

# Genetic Risk Score for Essential Hypertension and Risk of Preeclampsia

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## BACKGROUND

Preeclampsia is a hypertensive complication of pregnancy characterized by novel onset of hypertension after 20 weeks gestation, accompanied by proteinuria. Epidemiological evidence suggests that genetic susceptibility exists for preeclampsia; however, whether preeclampsia is the result of underlying genetic risk for essential hypertension has yet to be investigated. Based on the hypertensive state that is characteristic of preeclampsia, we aimed to determine if established genetic risk scores (GRSs) for hypertension and blood pressure are associated with preeclampsia.

## METHODS

Subjects consisted of 162 preeclamptic cases and 108 normotensive pregnant controls, all of Iowa residence. Subjects' DNA was extracted from buccal swab samples and genotyped on the Affymetrix Genome-wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA). Missing genotypes were imputed using MaCH and Minimac software. GRSs were calculated for hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) using

established genetic risk loci for each outcome. Regression analyses were performed to determine the association between GRS and risk of preeclampsia. These analyses were replicated in an independent US population of 516 cases and 1,097 controls of European ancestry.

## RESULTS

GRSs for hypertension, SBP, DBP, and MAP were not significantly associated with risk for preeclampsia ( $P > 0.189$ ). The results of the replication analysis also yielded nonsignificant associations.

## CONCLUSIONS

GRSs for hypertension and blood pressure are not associated with preeclampsia, suggesting that an underlying predisposition to essential hypertension is not on the causal pathway of preeclampsia.

**Keywords:** blood pressure; genetic epidemiology; genetic predisposition to disease; hypertension; maternal; preeclampsia; pregnancy.

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Preeclampsia is a complication of pregnancy characterized by novel onset of hypertension after 20 weeks gestation, accompanied by proteinuria. It affects 3%–8% of pregnancies in the Western world and is a major cause of morbidity and mortality for both mother and child.<sup>1,2</sup> Although the exact biological mechanism of preeclampsia remains unclear, it is generally accepted to be the result of a combination of endothelial dysfunction, excessive inflammation

beyond that of normal pregnancy and placental insufficiency.<sup>3</sup> There is evidence of genetic susceptibility to the condition, as women with a maternal history of preeclampsia are at a 2- to 5-fold increased risk of developing preeclampsia themselves.<sup>3</sup> Additionally, women who develop preeclampsia are at a significantly increased risk of future cardiovascular disease, including hypertension and stroke.<sup>4,5</sup> Chronic hypertension is an established risk

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factor for preeclampsia, although the onset of preeclampsia on a background of existing hypertension is referred to as superimposed preeclampsia.<sup>1,2</sup> First trimester systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) are significantly elevated in women who go on to develop preeclampsia compared to those with normotensive pregnancies.<sup>6,7</sup> These consistent phenomena led us to question whether underlying genetic risks for essential hypertension or higher first trimester blood pressure are predictors of the manifestation of preeclampsia.

The role of genetics in determining blood pressure has become clearer through genome-wide association studies (GWASs). The use of a genetic risk score (GRS) based on GWAS findings as an indicator of risk for a given condition is a novel method of investigating genetic susceptibility to a complex trait. These GRSs may be investigated for association with an intermediate phenotype, such as blood pressure, which may then be investigated for association with risk for a disease outcome<sup>8,9</sup> and *vice versa*.<sup>10</sup> Specifically, one study constructed a GRS for hypertension based on a meta-analysis of GWAS-identified single nucleotide polymorphisms (SNPs) and its association with ischemic stroke,<sup>9,11</sup> while another investigated a GRS for coronary artery disease and its association with hypertension.<sup>10</sup>

As preeclampsia is considered a hypertensive disorder of pregnancy and there is evidence of genetic susceptibility to the condition, including variants in vasoactive genes, it stands to reason that underlying genetic susceptibility to essential hypertension or higher first trimester blood pressure may contribute to the manifestation of preeclampsia. In this study, we investigate the association between an established GRS for essential hypertension and blood pressure and the outcome of preeclampsia in 2 different study populations. We hypothesize that women with higher genetic risk for elevated blood pressure and/or essential hypertension will be at increased risk of preeclampsia. To our knowledge, this is the first study to use GRS for essential hypertension and blood pressure in relation to preeclampsia.

## METHODS

### Study population

This study involved subjects from the Study of Pregnancy Hypertension in Iowa (SOPHIA) case-control population. The SOPHIA population is composed of nulliparous residents of 42 Iowa counties who had a live birth from August 2002 through April 2005. Two hundred seventy subjects, including 162 cases and 108 controls, were used in GRS analyses.

A replication population consisting of 516 preeclampsia cases and 1,097 normotensive controls of European ancestry was aggregated from 5 US sites. These sites were Institutional Review Board-approved hospital and internet-based collections and subjects were matched to population controls.

### Phenotype definition

The methods for classifying preeclampsia in the SOPHIA study have been described previously.<sup>12-14</sup> Cases were initially selected based on an indication of “pregnancy-induced

hypertension” or “eclampsia” on birth certificate records. Randomly selected control subjects had no record of hypertension on birth certificate records and were frequency matched to cases based on county of residence. Potential subjects were excluded for chronic hypertension, age <18 at delivery, non-English speaking, history of autoimmune disease, recurrent spontaneous abortion, multiple gestations, major congenital anomalies, infant death, or seriously ill infant.<sup>14</sup> Medical records were abstracted from the antenatal, intrapartum, and postpartum periods to identify all blood pressure and urinary protein measurements before, during, and after pregnancy; this information was used to classify patients with preeclampsia, gestational hypertension, or as normotensive controls. Preeclampsia was defined according to National Heart, Lung, and Blood Institute guidelines: (i) sustained *de novo* hypertension ( $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic on  $\geq 2$  occasions at least 6 hours apart) beginning no earlier than 20 weeks gestation and (ii) proteinuria, defined as urinary protein concentrations  $\geq 30$  mg/dL (equivalent to a dipstick value of 1+ from  $\geq 2$  specimens  $\geq 4$  hours apart or a 24-hour urine collection with  $\geq 300$  mg of protein).<sup>15</sup> Gestational hypertension was defined as *de novo* hypertension in the absence of proteinuria and preeclampsia as gestational hypertension with proteinuria. Normotensive controls consisted of women with no evidence of hypertension or proteinuria during their pregnancy.

In the replication population, preeclampsia was defined according to the same National Heart, Lung, and Blood Institute guidelines as the SOPHIA population. Boston and USC samples also included superimposed preeclampsia in their case definition. Normotensive controls consisted of pregnant women with no history of chronic hypertension and no evidence of hypertensive disorders of pregnancy or proteinuria.

### Genotyping

DNA collection, extraction, and genotyping methods for this study have been described previously.<sup>14</sup> A subset of samples ( $N = 270$ ) from the SOPHIA study underwent GWA analysis based on Caucasian race and consent for future research. Genotyping was performed at the Rockefeller University Genomics Resource Center using Affymetrix Genome-wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA). Samples with a call rate less than 86% were excluded ( $n = 1$ ).<sup>14</sup> The mean call rate among the remaining subjects was 94.4%.<sup>14</sup> SNPs on chromosomes 1–22 were imputed using MaCH software,<sup>16</sup> using the 379 samples of European ancestry (CEPH) from the 1000 Genomes Project phase 1 as the reference panel.<sup>17</sup> Haplotypes for the SOPHIA subjects were estimated using MaCH software, and imputation was performed using Minimac software.<sup>18</sup> All GRS SNPs were available in the SOPHIA population without requiring a proxy SNP.

DNA from the replication population was extracted from blood, saliva, or buccal samples according to standard procedures. Samples were genotyped on a cardiovascular gene-centric 50 K SNP array.<sup>19</sup> Genotypes were clustered using Illumina Beadstudio software and subjected to quality control filters at the sample and SNP level. Samples of European

ancestry were identified using principal component analysis using HapMap3 European (CEU), African (YRI), and Asian (JPT + CHB) panels as reference standards.<sup>20</sup> SNPs were removed for genotyping efficiency <95%, departure from Hardy–Weinberg equilibrium ( $P < 10^{-6}$ ) in controls, differential missingness between cases and controls ( $P < 0.05$ ), or batch effects ( $P < 10^{-6}$ ).<sup>14</sup> The cardiovascular disease gene-centric array contained a limited number of index SNPs for blood pressure measurements, so GRS analyses utilized proxy SNPs with the strongest correlation (pairwise  $r^2 > 0.8$ ) to the untyped index SNP in the 1KG CEU sample.

### Statistical analyses

GRSs for hypertension, SBP, DBP, and MAP were constructed for each subject based on the beta coefficients of GWAS-significant variants with a source-reported  $P$ -value <  $1.0E-04$ .<sup>11,21</sup> The number of source SNPs were 27, 28, 28, and 23 for hypertension, SBP, DBP, and MAP, respectively. After imputation of the SOPHIA genotypes, the GRS for hypertension consisted of 26 SNPs, the GRS for SBP and DBP consisted of 27 SNPs, and the GRS for MAP consisted of 22 SNPs. SNPs and beta coefficients used to construct these GRS are reported in [Supplementary Table 1](#). Specifically, GRSs were constructed based on the reported beta coefficient for the effect allele at the given SNP. Alleles were coded such that the reported beta coefficient would be a positive value; for SNPs where the source allele had a negative beta coefficient, the other allele was used and the beta coefficient was made positive. The beta coefficient of each effect allele was summed for each subject based on their genotypes, such that individuals homozygous for the noncoded allele would receive a value of 0 for that locus, heterozygous individuals would receive the value of the beta coefficient at that locus, and individuals homozygous for the coded allele would receive double the beta coefficient for that locus. Similar GRSs were constructed for the replication population. Due to the limited availability of index and proxy SNPs, the replication study used 6 SNPs for hypertension, SBP, and DBP, and 5 SNPs for MAP. SNPs and beta coefficients used to construct these GRS are reported in [Supplementary Table 2](#).

Logistic regression was performed to assess the association between the 4 GRSs and preeclampsia using Statistical Analysis Software version 9.3 (Cary, NC). Our primary analyses examined the relationship between each GRS, independently, and risk of preeclampsia. In a subset of our sample where first trimester blood pressure measurements were available ( $n = 131$  cases, 87 controls), we examined the relationship between first trimester DBP, SBP, and MAP with risk for preeclampsia. In addition, we examined the relationship between each GRS and its associated blood pressure measurement. First trimester MAP was calculated for each subject using the formula ( $\text{MAP} = \text{diastolic} + 1/3(\text{systolic} - \text{diastolic})$ ) based on subjects' first trimester average SBP and DBP. Analyses involving the blood pressure measurements for SBP, DBP, and MAP were performed unadjusted and adjusted for body mass index (BMI). Other covariates examined included maternal age at delivery, maternal education level, smoking during the first trimester, and leisure time physical activity. Our replication population did not

include any information on blood pressure measurements or information on maternal age, BMI, or smoking; therefore, these analyses were only examined in our primary population. GRSs for SBP, DBP, and MAP were also broken into quartiles based on their distributions among control subjects and then assessed for their association with SBP, DBP, and MAP, respectively, using linear regression.

### RESULTS

GRSs for hypertension, SBP, DBP, and MAP were not significantly associated with preeclampsia. Additionally, quartile analyses did not demonstrate a statistically significant trend for any of the GRSs ([Table 1](#)). Similar analyses in the replication population were also nonsignificant ([Table 2](#)).

To determine the effectiveness of each GRS in predicting its respective blood pressure measurement, GRSs for SBP, DBP, and MAP were analyzed against measured SBP, DBP, and MAP values, respectively, using linear regression. The GRS for DBP was significantly associated with DBP before and after adjustment for pre-pregnancy BMI and the GRS for SBP was marginally associated with SBP unadjusted ( $P = 0.07$ ) and significantly associated after adjustment for pre-pregnancy BMI ( $P < 0.05$ ) ([Supplementary Table 3](#)). The GRS for MAP was not significantly associated with first trimester MAP. In the quartile analyses, tests for trend demonstrated a significant trend for the DBP GRS and measured DBP ( $P < 0.05$ ), a marginally significant trend for the association between SBP GRS and SBP measurements ( $P = 0.11$ ) and no trend between the MAP GRS and MAP ([Supplementary Table 3](#)).

First trimester SBP, DBP, and MAP were significantly associated with preeclampsia in a subset of the SOPHIA population ( $P < 0.0001$ ), with increased first trimester blood pressures associated with increased risk of preeclampsia ([Supplementary Table 4](#)). These associations remained significant after adjustment for BMI. All 3 trends were highly significant ( $P \leq 0.0001$ ).

### DISCUSSION

Established GRSs for hypertension, SBP, DBP, and MAP were not associated with preeclampsia. This suggests that an alternative pathogenesis model is responsible for the relationship between first trimester blood pressure and risk for preeclamptic hypertension. In our primary study population, we demonstrate that first trimester SBP, DBP, and MAP measurements are significantly associated with preeclampsia. These results are consistent with existing knowledge.<sup>6,7,22,23</sup> Furthermore, GRSs for SBP and DBP were significantly associated with first trimester SBP and DBP, respectively, after adjustment for pre-pregnancy BMI ( $P < 0.05$ ), supporting that these GRSs are associated with blood pressure measurements in our cohort. Together, these data support the hypothesis that the increased risk of future cardiovascular disease, including hypertension and stroke, following a preeclamptic pregnancy is likely due to damage done during pregnancy rather than underlying genetic risk for hypertension. These findings shed light on the disputed pathophysiology of preeclampsia. Although chronic

**Table 1.** Association between genetic risk score (GRS) and risk of preeclampsia

Exposure	Continuous	Quartile				Trend test P value
		1	2	3	4	
<b>HTN GRS</b>						
n (case/control subjects)	270 (162/108)	68 (41/27)	69 (42/27)	65 (38/27)	68 (41/27)	
Median (range)	29.2 (21.4, 37.8)	25.6 (21.4, 26.9)	28.0 (26.9, 29.2)	30.4 (29.2, 31.4)	32.7 (31.4, 37.8)	
OR (95% CI) <sup>a</sup>	0.993 (0.916, 1.076)	1.00 (Ref)	1.024 (0.516, 2.033)	0.927 (0.464, 1.852)	1.000 (0.503, 1.988)	0.929
<b>SBP GRS</b>						
n (case/control subjects)	270 (162/108)	67 (40/27)	66 (39/27)	72 (45/27)	65 (38/27)	
Median (range)	29.1 (21.0, 37.2)	25.5 (21.0, 26.8)	28.0 (26.8, 29.0)	30.3 (29.1, 31.6)	33.0 (31.7, 37.2)	
OR (95% CI) <sup>a</sup>	1.004 (0.928, 1.086)	1.00 (Ref)	0.975 (90.488, 1.948)	1.125 (0.568, 2.226)	0.950 (0.475, 1.902)	1.000
<b>DBP GRS</b>						
n (case/control subjects)	270 (162/108)	63 (36/27)	80 (53/27)	65 (38/27)	62 (35/27)	
Median (range)	28.6 (21.7, 37.6)	25.2 (20.5, 26.3)	27.9 (26.4, 28.9)	30.1 (29.0, 31.3)	32.7 (31.3, 37.6)	
OR (95% CI) <sup>a</sup>	0.978 (0.904, 1.057)	1.00 (Ref)	1.472 (0.745, 2.909)	1.056 (0.523, 2.129)	0.972 (0.479, 1.973)	0.680
<b>MAP GRS</b>						
n (case/control subjects)	270 (162/108)	63 (36/27)	80 (53/27)	65 (38/27)	62 (35/27)	
Median (range)	22.7 (12.9, 28.3)	25.2 (20.5, 26.3)	27.9 (26.4, 28.9)	30.1 (29.0, 31.3)	32.7 (31.3, 37.6)	
OR (95% CI) <sup>a</sup>	1.042 (0.953, 1.140)	1.00 (Ref)	0.649 (0.309, 1.360)	1.595 (0.813, 3.127)	1.135 (0.568, 2.269)	0.262

Abbreviations: CI, confidence interval; HTN, hypertension; DBP, diastolic blood pressure; GRS, genetic risk score; MAP, mean arterial pressure; OR, odds ratio; Ref, reference; SBP, systolic blood pressure.

<sup>a</sup>Presented for unadjusted model.

**Table 2.** Association between genetic risk score (GRS) and risk of preeclampsia in the replication population

Exposure	Continuous	Quartile				Trend test P value
		1	2	3	4	
<b>HTN GRS</b>						
n (case/control subjects)	1,613 (516, 1,097)	117/252	134/299	125/264	140/282	
Median (range)	6.51 (3.36, 7.24)	7.84 (7.28, 8.36)	8.61 (8.37, 9.10)	9.60 (9.19, 11.47)		
OR (95% CI) <sup>a</sup>	1.01 (0.93, 1.10)	1.00 (Ref)	0.97 (0.71, 1.33)	0.96 (0.69, 1.32)	1.03 (0.75, 1.41)	0.83
<b>First trimester SBP GRS</b>						
n (case/control subjects)	1,613 (516, 1,097)	122/256	128/291	129/274	137/276	
Median (range)	6.36 (3.31, 7.00)	7.55 (7.00, 8.14)	8.16 (8.14, 8.91)	9.33 (8.91, 11.22)		
OR (95% CI) <sup>a</sup>	1.01 (0.93, 1.10)	1.00 (Ref)	0.93 (0.68, 1.27)	0.94 (0.69, 1.28)	0.99 (0.72, 1.36)	0.99
<b>First trimester DBP GRS</b>						
n (case/control subjects)	1,613 (516, 1,097)	117/263	130/275	134/281	135/278	
Median (range)	6.27 (3.12, 6.62)	7.46 (6.66, 7.71)	7.82 (7.75, 8.68)	9.41 (8.71, 11.33)		
OR (95% CI) <sup>a</sup>	1.02 (0.94, 1.11)	1.00 (Ref)	1.06 (0.77, 1.46)	1.03 (0.75, 1.41)	1.04 (0.76, 1.43)	0.84
<b>First trimester MAP GRS</b>						
n (case/control subjects)	1,613 (516, 1,097)	134/262	83/176	156/383	143/276	
Median (range)	4.42 (2.04, 5.05)	5.28 (5.10, 5.52)	6.10 (5.57, 6.39)	7.14 (6.56, 10.00)		
OR (95% CI) <sup>a</sup>	0.99 (0.90, 1.08)	1.00 (Ref)	0.88 (0.62, 1.25)	0.76 (0.57, 1.02)	0.96 (0.70, 1.31)	0.52

Abbreviations: CI, confidence interval; HTN, hypertension; DBP, diastolic blood pressure; GRS, genetic risk score; MAP, mean arterial pressure; OR, odds ratio; Ref, reference; SBP, systolic blood pressure.

<sup>a</sup>Adjusted for principal components.



hypertension is a risk factor for preeclampsia,<sup>2</sup> our findings suggest that genetic susceptibility for hypertension is not a necessary causal factor in the development of preeclampsia.

It is important to note that blood pressure is only one aspect of the pathophysiology of preeclampsia. Meta-analyses of the genetics of preeclampsia have identified several biological processes associated with risk for preeclampsia represented by only a handful of promising candidate genes.<sup>24,25</sup> Although genes involved with vasoactive processes have been implicated in the pathophysiology of preeclampsia, a recent meta-analysis found genes associated with thrombophilia to be more strongly associated with preeclampsia.<sup>24</sup> Another important contributor to the etiology of preeclampsia includes endothelial dysfunction, including insufficient spiral artery invasion and inappropriate endothelial cell activation,<sup>26</sup> which may be mediated by dyslipidemia.<sup>27</sup> Epidemiologic studies and GWASs, by our group and others, support the role of dyslipidemia in preeclampsia. This includes elevated triglycerides throughout pregnancy and decreased high density lipoprotein cholesterol in the third trimester.<sup>28,29</sup> Of interest, the lipoprotein lipase gene, *LPL*, is associated with both preeclampsia and cardiovascular disease.<sup>25</sup> We have previously reported an association between a GRS for decreased levels of high density lipoprotein cholesterol, which included a variant in *LPL*, and increased risk for preeclampsia.<sup>8</sup> Thus, the etiology of preeclampsia likely encompasses a myriad of factors on its causal pathway, and our current data, which are supported by other genetic studies, suggest that genes involved in the vasoactive process including those that predict blood pressure are not primary candidates on the causal pathway of preeclampsia.

A significant strength of our study was the availability of blood pressure values in addition to the rigorous assessment of preeclampsia status in our primary study population. The availability of first trimester blood pressure measurements allowed us to assess the relationship between first trimester blood pressure and preeclampsia and to evaluate the association between GRSs for SBP, DBP, and MAP and their respective first trimester blood pressure measurements. Although we were able to include maternal blood pressure measurements in our study, we lack blood pressure measurements prior to conception. Thus, although we excluded women with preexisting chronic hypertension, we cannot determine if subjects with preeclampsia had higher blood pressure while still being within the normotensive range prior to conception. An additional limitation is the lack of a standardized protocol for measuring blood pressure, given the nature of a retrospective case-control study design.

It is important to note that the SNPs involved in this study only explain a small fraction of the heritable variation in blood pressure (<3%); however, this was also the case in the meta-analysis of GWAS from which the SNPs came (~2.2%).<sup>11</sup> Furthermore, in our replication, we were only able to include a fraction of the SNPs in the initial GRS, and therefore, replication in other populations is warranted. As additional SNPs influencing blood pressure are identified and the genetic risk factors for hypertension and blood pressure are better understood, it will be important to reexamine the relationship between preeclampsia and the genetic risk for hypertension.

The SNPs used to generate GRS for this study were based on the results of the meta-analysis of multiple GWASs of hypertension and blood pressure-associated loci, demonstrating the reliability of these SNPs in their association with hypertension and blood pressure.<sup>11,21</sup> Further, most of these same SNPs were used in another GRS study of hypertension and ischemic stroke, demonstrating a precedent for the use of a GRS for blood pressure and its association with a disease outcome.<sup>9</sup> However, given that all of these studies were in a population of European ancestry and our study population is primarily Caucasian, it is necessary to evaluate these variants in other populations to determine their association with blood pressure in other racial and ethnic groups. Although our primary study population was relatively small, the fact that we find that (i) the GRSs of SBP and DBP are associated with their respective first trimester measurement, (ii) first trimester blood pressure measurements are associated with preeclampsia, and (iii) the results of nonsignificant associations between each GRS and preeclampsia were also observed in our replication population strengthens the conclusions of our study.

Our study suggests that elevated first trimester blood pressures are likely the result of early pathological changes of preeclampsia, rather than primary causal factors. Based on our findings, we propose that the hypertension present in preeclampsia is of a different etiology from essential hypertension. Our replication of the well-established association between elevated first trimester blood pressure and subsequent preeclampsia further supports our conclusion that this increase in blood pressure represents early pathological changes that eventually manifest as preeclampsia. Thus, since an established risk score for blood pressure was not associated with the development of preeclampsia and none of our subjects had a history of hypertension prior to conception, we can conclude that the hypertension present in preeclampsia is not due to a risk for chronic or “essential” hypertension but rather the early etiology of preeclampsia. Our previous genetic and epidemiologic studies suggest that other pathways such as dyslipidemia may play a causal role in preeclampsia. Given that the origins of preeclampsia are still not well understood, future research is needed on the etiology of preeclampsia in order to explain the origin of this early increase in blood pressure in pregnant subjects who go on to be diagnosed with preeclampsia. Although the complex pathophysiology of preeclampsia remains unclear, the results of our study suggest that the hypertensive state that is characteristic of preeclampsia is not due to genetic susceptibility for essential hypertension.

## SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (<http://ajh.oxfordjournals.org>).

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## DISCLOSURE

The authors declared no conflict of interest.

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