JAMA Cardiology | Original Investigation

Genetic Associations of Circulating Cardiovascular Proteins With Gestational Hypertension and Preeclampsia

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IMPORTANCE Hypertensive disorders of pregnancy (HDPs), including gestational hypertension and preeclampsia, are important contributors to maternal morbidity and mortality worldwide. In addition, women with HDPs face an elevated long-term risk of cardiovascular disease.

OBJECTIVE To identify proteins in the circulation associated with HDPs.

DESIGN, SETTING, AND PARTICIPANTS Two-sample mendelian randomization (MR) tested the associations of genetic instruments for cardiovascular disease–related proteins with gestational hypertension and preeclampsia. In downstream analyses, a systematic review of observational data was conducted to evaluate the identified proteins' dynamics across gestation in hypertensive vs normotensive pregnancies, and phenome-wide MR analyses were performed to identify potential non-HDP–related effects associated with the prioritized proteins. Genetic association data for cardiovascular disease–related proteins were obtained from the Systematic and Combined Analysis of Olink Proteins (SCALLOP) consortium. Genetic association data for the HDPs were obtained from recent European-ancestry genome-wide association study meta-analyses for gestational hypertension and preeclampsia. Study data were analyzed October 2022 to October 2023.

EXPOSURES Genetic instruments for 90 candidate proteins implicated in cardiovascular diseases, constructed using *cis*-protein quantitative trait loci (*cis*-pQTLs).

MAIN OUTCOMES AND MEASURES Gestational hypertension and preeclampsia.

RESULTS Genetic association data for cardiovascular disease–related proteins were obtained from 21 758 participants from the SCALLOP consortium. Genetic association data for the HDPs were obtained from 393 238 female individuals (8636 cases and 384 602 controls) for gestational hypertension and 606 903 female individuals (16 032 cases and 590 871 controls) for preeclampsia. Seventy-five of 90 proteins (83.3%) had at least 1 valid *cis*-pQTL. Of those, 10 proteins (13.3%) were significantly associated with HDPs. Four were robust to sensitivity analyses for gestational hypertension (cluster of differentiation 40, eosinophil cationic protein [ECP], galectin 3, N-terminal pro–brain natriuretic peptide [NT-proBNP]), and 2 were robust for preeclampsia (cystatin B, heat shock protein 27 [HSP27]). Consistent with the MR findings, observational data revealed that lower NT-proBNP (0.76- to 0.88-fold difference vs no HDPs) and higher HSP27 (2.40-fold difference vs no HDPs) levels during the first trimester of pregnancy were associated with increased risk of HDPs, as were higher levels of ECP (1.60-fold difference vs no HDPs). Phenome-wide MR analyses identified 37 unique non-HDP–related protein-disease associations, suggesting potential on-target effects associated with interventions lowering HDP risk through the identified proteins.

CONCLUSIONS AND RELEVANCE Study findings suggest genetic associations of 4 cardiovascular disease–related proteins with gestational hypertension and 2 associated with preeclampsia. Future studies are required to test the efficacy of targeting the corresponding pathways to reduce HDP risk.

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Supplemental content

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JAMA Cardiol. 2024;9(3):209-220. doi:10.1001/jamacardio.2023.4994
Published online January 3, 2024.

The hypertensive disorders of pregnancy (HDPs) are a leading cause of maternal and neonatal morbidity and mortality, affecting up to 15% of child-bearing female individuals and accounting for 14% of maternal deaths worldwide.[1,2] Gestational hypertension (new-onset hypertension after 20 weeks of gestation) and preeclampsia (gestational hypertension with proteinuria or other maternal end-organ dysfunction) account for approximately 90% of hypertensive pregnancies.[2,3] In addition to the immediate maternal and neonatal complications of HDPs, affected individuals also face an increased long-term risk of cardiovascular events and premature mortality.[2,4,5] Given the significant impact of HDPs on maternal and neonatal health, there is currently an unmet need for new therapeutics to prevent and treat these conditions.

The cardiovascular system plays a central role in the onset of HDPs.[6,7] For example, in preeclampsia, defective placental implantation and abnormal remodeling of the uterine spiral arteries lead to impaired placental perfusion later in gestation, which—in turn—leads to angiogenic factor imbalance, endothelial dysregulation, and systemic vasoconstriction. Consistent with this framework, genome-wide association studies (GWASs) suggest that most genetic loci associated with gestational hypertension and/or preeclampsia are related to cardiovascular processes.[7,8] However, it remains unclear whether cardiovascular disease-related pathways could represent potential drug targets for HDPs.

Although current management strategies for HDPs include blood pressure control, seizure prevention, and timed delivery,[6] none of these interventions targets underlying molecular pathways. This lack of disease-specific pharmacotherapeutic options can be partially ascribed to an incomplete understanding of the molecular mechanisms driving HDPs and the challenges associated with drug development for obstetric conditions.[9] For instance, although aspirin can be used to prevent preterm preeclampsia, mechanisms by which aspirin exerts its prophylactic effects remain unclear.[10] In addition, traditional methods to identify drug targets, such as animal models, have often been unsuccessful in capturing the complex pathophysiology underlying HDPs and, consequently, have not translated to effective interventions in clinical trials.[9]

Recent studies have identified genetic variants associated with plasma protein levels (protein quantitative trait loci [pQTLs]),[11] facilitating the identification of drug targets for human diseases using mendelian randomization (MR).[12-15] Given the limitations of traditional methods for identifying HDP drug targets, genetic approaches may help prioritize new therapeutic targets for these conditions. Here, we leveraged MR to identify therapeutic targets for HDPs. We constructed genetic instruments for candidate cardiovascular disease–related plasma proteins and estimated their association with gestational hypertension and preeclampsia. We evaluated observational associations between prioritized proteins and HDPs and conducted phenome-wide MR analyses to explore potential beneficial or adverse non-HDP–related effects associated with therapeutically targeting these proteins. Finally, we evaluated the potential druggability of the identified proteins as therapeutic targets for gestational hypertension and preeclampsia.

Key Points

Question Can mendelian randomization identify associations between circulating cardiovascular disease–related proteins and hypertensive disorders of pregnancy (HDPs)?

Findings In this genetic association study including data from 21 758 participants for cardiovascular disease–related proteins, 393 238 female individuals for gestational hypertension, and 606 903 female individuals for preeclampsia, using genetic variants associated with circulating proteins as instrumental variables, 6 biomarkers with robust genetic associations with gestational hypertension and/or preeclampsia representing different pathways (eg, natriuretic peptide signaling, inflammation) were identified. Observational data were consistent with mendelian randomization results for several proteins, with dynamic associations of these proteins with HDPs throughout gestation.

Meaning This study highlights novel biological mechanisms and identifies potential therapeutic targets for HDPs.

Methods

A detailed description of the methods can be found in the eMethods in Supplement 1 (as well as eFigures 2-3 in Supplement 1 and eTables 1-6 in Supplement 2). The Massachusetts General Brigham institutional review board approved these secondary data analyses. Participants in all studies contributing data for this analysis signed informed consent for participation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) reporting guidelines.

Study Design

The study design is summarized in eFigure 1 in Supplement 1. We used pQTLs as the exposures throughout all MR analyses. Because the use of *cis*-pQTLs (pQTLs near the protein-encoding gene) facilitates adherence to the core assumptions of MR,[15,16] all genetic instruments for circulating protein levels were constructed using *cis*-pQTLs (referred to as *cis*-MR). Additional information on the assumptions of MR and the impact of *cis*-pQTLs on those can be found in the eMethods in Supplement 1.

GWASs

Genetic association data for circulating protein levels were obtained from a meta-analysis including European-ancestry individuals enrolled in 13 cohorts from the Systematic and Combined Analysis of Olink Proteins (SCALLOP) consortium.[11] Participants were recruited from population-based studies,[17-25] a cohort of participants with metabolic syndrome,[26] a randomized clinical trial of coronary artery disease,[27] a population-based study with oversampling of participants with diabetes,[28] and a case-control study of bipolar disorder.[11,29]

Association data for HDPs were obtained from GWAS meta-analyses by Honigberg et al[8] for gestational hypertension and

preeclampsia/eclampsia. Participants were predominantly recruited from population-based or health system-linked cohort studies,[22,30-46] with HDP cases primarily identified using qualifying *International Statistical Classification of Diseases and Related Health Problems, Ninth* or *Tenth Revision* codes or phecodes; controls were primarily those with only normotensive pregnancies or all female individuals without codes for hypertension in pregnancy.[8,47] Biobanks and cohorts contributing data to the HDP GWAS meta-analyses began enrolling participants between 1989 and 2017; apart from a subset of cohorts contributing to the InterPregGen consortium, all other biobanks/cohorts began enrollment after 1999.

cis-MR Analyses

Genetic instruments for plasma proteins were constructed using region-wide significant, largely uncorrelated *cis*-pQTLs (±200 kilobases, $P < 1 \times 10^{-4}$, R^2 <0.4 in primary analyses).[15,16] Primary analyses used the inverse-variance–weighted (IVW) method with fixed effects for instruments with 2 to 3 variants and multiplicative random effects for instruments with more than 3 variants.

When the instrument included a single variant, we used the Wald ratio method. In addition, to avoid spurious associations due to residual correlation between variants, we adjusted for between-variant correlation structure in all primary IVW models as described previously.[48,49]

Multiple sensitivity analyses were conducted to probe robustness of our findings using different instrument selection parameters and MR methods.[12] First, because *cis*-MR analyses often rely on variants that are moderately correlated with each other,[50] we performed MR analyses using different correlation thresholds (R^2 <0.001, R^2 <0.01, R^2 <0.1, R^2 <0.2, R^2 <0.4, R^2 <0.6, and R^2 <0.8). Second, additional sensitivity analyses used stricter *P* value thresholds to construct genetic instruments ($P < 1 \times 10^{-4}$, $P < 1 \times 10^{-6}$, and $P < 5 \times 10^{-8}$). Third, we conducted analyses using MR models with principal components explaining 99% of the genetic variance.[48,50] Fourth, we calculated effect estimates using MR-Egger (adjusted for residual correlation between variants), which accounts for horizontal pleiotropy. Finally, we tested for reverse causation by performing Steiger filtering, which removes variants explaining more variance in the outcome than the exposure, and we tested the genetic associations of HDPs (exposure) with the indicated proteins (outcome).

Downstream Analyses

Downstream analyses further explored the proteins that survived sensitivity analyses. We (1) performed replication analyses using pQTL data from the UK Biobank Pharma Proteomics Project (UKB-PPP), (2) carried out colocalization analyses to test for shared causal variants between the prioritized proteins' *cis* loci and HDPs, (3) conducted a systematic review of observational data to gain insights into the identified proteins' dynamics across gestation in hypertensive vs normotensive pregnancies, (4) performed phenome-wide MR analyses to identify potential non-HDP-related outcomes (on-target beneficial or adverse effects), and (5) evaluated the druggability profiles of all identified target proteins (eMethods in Supplement 1).

Statistical Analysis

Two-sided, false discovery rate (FDR)–adjusted $P < .05$ was used to define statistical significance for the primary analyses. Associations of proteins with HDPs were considered robust if (1) the primary analysis was statistically significant, (2) all sensitivity analyses were directionally consistent, and (3) there was no evidence of reverse causation (unadjusted $P > .05$). MR analyses were performed using the TwoSampleMR and MendelianRandomization packages in R.[51,52] Study data were analyzed October 2022 to October 2023.

Results

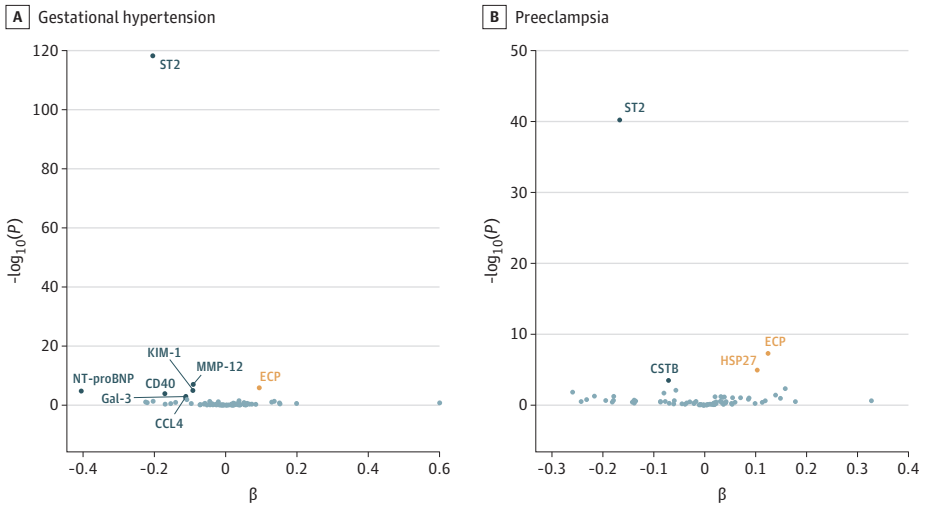
Genetic Associations of Cardiovascular Proteins With Gestational Hypertension and Preeclampsia

Genetic association data for cardiovascular disease–related proteins were obtained from 21 758 participants from the SCALLOP consortium.[11] Approximately 13 555 of 21 488 participants (63.1%) were recruited in population-based studies,[17-25] 3403 of 21 488 (15.8%) in a cohort of participants with metabolic syndrome,[26] 2967 of 21 488 (13.8%) in a randomized clinical trial of coronary artery disease,[27] 882 of 21 488 (4.1%) in a population-based study with oversampling of participants with diabetes,[28] and 681 of 21 488 (3.2%) in a case-control study of bipolar disorder (eTables 1 and 3 in Supplement 2).[11,29] Genetic association data for the HDPs were obtained from 393 238 female individuals (8636 cases and 384 602 controls) for gestational hypertension and 606 903 female individuals (16 032 cases and 590 871 controls) for preeclampsia.

Of the 90 candidate proteins, 85 were encoded by autosomal genes and had genetic association data available for the *cis*-regions of interest (eTable 2 in Supplement 2). Using the instrument selection parameters for our primary analyses ($P < 1 \times 10^{-4}$; R^2 <0.4), genetic instruments were constructed for 75 of 90 proteins (83.3%). The median number of variants included in the genetic instruments was 20 (IQR, 7-40). Genetic variants used for each protein-specific genetic instrument are listed in eTable 7 in Supplement 2. All *F* statistics were estimated to be greater than 15, suggesting low risk of weak instrument bias.

Primary analyses identified 10 of 75 proteins (13.3%) associated with gestational hypertension and/or preeclampsia at FDR-adjusted $P < .05$. Among those, 8 were associated with gestational hypertension: C-C motif chemokine 4 (CCL4), cluster of differentiation 40 (CD40), eosinophil cationic protein (ECP), galectin-3 (Gal-3), kidney injury molecule 1 (KIM-1), matrix metalloproteinase 12 (MMP-12), N-terminal pro-brain natriuretic peptide (NT-proBNP), and suppression of tumorigenicity 2 (ST2). Four proteins were associated with preeclampsia: cystatin B (CSTB), ECP, heat shock protein 27 (HSP27), and ST2. For ECP and HSP27, higher genetically predicted levels increased HDP risk, suggesting that higher levels of these proteins can lead to HDPs. The remaining proteins (including NT-proBNP) were negatively associated with HDPs, suggesting that higher levels are protective against HDPs (**Figure 1** and eTables 8-9 in Supplement 2).

Figure 1. Associations of Genetically Predicted Protein Levels With Hypertensive Disorders of Pregnancy (HDPs) in Primary Analyses



cis-Mendelian randomization analyses were performed using *cis*-variants at $P < 1 \times 10^{-4}$ clumped at R^2 <0.4. Associations are expressed per SD increase in genetically predicted protein levels. Biomarkers reaching statistical significance (false discovery rate–adjusted $P < .05$) are displayed in blue (if β <0) or orange (if β >0). CCL4 indicates C-C motif chemokine 4; CD40, cluster of differentiation 40; CSTB, cystatin B; ECP, eosinophil cationic protein; Gal-3, galectin 3; HSP27, heat shock protein 27; KIM-1, kidney injury molecule 1; MMP-12, matrix metalloproteinase 12; NT-proBNP, N-terminal pro–brain natriuretic peptide; ST2, suppression of tumorigenicity 2.

We performed multiple sensitivity analyses using different selection parameters and MR methods to probe the robustness of our findings (eTable 10 in Supplement 2). Robust associations (ie, directional consistency across all sensitivity analyses) were observed for 4 of 8 proteins associated with gestational hypertension (CD40, ECP, Gal-3, and NT-proBNP), and 2 of 4 proteins associated with preeclampsia (CSTB and HSP27) (**Figure 2**). All robustly associated proteins, except CD40 for gestational hypertension and CSTB for preeclampsia, had directionally consistent associations with the other HDP subtype (eTables 8-9 in Supplement 2). ECP, which was robust to all sensitivity analyses for gestational hypertension, was also robust to all but 1 sensitivity analysis for preeclampsia. Steiger filtering did not identify any *cis*-variants explaining more variance in the outcome (HDPs) than the exposure (protein levels) for most biomarkers; HSP27—the only protein with reverse-causal variants—was still strongly associated with preeclampsia after excluding a single variant identified using Steiger filtering (β = 0.12; 95% CI, 0.08-0.17; $P = 1.1 \times 10^{-8}$). Similarly, MR analyses testing the opposite direction of effects all yielded unadjusted *P* values >.05, further suggesting no bias from reverse causation (eTable 11 in Supplement 2).

All 6 robust associations replicated with $P < 1 \times 10^{-4}$ using pQTLs derived from the UK Biobank (eTable 12 in Supplement 2).[53] Colocalization was inconclusive for most proteins under study (eTable 13 in Supplement 2). There was strong evidence of a shared causal variant between Gal-3 and gestational hypertension in the UKB-PPP (posterior probability for H_4 >0.80). Colocalization evidence for NT-proBNP was mixed, with strong evidence of colocalization when examining variants within the *NPPB* gene but suggestion of distinct causal variants when broadening to a window of ±200 kilobases.

Observational Associations of Target Proteins With Gestational Hypertension and Preeclampsia

Observational studies suggest that the magnitude and direction of associations between HDPs and circulating proteins can change across gestation.[54] To gain insights into the identified proteins' dynamics during hypertensive vs normotensive pregnancies, we performed a systematic review of studies reporting observational associations of the prioritized proteins with HDPs. Forty-three studies[36-46,55-87] met our inclusion criteria (eFigure 3 in Supplement 1), encompassing 9749 pregnant individuals with protein measurements who enrolled from 1998 to 2020 in their respective studies. Of those, 3122 individuals (32.0%) experienced an HDP, including 939 (9.6%) with gestational hypertension, 2167 (22.2%) with preeclampsia, and 16 (0.2%) without information on HDP subtype. The most frequently tested biomarker was NT-proBNP (n = 8940; 30 studies[38,39,42,44,45,56-59,61,63,64,67-77,79,80,82-85,87]), followed by Gal-3 (n = 921; 11 studies[37,40,41,46,55,62,63,66,71,86,88]), HSP27 (n = 363; 5 studies[46,60,63,65,81]), and CD40 (n = 81; 2 studies[63,78]). CSTB and ECP were both evaluated by a single study[63] including 66 participants. Detailed information on each study's design and participants can be found in eTables 14 and 15 in Supplement 2.

Information on observational protein levels in pregnant individuals with vs without HDPs is provided in eTable 16 in Supplement 2. In contrast with the established associations of higher NT-proBNP levels with cardiac dysfunction and heart failure,[89] lower first-trimester NT-proBNP level was associated with subsequent development of HDPs (0.76- to 0.88-fold difference vs no HDPs). The direction of this association reversed during the second and third trimesters of pregnancy, with higher NT-proBNP levels in those with vs without HDPs (**Figure 3**A). We did not observe a similar temporal trend for Gal-3 in individuals with preeclampsia (Figure 3B). There were no data available on Gal-3 in individuals with gestational hypertension. For HSP27, higher levels early in pregnancy were associated with the subsequent development of preeclampsia (2.40-fold difference in the first trimester vs no HDPs) (Figure 3C). Temporal trends across gestation were observed for NT-proBNP and HSP27 in both linear and nonlinear models (eFigure 4 in Supplement 1). CD40 and ECP, al-

Figure 2. Genetic Associations of Protein Levels With Hypertensive Disorders of Pregnancy (HDPs) Robust to Sensitivity Analyses

A Gestational hypertension

Biomarker	Odds ratio (95% CI)
NT-proBNP	
Main analysis: IVW using P <1×10^{-4} and R^2 <0.4	0.67 (0.55-0.80)
Sensitivity analysis: IVW-PCA using P <1×10^{-4} and R^2 <0.4	0.72 (0.60-0.86)
Sensitivity analysis: MR-Egger using P <1×10^{-4} and R^2 <0.4	0.67 (0.56-0.79)
Sensitivity analysis: IVW using P <5×10^{-8} and R^2 <0.4	0.63 (0.50-0.79)
Sensitivity analysis: IVW using P <1×10^{-6} and R^2 <0.4	0.66 (0.53-0.82)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.001	0.74 (0.63-0.87)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.01	0.67 (0.58-0.77)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.1	0.66 (0.51-0.86)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.2	0.71 (0.56-0.89)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.6	0.51 (0.44-0.59)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.8	0.69 (0.71-0.69)
CD40	
Main analysis: IVW using P <1×10^{-4} and R^2 <0.4	0.84 (0.77-0.92)
Sensitivity analysis: IVW-PCA using P <1×10^{-4} and R^2 <0.4	0.96 (0.89-1.03)
Sensitivity analysis: MR-Egger using P <1×10^{-4} and R^2 <0.4	0.85 (0.79-0.92)
Sensitivity analysis: IVW using P <5×10^{-8} and R^2 <0.4	0.86 (0.78-0.95)
Sensitivity analysis: IVW using P <1×10^{-6} and R^2 <0.4	0.86 (0.78-0.95)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.001	0.97 (0.90-1.04)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.01	0.97 (0.90-1.04)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.1	0.96 (0.89-1.04)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.2	0.96 (0.89-1.03)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.6	0.71 (0.66-0.77)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.8	0.71 (0.66-0.76)
Gal-3	
Main analysis: IVW using P <1×10^{-4} and R^2 <0.4	0.89 (0.84-0.96)
Sensitivity analysis: IVW-PCA using P <1×10^{-4} and R^2 <0.4	0.89 (0.82-0.97)
Sensitivity analysis: MR-Egger using P <1×10^{-4} and R^2 <0.4	0.94 (0.88-1.01)
Sensitivity analysis: IVW using P <5×10^{-8} and R^2 <0.4	0.90 (0.83-0.96)
Sensitivity analysis: IVW using P <1×10^{-6} and R^2 <0.4	0.90 (0.83-0.96)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.001	0.96 (0.82-1.12)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.01	0.89 (0.78-1.02)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.1	0.89 (0.81-0.97)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.2	0.89 (0.83-0.97)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.6	0.91 (0.85-0.97)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.8	0.86 (0.79-0.95)
ECP	
Main analysis: IVW using P <1×10^{-4} and R^2 <0.4	1.10 (1.06-1.14)
Sensitivity analysis: IVW-PCA using P <1×10^{-4} and R^2 <0.4	1.11 (1.06-1.16)
Sensitivity analysis: MR-Egger using P <1×10^{-4} and R^2 <0.4	1.08 (0.99-1.18)
Sensitivity analysis: IVW using P <5×10^{-8} and R^2 <0.4	1.06 (0.94-1.20)
Sensitivity analysis: IVW using P <1×10^{-6} and R^2 <0.4	1.07 (1.00-1.14)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.001	1.10 (1.05-1.15)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.01	1.09 (1.05-1.14)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.1	1.10 (1.06-1.14)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.2	1.10 (1.06-1.14)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.6	1.08 (1.07-1.10)
Sensitivity analysis: IVW using P <1×10^{-4} and R^2 <0.8	1.10 (1.05-1.15)

B Preeclampsia

Odds ratio (95% CI)
CSTB
0.93 (0.90-0.97)
0.95 (0.90-1.00)
0.93 (0.89-0.97)
0.93 (0.89-0.97)
0.93 (0.89-0.97)
0.95 (0.88-1.02)
0.95 (0.90-1.01)
0.93 (0.88-0.98)
0.92 (0.88-0.97)
0.90 (0.87-0.92)
0.77 (0.75-0.79)
HSP27
1.11 (1.06-1.16)
1.06 (0.97-1.16)
1.08 (1.03-1.13)
1.09 (1.04-1.15)
1.09 (1.04-1.14)
1.06 (0.97-1.16)
1.08 (0.99-1.17)
1.08 (1.00-1.16)
1.07 (0.99-1.15)
1.04 (0.99-1.10)
1.11 (1.06-1.15)

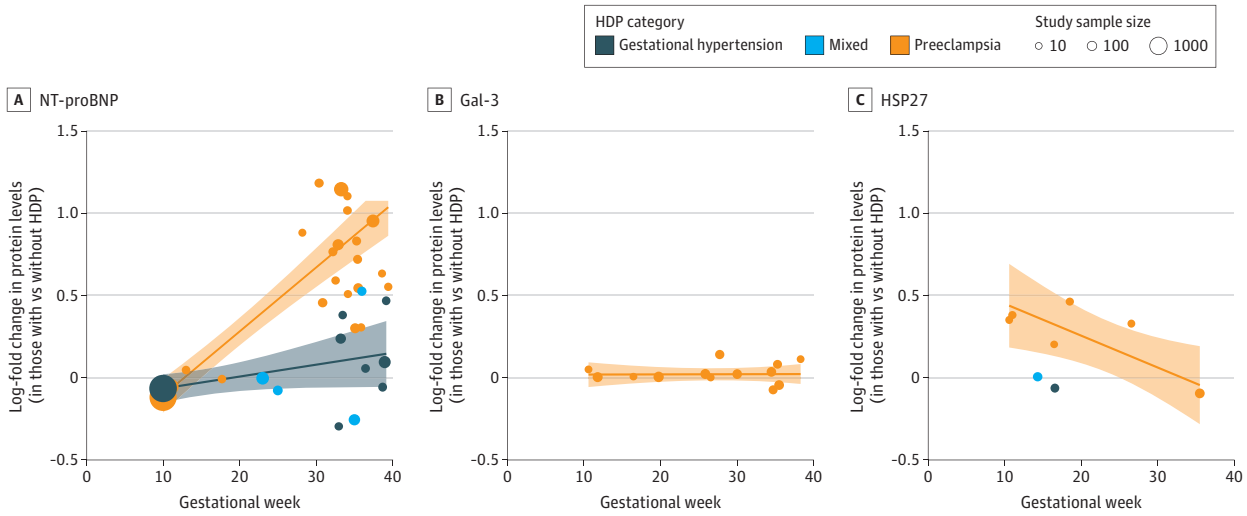
Forest plots show associations that were significant in primary analyses (orange squares) with directionally consistent sensitivity analyses (blue squares). Associations are expressed per SD increase in genetically predicted protein levels. Main analyses included *cis*-protein quantitative trait loci with $P < 1 \times 10^{-4}$ at R^2 <0.4 and used inverse-variance–weighted (IVW) adjusting for between-variant correlation. From top to bottom, sensitivity analyses used IVW with principal component analysis ([IVW-PCA] 99% of variance); mendelian randomization–Egger (MR-Egger); IVW adjusting for between-variant correlation using different linkage disequilibrium R^2 thresholds (0.001, 0.01, 0.1, 0.2, 0.6, and 0.8); and IVW adjusting for between-variant correlation using different P-value thresholds (1×10^{-6} and 5×10^{-8}). CD40 indicates cluster of differentiation 40; CSTB, cystatin B; ECP, eosinophil cationic protein; Gal-3, galectin 3; HSP27, heat shock protein 27; NT-proBNP, N-terminal pro–brain natriuretic peptide.

though only measured in fewer than 100 participants each, were higher among participants with preeclampsia vs no HDPs (eTable 16 in Supplement 2). Overall, observational data were available and consistent with MR analyses for 3 of 6 prioritized biomarkers (NT-proBNP, HSP27, and ECP), including both biomarkers (NT-proBNP and HSP27) with available first trimester data.

Phenome-Wide MR Analyses of Therapeutic Targets

Next, we performed phenome-wide MR analyses to investigate potential non-HDP–related outcomes (ie, on-target beneficial or adverse effects) associated with therapeutic targeting of the identified proteins. Using a lenient significance threshold of $P < .0083$ (ie, $P < .05/6$ [for 6 tested proteins]), which may increase the sensitivity to detect potential beneficial or adverse effects but may

Figure 3. Observational Associations Between Hypertensive Disorders of Pregnancy (HDPs) and N-Terminal Pro–Brain Natriuretic Peptide (NT-proBNP), Galectin 3 (Gal-3), and Heat Shock Protein 27 (HSP27) Across Gestation



Scatterplots illustrate the association between protein levels and gestational age at blood sampling. Protein levels were compared by $\log_{10}$-transforming the ratio of mean protein concentration in the HDP vs non-HDP group. Lines depict linear regression estimates (and corresponding 95% confidence bands) for HDP subgroups (preeclampsia or gestational hypertension) weighted by each study's sample size, generated using *ggplot2* in R. Studies with data labeled as mixed did not distinguish between preeclampsia and gestational hypertension. Each 1-week increase in gestational age was associated with a 0.039-point increase (95% CI, 0.032-0.046; $P = 4.4 \times 10^{-10}$) in NT-proBNP abundance (log-fold change in women with vs without HDP) for preeclampsia; a 0.007-point increase (95% CI, −0 to 0.015; $P = .06$) in NT-proBNP abundance for gestational hypertension; a 0-point increase (95% CI, −0.003 to 0.004; $P = .94$) in Gal-3 abundance for preeclampsia; and a 0.019-point decrease (β = −0.019; 95% CI, −0.035 to −0.005; $P = .03$) in HSP27 abundance for preeclampsia.

Table 1. Summary of Phenome-Wide Mendelian Randomization (MR) Analyses Evaluating Potential On-Target Outcome Effects Associated With Therapeutic Interventions on the Identified Proteins

Circulating protein	No. of potential beneficial or adverse side effects, No.	Beneficial effects, No. (%)[a]	Strongest associations (beneficial or adverse)[b]
CD40	5	4 (80.0)	Hemoptysis (beneficial); non-Hodgkin lymphoma (beneficial); back pain (beneficial)
CSTB	5	3 (60.0)	Melanoma (adverse); viral hepatitis (beneficial); infections of skin and subcutaneous tissue (beneficial)
ECP	9	5 (55.6)	Glaucoma (adverse); intestinal obstruction (beneficial); inguinal hernia (beneficial)
Gal-3	13	3 (23.1)	Upper respiratory tract disease (adverse); ganglion/cyst of synovium, tendon, or bursa (adverse); osteoarthrosis (adverse)
HSP27	4	1 (25.0)	Acute/chronic tonsillitis (adverse); acquired toe deformities (beneficial); age-related cataract (adverse)
NT-proBNP	1	1 (100)	Edema (beneficial)

Abbreviations: CD40 indicates cluster of differentiation 40; CSTB, cystatin B; ECP, eosinophil cationic protein; Gal-3, galectin 3; HSP27, heat shock protein 27; NT-proBNP, N-terminal pro–brain natriuretic peptide.

[a] A protein-disease association was considered beneficial if there were genetically predicted alterations in protein levels, consistent with reduced risk of hypertensive disorders of pregnancy and associated with a lower risk of the corresponding phecode-based disease phenotype.

[b] Protein-disease associations were considered significant if the inverse-variance–weighted method (correcting for between-variant correlation structure) yielded a $P < .0083$ ($P < .05/6$).

also lead to more false-positive findings, we identified 37 unique protein-disease associations (eTables 17-18 in Supplement 2). Among these, 17 protein-disease associations (45.9%) were beneficial, indicating that therapeutic targeting of these proteins to reduce HDP risk was associated with a lower risk of the corresponding diseases. Musculoskeletal disorders constituted the most frequently implicated phecode-based disease category (8 of 37 [21.6%]).

Table 1 summarizes protein-specific findings from our phenome-wide MR analyses. Gal-3 had the highest number of potential on-target effects (n = 13), the majority of which were adverse (9 of 13 [69.2%]). Each SD increase in genetically predicted protein levels was associated with 1.20-fold odds of having upper respiratory tract infections (β = 0.18; 95% CI, 0.09-0.28; $P = 2.2 \times 10^{-4}$), consistent with clinical trials testing Gal-3 inhibitors for the treatment of respiratory tract infections.[90] NT-proBNP had the fewest disease associations, with only a single beneficial association identified: each SD increase in genetically predicted levels was associated with 0.58-fold odds of having edema symptoms (β = −0.55; 95% CI, −0.84 to −0.26 per SD increase in genetically predicted protein levels; $P = 2.4 \times 10^{-4}$).

Table 2. Druggability of the Identified Proteins Representing Therapeutic Targets for Gestational Hypertension and/or Preeclampsia

Gene	Corresponding circulating protein	Druggability	Clinical development status	Molecule type	Compound names
CD40	CD40	Listed as druggable	Target of clinical-phase drug candidates (phase I and II)	Biotherapeutics (antibodies, recombinant ligands)	CDX-1140, cifurtilimab, giloralimab, mitazalimab, recombinant CD40 ligand, selicrelumab, sotigalimab
CSTB	CSTB	Not currently listed as druggable	NA	NA	NA
RNASE3	ECP	Listed as druggable	Not a current target of clinically approved compounds or clinical-phase drug candidates	Biotherapeutics	NA
LGALS3	Gal-3	Listed as druggable	Not a current target of clinically approved compounds or clinical-phase drug candidates	Biotherapeutics	NA
HSPB1	HSP27	Listed as druggable	Target of clinical-phase drug candidates (phase I and II)	Small molecules	Apatorsen
NPPB	NT-proBNP	Listed as druggable	Not a current target of clinically approved compounds or clinical-phase drug candidates	Biotherapeutics	NA
NPR1[a]	GC-A	Listed as druggable	Target of clinically approved compounds and clinical-phase drug candidates (phase I and II)	Biotherapeutics and small molecules	ANX-042, cenderitide, CRRL408, MANP, nesiritide, PL-3994

Abbreviations: CD40 indicates cluster of differentiation 40; CSTB, cystatin B; ECP, eosinophil cationic protein; Gal-3, galectin 3; GC-A, particulate guanylyl cyclase receptor A; HSP27, heat shock protein 27; NA, not applicable; NT-proBNP, N-terminal pro–brain natriuretic peptide.

[a] Designer natriuretic peptides targeting GC-A (encoded by *NPR1*) have mechanisms that align with higher NT-proBNP levels.

Druggability of Potential Therapeutic Targets

To determine whether the identified proteins could serve as therapeutic targets for gestational hypertension and/or preeclampsia, we extracted their druggability profiles from a recently published list of druggable genes.[91] All prioritized proteins except CSTB were considered druggable (**Table 2** and eTable 19 in Supplement 2).

Discussion

We used MR to test the genetic associations of various candidate cardiovascular disease–related proteins with gestational hypertension and preeclampsia. Primary analyses identified 10 proteins reflecting pathways with potential roles in the development of HDPs, 6 of which were robust to sensitivity analyses for gestational hypertension (CD40, ECP, Gal-3, NT-proBNP) or preeclampsia (CSTB, HSP27). Consistent with these findings, observational data revealed that pregnant individuals with lower NT-proBNP and higher HSP27 levels during early gestation had an associated higher risk of experiencing HDPs, as were those with higher levels of ECP. Phenome-wide MR analyses suggested potential on-target effects, both beneficial and adverse, associated with interventions to lower HDP risk through the identified proteins. Collectively, these findings provided insights into biological mechanisms and identified potential therapeutic targets for HDPs.

First, our findings identified natriuretic peptide signaling as a potential therapeutic target for HDPs. NT-proBNP and BNP, members of the natriuretic peptide family, are derived from a common prohormone (proBNP) encoded by the *NPPB* gene.[92] ProBNP is primarily synthesized and secreted by cardiac myocytes in response to increased myocardial wall tension, after which it is cleaved in equimolar quantities into inert NT-proBNP and bioactive BNP, which enhances natriuresis and reduces vascular tone. NT-proBNP levels change during uncomplicated pregnancies: they increase during the first trimester and decline thereafter,[93] likely reflecting physiological adaptations to volume expansion early in gestation. Recent data from the Nulliparous Pregnancy Outcomes Study Monitoring Mothers to Be (nuMoM2b) study,[94] a large prospective US cohort study of pregnant individuals, revealed that lower first trimester NT-proBNP levels were associated with increased risks of gestational hypertension, preeclampsia, and hypertension after delivery. Our *cis*-MR analyses affirmed and extended these findings by demonstrating that lower geneti-

cally predicted NT-proBNP levels were associated with an increased risk of developing gestational hypertension. Furthermore, genetic studies implicate lower expression of *NPPA* (which encodes atrial natriuretic peptide [ANP] and has strong shared genetic regulation mechanisms with *NPPB*[95]) in the development of HDPs,[8] with ANP-deficient mice demonstrating impaired trophoblast invasion and uterine spiral artery remodeling.[96,97] These findings collectively suggest that the HDPs may represent a syndrome of deficient natriuretic peptide signaling, potentially implicating a paradigm of cardiac-placental crosstalk underlying the core pathobiology of HDPs. Importantly, designer natriuretic peptides mimicking the effects of BNP or ANP are currently under development for cardiovascular diseases such as hypertension and heart failure.[92] Future studies are required to test the effectiveness of direct modulation (eg, designer natriuretic peptides), indirect modulation, or tailored management (eg, conservative fluid management in high-risk patients) of these pathways to prevent the onset and/or long-term cardiovascular consequences of HDPs.

Second, our findings provided novel insights into inflammatory mechanisms underlying HDPs. Specifically, we observed that higher genetically predicted ECP levels were associated with an increased risk of gestational hypertension. ECP is a cytotoxic protein involved in immune regulation and serves as an established biomarker for eosinophil activation.[98] Previous observational and MR studies have indicated that ECP plays a role in the onset and progression of asthma,[98] a known risk factor for HDPs.[99] As recent research implicates a role for ECP in atherogenesis and vascular calcification,[100] it is possible that ECP contributes to accelerated atherosclerosis in individuals with prior HDPs.[2,5] Furthermore, we also identified HSP27—an intracellular protein involved in stress response and cell survival—as a potential biomarker associated with preeclampsia. When released extracellularly, HSP27 promotes inflammation through increased expression of interleukin 1β and tumor necrosis factor α.[101] Experiments in mice indicate that HSP27 is upregulated from conception to delivery in response to physiologic stress associated with pregnancy.[102] It has been proposed that homeostasis of extracellular heat shock proteins is important for immune tolerance during pregnancy, with increased heat shock protein levels predisposing to an immunogenic rather than tolerant phenotype toward the fetus.[103] Consistent with this framework, human genetic data suggest that heat shock proteins are important contributors to spontaneous preterm delivery.[104] These data, together with the genetic and observational findings from the present study, suggest a role for HSP27 in pregnancy-associated inflammation.

Third, this study corroborated the notion that the relevance of circulating proteins with HDPs can change throughout gestation. Pregnancy is a dynamic process, reflected by longitudinal changes in the plasma concentrations of certain proteins.[54,93] Previous research has shown that associations of placental proteins with HDPs change throughout pregnancy.[54] The present analysis extended these findings by demonstrating that the direction of observational biomarker associations with HDPs may reverse between early and late pregnancy. In addition to longitudinal changes throughout gestation, emerging evidence suggests a complex interplay between fetal- and maternally encoded proteins in human pregnancy.[105] Further research is necessary to elucidate the relative contributions of other fetal- and maternal-encoded proteins to the development of HDPs, underscoring the need for additional efforts (eg, regulatory incentives) to include pregnant individuals at various stages of gestation in clinical research.

Limitations

Although our study benefits from large genetic data sets and a robust *cis*-MR framework, findings must be interpreted in the context of limitations. First, we only examined 90 proteins within the Target 96 Olink CVD-I panel; this targeted approach has advantages but only examines candidate proteins. Second, our analysis only included genetic instruments identified in European-ancestry cohorts, limiting generalizability to other ancestries. Similarly, there was limited racial and ethnic diversity among the studies included in our systematic review. Although data from the nuMoM2b study suggest that the associations of low NT-proBNP levels early in pregnancy with the subsequent development of HDPs and hypertension after delivery are similar across self-reported races and ethnicities,[94] further studies are warranted to evaluate potential differences across races and ethnicities. Third, although MR can be used to infer causality in given exposure-outcome associations, any causal inference relies on the justification of the underlying MR assumptions. The present study used a robust *cis*-MR framework facilitating adherence to these assumptions,[12-14] probed the robustness of the study findings through multiple sensitivity and replication analyses, and found no substantial evidence of pleiotropic associations. Nevertheless, candidate therapeutic targets remain to be validated in intervention trials, and additional efforts are needed to overcome barriers to the inclusion of pregnant individuals in scientific trials and further scientific progress on reducing pregnancy complications.[106] Fourth, genetic association data for HDPs were predominantly based on diagnostic code–based definitions, the use of which may differ across studies and change over time. Finally, we constructed genetic instruments using pQTLs derived from nonpregnant individuals.[11] Although we speculate that our analysis (using pQTLs from the general population) may more closely represent first-trimester biology, the genetic regulation of plasma proteins during pregnancy has not been studied at scale. Recent data suggest that between-sex differences in pQTLs are limited[107,108] with few sex-specific effects on protein-disease associations,[109] but whether sex-stratified pQTLs may yield additional insights warrants future investigation. However, our MR findings were consistent with observational associations between HDPs and first-trimester protein levels for NT-proBNP and HSP27, suggesting that pQTLs derived from nonpregnant individuals can recapitulate associations between proteins and outcomes in pregnancy.

Conclusions

Although, to the authors' knowledge, there are currently no pharmacotherapeutic options available that specifically tar-

get the underlying causal pathways leading to HDPs, disease-specific therapeutics could potentially benefit many high-risk pregnant individuals. In this study, we used MR to infer associations of various candidate proteins with gestational hypertension and preeclampsia. Our analysis revealed druggable proteins involved in cardiovascular and inflammatory processes. Future studies should evaluate the efficacy of targeting these pathways in animal models and human trials.

ARTICLE INFORMATION

Accepted for Publication: November 1, 2023.

Published Online: January 3, 2024. doi:10.1001/jamacardio.2023.4994

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Obtained funding: Roh, Natarajan.
Administrative, technical, or material support: Truong, Ardissino, Cho, Hornsby, Lannery, Postupaka, Wood, Sarma, Roh.
Supervision: Small, Butterworth, Wood, Sarma, Januzzi, Natarajan, Honigberg.

Conflict of Interest Disclosures: Dr Nakao reported receiving grants from Japan Society for the Promotion of Science Overseas Fellowship and the National Heart, Lung, and Blood Institute outside the submitted work. Dr Gray reported receiving personal fees from BillionToOne, Roche, and Aetion outside the submitted work. Dr Butterworth reported receiving grants from AstraZeneca, Bayer, Biogen, BioMarin, and Sanofi outside the submitted work. Dr Scott reported receiving personal fees from HOPE registry and grants from the REBIRTH study during the conduct of the study. Dr Sarma reported receiving grants from CRICO and the American Heart Association and consulting fees from Pfizer during the conduct of the study. Dr Lau reported receiving grants from the National Institutes of Health/National Heart, Lung, and Blood Institute and the American Heart Association and advisory board fees from Astellas Pharma outside the submitted work. Dr Natarajan reported receiving grants from Allelica, Amgen, Apple, Boston Scientific, Genentech/Roche, and Novartis; personal fees from Allelica, Apple, AstraZeneca, Blackstone Life Sciences, Eli Lilly & Co, Foresite Labs, Genentech/Roche, GV, HeartFlow, Magnet Biomedicine, and Novartis; advisory board fees from Esperion Therapeutics, TenSixteen Bio, and MyOme; and equity from Preciseli, TenSixteen Bio, and MyOme outside the submitted work. Dr Honigberg reported receiving advisory board fees from Miga Health; personal fees from Comanche Biopharma; and grants from the National Heart, Lung, and Blood Institute, the American Heart Association, and Genentech outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported in part by the Belgian American Educational Foundation (Mr Schuermans); a Japan Society for the Promotion of Science overseas fellowship (Dr Nakao); a National Institute for Health and Care research academic clinical fellowship (Dr Ardissino); grant T32HG010464 from the Partners Healthcare Training Program in Precision and Genomic Medicine (Dr Small); grant HI19C1330 from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (Dr Cho); grant 225790/Z/22/Z from the Wellcome Trust and grant MC_UU_00002/7 from the UK Research and Innovation Medical Research Council (Dr Burgess); grants K08HL146963, R03HL162756, and R01HL163234 from the US National Heart, Lung, and Blood Institute (Dr Gray); funding from the Ellertson Family Endowed Chair in Cardiovascular Medicine and the HOPE registry and REBIRTH study (Dr Scott); grant K23HL159243 from the US National Heart, Lung, and Blood Institute and grant 853922 from the American Heart Association (Dr Lau); grant K76AG064328 from the US National Institute on Aging, an MGH Transformative Scholars Award, and the Yeatts Fund for Innovative Research (Dr Roh); the Hutter Family Professorship (Dr Januzzi); funding from the Hassenfeld Scholar Award and the Paul & Phyllis Fireman Endowed Chair in Vascular Medicine from the Massachusetts General Hospital, grants R01HL142711, R01HL148565 and R01HL148050 from the US National Heart, Lung, and Blood Institute, grant R01DK125782 from the National Institute of Diabetes and Digestive and Kidney Diseases, and grant TNE-18CVD04 from Fondation Leducq (Dr Natarajan); and grants K08HL166687 from the US National Heart, Lung, and Blood Institute and 940166 and 979465 from the American Heart Association (Dr Honigberg).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank all participants and investigators from the studies contributing to the present analyses.

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Editor's Note

Precision Medicine for Hypertensive Disorders of Pregnancy—Are We There Yet?

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New-onset hypertensive disorders of pregnancy (HDPs) are a heterogeneous syndrome of interrelated vascular conditions. HDPs include gestational hypertension, preeclampsia, and eclampsia and are defined by elevated blood pressure (BP) beginning after 20 weeks' gestation with or without end-organ damage. HDPs affect nearly 1 in 6 pregnancies, represent an important risk factor for short- and long-term risk of cardiovascular disease (CVD), and share antecedent determinants with CVD. However, disease-modifying therapies for HDPs do not currently exist, and contemporary management approaches for HDPs focus primarily on targeting BP. Although a precision medicine approach to HDPs has garnered much enthusiasm, a better understanding of the underlying pathophysiology is first needed, which was recently highlighted by the Society for Maternal-Fetal Medicine and the Preeclampsia Foundation.[1]

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The present study by Schuermans et al[2] leverages data from 21 758 individuals of European ancestry to examine the role of 75 candidate CVD proteins in the development of HDPs. Overall, 10 proteins were associated with either gestational hypertension or preeclampsia; 2 of them had consistent asso-