151 (13.3%)	1,057 (15.0%)	2,498 (14.8%)
No	1,723 (87.5%)	176 (83.0%)	1,554 (91.7%)	2,977 (80.5%)	912 (84.9%)	985 (88.5%)	6,013 (85.0%)	14,340 (84.6%)
Biological risk factors								
Age								
17-19	112 (5.7%)	17 (8.1%)	11 (0.7%)	183 (4.9%)	55 (5.1%)	70 (6.2%)	103 (1.5%)	551 (3.3%)
20-24	436 (22.1%)	47 (22.2%)	88 (5.2%)	709 (19.2%)	224 (20.9%)	221 (19.5%)	665 (9.4%)	2,390 (14.2%)
25-29	531 (27.0%)	60 (28.3%)	384 (22.9%)	1,141 (30.9%)	298 (27.7%)	312 (27.5%)	1,665 (23.4%)	4,381 (26.0%)
30-34	497 (25.2%)	53 (25.0%)	745 (44.4%)	948 (25.6%)	284 (26.4%)	299 (26.3%)	2,801 (39.6%)	5,627 (33.4%)
35-39	306 (15.5%)	27 (12.7%)	364 (21.7%)	571 (15.4%)	174 (16.2%)	179 (15.8%)	1,552 (22.0%)	3,173 (18.8%)
40+	88 (4.5%)	8 (3.8%)	86 (5.1%)	146 (3.9%)	39 (3.6%)	55 (4.8%)	294 (4.2%)	716 (4.3%)
BMI								

<18.5	43 (2.2%)	7 (3.3%)	111 (6.6%)	101 (2.7%)	26 (2.4%)	35 (3.1%)	212 (3.0%)	535 (3.2%)
18.5-24.9	761 (38.6)	73 (34.4%)	995 (59.3%)	1,156 (31.3%)	427 (39.8%)	402 (35.4%)	3,533 (50.0%)	7,347 (43.6%)
25.0-29.9	584 (29.6%)	53 (25.0%)	390 (23.2%)	972 (26.3%)	270 (25.1%)	382 (33.6%)	1,681 (23.8%)	4,332 (25.7%)
30+	582 (29.5%)	79 (37.3%)	182 (10.8%)	1,469 (39.7%)	351 (32.7%)	317 (26.4%)	1,644 (23.3%)	4,624 (27.5%)
Hypertension before pregnancy?								
Yes	83 (4.2%)	13 (6.1%)	45 (2.7%)	335 (9.1%)	54 (5.0%)	50 (4.4%)	295 (4.2%)	875 (5.2%)
No	1,887 (95.8%)	199 (93.9%)	1,633 (97.3%)	3,363 (90.9%)	1,020 (95.0%)	1,086 (95.6%)	6,775 (95.8%)	15,963 (94.8%)
Diabetes before pregnancy?								
Yes	58 (2.9%)	4 (1.9%)	48 (2.9%)	115 (3.1%)	27 (2.5%)	41 (3.6%)	154 (2.2%)	447 (2.7%)
No	1,912 (97.1%)	208 (98.1%)	1,630 (97.1%)	3,583 (96.9%)	1,047 (96.8%)	1,095 (96.4%)	6,916 (97.8%)	16,391 (97.3%)
Infertility treatment?								
Yes	26 (1.3%)	3 (1.4%)	59 (3.5%)	37 (1.0%)	15 (1.4%)	9 (0.8%)	245 (3.5%)	394 (2.3%)
No	1,944 (98.7%)	209 (98.6%)	1,619 (96.5%)	3,661 (99.3%)	1,059 (98.6%)	1,127 (99.2%)	6,825 (96.5%)	16,444 (98.1%)
Birth order								
1	1.959 (99.4%)	210 (99.1%)	1,659 (98.9%)	3,650 (98.7%)	1,066 (99.3%)	1,123 (98.9%)	6,940 (98.2%)	16,607 (98.6%)
2+	11 (0.6%)	2 (0.9%)	19 (1.1%)	48 (1.3%)	8 (0.7%)	13 (1.1%)	130 (1.8%)	231 (1.4%)
Plurality								
1	1,944 (98.7%)	209 (98.6%)	1,651 (98.4%)	3,602 (97.4%)	1,055 (98.2%)	1,113 (98.0%)	6,819 (96.4%)	16,393 (97.4%)
2+	26 (1.3%)	3 (1.4%)	27 (1.6%)	96 (2.6%)	19 (1.8%)	23 (2.0%)	251 (3.6%)	445 (2.6%)
Gestational diabetes?								
Yes	252 (12.8%)	29 (13.7%)	311 (18.5%)	367 (9.9%)	100 (9.3%)	145 (12.8%)	571 (8.1%)	1,775 (10.5%)
No	1,718 (87.2%)	183 (86.3%)	1,367 (81.5%)	3,331 (90.1%)	974 (90.7%)	991 (87.2%)	6,499 (91.9%)	15,063 (89.5%)
Socioeconomic factors								
Mother use WIC?								
Yes	1,118 (56.8%)	112 (52.8%)	204 (12.2%)	1,917 (51.8%)	436 (40.6%)	636 (56.0%)	920 (13.0%)	5,343 (31.7%)
No	852 (43.2%)	100 (47.2%)	1,474 (87.8%)	1,781 (48.2%)	638 (59.4%)	500 (44.0%)	6,150 (87.0%)	11,495 (68.3%)
Insurance type								
Medicaid	1,029 (52.2%)	128 (60.4%)	311 (18.5%)	2,417 (65.4%)	550 (51.2%)	642 (56.5%)	1,316 (18.6%)	6,393 (38.0%)
Private insurance	543 (27.6%)	56 (26.4%)	1,326 (79.0%)	1,146 (31.0%)	473 (44.0%)	291 (25.6%)	5,473 (77.4%)	9,308 (55.3%)
Self-pay	341 (17.3%)	15 (7.1%)	21 (1.3%)	67 (1.8%)	25 (2.3%)	146 (12.9%)	134 (1.9%)	749 (4.4%)
Government	23 (1.2%)	4 (1.9%)	14 (0.8%)	38 (1.0%)	17 (1.6%)	19 (1.7%)	89 (1.3%)	204 (1.2%)

Other	34 (1.7%)	9 (4.2%)	6 (0.4%)	30 (0.8%)	9 (0.8%)	38 (3.3%)	89 (0.8%)	184 (1.1%)
Psychosocial factor								
Experience discrimination?								
Yes	338 (17.2%)	79 (37.3%)	243 (14.5%)	560 (15.1%)	399 (37.2%)	187 (16.5%)	817 (11.6%)	2,623 (15.6%)
No	1,632 (82.8%)	133 (62.7%)	1,435 (85.5%)	3,138 (84.9%)	675 (66.2%)	949 (83.5%)	6,253 (88.4%)	14,215 (84.4%)

Table 6: Association (odds ratio and 95% confidence interval) of race/ethnicity, biological risk factors, socioeconomic factors, and psychosocial factors with hypertension during pregnancy. *Non-Hispanic White individuals are the reference group.*

Unadjusted Model	
Race and Ethnicity	
Hispanic White	**0.78 (0.68, 0.89)**
Non-Hispanic & Hispanic American Indian & Hawaiian	1.21 (0.84,1.73)
Non-Hispanic & Hispanic Asian	**0.47 (0.40, 0.56)**
Non-Hispanic and Hispanic Black	**1.47 (1.35, 1.59)**
Non-Hispanic and Hispanic Mixed Race	1.05 (0.88, 1.25)
Non-Hispanic and Hispanic Other Non-White	**0.83 (0.71, 0.96)**
Adjusted Model 1: Adjusted without racism or discrimination	
Race and Ethnicity	
Hispanic White	**0.75 (0.63, 0.83)**
Non-Hispanic & Hispanic American Indian & Hawaiian	0.89 (0.59, 1.34)

Non-Hispanic & Hispanic Asian	**0.53 (0.45, 0.63)**
Non-Hispanic and Hispanic Black	**1.13 (1.03, 1.24)**
Non-Hispanic and Hispanic Mixed Race	0.92 (0.76, 1.11)
Non-Hispanic and Hispanic Other Non-White	**0.74 (0.63, 0.88)**
Biological risk factors	
Maternal age	**0.91 (0.88, 0.94)**
BMI	**1.60 (1.53, 1.67)**
Hypertension before pregnancy	**6.00 (5.20, 6.92)**
Diabetes before pregnancy	**0.55 (0.45, 0.69)**
Infertility treatment	**1.43 (1.15, 1.78)**
Birth order	1.15 (0.81, 1.65)
Plurality	**1.62 (1.26, 2.09)**
Gestational diabetes	**2.05 (1.85, 2.29)**
Socioeconomic factors	
WIC status	0.94 (0.86, 1.02)
Insurance type	0.97 (0.91, 1.02)
Adjusted Model 2: Adjusted, with racism	
Race and Ethnicity	
Hispanic White	**0.73 (0.62, 0.86)**
Non-Hispanic & Hispanic American Indian & Hawaiian	0.91 (0.55, 1.51)
Non-Hispanic & Hispanic Asian	**0.54 (0.45, 0.65)**
Non-Hispanic and Hispanic Black	**1.15 (1.03, 1.28)**

Non-Hispanic and Hispanic Mixed Race	0.96 (0.77, 1.20)
Non-Hispanic and Hispanic Other Non-White	**0.72 (0.60, 0.87)**
Biological risk factors	
Maternal age	**0.92 (0.89, 0.96)**
BMI	**1.58 (1.50, 1.66)**
Hypertension before pregnancy	**5.98 (5.09, 7.01)**
Diabetes before pregnancy	**0.58 (0.45, 0.73)**
Infertility treatment	**1.46 (1.14, 1.86)**
Birth order	1.28 (0.87, 1.90)
Plurality	**1.56 (1.18, 2.07)**
Gestational diabetes	**2.11 (1.87, 2.36)**
Socioeconomic factors	
Insurance type	0.97 (0.91, 1.03)
WIC status	0.96 (0.87, 1.05)
Psychosocial factor	
Experience racism	**1.14 (1.00, 1.31)**
Adjusted Model 3: Adjusted, with discrimination	
Race and Ethnicity	
Hispanic White	**0.67 (0.51, 0.88)**
Non-Hispanic & Hispanic American Indian & Hawaiian	**0.53 (0.29, 0.97)**
Non-Hispanic & Hispanic Asian	**0.40 (0.29, 0.97)**
Non-Hispanic and Hispanic Black	1.09 (0.85, 1.38)

Non-Hispanic and Hispanic Mixed Race	0.78 (0.57, 1.07)
Non-Hispanic and Hispanic Other Non-White	0.82 (0.56, 1.20)
Biological risk factors	
Maternal Age	**0.88 (0.81, 0.96)**
BMI	**1.61 (1.45, 1.78)**
Hypertension before pregnancy	**5.48 (3.92, 7.65)**
Diabetes before pregnancy	**0.57 (0.34, 0.96)**
Infertility treatment	1.59 (0.97, 2.63)
Birth order	0.85 (0.35, 2.07)
Plurality	**2.11 (1.10, 4.04)**
Gestational diabetes	**2.04 (1.57, 2.65)**
Socioeconomic factors	
WIC status	**0.77 (0.62, 0.97)**
Insurance type	0.89 (0.76, 1.03)
Psychosocial factor	
Experience discrimination	**1.30 1.02, 1.65)**

2.6 Discussion

In this work, most models showed a racial disparity with non-Hispanic and Hispanic Black participants having a higher odds of having hypertension in pregnancy compared to non-Hispanic White individuals. This mirrors many previous studies as well as our original hypotheses [154]–[156]. However, when controlling for experiences of discrimination,

these racial disparities were eliminated, providing new evidence for the role of psychosocial factors on perinatal clinical outcomes.

Discrimination can be conceived as the enaction of racial biases, and has a long history in the United States due to its founding as an enslaving republic and colonial-settler nation [174]. In terms of racism in healthcare, Hamed et al. found that the oldest article on the topic was from 2001 and the number of research studies published per year has increased since then [175]. Parallels can be drawn between previous studies and the one conducted here to explain pathways as to why those who experience racism and/or discrimination are at a higher risk of having hypertension during pregnancy. Sonderlund et al.'s systematic review found that maternal experiences of interpersonal discrimination was positively associated with adverse birth outcomes [165]. Notably, they highlighted evidence of increased allostatic load markers and longer lengths of exposure to discrimination based on exposure increased one's likelihood of adverse birth outcomes. Those who have gestational diabetes mellitus have reported stigma when seeking healthcare but also with their friends and families [176]. Davidsen et al. found that the experience of stigma for those with gestational diabetes mellitus was similar to that of those who experience weight stigma. Experiencing stigma and discrimination affected these patients by leading to increased levels of chronic stress, poor cardiometabolic outcomes, and increased risk of other adverse health outcomes. Additionally, those who experienced weight stigma felt discouraged to attend healthcare appointments [176].

To reduce racial/ethnic disparities in healthcare large, structural changes will have to be made, not only within healthcare but in other aspects of society like workplaces, schools, laws, and housing. Changes such as increasing access to affordable health care, enforcing anti-racist housing policies (which affects K-12 schooling), ensuring workplaces are equitable and inclusive, and more are just a few examples of ways to work towards a

more equitable society in the US [177]. In terms of healthcare, there have been a few anti-racism interventions that have been published and reviewed by Hassen et al. [178]. This includes many individual-level trainings, but organizations must make changes at an organizational level [178]. Many of the interventions that target racism would likely be effective against various types of discrimination that the participants in this study experienced.

Aside from race/ethnicity and racism/discrimination, when the biological risk factors of hypertension during pregnancy were included in the various models, some risk factors were shown to be protective and some were shown to increase the risk of hypertension during pregnancy. Lower socioeconomic status did not increase one's risk in most of the models, according to the parameters we used to define socioeconomic status. In the discrimination model, one's use of WIC was protective, which highlights the importance of social programs to help support pregnant individuals. In all models, age and being diagnosed with diabetes before pregnancy were protective. These were surprising results and further analyses, both qualitative and quantitative, would need to be done to understand this, as most literature states that a higher age and having diabetes before pregnancy would increase one's odds of having hypertension during pregnancy [2]. Our results showed that age and pregestational diabetes may have to be present with another comorbidity to lead to hypertension during pregnancy. Another hypothesis for this result is that these are two populations that are typically considered at risk for adverse pregnancy outcomes, thus more focused prenatal care is offered to them, which may aid in reducing their risk of developing hypertension during pregnancy. For example, those with pregestational diabetes have very specific preconception health counseling and management as recommended by the American College of Obstetricians and

Gynecologists (ACOG) [179] to reduce risk of adverse pregnancy outcomes, even before one becomes pregnant.

Overall, this study showed the importance of considering how one's experience with racism and discrimination affects one's health outcomes. In quantitative work race is often described as a biological risk factor and this study adds to the discourse around instead conceptualizing race as a proxy for racism [180]. It is essential for researchers to consider how one's race, ethnicity, weight, sexuality, culture, and other psychosocial factors influence how one is treated in their societal context, which has implications in various health outcomes.

2.7 Strengths & Limitations

This study has several strengths. Firstly, the sites that were included in the study were from various locations across the USA, which allows for geographical differences to be considered in peoples' experiences. Additionally, the confounders were chosen in a hypothesis-driven manner, with biological risk factors that have been shown in the literature of leading to a higher risk of developing hypertension during pregnancy. Also, the number of confounders allowed for in-depth analysis of these risk factors and this study was the first, to our knowledge, to include all of the risk factors identified by ACOG. A limitation of this work is that 34.3% of participants did not answer the racism question and 76% of participants did not respond to the discrimination questions. In general, more sites need to ask questions about experiences with racism and discrimination, which is a limitation of the current version (Phase 8) of the PRAMS questionnaire. Experiences with racism and discrimination questions are not required of all PRAMS sites to be asked. Almeida et al. called for action regarding this important issue and the CDC responded stating that they would include Core Questions (asked by all PRAMS sites) [181], [182], which is important for including these factors in future, more expansive research. Lastly,

due to the way we classified the participants in terms of race and ethnicity makes it difficult to directly compare some of our results to other studies. The classifications of ethnicity and race in research and beyond have oversimplified a very complex social concept [168], which is an important consideration for future studies examining racial and ethnic disparities.

2.8 Public Health Implications

Identifying and eventually uncovering the reasons behind disparities in gestational hypertension diagnoses will lead to more targeted interventions to high-risk groups and healthcare models to reduce maternal mortality in the US.

2.9 Conclusions

Hypertensive conditions of pregnancy are a leading cause of maternal mortality and are complex biologically. This study explored biological, socioeconomic, and psychosocial factors that may affect one's risk of developing hypertension during pregnancy. Experiencing discrimination and/or racism affects how one seeks care, their stress levels, and more. Further biological, quantitative, and qualitative studies should be done to mechanistically understand the effects of discrimination on health outcomes (especially using an intersectionality framework). These systemic issues must be addressed at the individual, organizational, and political levels to make legitimate strides toward equitable healthcare.

REFERENCES

[1] F. G. Cunningham *et al.*, “Hypertensive Disorders,” in *Williams Obstetrics, 25e*, New York, NY: McGraw-Hill Education, 2018.

[2] Committee on Practice Bulletins--Obstetrics, “ACOG Practice Bulletin: Gestational Hypertension and Preeclampsia,” *Clin. Manag. Guidel. Obestetrician-Gynecologists*, vol. 133, no. 76, pp. 168–186, 2019.

[3] N. I. for H. and C. Excellence, “Hypertension in pregnancy : diagnosis and management,” *Am J Obs. Gynecol*, vol. 77, no. 1, pp. S1-s22, 2019, doi: 10.1111/j.1479-828X.2009.01003.x.

[4] M. A. Brown *et al.*, “The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice,” *Pregnancy Hypertens.*, vol. 13, no. May 2018, pp. 291–310, 2018, doi: 10.1016/j.preghy.2018.05.004.

[5] World Health Organization, *WHO recommendations for: Prevention and treatment of pre-eclampsia and eclampsia*. 2011.

[6] World Health Organization, “WHO recommendations on antenatal care for a positive pregnancy experience.” 2016.

[7] L. Ghulmiyyah and B. Sibai, “Maternal Mortality From Preeclampsia/Eclampsia,” *Semin. Perinatol.*, vol. 36, no. 1, pp. 56–59, 2012, doi: 10.1053/j.semperi.2011.09.011.

[8] V. L. Bilano, E. Ota, T. Ganchimeg, R. Mori, and J. P. Souza, “Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: A WHO secondary analysis,” *PLoS One*, vol. 9, no. 3, Mar. 2014, doi: 10.1371/journal.pone.0091198.

[9] P. Chaemsaithong, D. Sahota, and L. Poon, “First trimester preeclampsia screening and prediction,” *Am. J. Obstet. Gynecol.*, Jul. 2020, doi: 10.1016/j.ajog.2020.07.020.

[10] N. O’Gorman *et al.*, “Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks’ gestation: comparison with NICE guidelines and ACOG recommendations,” *Ultrasound Obstet. Gynecol.*, vol. 49, no. 6, pp. 756–760, 2017, doi: 10.1002/uog.17455.

[11] N. Denicola, “Implementing Telehealth in Practice,” *Obstet. Gynecol.*, vol. 135, no. 2, pp. e73–e79, 2020, doi: 10.1097/AOG.0000000000003671.

[12] J. R. Barton, G. R. Saade, and B. M. Sibai, “A Proposed Plan for Prenatal Care to Minimize Risks of COVID-19 to Patients and Providers: Focus on Hypertensive Disorders of Pregnancy,” *Am. J. Perinatol.*, vol. 37, no. 8, pp. 837–844, 2020, doi: 10.1055/s-0040-1710538.

[13] A. Aziz *et al.*, “Telehealth for High-Risk Pregnancies in the Setting of the COVID-19 Pandemic,” *Am. J. Perinatol.*, vol. 37, no. 8, pp. 800–808, 2020, doi: 10.1055/s-0040-1712121.

[14] P. Von Dadelszen, L. A. Magee, and J. M. Roberts, “Subclassification of Preeclampsia,” *Hypertens. Pregnancy*, vol. 22, no. 2, pp. 143–148, 2003, doi: 10.1081/PRG-120021060.

[15] A. L. Tranquilli, M. A. Brown, G. G. Zeeman, G. Dekker, and B. M. Sibai, “Pregnancy Hypertension : An International Journal of Women ’ s Cardiovascular Health The definition of severe and early-onset preeclampsia . Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP),” *Pregnancy Hypertens. An Int. J. Women’s Cardiovasc. Heal.*, vol. 3, no. 1, pp. 44–47, 2013, doi: 10.1016/j.preghy.2012.11.001.

[16] A. Wójtowicz, M. Zembala-Szczerba, D. Babczyk, M. Kołodziejczyk-Pietruszka, O. Lewaczyńska, and H. Huras, “Early-and Late-Onset Preeclampsia: A Comprehensive Cohort Study of Laboratory and Clinical Findings according to the New ISHHP Criteria,” *Int. J. Hypertens.*, vol. 2019, 2019, doi: 10.1155/2019/4108271.

[17] D. Raymond and E. Peterson, “A Critical Review of Early-Onset and Late-Onset Preeclampsia,” *Obstet. Gynecol. Surv.*, vol. 66, no. 8, pp. 497–506, 2011, doi: 10.1017/s0021849905050130.

[18] A. Bokslag, M. van Weissenbruch, B. W. Mol, and C. J. M. de Groot, “Preeclampsia; short and long-term consequences for mother and neonate,” *Early Human Development*, vol. 102. Elsevier Ireland Ltd, pp. 47–50, Nov. 01, 2016, doi: 10.1016/j.earlhumdev.2016.09.007.

[19] J. M. Pauli and J. T. Repke, “Preeclampsia: Short-term and Long-term Implications,” *Obstetrics and Gynecology Clinics of North America*, vol. 42, no. 2. W.B. Saunders, pp. 299–313, Jun. 01, 2015, doi: 10.1016/j.ogc.2015.01.007.

[20] B. Jim and S. A. Karumanchi, “Preeclampsia: Pathogenesis, Prevention, and Long-Term Complications,” *Semin. Nephrol.*, vol. 37, no. 4, pp. 386–397, Jul. 2017, doi: 10.1016/j.semnephrol.2017.05.011.

[21] D. Williams, “Pre-eclampsia and long-term maternal health,” *Obstet. Med.*, vol. 5, no. 3, pp. 98–104, Sep. 2012, doi: 10.1258/om.2012.120013.

[22] L. Brouwers *et al.*, “Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis,” *BJOG An Int. J. Obstet. Gynaecol.*, vol. 125, no. 13, pp. 1642–1654, 2018, doi: 10.1111/1471-0528.15394.

[23] A. D. Lane-Cordova, S. S. Khan, W. A. Grobman, P. Greenland, and S. J. Shah, “Long-Term Cardiovascular Risks Associated With Adverse Pregnancy Outcomes: JACC Review Topic of the Week,” *J. Am. Coll. Cardiol.*, vol. 73, no. 16, pp. 2106–2116, Apr. 2019, doi: 10.1016/j.jacc.2018.12.092.

[24] H. Okada, T. Tsuzuki, and H. Murata, “Decidualization of the human endometrium,” *Reproductive Medicine and Biology*, vol. 17, no. 3. John Wiley and Sons Ltd, pp. 220–227, Jul. 01, 2018, doi: 10.1002/rmb2.12088.

[25] F. G. Cunningham, S. L. Leveno, Kenneth J. Bloom, J. S. Dashe, B. L. Hoffman, B. M. Casey, and C. Y. Spong, “Implantation and Placental Development,” in *Williams Obstetrics, 25e*, New York, NY: McGraw-Hill Education, 2018.

[26] L. P. Reynolds, A. T. Grazul-Bilska, and D. A. Redmer, “Angiogenesis in the corpus luteum,” *Endocrine*, vol. 12, no. 1, pp. 1–9, 2000, doi: 10.1385/endo:12:1:1.

[27] E. Lu, C. Li, J. Wang, and C. Zhang, “Inflammation and angiogenesis in the corpus luteum,” *J. Obstet. Gynaecol. Res.*, vol. 45, no. 10, pp. 1967–1974, 2019, doi: 10.1111/jog.14076.

[28] M. Y. Turco and A. Moffett, “Development of the human placenta,” *Dev.*, vol. 146, no. 22, pp. 1–14, 2019, doi: 10.1242/dev.163428.

[29] M. S. Johnson, D. L. Jackson, and D. J. Schust, “Endocrinology of pregnancy,” in *Encyclopedia of Reproduction*, Elsevier, 2018, pp. 469–476.

[30] L. A. Vodstrcil *et al.*, “Relaxin mediates uterine artery compliance during pregnancy and increases uterine blood flow,” *FASEB J.*, vol. 26, no. 10, pp. 4035–4044, 2012, doi: 10.1096/fj.12-210567.

[31] K. P. Conrad and J. M. Davison, “The renal circulation in normal pregnancy and preeclampsia: Is there a place for relaxin?,” *Am. J. Physiol. - Ren. Physiol.*, vol. 306, no. 10, 2014, doi: 10.1152/ajprenal.00042.2014.

[32] G. A. Dekker and B. M. Sibai, “Etiology and pathogenesis of preeclampsia: Current concepts,” 1998, doi: 10.1016/S0002-9378(98)70160-7.

[33] J. M. Roberts, “Pathophysiology of ischemic placental disease,” *Semin. Perinatol.*, vol. 38, no. 3, pp. 139–145, 2014, doi: 10.1038/jid.2014.371.

[34] N. M. Gude, C. T. Roberts, B. Kalionis, and R. G. King, “Growth and function of the normal human placenta,” *Thromb. Res.*, vol. 114, no. 5-6 SPEC. ISS., pp. 397–407, 2004, doi: 10.1016/j.thromres.2004.06.038.

[35] S. A. Robertson, A. S. Care, and L. M. Moldenhauer, “Regulatory T cells in embryo implantation and the immune response to pregnancy,” *J. Clin. Invest.*, vol. 128, no. 10, pp. 4224–4235, 2018, doi: 10.1172/JCI122182.

[36] C. W. G. Redman, “Current Topic: Pre-eclampsia and the Placenta,” *Placenta*, vol. 12, pp. 301–308, 1991.

[37] A. C. Staff, “The two-stage placental model of preeclampsia: An update,” *J. Reprod. Immunol.*, vol. 134–135, no. June, pp. 1–10, 2019, doi: 10.1016/j.jri.2019.07.004.

[38] D. Wertaschnigg, M. Reddy, B. W. J. Mol, D. L. Rolnik, and F. da Silva Costa, “Prenatal screening for pre-eclampsia: Frequently asked questions,” *Aust. New Zeal. J. Obstet. Gynaecol.*, vol. 59, no. 4, pp. 477–483, 2019, doi: 10.1111/ajo.12982.

[39] J. R. Barton and B. M. Sibai, “Prediction and Prevention of Recurrent Preeclampsia,” vol. 112, no. 2, pp. 359–372, 2008.

[40] K. Bramham, A. L. Briley, P. Seed, L. Poston, A. H. Shennan, and L. C. Chappell, “Adverse maternal and perinatal outcomes in women with previous preeclampsia: A prospective study,” *Am. J. Obstet. Gynecol.*, vol. 204, no. 6, pp. 512.e1-512.e9, 2011, doi: 10.1016/j.ajog.2011.02.014.

[41] C. W. G. Redman and A. C. Staff, “Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity,” *Am. J. Obstet. Gynecol.*, vol. 213, no. 4, p. S9.e1-

S9.e4, 2015, doi: 10.1016/j.ajog.2015.08.003.

[42] F. J. Broekmans, E. A. H. Knauff, E. R. te Velde, N. S. Macklon, and B. C. Fauser, “Female reproductive ageing: current knowledge and future trends,” *Trends in Endocrinology and Metabolism*, vol. 18, no. 2. Elsevier Current Trends, pp. 58–65, Mar. 01, 2007, doi: 10.1016/j.tem.2007.01.004.

[43] Z. Sultana, K. Maiti, L. Dedman, and R. Smith, “Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction?,” *American Journal of Obstetrics and Gynecology*, vol. 218, no. 2. Mosby Inc., pp. S762–S773, Feb. 01, 2018, doi: 10.1016/j.ajog.2017.11.567.

[44] P. E. Parra-Pingel, L. A. Quisiguiña-Avellán, L. Hidalgo, P. Chedraui, and F. R. Pérez-López, “Pregnancy outcomes in younger and older adolescent mothers with severe preeclampsia,” *Adolesc. Health. Med. Ther.*, vol. Volume 8, pp. 81–86, Jun. 2017, doi: 10.2147/ahmt.s131050.

[45] I. Brosens *et al.*, “Adolescent Preeclampsia: Pathological Drivers and Clinical Prevention,” *Reproductive Sciences*, vol. 26, no. 2. SAGE Publications Inc., pp. 159–171, Feb. 01, 2019, doi: 10.1177/1933719118804412.

[46] K. Ndiaye, E. Portillo, D. Ouedraogo, A. Mobley, and S. Babalola, “High-risk advanced maternal age and high parity pregnancy: Tackling a neglected need through formative research and action,” *Glob. Heal. Sci. Pract.*, vol. 6, no. 2, pp. 370–380, 2018, doi: 10.9745/GHSP-D-17-00417.

[47] M. Y. Tan *et al.*, “Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE,” *Ultrasound Obstet. Gynecol.*, vol. 52, no. 1, pp. 52–59, 2018, doi: 10.1002/uog.19077.

[48] C. W. G. Redman and I. L. Sargent, “Immunology of Pre-Eclampsia,” *Am. J. Reprod. Immunol.*, vol. 63, no. 6, pp. 534–543, 2010, doi: 10.1111/j.1600-0897.2010.00831.x.

[49] S. A. Robertson and D. J. Sharkey, “Seminal fluid and fertility in women,” *Fertility and Sterility*, vol. 106, no. 3. Elsevier Inc., pp. 511–519, Sep. 01, 2016, doi: 10.1016/j.fertnstert.2016.07.1101.

[50] C. Thomopoulos *et al.*, “Risk of hypertensive disorders in pregnancy following assisted reproductive technology: overview and meta-analysis,” *J. Clin. Hypertens.*, vol. 19, no. 2, pp. 173–183, Feb. 2017, doi: 10.1111/jch.12945.

[51] M. Storgaard *et al.*, “Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis,” *BJOG An Int. J. Obstet. Gynaecol.*, vol. 124, no. 4, pp. 561–572, 2017, doi: 10.1111/1471-0528.14257.

[52] D. Alecsandru *et al.*, “Parental human leukocyte antigen-C allotypes are predictive of live birth rate and risk of poor placentation in assisted reproductive treatment,” *Fertil. Steril.*, vol. 114, no. 4, pp. 809–817, Oct. 2020, doi: 10.1016/j.fertnstert.2020.05.008.

[53] K. van Bentem *et al.*, “The development of preeclampsia in oocyte donation pregnancies is related to the number of fetal-maternal HLA class II mismatches,” *J. Reprod. Immunol.*, vol. 137, p. 103074, Feb. 2020, doi: 10.1016/j.jri.2019.103074.

[54] C. Thomopoulos, C. Tsioufis, H. Michalopoulou, T. Makris, V. Papademetriou, and C. Stefanadis, “Assisted reproductive technology and pregnancy-related hypertensive complications: A systematic review,” *J. Hum. Hypertens.*, vol. 27, no. 3, pp. 148–157, 2013, doi: 10.1038/jhh.2012.13.

[55] M. J. Kupferminc, “Thrombophilia and pregnancy,” *Reprod. Biol. Endocrinol.*, vol. 1, no. 111, Nov. 2003, doi: 10.1186/1477-7827-1-111.

[56] A. Lateef and M. Petri, “Systemic Lupus Erythematosus and Pregnancy,” *Rheum. Dis. Clin. North Am.*, vol. 43, no. 2, pp. 215–226, 2017, doi: 10.1016/j.rdc.2016.12.009.

[57] A. N. Baer, F. R. Witter, and M. Petri, “Lupus and pregnancy,” *Obstet. Gynecol. Surv.*, vol. 66, no. 10, pp. 639–653, 2011, doi: 10.1097/OGX.0b013e318239e1ee.

[58] E. Stolarczyk, “Adipose tissue inflammation in obesity: a metabolic or immune response?,” *Current Opinion in Pharmacology*, vol. 37. Elsevier Ltd, pp. 35–40, Dec. 01, 2017, doi: 10.1016/j.coph.2017.08.006.

[59] P. M. Catalano and K. Shankar, “Obesity and pregnancy: Mechanisms of short term and long term adverse consequences for mother and child,” *BMJ (Online)*, vol. 356. BMJ Publishing Group, p. 1, Feb. 08, 2017, doi: 10.1136/bmj.j1.

[60] D. Williams and J. Davison, “Pregnancy plus: Chronic kidney disease in pregnancy,” *BMJ*, vol. 336, no. 7637. BMJ Publishing Group, pp. 211–215, Jan. 26, 2008, doi: 10.1136/bmj.39406.652986.BE.

[61] E. R. Lumbers, S. J. Delforce, A. L. Arthurs, and K. G. Pringle, “Causes and Consequences of the Dysregulated Maternal Renin-Angiotensin System in Preeclampsia,” *Frontiers in Endocrinology*, vol. 10. Frontiers Media S.A., p. 563, Sep. 10, 2019, doi: 10.3389/fendo.2019.00563.

[62] G. M. Egeland, K. Klungsøyr, N. Øyen, G. S. Tell, Ø. Næss, and R. Skjærven, “Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension and Preeclampsia: Cohort Norway Study.,” *Hypertens. (Dallas, Tex. 1979)*, vol. 67, no. 6, pp. 1173–80, Jun. 2016, doi: 10.1161/HYPERTENSIONAHA.116.07099.

[63] G. Leguizamón, D. Trigubo, J. I. Pereira, M. F. Vera, and J. A. Fernández, “Vascular Complications in the Diabetic Pregnancy,” *Current Diabetes Reports*, vol. 15, no. 4. Current Medicine Group LLC 1, pp. 1–10, Mar. 04, 2015, doi: 10.1007/s11892-015-0586-5.

[64] C. Smith, F. Teng, E. Branch, S. Chu, and K. S. Joseph, “Maternal and Perinatal Morbidity and Mortality Associated with Anemia in Pregnancy,” *Obstet. Gynecol.*, vol. 134, no. 6, pp. 1234–1244, 2019, doi: 10.1097/AOG.0000000000003557.

[65] K. J. Gray, R. Saxena, and S. A. Karumanchi, “Genetic predisposition to preeclampsia is conferred by fetal DNA variants near FLT1, a gene involved in the regulation of angiogenesis,” *Am. J. Obstet. Gynecol.*, vol. 218, no. 2, pp. 211–218, 2018, doi: 10.1016/j.physbeh.2017.03.040.

[66] L. C. CHESLEY and D. W. COOPER, “Genetics of hypertension in pregnancy: possible single gene control of pre-eclampsia and eclampsia in the descendants of eclamptic women,” *BJOG An Int. J. Obstet. Gynaecol.*, vol. 93, no. 9, pp. 898–908,

1986, doi: 10.1111/j.1471-0528.1986.tb08006.x.

[67] A. Nejatizadeh, T. Stobdan, N. Malhotra, and M. A. Q. Pasha, “The genetic aspects of pre-eclampsia: Achievements and limitations,” *Biochemical Genetics*, vol. 46, no. 7–8. Springer, pp. 451–479, Aug. 24, 2008, doi: 10.1007/s10528-008-9163-9.

[68] P. A. Benny, F. M. Alakwaa, R. J. Schlueter, C. B. Lassiter, and L. X. Garmire, “A review of omics approaches to study preeclampsia,” *Placenta*, vol. 92, no. January, pp. 17–27, 2020, doi: 10.1016/j.placenta.2020.01.008.

[69] J. A. M. Graves, “Genomic imprinting, development and disease -- is pre-eclampsia caused by a maternal imprinted gene?,” *Reprod. Fertil. Dev.*, vol. 10, pp. 23–29, 1998, doi: 10.1071/RD98014.

[70] J. H. Flaskerud and C. R. Delilly, “Social determinants of health status,” *Issues Ment. Health Nurs.*, vol. 33, no. 7, pp. 494–497, Jul. 2012, doi: 10.3109/01612840.2012.662581.

[71] S. Artiga and E. Hinton, “Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity | The Henry J. Kaiser Family Foundation,” *Kaiser Family Foundation*, no. May. 2018, [Online]. Available: https://www.kff.org/disparities-policy/issue-brief/beyond-health-care-the-role-of-social-determinants-in-promoting-health-and-health-equity/.

[72] M. Zhang *et al.*, “Preeclampsia Among African American Pregnant Women,” *Obstet. Gynecol. Surv.*, vol. 75, no. 2, pp. 111–120, Feb. 2020, doi: 10.1097/OGX.0000000000000747.

[73] K. M. Ross, C. Guardino, C. Dunkel Schetter, and C. J. Hobel, “Interactions between race/ethnicity, poverty status, and pregnancy cardio-metabolic diseases in prediction of postpartum cardio-metabolic health,” *Ethn. Heal.*, pp. 1–16, Jul. 2018, doi: 10.1080/13557858.2018.1493433.

[74] M. Tanaka *et al.*, “Racial disparity in hypertensive disorders of pregnancy in New York state: A 10-year longitudinal population-based study,” *Am. J. Public Health*, vol. 97, no. 1, pp. 163–170, Jan. 2007, doi: 10.2105/AJPH.2005.068577.

[75] K. M. Ross *et al.*, “Socioeconomic Status, Preeclampsia Risk and Gestational Length in Black and White Women,” *J. Racial Ethn. Heal. Disparities*, vol. 6, no. 6, pp. 1182–1191, Dec. 2019, doi: 10.1007/s40615-019-00619-3.

[76] M. E. B. Clowse and C. Grotegut, “Racial and Ethnic Disparities in the Pregnancies of Women With Systemic Lupus Erythematosus,” *Arthritis Care Res.*, vol. 68, no. 10, pp. 1567–1572, 2016, doi: 10.1002/acr.22847.

[77] A. Barnado, L. Wheless, A. K. Meyer, G. S. Gilkeson, and D. L. Kamen, “Pregnancy outcomes among African-American patients with systemic lupus erythematosus compared with controls,” *Lupus Sci. Med.*, vol. 1, no. 1, p. 20, Jun. 2014, doi: 10.1136/lupus-2014-000020.

[78] L. C. Chappell, S. Enye, P. Seed, A. L. Briley, L. Poston, and A. H. Shennan, “Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: A prospective study,” *Hypertension*, vol. 51, no. 4 PART 2 SUPPL., pp. 1002–1009, Apr. 2008, doi: 10.1161/HYPERTENSIONAHA.107.107565.

[79] A. R. Samadi, R. M. Mayberry, A. A. Zaidi, J. C. Pleasant, N. McGhee, and R. J. Rice, “Maternal hypertension and associated pregnancy complications among african-american and other women in the united states,” *Obstet. Gynecol.*, vol. 87, no. 4, pp. 557–563, 1996, doi: 10.1016/0029-7844(95)00480-7.

[80] C. D. Odell *et al.*, “Maternal hypertension as a risk factor for low birth weight infants: Comparison of Haitian and African-American women,” *Matern. Child Health J.*, vol. 10, no. 1, pp. 39–46, Jan. 2006, doi: 10.1007/s10995-005-0026-2.

[81] B. T. Nguyen, Y. W. Cheng, J. M. Snowden, T. F. Esakoff, A. E. Frias, and A. B. Caughey, “The effect of race/ethnicity on adverse perinatal outcomes among patients with gestational diabetes mellitus,” *Am. J. Obstet. Gynecol.*, vol. 207, no. 4, pp. 322.e1-322.e6, Oct. 2012, doi: 10.1016/j.ajog.2012.06.049.

[82] T. James-Todd, T. Janevic, F. M. Brown, and D. A. Savitz, “Race/ethnicity, educational attainment, and pregnancy complications in New York City women with pre-existing diabetes,” *Paediatr. Perinat. Epidemiol.*, vol. 28, no. 2, pp. 157–165, 2014, doi: 10.1111/ppe.12100.

[83] K. J. Reidy *et al.*, “Fetal—Not Maternal—APOL1 Genotype Associated with Risk for Preeclampsia in Those with African Ancestry,” *Am. J. Hum. Genet.*, vol. 103, no. 3, pp. 367–376, Sep. 2018, doi: 10.1016/j.ajhg.2018.08.002.

[84] D. J. Rouse, “The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus: Commentary,” *Obstet. Gynecol. Surv.*, vol. 61, no. 2, pp. 78–79, 2006, doi: 10.1097/01.ogx.0000197814.31769.3b.

[85] G. J. Burton, C. W. Redman, J. M. Roberts, and A. Moffett, “Pre-eclampsia: pathophysiology and clinical implications,” *The BMJ*, vol. 366. BMJ Publishing Group, 2019, doi: 10.1136/bmj.l2381.

[86] O. O. Osuchukwu and D. J. Reed, *Small for Gestational Age*. StatPearls Publishing, 2020.

[87] L. E. Frederiksen *et al.*, “Risk of Adverse Pregnancy Outcomes at Advanced Maternal Age,” *Obstet. Gynecol.*, vol. 131, no. 3, pp. 457–463, Mar. 2018, doi: 10.1097/AOG.0000000000002504.

[88] Z. C. Luo, N. An, H. R. Xu, A. Larante, F. Audibert, and W. D. Fraser, “The effects and mechanisms of primiparity on the risk of pre-eclampsia: A systematic review,” *Paediatr. Perinat. Epidemiol.*, vol. 21, no. SUPPL. 1, pp. 36–45, 2007, doi: 10.1111/j.1365-3016.2007.00836.x.

[89] Z. Jie, D. Yiling, and Y. Ling, “Association of assisted reproductive technology with adverse pregnancy outcomes,” *Iran. J. Reprod. Med.*, vol. 13, no. 3, pp. 169–180, 2015, Accessed: Nov. 03, 2020. [Online]. Available: /pmc/articles/PMC4426157/?report=abstract.

[90] A. Almasi-Hashiani *et al.*, “Assisted reproductive technology and the risk of preeclampsia: An updated systematic review and meta-analysis,” *BMC Pregnancy and Childbirth*, vol. 19, no. 1. BioMed Central Ltd., May 02, 2019, doi: 10.1186/s12884-019-2291-x.

[91] R. Omani-Samani *et al.*, “Risk of preeclampsia following assisted reproductive technology: systematic review and meta-analysis of 72 cohort studies,” *J. Matern.*

Neonatal Med., vol. 33, no. 16, pp. 2826–2840, Aug. 2020, doi: 10.1080/14767058.2018.1560406.

[92] K. Liu *et al.*, “Advanced Reproductive Age and Fertility,” *J. Obstet. Gynaecol. Canada*, vol. 33, no. 11, pp. 1165–1175, 2011, doi: 10.1016/S1701-2163(16)35087-3.

[93] S. Y. Choo, “The HLA system: Genetics, immunology, clinical testing, and clinical implications,” *Yonsei Med. J.*, vol. 48, no. 1, pp. 11–23, Feb. 2007, doi: 10.3349/ymj.2007.48.1.11.

[94] L. M. Sun, M. C. Walker, H. L. Cao, Q. Yang, T. Duan, and J. C. P. Kingdom, “Assisted reproductive technology and placenta-mediated adverse pregnancy outcomes,” *Obstet. Gynecol.*, vol. 114, no. 4, pp. 818–824, 2009, doi: 10.1097/AOG.0b013e3181b76bd1.

[95] G. Hawthorne, “Maternal complications in diabetic pregnancy,” *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 25, no. 1, pp. 77–90, Feb. 2011, doi: 10.1016/j.bpobgyn.2010.10.015.

[96] P. J. Williams and F. Broughton Pipkin, “The genetics of pre-eclampsia and other hypertensive disorders of pregnancy,” *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 25, no. 4, pp. 405–417, 2011, doi: 10.1016/j.bpobgyn.2011.02.007.

[97] K. Bibbins-Domingo *et al.*, “Screening for Preeclampsia US preventive services task force recommendation statement,” *JAMA - J. Am. Med. Assoc.*, vol. 317, no. 16, pp. 1661–1667, Apr. 2017, doi: 10.1001/jama.2017.3439.

[98] P. Wu *et al.*, “Early Pregnancy Biomarkers in Pre-Eclampsia: A Systematic Review and Meta-Analysis.,” *Int. J. Mol. Sci.*, vol. 16, no. 9, pp. 23035–56, Sep. 2015, doi: 10.3390/ijms160923035.

[99] F. P. McCarthy, R. M. Ryan, and L. C. Chappell, “Prospective biomarkers in preterm preeclampsia: A review,” *Pregnancy Hypertens.*, vol. 14, pp. 72–78, Oct. 2018, doi: 10.1016/j.preghy.2018.03.010.

[100] A. Umapathy, L. W. Chamley, and J. L. James, “Reconciling the distinct roles of angiogenic/anti-angiogenic factors in the placenta and maternal circulation of normal and pathological pregnancies,” *Angiogenesis*, vol. 23, no. 2. Springer, pp. 105–117, May 01, 2020, doi: 10.1007/s10456-019-09694-w.

[101] P. Gathiram and J. Moodley, “Pre-eclampsia: Its pathogenesis and pathophysiolgy,” *Cardiovascular Journal of Africa*, vol. 27, no. 2. Clinics Cardive Publishing (PTY)Ltd, pp. 71–78, Mar. 01, 2016, doi: 10.5830/CVJA-2016-009.

[102] R. T. Michita, V. de L. Kaminski, and J. A. B. Chies, “Genetic Variants in Preeclampsia: Lessons From Studies in Latin-American Populations,” *Front. Physiol.*, vol. 9, p. 1771, Dec. 2018, doi: 10.3389/fphys.2018.01771.

[103] A. C. De Kat, J. Hirst, M. Woodward, S. Kennedy, and S. A. Peters, “Prediction models for preeclampsia: A systematic review,” *Pregnancy Hypertens.*, vol. 16, no. March, pp. 48–66, 2019, doi: 10.1016/j.preghy.2019.03.005.

[104] I. Marić *et al.*, “Early prediction of preeclampsia via machine learning,” *Am. J. Obstet. Gynecol. MFM*, vol. 2, no. 2, p. 100100, 2020, doi: 10.1016/j.ajogmf.2020.100100.

[105] D. Wright *et al.*, “Predictive performance of the competing risk model in screening for preeclampsia,” *Am. J. Obstet. Gynecol.*, vol. 220, no. 2, pp. 199.e1-199.e13, Feb. 2019, doi: 10.1016/j.ajog.2018.11.1087.

[106] D. L. Rolnik *et al.*, “Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia,” *N. Engl. J. Med.*, vol. 377, no. 7, pp. 613–622, Aug. 2017, doi: 10.1056/nejmoa1704559.

[107] T. Firoz, H. Sanghvi, M. Merialdi, and P. Von Dadelszen, “Pre-eclampsia in low and middle income countries,” *Best Practice and Research: Clinical Obstetrics and Gynaecology*, vol. 25, no. 4. Bailliere Tindall Ltd, pp. 537–548, Aug. 01, 2011, doi: 10.1016/j.bpobgyn.2011.04.002.

[108] D. Wright, A. Wright, and K. H. Nicolaides, “The competing risk approach for prediction of preeclampsia,” *American Journal of Obstetrics and Gynecology*, vol. 223, no. 1. Mosby Inc., pp. 12–23, Jul. 01, 2020, doi: 10.1016/j.ajog.2019.11.1247.

[109] C. McSpedon, “Reproductive Care During COVID-19,” *Am. J. Nurs.*, vol. 120, no. 9, pp. 19–20, 2020, doi: 10.1097/01.NAJ.0000697600.29112.22.

[110] Z. M. McLaren *et al.*, “Cost effectiveness of medical devices to diagnose pre-eclampsia in low-resource settings,” *Dev. Eng.*, vol. 2, pp. 99–106, 2017, doi: 10.1016/j.deveng.2017.06.002.

[111] C. E. Majors, C. A. Smith, M. E. Natoli, K. A. Kundrod, and R. Richards-Kortum, “Point-of-care diagnostics to improve maternal and neonatal health in low-resource settings,” *Lab Chip*, vol. 17, no. 20, pp. 3351–3387, 2017, doi: 10.1039/c7lc00374a.

[112] H. L. Nathan *et al.*, “The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings,” *Reprod. Health*, vol. 15, no. 1, p. 5, Jan. 2018, doi: 10.1186/s12978-017-0450-y.

[113] L. A. Magee, A. Khalil, and P. von Dadelszen, “Pregnancy hypertension diagnosis and care in COVID-19 era and beyond,” *Ultrasound Obstet. Gynecol.*, vol. 56, no. 1, pp. 7–10, 2020, doi: 10.1002/uog.22115.

[114] K. A. Stewart *et al.*, “Trends in Ultrasound Use in Low and Middle Income Countries: A Systematic Review.,” *Int. J. MCH AIDS*, vol. 9, no. 1, pp. 103–120, 2020, doi: 10.21106/ijma.294.

[115] A. Hurrell, A. Beardmore-Gray, K. Duhig, L. Webster, L. Chappell, and A. Shennan, “Placental Growth Factor in Suspected Preterm Pre-eclampsia: A Review of the Evidence and Practicalities of Implementation,” *BJOG An Int. J. Obstet. Gynaecol.*, pp. 1471–0528.16425, Jul. 2020, doi: 10.1111/1471-0528.16425.

[116] G. F. Grauer, “Proteinuria: Measurement and Interpretation,” *Top. Companion Anim. Med.*, vol. 26, no. 3, pp. 121–127, Aug. 2011, doi: 10.1053/j.tcam.2011.04.002.

[117] E. J. Lamb, F. MacKenzie, and P. E. Stevens, “How should proteinuria be detected and measured?,” *Ann. Clin. Biochem.*, vol. 46, no. 3, pp. 205–217, 2009, doi: 10.1258/acb.2009.009007.

[118] I. A. Buhimschi *et al.*, “Protein misfolding, congophilia, oligomerization, and

defective amyloid processing in preeclampsia," *Sci. Transl. Med.*, vol. 6, no. 245, pp. 245ra92-245ra92, Jul. 2014, doi: 10.1126/scitranslmed.3008808.

[119] E. A. P. Steegers, P. Von Dadelszen, J. J. Duvekot, and R. Pijnenborg, "Pre-eclampsia," *Lancet*, vol. 376, no. 9741, pp. 631–644, 2010, doi: 10.1016/S0140-6736(10)60279-6.

[120] L. De Oliveira *et al.*, "Creating biobanks in low and middle-income countries to improve knowledge – The PREPARE initiative," *Pregnancy Hypertens.*, vol. 13, pp. 62–64, Jul. 2018, doi: 10.1016/j.preghy.2018.05.007.

[121] F. R. Giachini *et al.*, "Vascular Dysfunction in Mother and Offspring During Preeclampsia: Contributions from Latin-American Countries," *Current Hypertension Reports*, vol. 19, no. 10. Current Medicine Group LLC 1, p. 83, Oct. 01, 2017, doi: 10.1007/s11906-017-0781-7.

[122] A. Conde-Agudelo and J. M. Belizán, "Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women," *BJOG An Int. J. Obstet. Gynaecol.*, vol. 107, no. 1, pp. 75–83, Jan. 2000, doi: 10.1111/j.1471-0528.2000.tb11582.x.

[123] M. W. Meazaw, C. Chojenta, M. D. Muluneh, and D. Loxton, "Systematic and meta-analysis of factors associated with preeclampsia and eclampsia in sub-Saharan Africa," *PLoS One*, vol. 15, no. 8, p. e0237600, Aug. 2020, doi: 10.1371/journal.pone.0237600.

[124] M. P. Rambaldi, E. Weiner, F. Mecacci, J. Bar, and F. Petraglia, "Immunomodulation and preeclampsia," *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 60, pp. 87–96, 2019, doi: 10.1016/j.bpobgyn.2019.06.005.

[125] K. J. Askelund and L. W. Chamley, "Trophoblast deportation part I: Review of the evidence demonstrating trophoblast shedding and deportation during human pregnancy," *Placenta*, vol. 32, no. 10, pp. 716–723, 2011, doi: 10.1016/j.placenta.2011.07.081.

[126] R. Ganapathy, L. J. Ayling, G. S. J. Whitley, J. E. Cartwright, and B. Thilaganathan, "Effect of first-trimester serum from pregnant women with high-resistance uterine artery Doppler resistance on extravillous trophoblast invasion," *Hum. Reprod.*, vol. 21, no. 5, pp. 1295–1298, May 2006, doi: 10.1093/humrep/dei482.

[127] S. Kalkunte *et al.*, "Sera from preeclampsia patients elicit symptoms of human disease in mice and provide a basis for an in vitro predictive assay," *Am. J. Pathol.*, vol. 177, no. 5, pp. 2387–2398, Nov. 2010, doi: 10.2353/ajpath.2010.100475.

[128] K. A. Pennington, J. M. Schlitt, D. L. Jackson, L. C. Schulz, and D. J. Schust, "Preeclampsia: Multiple approaches for a multifactorial disease," *DMM Dis. Model. Mech.*, vol. 5, no. 1, pp. 9–18, Jan. 2012, doi: 10.1242/dmm.008516.

[129] P. J. Garcia, P. You, G. Fridley, D. Mabey, and R. Peeling, "Point-of-care diagnostic tests for low-resource settings," *Lancet Glob. Heal.*, vol. 3, no. 5, pp. e257–e258, 2015, doi: 10.1016/S2214-109X(15)70089-6.

[130] M. G. Da Broi, V. S. I. Giorgi, F. Wang, D. L. Keefe, D. Albertini, and P. A. Navarro, "Influence of follicular fluid and cumulus cells on oocyte quality: Clinical implications," *J. Assist. Reprod. Genet.*, vol. 35, no. 5, pp. 735–751, 2018, doi:

10.1007/s10815-018-1143-3.

[131] A. L. Tarca *et al.*, “Maternal whole blood mRNA signatures identify women at risk of early preeclampsia: a longitudinal study,” *J. Matern. Neonatal Med.*, 2020, doi: 10.1080/14767058.2019.1685964.

[132] K. Breathett, D. Muhlestein, R. Foraker, and M. Gulati, “Differences in Preeclampsia Rates Between African American and Caucasian Women: Trends from the National Hospital Discharge Survey,” *J. Women’s Heal.*, vol. 23, no. 11, pp. 886–893, Nov. 2014, doi: 10.1089/jwh.2014.4749.

[133] J. A. Pellowski *et al.*, “Perinatal depression among mothers in a South African birth cohort study: Trajectories from pregnancy to 18 months postpartum,” *J. Affect. Disord.*, vol. 259, no. June, pp. 279–287, 2019, doi: 10.1016/j.jad.2019.08.052.

[134] L. J. Lee *et al.*, “Role of maternal occupational physical activity and psychosocial stressors on adverse birth outcomes,” *Occup. Environ. Med.*, vol. 74, no. 3, pp. 192–199, Mar. 2017, doi: 10.1136/oemed-2016-103715.

[135] C. Giurgescu and D. P. Misra, “Psychosocial Factors and Preterm Birth Among Black Mothers and Fathers,” *MCN, Am. J. Matern. Nurs.*, vol. 43, no. 5, pp. 245–251, Sep. 2018, doi: 10.1097/NMC.0000000000000458.

[136] C. Giurgescu *et al.*, “Relationships among psychosocial factors, biomarkers, preeclampsia, and preterm birth in African American women: A pilot,” *Appl. Nurs. Res.*, vol. 28, no. 1, pp. e1–e6, Feb. 2015, doi: 10.1016/j.apnr.2014.09.002.

[137] M. C. Arcaya, A. L. Arcaya, and S. V. Subramanian, “Inequalities in health: definitions, concepts, and theories,” *Rev. Panam. Salud Publica*, vol. 38, no. 4, pp. 261–271, 2015, doi: 10.3402/gha.v8.27106.

[138] R. R. Hardeman, K. A. Murphy, J. Karbeah, and K. B. Kozhimannil, “Naming Institutionalized Racism in the Public Health Literature: A Systematic Literature Review,” *Public Health Rep.*, vol. 133, no. 3, p. 240, 2018, doi: 10.1177/0033354918760574.

[139] L. Sheets, J. Johnson, T. Todd, T. Perkins, C. Gu, and M. Rau, “Unsupported Labeling of Race as a Risk Factor for Certain Diseases in a Widely Used Medical Textbook,” *Acad. Med.*, vol. 86, no. 10, pp. 1300–1303, Oct. 2011, doi: 10.1097/ACM.0b013e31822bbdb5.

[140] A. T. Geronimus, “The weathering hypothesis and the health of African-American women and infants: evidence and speculations.,” *Ethnicity & disease*, vol. 2, no. 3. pp. 207–221, Jun. 01, 1992, Accessed: Nov. 23, 2020. [Online]. Available: https://europepmc.org/article/med/1467758.

[141] A. Roeder, “America is Failing its Black Mothers | Harvard Public Health Magazine | Harvard T.H. Chan School of Public Health,” *Magazine of the Harvard T.H. Chan School of Public Health*, 2019.

[142] R. Walker, J. Williams, and L. Egede, “Impact of Race/Ethnicity and Social Determinants of Health on Diabetes Outcomes,” *Am J Med Sci*, vol. 35, no. 4, pp. 366–373, 2016, doi: 10.1016/j.amjms.2016.01.008.Impact.

[143] M. Hanson, “The inheritance of cardiovascular disease risk,” *Acta Paediatr.*, vol. 108, no. 10, pp. 1747–1756, Oct. 2019, doi: 10.1111/apa.14813.

[144] S. Sullivan, “Inheriting Racist Disparities in Health: Epigenetics and the Transgenerational Effects of White Racism,” *Crit. Philos. Race*, vol. 1, no. 2, pp. 190–218, 2013.

[145] J. Gong, D. A. Savitz, C. R. Stein, and S. M. Engel, “Maternal ethnicity and pre-eclampsia in New York City, 1995-2003,” *Paediatr. Perinat. Epidemiol.*, vol. 26, no. 1, pp. 45–52, Jan. 2012, doi: 10.1111/j.1365-3016.2011.01222.x.

[146] S. M. Cripe, W. O’Brien, B. Gelaye, and M. A. Williams, “Perinatal outcomes of Southeast Asians with pregnancies complicated by gestational diabetes mellitus or preeclampsia,” *J. Immigr. Minor. Heal.*, vol. 14, no. 5, pp. 747–753, Oct. 2012, doi: 10.1007/s10903-011-9537-7.

[147] K. M. Flegal *et al.*, “Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults,” *Am. J. Clin. Nutr.*, vol. 89, no. 2, pp. 500–508, Feb. 2009, doi: 10.3945/ajcn.2008.26847.

[148] A. M. Prentice and S. A. Jebb, “Beyond body mass index,” *Obes. Rev.*, vol. 2, no. 3, pp. 141–147, 2001, doi: 10.1046/j.1467-789x.2001.00031.x.

[149] D. Gallagher, S. B. Heymsfield, M. Heo, S. A. Jebb, P. R. Murgatroyd, and Y. Sakamoto, “Healthy percentage body fat ranges: An approach for developing guidelines based on body mass index,” *Am. J. Clin. Nutr.*, vol. 72, no. 3, pp. 694–701, Sep. 2000, doi: 10.1093/ajcn/72.3.694.

[150] S. Humphreys, “The unethical use of BMI in contemporary general practice,” *Br. J. Gen. Pract.*, vol. 60, no. 578, pp. 696–697, Sep. 2010, doi: 10.3399/bjgp10X515548.

[151] F. L. Foo *et al.*, “Association between prepregnancy cardiovascular function and subsequent preeclampsia or fetal growth restriction,” *Hypertension*, vol. 72, no. 2, pp. 442–450, 2018, doi: 10.1161/HYPERTENSIONAHA.118.11092.

[152] OECD, “OECD (2022), Health spending (indicator),” *OECD*, Nov. 09, 2021. https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2021_ae3016b9-en (accessed Sep. 19, 2022).

[153] World Health Organization, “Maternal mortality ratio (per 100 000 live births),” *World Health Organization*. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/maternal-mortality-ratio-(per-100-000-live-births) (accessed Sep. 19, 2022).

[154] D. L. Hoyert, “Maternal mortality rates in the United States, 2020,” *Natl. Cent. Heal. Stat.*, no. 3, p. 1, 2021, doi: https://dx.doi.org/10.15620/cdc:113967.

[155] M. Harris, C. Henke, M. Hearst, and K. Campbell, “Future Directions: Analyzing Health Disparities Related to Maternal Hypertensive Disorders,” *Journal of Pregnancy*, vol. 2020. Hindawi Limited, 2020, doi: 10.1155/2020/7864816.

[156] C. V. Ananth, C. M. Duzyj, S. Yadava, M. Schwebel, A. T. N. Tita, and K. S. Joseph, “Changes in the prevalence of chronic hypertension in Pregnancy, United States, 1970 to 2010,” *Hypertension*, vol. 74, no. 5, pp. 1089–1095, Nov. 2019, doi: 10.1161/HYPERTENSIONAHA.119.12968.

[157] M. Wolf, A. Shah, R. Jimenez-Kimble, J. Sauk, J. L. Ecker, and R. Thadhani, “Differential Risk of Hypertensive Disorders of Pregnancy among Hispanic

Women," *J. Am. Soc. Nephrol.*, vol. 15, no. 5, pp. 1330–1338, 2004, doi: 10.1097/01.ASN.0000125615.35046.59.

[158] J. J. Shen, Z. Mojtahedi, J. Vanderlaan, and S. Rathi, "Disparities in Adverse Maternal Outcomes Among Five Race and Ethnicity Groups," *J. Women's Heal.*, vol. 00, no. 00, pp. 1–8, 2022, doi: 10.1089/jwh.2021.0495.

[159] H. O. Fasanya, C. J. Hsiao, K. R. Armstrong-Sylvester, and S. G. Beal, "A Critical Review on the Use of Race in Understanding Racial Disparities in Preeclampsia," *J. Appl. Lab. Med.*, vol. 6, no. 1, pp. 247–256, Jan. 2021, doi: 10.1093/jalm/jfaa149.

[160] N. E. Marshall, C. Guild, Y. W. Cheng, A. B. Caughey, and D. R. Halloran, "Racial disparities in pregnancy outcomes in obese women," *J. Matern. Neonatal Med.*, vol. 27, no. 2, pp. 122–126, Jan. 2014, doi: 10.3109/14767058.2013.806478.

[161] G. I. Oribhabor, M. L. Nelson, K.-A. R. Buchanan-Peart, and I. Cancarevic, "A Mother's Cry: A Race to Eliminate the Influence of Racial Disparities on Maternal Morbidity and Mortality Rates Among Black Women in America," *Cureus*, vol. 12, no. 7, Jul. 2020, doi: 10.7759/cureus.9207.

[162] H. Hu, H. Xiao, Y. Zheng, and B. (Bonnie) Yu, "A Bayesian spatio-temporal analysis on racial disparities in hypertensive disorders of pregnancy in Florida, 2005–2014," *Spat. Spatiotemporal. Epidemiol.*, vol. 29, pp. 43–50, Jun. 2019, doi: 10.1016/j.sste.2019.03.002.

[163] L. M. Christian, J. Koenig, D. P. Williams, G. Kapuku, and J. F. Thayer, "Impaired vasodilation in pregnant African Americans: Preliminary evidence of potential antecedents and consequences," *Psychophysiology*, vol. 58, no. 1, p. e13699, Jan. 2021, doi: 10.1111/psyp.13699.

[164] T. M. Spruill, "Chronic psychosocial stress and hypertension," *Current Hypertension Reports*, vol. 12, no. 1. NIH Public Access, pp. 10–16, Feb. 2010, doi: 10.1007/s11906-009-0084-8.

[165] A. L. Sonderlund, A. Schoenthaler, and T. Thilsing, "The Association between Maternal Experiences of Interpersonal Discrimination and Adverse Birth Outcomes: A Systematic Review of the Evidence," *Int. J. Environ. Res. Public Health*, vol. 18, no. 4, pp. 1–31, Feb. 2021, doi: 10.3390/IJERPH18041465.

[166] S. Zhang *et al.*, "Association Between Mental Stress and Gestational Hypertension/Preeclampsia: A Meta-Analysis," *Pediatr. Emerg. Care*, vol. 68, no. 12, pp. 825–834, 2013.

[167] K. F. Barrber Smith and B. Meagan, "Examining the Influence of Racial Discrimination on Adverse Birth Outcomes : An Analysis of the Virginia Pregnancy Risk Assessment Monitoring System (PRAMS), 2016 – 2018," *Matern. Child Health J.*, vol. 26, no. 4, pp. 691–699, 2022, doi: 10.1007/s10995-021-03223-2.

[168] J. D. Johnson and J. M. Louis, "Does race or ethnicity play a role in the origin, pathophysiology, and outcomes of preeclampsia? An expert review of the literature," *Am. J. Obstet. Gynecol.*, vol. 226, no. 2, pp. S876–S885, 2022, doi: 10.1016/j.ajog.2020.07.038.

[169] L. D. Arnold, L. Luong, T. Rebmann, and J. J. Chang, "Racial disparities in U.S. maternal influenza vaccine uptake: Results from analysis of Pregnancy Risk

Assessment Monitoring System (PRAMS) data, 2012–2015," *Vaccine*, vol. 37, no. 18, pp. 2520–2526, Apr. 2019, doi: 10.1016/j.vaccine.2019.02.014.

[170] S. Kim, E. O. Im, J. Liu, and C. Ulrich, "Maternal Age Patterns of Preterm Birth: Exploring the Moderating Roles of Chronic Stress and Race/Ethnicity," *Ann. Behav. Med. A Publ. Soc. Behav. Med.*, vol. 54, no. 9, p. 653, Mar. 2020, doi: 10.1093/ABM/KAAA008.

[171] A. S. Bossick, N. R. Bossick, L. S. Callegari, C. M. Carey, H. Johnson, and J. G. Katon, "Experiences of racism and postpartum depression symptoms, care-seeking, and diagnosis," *Arch. Womens. Ment. Health*, pp. 717–727, 2022, doi: 10.1007/s00737-022-01232-w.

[172] S. W. Masho, P. Urban, S. Cha, and R. Ramus, "Body Mass Index, Weight Gain, and Hypertensive Disorders in Pregnancy," *Am. J. Hypertens.*, vol. 29, no. 6, pp. 763–771, Jun. 2016, doi: 10.1093/ajh/hpv184.

[173] H. B. Shulman, D. V. D'Angelo, L. Harrison, R. A. Smith, and L. Warner, "The Pregnancy Risk Assessment Monitoring System (PRAMS): Overview of Design and Methodology," *Am. J. Public Health*, vol. 108, no. 10, p. 1305, Oct. 2018, doi: 10.2105/AJPH.2018.304563.

[174] Z. D. Bailey, N. Krieger, M. Agénor, J. Graves, N. Linos, and M. T. Bassett, "Structural racism and health inequities in the USA: evidence and interventions," *Lancet*, vol. 389, no. 10077, pp. 1453–1463, Apr. 2017, doi: 10.1016/S0140-6736(17)30569-X.

[175] S. Hamed, H. Bradby, B. M. Ahlberg, and S. Thapar-Björkert, "Racism in healthcare: a scoping review," *BMC Public Health*, vol. 22, no. 1, Dec. 2022, doi: 10.1186/S12889-022-13122-Y.

[176] E. Davidsen *et al.*, "The stigma associated with gestational diabetes mellitus: A scoping review," *eClinicalMedicine*, vol. 52, Oct. 2022, doi: 10.1016/J.ECLINM.2022.101614.

[177] K. Churchwell *et al.*, "Call to Action: Structural Racism as a Fundamental Driver of Health Disparities: A Presidential Advisory From the American Heart Association," *Circulation*, vol. 142, no. 24, pp. E454–E468, Dec. 2020, doi: 10.1161/CIR.0000000000000936.

[178] N. Hassen, A. Lofters, S. Michael, A. Mall, A. D. Pinto, and J. Rackal, "Implementing anti-racism interventions in healthcare settings: A scoping review," *Int. J. Environ. Res. Public Health*, vol. 18, no. 6, pp. 1–15, Mar. 2021, doi: 10.3390/IJERPH18062993.

[179] A. C. of O. and Gynecologists, "ACOG Practice Bulletin: Pregestational Diabetes Mellitus," *Obestrics Gynecol.*, vol. 132, no. 6, pp. 228–248, 2018.

[180] E. Lett, E. Asabor, S. Beltrán, A. M. Cannon, and O. A. Arah, "Conceptualizing, Contextualizing, and Operationalizing Race in Quantitative Health Sciences Research," *Ann. Fam. Med.*, vol. 20, no. 2, pp. 157–163, 2022, doi: 10.1370/afm.2792.

[181] J. Almeida, C. Belanoff, and K. F. Erbetta, "The Time has Come for All States to Measure Racial Discrimination: A Call to Action for the Pregnancy Risk Assessment

Monitoring System (PRAMS),” *Matern. Child Health J.*, vol. 26, no. 1, pp. 7–11, 2022, doi: 10.1007/s10995-021-03160-0.

[182] D. V. D’Angelo *et al.*, “Response to ‘The Time has Come for All States to Measure Racial Discrimination: A Call to Action for the Pregnancy Risk Assessment Monitoring System (PRAMS),’” *Matern. Child Health J.*, vol. 26, no. 1, pp. 12–14, 2022, doi: 10.1007/s10995-021-03279-0.