

Genetic Predisposition to Dyslipidemia and Risk of Preeclampsia

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BACKGROUND

Large epidemiologic studies support the role of dyslipidemia in preeclampsia; however, the etiology of preeclampsia or whether dyslipidemia plays a causal role remains unclear. We examined the association between the genetic predisposition to dyslipidemia and risk of preeclampsia using validated genetic markers of dyslipidemia.

METHODS

Preeclampsia cases ($n = 164$) and normotensive controls ($n = 110$) were selected from live birth certificates to nulliparous Iowa women during the period August 2002 to May 2005. Disease status was verified by medical chart review. Genetic predisposition to dyslipidemia was estimated by 4 genetic risk scores (GRS) (total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides) on the basis of established loci for blood lipids. Logistic regression analyses were used to evaluate the relationships between each of the 4 genotype scores and preeclampsia. Replication analyses were performed in an independent, US population of preeclampsia cases ($n = 516$) and controls ($n = 1,097$) of European ancestry.

RESULTS

The GRS related to higher levels of TC, LDL-C, and triglycerides demonstrated no association with the risk of preeclampsia in either the lowa or replication population. The GRS related to lower HDL-C was marginally associated with an increased risk for preeclampsia (odds ratio (OR) = 1.03, 95% confidence interval (CI) = 0.99–1.07; $P = 0.10$). In the independent replication population, the association with the HDL-C GRS was also marginally significant (OR = 1.03, 95% CI: 1.00–1.06; $P = 0.04$).

CONCLUSIONS

Our data suggest a potential effect between the genetic predisposition to dyslipidemic levels of HDL-C and an increased risk of preeclampsia, and, as such, suggest that dyslipidemia may be a component along the causal pathway to preeclampsia.

Keywords: blood pressure; dyslipidemia; genetic epidemiology; genetic risk score; hypertension; preeclampsia.

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Preeclampsia is a multisystem disorder of pregnancy characterized by *de novo* hypertension and proteinuria with onset after 20 weeks gestation.¹ In the absence of proteinuria, *de novo* hypertension with new onset of any of the following will also qualify a woman for a diagnosis of preeclampsia:

thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual disturbances.² Complicating approximately 3% of all deliveries in the United States,^{3,4} preeclampsia is a leading cause of maternal and infant morbidity and mortality worldwide.^{5,6} Without

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intervention, the mother is at substantial risk for seizures (eclampsia), renal and liver failure, stroke, and death.⁴ In the infant, preeclampsia increases the risk for intrauterine growth restriction, prematurity, and perinatal death.⁵ Despite considerable research, there are no clinically useful screening tools for identifying women in whom preeclampsia will develop¹; the only “cure” is delivery.⁵

Evidence of the heritability of preeclampsia is apparent. Family studies have demonstrated that preeclampsia is more common among daughters and sisters of previously preeclamptic women.^{7–12} However, the underlying genetics are complex, and the extent to which genes and pathways contribute to preeclampsia remains unknown.¹³ Numerous candidate gene studies and a few genome-wide association studies (GWAS) have been performed to identify genetic markers of preeclampsia.¹³ A recent meta-analysis reported 7 variants in 6 genes that were significantly associated with preeclampsia. Some of these variants are also independent genetic risk factors for dyslipidemia and are involved in lipid metabolism.¹³ One identified genetic variant, rs268 of the *LPL* gene, is also associated with reduced lipoprotein lipase activity and dyslipidemia.¹⁴ Because dyslipidemia can play a role in endothelial cell dysfunction,¹⁵ a known mechanism in the pathophysiology of preeclampsia, evaluating the genetic components of lipid metabolism, and of dyslipidemia specifically, may help to elucidate the pathophysiology of preeclampsia.

A recent meta-analysis of 46 lipid GWAS comprising more than 100,000 individuals of European descent established a comprehensive genetic profile of 95 loci for various blood lipids.¹⁶ In 2013, this meta-analysis was updated with an additional 62 loci.¹⁷ In the current study, we calculated 4 genetic risk scores (GRS) on the basis of the well-established single nucleotide polymorphisms (SNPs) for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides as proxies for the genetic predisposition to dyslipidemia. We then evaluated the effects of these dyslipidemia GRS on the risk of preeclampsia. To our knowledge, this is the first study to assess the relationship between a GRS for dyslipidemia and risk for preeclampsia.

METHODS

SOPHIA

Study population and phenotype definition. The Study of Pregnancy Hypertension in Iowa, SOPHIA, is a population-based case-control study designed to examine the roles of maternal-fetal human leukocyte antigen sharing and sexual history with the baby's father in preeclampsia. A detailed description of this study has been described elsewhere.^{18–20} Briefly, 3,078 primiparous women who resided in one of 42 Iowa counties and delivered a live, singleton birth from August 2002 to May 2005 were identified from electronic birth certificates. Final case-control status was determined based on computer-assisted telephone interviews and review of prenatal and hospital records.

Based on information abstracted from the telephone interviews and medical charts, 274 preeclampsia cases and 190 normotensive controls were ascertained. DNA samples

belonging to Caucasian women who consented to future genetic studies with sufficient DNA were genotyped and analyzed in a GWAS ($n = 177$ preeclampsia cases and $n = 116$ normotensive controls).²⁰

Preeclampsia was defined according to National Heart, Lung, and Blood Institute guidelines: (i) sustained *de novo* hypertension (systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) on at least 2 occasions at least 6 h apart after the 20th week of pregnancy, and (ii) accompanying proteinuria defined as a urine protein concentration ≥ 300 mg/l (equivalent to a 24-h urine sample containing >300 mg of protein; a urine sample concentration of ≥ 30 mg/dl urinary protein or dipstick protein test value of 1+ or greater based on 2 or more samples collected at least 4 h apart; 1 or more urinary dipstick value of 2+ near the end of pregnancy; or 1 or more catheterized dipstick value of 1+ during delivery hospitalization).²¹ Only women who had no evidence of hypertension or proteinuria during their pregnancy were included as normotensive controls.

GWAS genotyping and imputation. The genotyping methods have been described in detail elsewhere.²⁰ Briefly, buccal cell DNA was extracted from cytobrush samples using Puregene DNA tissue kits (Gentra Systems, Minneapolis, MN) following the manufacturer's protocol with minor modifications.²² After extraction, DNA samples were assessed for quality. Genotyping of the buccal cell DNA was performed at the Rockefeller University Genomics Resource Center using Affymetrix Genome-wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA). Sample quality was assessed using the Dynamic Model algorithm, and genotyping calls were generated using the Birdseed algorithm available in Genotyping Console 4.0 (Affymetrix). We used MaCH²³ to impute SNPs on chromosome 1–22 using the 379 samples of European ancestry from the 1000 Genomes Project²⁴ as the referent panel. Haplotypes for the SOPHIA subjects were estimated using MaCH, and imputation was performed using minimac.²⁵ After accounting for imputation quality, we included 164 preeclampsia cases and 110 normotensive controls in our final analysis.

Exposure assessment—GRS calculation. To estimate the genetic predisposition to dyslipidemia, 4 lipid (TC, triglycerides, LDL-C, and HDL-C) GRS were calculated based on well-established SNPs for blood lipids reported by 2 recent meta-analyses of GWAS.^{16,17} These GRS represent the genetic contribution for increased levels of TC, triglycerides, and LDL-C, as well as decreased levels of HDL-C. Only SNPs with genotyped data or high imputation quality scores (MACH $r^2 \geq 0.8$) were included; 17 SNPs were excluded due to poor genotyping quality in the SOPHIA population. A total of 68, 40, 50, and 69 SNPs for TC, triglycerides, LDL-C, and HDL-C, respectively, were included in the GRS analysis (Supplementary Table 1). We assumed that each SNP acted independently and in an additive manner.

The genotype scores were calculated using a weighted method in a manner similar to that described by other researchers.^{26–29} Each SNP was weighted by its relative effect size (β coefficient) obtained from the reported meta-analysis data.^{16,30} The genotype scores were then calculated by

multiplying each β coefficient by the number of corresponding risk alleles and then summing the products. This calculation resulted in a TC genotype score out of 198.65, an LDL-C score out of 120.88, an HDL-C score out of 72.17, and a triglyceride score out of 263.67, twice the sum of the β coefficients. To make the genotype scores easier to interpret, these values were divided by 198.65, 120.88, 72.17, and 263.67 and multiplied by 136, 100, 138, and 80 (the total number of the risk alleles), respectively. This allowed us to interpret the β coefficients as per-1 risk allele increase in the GRS.

Replication population

Study population. A total of 516 preeclampsia cases and 449 normotensive controls of European ancestry were selected from Institutional Review Board-approved hospital- and internet-based collections at 5 US sites and matched to population controls (Supplementary Table 2).

Case status was verified by review of medical records at each site. Preeclampsia was defined as new onset of hypertension after 20 weeks of gestation with systolic BP ≥ 140 or diastolic BP ≥ 90 on 2 occasions at least 6 h apart in the presence of proteinuria of 300 mg/dl on a 24-h collection or at least +1 on a dipstick. In Boston and University of Southern California samples, case definition included superimposed preeclampsia (onset of hypertension after 20 weeks and new onset proteinuria in women with chronic hypertension). Pregnant women without a history of chronic hypertension and with no evidence of hypertensive disorders of pregnancy were defined as normotensive controls.

Cardiovascular disease array genotyping. DNA was extracted from blood, saliva, or buccal samples at each site using standard protocols. Samples were genotyped on a cardiovascular gene-centric 50 K SNP array v1.0.³¹ SNPs were clustered into genotypes using the Illumina Beadstudio software and subjected to quality control filters at the sample and SNP level. For this study, samples of European ancestry were identified by principal component (PC) analysis, including HapMap3 European (CEU), African (YRI), and Asian (JPT+CHB) panels as reference standards.³² To increase power, cardiovascular disease array genotypes from 648 additional EA population-based women from the Atherosclerosis Risk in Communities study from the CARE study³³ were individually matched to cases using nearest-neighbor genetic matching at each site. Samples were excluded for individual call rates $< 90\%$, duplicate discordance, heterozygosity > 3 SD from the mean, any of the first 3 PCs > 3 SD from the mean, and excess relatedness (π -hat > 0.125). SNPs were removed for call rates $< 95\%$, departure from Hardy-Weinberg equilibrium with $P < 10^{-6}$ in controls, differential missingness between cases and controls ($P < 0.05$), or batch effects ($P < 10^{-6}$).

GRS calculation. GRS were calculated as described for the SOPHIA population with some modifications. Since the cardiovascular disease gene-centric array was designed before recent lipid GWAS discoveries, only a limited number of index SNPs for TC, HDL-C, LDL-C, and triglycerides were directly genotyped. Thus, in order to improve power

to detect association of a lipid GRS with preeclampsia, we included a proxy SNP with the strongest correlation (pairwise $r^2 > 0.8$) to the untyped index SNP in the 1KG CEU sample. Using this approach, 27 loci for TC, 19 loci for LDL-C, 23 loci for HDL-C, and 16 loci for triglycerides were available for assessment. A weighted GRS for each trait was calculated for each individual. If a genotype in the score was missing for a particular individual, then the expected value was imputed based on the sample allele frequency. Division by twice the sum of the β coefficients (118.46 for TC, 65.79 for LDL-C, 37.25 for HDL-C, and 150.11 for triglyceride) and multiplication by the number of risk alleles (54, 38, 46, and 32) allowed us to interpret the β coefficients as per-1 risk allele increase in the GRS.

Statistical analysis

Chi-square and *t*-tests were run to compare proportions and means between case and control groups. Four GRS were modeled—one for each of the lipid types. Logistic regression was used to estimate the odds ratios (ORs) for preeclampsia risk. Multivariate logistic regression was used in order to evaluate and adjust for potential confounders. *A priori*, only variables that produced at least a 10% change in the OR for preeclampsia would be retained in the final models. The covariates examined included body mass index (BMI) (continuous), maternal age at delivery (continuous), education, preconception smoking (yes/no), smoking during pregnancy (nonsmoker, 1st trimester only, and 2nd/3rd trimester), physical activity (metabolic equivalents per week; continuous), paternal seminal fluid exposure,¹⁹ and human leukocyte antigen sharing. Ultimately, none of the evaluated covariates met the threshold for retention in any of the models. However, due to its significant difference between preeclamptic and normotensive women and biologic relevance to the associations tested, bivariate models for the SOPHIA population are also presented with an adjustment for prepregnancy BMI. Finally, assessment of the relationship between each SNP and the risk of preeclampsia was evaluated with univariate logistic regression using PLINK. Adequacy of model fit was examined using the Hosmer and Lemeshow goodness of fit test.

In the replication study, multivariate logistic regression analysis was used to test for association of each lipid GRS with preeclampsia, adjusting for 10 PCs and collection site. BMI and other relevant covariates were not available for the replication population.

RESULTS

Characteristics of the study participants are shown in Table 1. Women who developed preeclampsia had a significantly higher prepregnancy BMI, engaged in significantly less leisure time physical activity, and were less likely to smoke than the normotensive control women. Preeclamptic women and women who remained normotensive during pregnancy did not differ with respect to age at delivery, level of education, or mean GRS for TC, LDL-C, HDL-C, or triglycerides. In addition, all 4 genotype scores were normally distributed among study participants (Figure 1).

Table 1. Characteristics of study participants by case status, Study of Pregnancy-induced Hypertension in Iowa, 2004–2005

Variable	Preeclampsia	Normotensive controls	P
N	164	110	
Age at birth (years)	26.2 (4.9)	26.4 (5.2)	0.85
Prepregnancy BMI (kg/m ²)	27.3 (5.9)	23.9 (4.9)	<0.0001
Smoked during pregnancy, n (%)			
Nonsmoker	129 (78.7)	86 (78.2)	0.02
First trimester only	22 (13.4)	6 (5.5)	
Second/third trimester	13 (7.9)	18 (16.4)	
Education, n (%)			
High school diploma or less	28 (17.1)	20 (18.2)	0.27
Some college	66 (40.2)	34 (30.9)	
College graduate	70 (42.7)	56 (50.9)	
Physical activity (metabolic equivalent hours/week)	6.2 (10.3)	11.2 (17.8)	0.001
Total cholesterol genotype score	68.8 (6.3)	69.0 (5.3)	0.81
LDL cholesterol genotype score	50.2 (6.0)	49.8 (5.6)	0.57
HDL cholesterol genotype score	66.2 (6.6)	64.9 (7.4)	0.12
Triglyceride genotype score	40.5 (5.1)	40.3 (4.8)	0.80

Data are means (SD) or percent, unless otherwise indicated; *t*-tests used to test difference between cases and controls for continuous variables. Chi-square tests were performed to test differences between cases and controls for categorical variables. Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

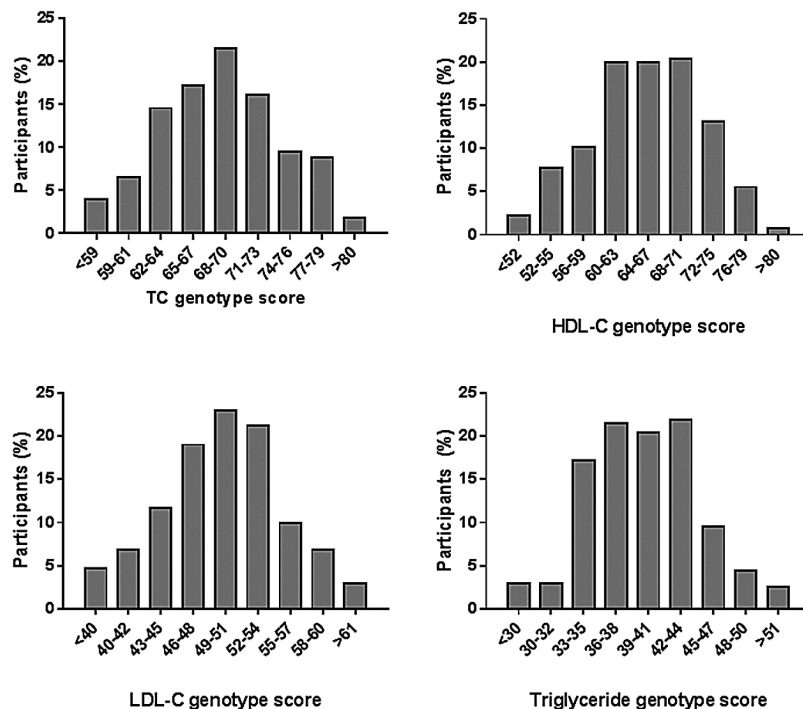


Figure 1. Lipid genotype scores in pre-eclamptic and normotensive women from the Study of Pregnancy Hypertension in Iowa. The histograms represent the percentage of participants whose genotype score falls within a particular category. Abbreviations: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

Table 2 presents the results from the analyses of the TC, LDL-C, HDL-C, and triglyceride genotype scores and the associated risk of preeclampsia. No significant associations were observed between the GRS for increased levels of TC, LDL-C,

or triglycerides and the risk for preeclampsia: TC (OR = 1.00, 95% confidence interval (CI) = 0.96, 1.04), LDL-C (OR = 1.01, 95% CI = 0.97, 1.06), or triglycerides (OR = 1.01, 95% CI = 0.96, 1.06). Additionally, the risk of preeclampsia among women

Table 2. Association between the lipid genotype scores and risk for preeclampsia, Study of Pregnancy-induced Hypertension in Iowa, 2004–2005

	Continuous	Quartile				P for trend
		1	2	3	4	
Total cholesterol						
n (case/control subjects)		43/28	40/28	43/27	38/27	
Median (range)		62.5 (49.6–65.0)	67.1 (65.0–69.4)	71.0 (69.4–73.1)	76.2 (73.2–81.1)	
OR (95% CI)						
Unadjusted	1.00 (0.96, 1.04)	1.00 (Ref)	0.93 (0.47, 1.83)	1.04 (0.53, 2.04)	0.92 (0.46, 1.82)	0.89
BMI adjusted	1.01 (0.96, 1.05)	1.00 (Ref)	1.11 (0.54, 2.27)	1.23 (0.60, 2.52)	1.09 (0.53, 2.24)	0.75
LDL cholesterol						
n (case/control subjects)		43/28	27/29	46/26	48/27	
Median (range)		43.7 (30.6–46.4)	48.0 (46.5–49.5)	51.2 (49.6–53.8)	56.8 (53.8–65.4)	
OR (95% CI)						
Unadjusted	1.01 (0.97, 1.06)	1.00 (Ref)	0.61 (0.30, 1.23)	1.15 (0.59, 2.27)	1.16 (0.59, 2.26)	0.35
BMI adjusted	1.03 (0.98, 1.07)	1.00 (Ref)	0.69 (0.32, 1.45)	1.39 (0.68, 2.84)	1.39 (0.69, 2.81)	0.15
HDL cholesterol						
n (case/control subjects)		39/27	29/28	53/27	43/28	
Median (range)		57.0 (47.6–60.6)	63.0 (60.6–64.9)	67.8 (64.9–70.6)	73.6 (70.6–81.5)	
OR (95% CI)						
Unadjusted	1.03 (0.99, 1.07)	1.00 (Ref)	0.72 (0.35, 1.47)	1.36 (0.69, 2.67)	1.06 (0.54, 2.11)	0.46
BMI adjusted	1.03 (0.99, 1.07)	1.00 (Ref)	0.73 (0.34, 1.55)	1.47 (0.72, 2.98)	1.16 (0.57, 2.37)	0.33
Triglycerides						
n (case/control subjects)		47/28	22/27	46/27	49/28	
Median (range)		35.1 (27.8–37.1)	38.6 (37.2–39.4)	41.7 (39.5–43.2)	45.6 (43.2–53.7)	
OR (95% CI)						
Unadjusted	1.01 (0.96, 1.06)	1.00 (Ref)	0.49 (0.23, 1.01)	1.02 (0.52, 1.98)	1.04 (0.54, 2.02)	0.52
BMI adjusted	1.00 (0.95, 1.05)	1.00 (Ref)	0.42 (0.19, 0.90)	0.88 (0.44, 1.76)	0.90 (0.45, 1.79)	0.84

P value for test for trend from Cochran–Armitage test for trend. Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio.

with GRS in the second, third, and fourth quartiles did not significantly differ from the risk among women with GRS in the first quartile (P for trend = 0.89, TC = 0.35, LDL-C = 0.52, triglycerides). However, a marginally significant association was observed between the GRS associated with lower levels of HDL-C and preeclampsia risk (OR = 1.03, 95% CI = 0.99, 1.07; P = 0.10), though the test for trend across the quartiles was not significant (P for trend = 0.46). Results were consistent with multivariate adjustment for prepregnancy BMI. Each of the GRS explained <1% of the deviance in preeclampsia outcomes whereas BMI, smoking, and physical activity explained 11% of the deviance in preeclampsia outcome.

To ensure that an individual SNP was not driving the results, logistic regression analysis was conducted to evaluate the relationship between each SNP and preeclampsia risk. While none of the SNPs assessed reached statistical significance after the Bonferroni correction (P < 0.0003), 1 SNP (rs964184) did achieve a P value of 0.0088 (OR = 1.90 for every addition of a G allele); as such, sensitivity analyses were performed excluding rs964184 from all 4 GRS. Results were consistent with those of the main analyses (data not shown).

Replication analysis

Table 3 presents the results from the replication analyses of the GRS for TC, LDL-C, HDL-C, and triglyceride genotype scores and the associated risk of preeclampsia. The GRS results were similar to those from the original SOPHIA analysis: TC (OR = 0.98, 95% CI = 0.95, 1.01), LDL-C (OR = 0.98, 95% CI = 0.95, 1.02), or triglycerides (OR = 1.00, 95% CI = 0.96, 1.05). Effect estimates from the GRS analysis of HDL-C were not only similar to those from the SOPHIA analysis, but were statistically significant (OR = 1.03, 95% CI = 1.00, 1.06). The risk of preeclampsia among women with GRS in the second, third, and fourth quartiles did not significantly differ from the risk among women with GRS in the first quartile (P for trend = 0.26, TC = 0.16, LDL-C = 0.12, HDL-C = 0.84, triglycerides). Meta-analysis of the HDL-C results between SOPHIA and the replication population also demonstrated a significant association between the HDL-C GRS and preeclampsia risk (OR = 1.03, 95% CI = 1.01, 1.05).

Table 3. Association between the lipid genotype scores and risk for preeclampsia, preeclampsia replication population

	Continuous	Quartile				P for trend
		1	2	3	4	
Total cholesterol						
<i>n</i> (case/control subjects)		136/267	133/270	122/280	125/280	
Median (range)		29.5 (20.4–31.2)	32.5 (31.2–33.6)	34.6 (33.6–35.9)	37.6 (35.9–43.5)	
OR (95% CI)						
PCA adjusted	0.98 (0.95, 1.01)	1.00 (Ref)	1.01 (0.74, 1.38)	0.91 (0.67, 1.25)	0.85 (0.63, 1.16)	0.26
LDL cholesterol						
<i>n</i> (case/control subjects)		130/273	140/263	131/272	115/289	
Median (range)		15.8 (7.5–17.5)	18.8 (17.5–19.9)	21.0 (19.9–22.4)	23.9 (22.4–29.4)	
OR (95% CI)						
PCA adjusted	0.98 (0.95, 1.02)	1.00 (Ref)	1.02 (0.75, 1.40)	1.07 (0.78, 1.46)	0.81 (0.59, 1.10)	0.16
HDL cholesterol						
<i>n</i> (case/control subjects)		125/278	122/281	127/276	142/262	
Median (range)		19.4 (10.7–21.8)	23.2 (21.8–24.6)	25.9 (24.6–27.1)	28.7 (27.2–34.0)	
OR (95% CI)						
PCA adjusted	1.03 (1.00, 1.06)	1.00 (Ref)	0.98 (0.72, 1.35)	1.06 (0.77, 1.46)	1.31 (0.95, 1.81)	0.12
Triglycerides						
<i>n</i> (case/control subjects)		133/270	133/270	113/290	137/267	
Median (range)		18.0 (11.0–19.2)	20.1 (19.2–21.0)	21.8 (21.0–22.8)	24.0 (22.8–29.6)	
OR (95% CI)						
PCA adjusted	1.00 (0.96, 1.05)	1.00 (Ref)	1.00 (0.73, 1.36)	0.76 (0.55, 1.05)	1.00 (0.73, 1.37)	0.84

P value for test for trend from Cochran–Armitage test for trend. Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; PCA, principal components analysis for population stratification.

Logistic regression was performed in the replication population to evaluate for potential associations between individual SNPs and preeclampsia risk; 3 SNPs were identified (rs11024739, $P < 0.0001$; rs103294, $P = 0.0009$; and rs6073952, $P = 0.007$). As such, sensitivity analyses were performed for each applicable GRS without these loci. Results were consistent with those from the main analyses (data not shown).

Because the replication population included only a subset of the SNPs included in the SOPHIA analysis (Supplementary Table 3), a sensitivity analysis was performed in the SOPHIA dataset evaluating only those SNPs utilized in the replication set. Results were similar to the original SOPHIA results.

DISCUSSION

Several GWAS and many candidate gene studies have been performed to identify underlying genetic risk factors for preeclampsia; however, results have been inconsistent. One meta-analysis found a validated association between the *LPL* gene and risk for preeclampsia, potentially implicating dyslipidemia in the etiology of preeclampsia. Despite the emerging evidence of a strong role of dyslipidemia in the etiology of preeclampsia, no studies to our knowledge have examined genetic predisposition to dyslipidemia and preeclampsia. Our study is the first, to examine the relationships

between well-established GRS for circulating lipid levels and preeclampsia. We did not find a statistically significant association between the GRS for elevated levels of LDL-C, TC, and triglycerides and preeclampsia risk in either the main study population or in the replication population. We did, however, identify a statistically significant relationship between the genetic predisposition for decreased levels of HDL-C and increased risk for preeclampsia.

It is important to note that the loci included in each of the risk scores only explain ~12% of the variation in plasma lipid levels.^{17,26} Therefore, as additional variants, particularly rare variants, are discovered, the association between the GRS for circulating lipid levels and risk of preeclampsia will need to be reevaluated. As lipid measures during pregnancy were not collected in SOPHIA, we could not directly measure the association between the GRS and lipid levels in our population of women; however, large GWAS have demonstrated the validity of the GRS used for this analysis based on their ability to predict circulating levels of lipids.

Epidemiologic studies have shown a strong association between dyslipidemia and preeclampsia; however, most studies examined levels in the third trimester of pregnancy and the ability of lipid levels to predict preeclampsia remains unclear.³⁴ Women who experience preeclampsia are more likely to develop dyslipidemia later-in-life suggesting a potential shared etiology for both preeclampsia and

dyslipidemia. The most common patterns of dyslipidemia experienced during preeclamptic pregnancies are elevated triglycerides and reduced HDL-C levels.^{34–36} Levels of circulating lipids indicative of dyslipidemia have been implicated in the pathogenesis of endothelial dysfunction in atherosclerosis.³⁷ Because one of the classic hallmarks of preeclampsia is endothelial dysfunction, dyslipidemia is a plausible candidate in the pathogenesis of preeclampsia.¹⁵ Our data suggest that lower levels of HDL-C may be a component or an effect modifier along the causal pathway to preeclampsia. This finding is intriguing as HDL-C has antithrombotic properties, the ability to inhibit inflammation and oxidation, and is reported to enhance endothelial repair. However, it should be noted that the observed effects explain an extremely small (<1%) percentage of risk for preeclampsia. In comparison, anthropometric measures such as BMI and lifestyle risk factors such as smoking and low physical activity explains just over 11% of the preeclampsia risk in our population. As such, the clinical utility of this GRS to identify women at risk for preeclampsia is low compared to other well-known risk factors.

A major strength of our study includes the strict case definition of preeclampsia confirmed by BP measures and urinary protein levels recorded in the medical charts in our initial study population. We also used a population-based, nonhypertensive control group that underwent the same strict protocol of medical chart abstraction to verify normotensive status. In addition, we had high-quality genotype data from a large replication cohort to confirm our findings.

In conclusion, we found that genetic predisposition for decreased levels of HDL-C, estimated by a GRS, were associated with increased risk for preeclampsia. In contrast, genetic predisposition for elevated levels of TC, triglycerides, and LDL-C was not associated with the risk of preeclampsia in our study. Future research should focus on additional loci, particularly rare variants, associated with circulating lipid levels measured during pregnancy.

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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