



Increased Risk of Preeclampsia in Women With a Genetic Predisposition to Elevated Blood Pressure

Anna Kivioja¹, Elli Toivonen¹*, Jaakko Tyrmi¹*, Sanni Ruotsalainen, Samuli Ripatti¹, Heini Huhtala¹, Tiina Jääskeläinen¹, Seppo Heinonen, Eero Kajantie¹, Juha Kere, Katja Kivinen¹, Anneli Pouta, Tanja Saarela¹, Hannele Laivuori¹

BACKGROUND: Preeclampsia causes significant maternal and perinatal morbidity. Genetic factors seem to affect the onset of the disease. We aimed to investigate whether the polygenic risk score for blood pressure (BP; BP-PRS) is associated with preeclampsia, its subtypes, and BP values during pregnancy.

METHODS: The analyses were performed in the FINNPEC study (Finnish Genetics of Pre-Eclampsia Consortium) cohort of 1514 preeclamptic and 983 control women. In a case-control setting, the data were divided into percentiles to compare women with high BP-PRS (HBP-PRS; >95th percentile) or low BP-PRS (≤5th percentile) to others. Furthermore, to evaluate the effect of BP-PRS on BP, we studied 3 cohorts: women with preeclampsia, hypertensive controls, and normotensive controls.

RESULTS: BP values were higher in women with HBP-PRS throughout the pregnancy. Preeclampsia was more common in women with HBP-PRS compared with others (71.8% and 60.1%, respectively; $P=0.009$), and women with low BP-PRS presented with preeclampsia less frequently than others (44.8% and 61.5%, respectively; $P<0.001$). HBP-PRS was associated with an increased risk for preeclampsia (odds ratio, 1.7 [95% CI, 1.1–2.5]). Furthermore, women with HBP-PRS presented with recurrent preeclampsia and preeclampsia with severe features more often.

CONCLUSIONS: Our results suggest that HBP-PRS is associated with an increased risk of preeclampsia, recurrent preeclampsia, and preeclampsia with severe features. Furthermore, women with HBP-PRS present higher BP values during pregnancy. The results strengthen the evidence pointing toward the role of genetic variants associated with BP regulation in the etiology of preeclampsia, especially its more severe forms. (*Hypertension*. 2022;79:2008–2015. DOI: 10.1161/HYPERTENSIONAHA.122.18996.) • [Supplemental Material](#)

Key Words: blood pressure ■ hypertension ■ preeclampsia ■ pregnancy ■ pregnancy complications

Preeclampsia affects 2% to 8% of pregnancies in developed countries and is defined by new-onset hypertension and proteinuria after 20 weeks of gestation, or, in the absence of proteinuria, impaired organ function or subjective symptoms of preeclampsia.¹ Risks of stillbirth, preterm birth, and intrauterine growth restriction increase in hypertensive disorders of pregnancy.^{2–4} Preeclampsia is a systemic vascular disorder involving

endothelial dysfunction,⁵ oxidative stress, and immunologic intolerance.⁶ Hypertensive disorders of pregnancy are risk factors for maternal and offspring cardiovascular morbidity.^{2,3} With efficient predicting methods, early diagnosis and in some cases even disease prevention could be possible, leading to improved maternal and neonatal outcome.⁷

Preeclampsia has multiple subtypes with different etiologies. Early-onset preeclampsia manifests before 34+0

Correspondence to: Elli Toivonen, Tampere University Hospital, PL2000, 33521 Tampere, Finland. Email elli.toivonen@tuni.fi

*E. Toivonen and J. Tyrmi contributed equally.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.122.18996>.

For Sources of Funding and Disclosures, see page 2014.

© 2022 The Authors. *Hypertension* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

Hypertension is available at www.ahajournals.org/journal/hyp

NOVELTY AND RELEVANCE

What Is New?

This study is among the first to investigate the role of polygenic risk scores (PRSs) in the onset of preeclampsia (PE).

What Is Relevant?

Our results show the association between PRS for for blood pressure (BP) and gestational BP values and highlight the increased risk for PE in women with the highest

BP-PRS. Our study is, to our knowledge, the first to note the association between certain PE subtypes (PE with severe features and recurrent PE) and BP-PRS.

Clinical/Pathophysiological Implications?

Women whose genetics predispose them to higher BP values are also at higher risk for PE and its more severe forms. The use of BP-PRS as a predictive tool is a target for further research.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
BP-PRS	polygenic risk score for blood pressure
CVD	cardiovascular disease
FINNPEC	Finnish Genetics of Pre-Eclampsia Consortium
HBP-PRS	high polygenic risk score for blood pressure (>95th percentile)
LBP-PRS	low polygenic risk score for blood pressure (≤5th percentile)
OR	odds ratio
PRS	polygenic risk score

weeks of gestation.⁸ Preeclampsia is considered to be associated with severe symptoms if significantly increased blood pressure (BP) level ($\geq 160/110$ mmHg) is combined with severe headache, visual disturbances, impaired liver function, renal insufficiency, pulmonary edema, or thrombocytopenia.¹ Early-onset preeclampsia,^{9,10} preeclampsia with severe features,¹¹ as well as recurrent preeclampsia¹²⁻¹⁴ are strongly related to chronic hypertension and future cardiovascular disease (CVD) risk.

The genetics of underlying preeclampsia is incompletely understood. However, a family history of preeclampsia increases the risk, suggesting a genetic background. In a systematic review,¹⁵ preeclampsia in the family was shown to increase the risk of preeclampsia 3-fold. In a recent study by the InterPregGen consortium, the maternal single-nucleotide polymorphism heritability of preeclampsia on the liability scale in Europeans was shown to be 38.1%, and certain maternal DNA variants were identified as risk factors for preeclampsia.¹⁶ Variants of these genes have previously been associated with BP¹⁷ and body mass index.^{18,19} The consortium previously reported the first genetic variants in fetal genomes predisposing mothers to preeclampsia.²⁰ In addition, epigenetic changes have been suggested to account for the onset of preeclampsia.^{21,22}

A polygenic risk score (PRS) demonstrates an individual's genetic risk of a disease affected by multiple genetic variants. A PRS is formed as a weighted sum of the risk alleles found in genome-wide association studies to be associated with the disease.²³ PRSs are an extended method as opposed to traditional genetic risk scores in which only genome-wide significant associations are taken into account in calculating the score.²⁴ In a recent study, the PRS for hypertension was shown to be associated with preeclampsia.¹⁶ This suggests that women genetically susceptible to hypertension might be at a higher risk for preeclampsia.

This study had 2 aims. First, we evaluated the impact of PRS for BP (BP-PRS) on the risks of preeclampsia, its subtypes, and other hypertensive disorders of pregnancy in a case-control setting. Another aim of the study was to assess the effect of BP-PRS on BP during pregnancy.

METHODS

Population

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers may be sent to H.L. at the Tampere University. Data requests may require further review by national register authorities and ethical committees. A.K. had access to all data.

Nulliparous and multiparous women with a singleton pregnancy were recruited at 5 university hospitals in Finland during 2008 to 2011 in the FINNPEC study (Finnish Genetics of Preeclampsia Consortium). A detailed description of the FINNPEC cohort has been published elsewhere.²⁵ Our study included those women whose genetic data were available. After the cohort description was published, additional women were included since their data were processed in accordance with the FINNPEC study protocol. Our study, therefore, includes more women than reported in the original cohort description, a total of 1514 women in the preeclampsia group and 983 women as controls. All participants provided written informed consent, and the FINNPEC study protocol was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (149/EO/2007).

Preeclampsia was defined as hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) and proteinuria

occurring after 20+0 weeks of gestation. Proteinuria was defined as urinary excretion of ≥ 0.3 g protein in a 24-hour specimen or 0.3 g/L or two $\geq 1+$ readings on a dipstick in a random urine determination in the absence of urinary tract infection. Preeclampsia was classified as early onset if diagnosed before 34+0 weeks of gestation.⁸ Preeclampsia with severe features was diagnosed with either markedly increased BP ($\geq 160/110$ mmHg) or severe proteinuria (≥ 5 g/24 hours) combined with subjective symptoms and, preferably, objective findings referring to a severe disease form.⁸

The FINNPEC cohort includes data on participating women and their pregnancies, including detailed data on BP and maternal biological samples. BP information was obtained from maternity cards or hospital records. Measurements were performed by medical professionals.

Genotyping and Imputation

FINNPEC samples have been genotyped using the Infinium Global Screening Array-24 v2.0 BeadChip (Illumina, Inc, San Diego, CA) at the Institute for Molecular Medicine Finland FIMM Technology Centre (University of Helsinki, Finland). Preimputation quality control has been performed with Plink, versions 1.07 and 1.9.²⁶ The genome option of Plink was used to test for unexpected genetic relationships in duplicated samples, triads, and dyads. Samples with unresolved sex mismatch, a missingness rate $>5\%$, or heterozygosity rate ± 4 SDs were omitted. Also samples with non-Finnish ancestry based on MDS analysis were excluded. Variants with a missing call rate $>2\%$, Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$, or minor allele count < 3 were removed. The genotyped samples were then phased using the Eagle 2.3.5 software²⁷ and imputed with Beagle, version 4.1,²⁸ using a population-specific reference panel SiSu v3 imputation reference panel, which consisted of 3775 whole-genome sequenced individuals of Finnish ancestry.

Polygenic Risk Scores

We built a BP-PRS with the PRS-CS software,²⁹ which recalculates single-nucleotide polymorphism weights from genome-wide association study summary statistics and a linkage disequilibrium reference panel by utilizing a Bayesian regression framework and placing continuous shrinkage priors on single-nucleotide polymorphism effect sizes. In the PRS-CS pipeline, default parameters and a European linkage disequilibrium reference panel with 1.1 million variants derived from samples from the 1000 Genomes Project³⁰ were used. Input weights came from the publicly available genome-wide association study for SBP.¹⁷ A total of 1 073 588 genetic variants common for the FINNPEC cohort and the linkage disequilibrium reference panel were included in the PRSs.

Study Groups and Settings

To assess the effect of high BP-PRS (HBP-PRS) or low BP-PRS (LBP-PRS) on the risk of preeclampsia and hypertensive disorders in a case-control setting, the participants were divided into percentiles based on their BP-PRS: women with HBP-PRS (>95 th percentile) were compared with those with LBP-PRS, and women with LBP-PRS (≤ 5 th percentile) were compared with those with HBP-PRS. PRS was

categorized into HBP-PRS and LBP-PRS percentiles for ease of interpretation.³¹

To evaluate BP levels in cohorts, 1514 women experiencing preeclampsia were compared with 2 control groups. Women with chronic hypertension, gestational hypertension or gestational proteinuria were counted as hypertensive controls ($n=219$), whereas normotensive controls ($n=764$) presented none of these. Women with preeclampsia in a previous but not in the current pregnancy were excluded from both control groups to control for potential confounding in genetic samples. In the cohort setting, we investigated the differences in BP values in the 3 cohorts between women with HBP-PRS and others and between women with LBP-PRS and others.

In this study, we used BP measurements from the first antenatal visit and the highest BP throughout the pregnancy. Furthermore, we calculated BP change as BP measured at first antenatal visit subtracted from the highest BP during pregnancy. We calculated whether BP-PRS correlates with BP values during pregnancy.

Statistical Analyses

Statistical analyses were performed using IBM SPSS for Windows, version 27 (IBM Corp, Armonk, NY). Women with HBP-PRS were compared with those whose BP-PRS was lower, and similarly, women with LBP-PRS were compared with those whose BP-PRS was higher. BP values were compared in a similar manner and, in addition, in 3 groups (preeclampsia women, hypertensive controls, and normotensive controls). Correlations were calculated using the Pearson method. Normally distributed quantitative data are expressed as means and SD, whereas medians and quartiles are reported for skewed distributions. Categorical data are shown in percentages. The normality of continuous variables was assessed with the Kolmogorov-Smirnov test. Student *t* test and 1-way ANOVA were used to compare means where appropriate, and for skewed distributions, the Kruskal-Wallis test was used. The χ^2 test was used to analyze the associations between the categorical variables. Binary logistic regression was used to calculate odds ratios (ORs) with 95% CIs. Women with preeclampsia were compared with controls (dependent variable), whereas HBP-PRS and LBP-PRS were used as independent variables. A linear regression model was used to adjust results of BP value comparisons using BP-PRS for age, body mass index, and principal components. Homoscedasticity of errors was assessed by plotting the residuals.

RESULTS

Preeclamptic women and hypertensive controls were older and more obese compared with normotensive control women (Table 1). There were more primiparous women in the preeclampsia group compared with the 2 control groups. Furthermore, fewer women were smokers in the preeclampsia group compared with the control groups. Family history of preeclampsia was more common in preeclamptic women. Women experiencing preeclampsia delivered at earlier gestational weeks than control women. Newborns of preeclampsia and hypertensive control women were more often small for

Table 1. Maternal and Perinatal Characteristics

Maternal or perinatal characteristics	Preeclampsia (n=1514)	Hypertensive control n=219	Normotensive control (n=764)	P value
	Median (Q1–Q3)/n (%)	Median (Q1–Q3)/n (%)	Median (Q1–Q3)/n (%)	
Age at delivery, y	30.0 (26.0–34.0)	30.0 (27.0–34.8)	29.0 (26.0–33.0)	0.002
Nulliparous	1128 (74.5)	148 (67.6)	419 (54.8)	<0.001
BMI* >30 kg/m ²	283 (18.7)	47 (21.5)	60 (7.9)	<0.001
Smoking during pregnancy	119 (8.0)	27 (12.5)	81 (10.6)	0.003
Systolic BP at the first antenatal visit, mmHg	124.0 (116.0–132.0)	128.5 (120.0–138.0)	117.0 (109.0–124.0)	<0.001
Diastolic BP at the first antenatal visit, mmHg	78.0 (70.0–84.0)	80.0 (72.3–88.0)	71.0 (66.0–77.0)	<0.001
Highest systolic BP, mmHg	165.0 (153.0–179.0)	150 (140.0–164.0)	125.0 (119.0–133.0)	<0.001
Highest diastolic BP, mmHg	109.0 (104.0–116.0)	101.50 (96.0–110.0)	83.0 (78.0–87.0)	<0.001
Chronic hypertension	263 (17.4)	61 (27.9)	0 (0)	<0.001
Gestational hypertension	0 (0)	139 (63.5)	0 (0)	<0.001
Proteinuria during pregnancy without elevated BP	0 (0)	20 (9.1)	0 (0)	<0.001
Small for gestational age	333 (22.0)	47 (21.5)	29 (3.8)	<0.001
Gestational age at delivery, wk+d	37+5 (35+1 to 39+1)	39+1 (37+6 to 40+4)	40+2 (39+3 to 41+2)	<0.001
Delivery before 34+0 GW	253 (16.7)	16 (7.3)	6 (0.8)	<0.001
Recurrent preeclampsia	189 (12.8)	0 (0)	0 (0)	<0.001
Preeclampsia in family†	141 (9.3)	10 (4.6)	32 (4.2)	<0.001

P values were calculated with the χ^2 test for categorical variables and with the Kruskal-Wallis test for continuous variables. BMI indicates body mass index; BP, blood pressure; and GW, gestational weeks.

*Self-reported, prepregnancy.

†Family meaning the mother's or father's mother.

gestational age compared with newborns of normotensive control women. In addition, in the preeclamptic group, delivery before gestational week 34+0 was more common compared with the control groups.

Women with HBP-PRS (>95th percentile) displayed higher BP values throughout pregnancy compared with women with LBP-PRS (Table 2).

Among women experiencing preeclampsia, those with HBP-PRS displayed higher BP values throughout pregnancy compared with those with LBP-PRS (Table S1). The difference in BPs remained statistically significant after adjusting for age, body mass index, and genetic principal components. The increase in BP from the first antenatal visit to highest measured BP did not differ between women with HBP-PRS or LBP-PRS when analyzed within subgroups. Figure 1 shows the difference

in BP between women with HBP-PRS and LBP-PRS across the 3 study groups.

Women with HBP-PRS (>95th percentile) had preeclampsia more often compared with women whose BP-PRS was lower (71.8% versus 60.1%; $P=0.009$), and women with HBP-PRS were more often hypertensive (12.9% versus 8.6%; $P<0.001$). Additionally, women with HBP-PRS were less often normotensive compared with women with LBP-PRS (15.3% versus 31.4%; $P<0.001$). In the preeclamptic group, those with HBP-PRS more often displayed preeclampsia with severe features (58.1% versus 42.4%; $P=0.003$) or recurrent preeclampsia (10.0% versus 7.7%; $P<0.001$) compared with those with LBP-PRS. Table 3 shows the proportion of women with HBP-PRS in study groups and with subtypes of preeclampsia.

Table 2. Mean BP Values Compared in Women With Low (at or Below Fifth Percentile) BP-PRS to Women With Higher BP-PRS, As Well As Women With High (Above 95th Percentile) BP-PRS to Women With Lower BP-PRS

BP value, mmHg	BP-PRS \leq 5th percentile (n=125)	BP-PRS >5th percentile (n=2372)	P value	BP-PRS \leq 95th percentile (n=2373)	BP-PRS >95th percentile (n=124)	P value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
At first antenatal visit systolic BP	115.6 (12.3)	122.8 (12.8)	<0.001	122.0 (12.6)	130.8 (15.1)	<0.001
At first antenatal visit diastolic BP	71.2 (7.8)	76.2 (9.8)	<0.001	75.6 (9.7)	82.0 (10.6)	<0.001
Highest systolic BP during pregnancy	140.9 (23.6)	153.8 (24.7)	<0.001	152.5 (24.6)	166.7 (25.4)	<0.001
Highest diastolic BP during pregnancy	92.7 (15.5)	101.3 (14.9)	<0.001	100.4 (15.0)	109.0 (14.2)	<0.001
Mean change in systolic BP	25.6 (22.2)	31.0 (23.0)	0.012	30.5 (22.8)	35.6 (26.8)	0.046
Mean change in diastolic BP	21.9 (13.6)	25.1 (13.5)	0.011	24.8 (13.5)	27.0 (13.6)	0.098

P values were calculated with the Student *t* test. BP indicates blood pressure; and BP-PRS, polygenic risk score for blood pressure.

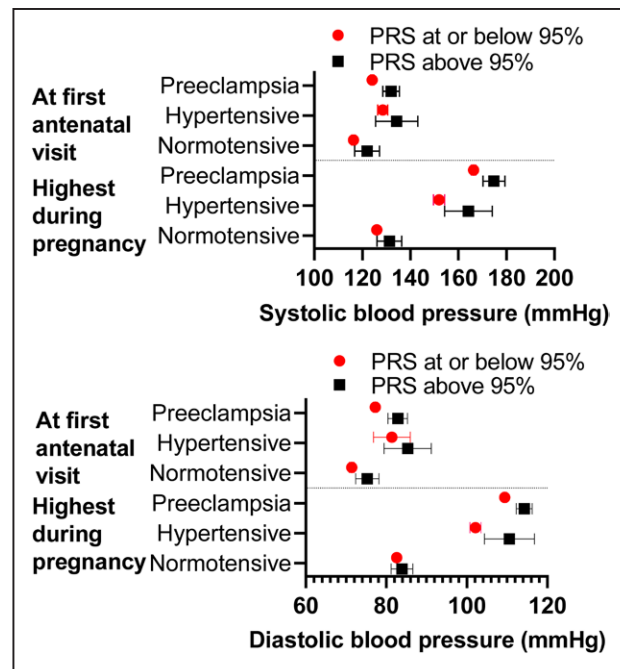


Figure 1. Systolic and diastolic blood pressure (BP) values at the first antenatal visit and highest BP values during pregnancy presented in women with high (>95th percentile) polygenic risk score (PRS) for systolic BP and women with lower BP-PRS across the 3 study groups (1514 women with preeclampsia, 219 hypertensive and 764 normotensive control women).

Data are presented as means with 95% CI. Detailed data on BP values can be found in [Table S1](#).

Our results demonstrate an association between HBP-PRS and preeclampsia (OR, 1.7 [95% CI, 1.1–2.5]). However, when the first antenatal BP value was included in the model, the association between HBP-PRS and preeclampsia was not statistically significant (OR, 1.33 [95% CI, 0.87–2.04]).

Women with LBP-PRS (≤ 5 th percentile) had lower BP values throughout pregnancy compared with women with HBP-PRS. Moreover, the increase in BP from the first antenatal visit to the highest measured BP was smaller in women with LBP-PRS (Table 2).

In the preeclamptic group, BP values were significantly lower in women with LBP-PRS compared with others, but BP change did not show the same tendency (Table S2). The difference in BP values remained statistically significant after adjusting for age, body mass index, and genetic principal components. Figure 2 shows the difference in BP between women with LBP-PRS compared with women with HBP-PRS across the 3 study groups.

Women with LBP-PRS (≤ 5 th percentile) had preeclampsia less frequently than those with HBP-PRS (44.8% versus 61.5%; $P < 0.001$). Women with LBP-PRS had hypertensive disorders less often (5.6% versus 8.9%; $P < 0.001$) and were more often normotensive (49.6% versus 29.6%; $P < 0.001$) compared with those

with HBP-PRS. Additionally, in the preeclampsia group, women with LBP-PRS less frequently had preeclampsia with severe features compared with those with HBP-PRS (31.2% versus 43.8%; $P < 0.001$). Table 3 shows the proportion of women with LBP-PRS in study groups and with subtypes of preeclampsia.

Our results show a negative association between LBP-PRS and preeclampsia (OR, 0.51 [95% CI, 0.35–0.73]). After including the first antenatal BP value in the model, the negative association between LBP-PRS and preeclampsia remained statistically significant (OR, 0.66 [95% CI, 0.45–0.97]).

BP values from the first antenatal visit correlated with BP-PRS (correlation coefficient for SBP, 0.268; $P < 0.001$). A similar correlation was seen between the highest measured BP and HBP-PRS (0.216; $P < 0.001$). There was a positive correlation between BP-PRS and BP values. Correlation coefficients varied between 0.216 and 0.293 ($P < 0.001$) and were convergent for both SBP and DBP values.

DISCUSSION

Our study of 1514 women affected by preeclampsia and 983 control women showed that preeclampsia was more common in those with HBP-PRS (BP-PRS >95th percentile) compared with others. Additionally, women with LBP-PRS (BP-PRS ≤ 5 th percentile) were affected less frequently than others. Recurrent preeclampsia and preeclampsia with severe features were more common in women with HBP-PRS compared with others. BP values were higher in women with HBP-PRS, and the difference was observed throughout the pregnancy.

This study supports the evidence that women genetically susceptible to hypertension have an increased risk for preeclampsia in their pregnancies. In a recent meta-analysis, BP-PRS was linked to a higher risk for preeclampsia,¹⁶ and in previous studies, genetic variants related to hypertension have been shown to be associated with preeclampsia.^{16,17} In our study, along with the increase in preeclampsia risk, women with HBP-PRS also had higher BP values and the difference was already seen in the first antenatal visit. After adjusting for preeclampsia risk with the first antenatal BP value in women with HBP-PRS and other women, the association between HBP-PRS and preeclampsia was not statistically significant. Hence, the increase in the preeclampsia risk in women with HBP-PRS seems to be more strongly associated with prepregnancy BP levels. In our data, HBP-PRS was associated with preeclampsia with severe features and recurrent preeclampsia, supporting the evidence of genetic background in these subtypes, whereas milder forms of the disease might be linked to preexisting complex maternal conditions, such as obesity and diabetes.^{6,32} However, in our study, the incidence of early-onset preeclampsia was not associated

Table 3. Proportions of Women With PE, Hypertensive and Normotensive Women, and PE Subtypes Compared Between Women With BP-PRS Above the 95th Percentile and Women With Lower BP-PRS and Between Women With BP-PRS at or Below 5th Percentile and Women With Higher BP-PRS

Study group or PE subtype	n (%)	n (%)	Total	P value
			n (%)	
	BP-PRS >95th percentile (n=124)	BP-PRS ≤95th percentile (n=2373)		
PE	89 (5.9)	1425 (94.1)	1514 (100)	<0.001
Hypertensive controls	16 (7.3)	203 (92.7)	219 (100)	
Normotensive controls	19 (2.5)	745 (97.5)	764 (100)	
PE with severe features	72 (6.7)	1005 (93.3)	1077 (100)	0.003
Early-onset PE	27 (5.9)	428 (94.1)	455 (100)	0.294
Recurrent PE	12 (6.3)	177 (93.7)	189 (100)	<0.001
Eclampsia	1 (7.7)	12 (92.3)	13 (100)	0.650
	BP-PRS ≤5th percentile (n=125)	BP-PRS >5th percentile (n=2372)		
PE	56 (3.7)	1458 (96.3)	1514 (100)	<0.001
Hypertensive controls	7 (3.2)	212 (96.8)	219 (100)	
Normotensive controls	62 (8.1)	702 (91.9)	764 (100)	
PE with severe features	39 (3.6)	1038 (96.4)	1077 (100)	<0.001
Early-onset PE	21 (4.6)	434 (95.4)	455 (100)	0.671
Recurrent PE	4 (2.1)	185 (97.9)	189 (100)	0.095
Eclampsia	1 (7.7)	12 (92.3)	13 (100)	0.656

Two women had BP-PRS at exactly the 95th percentile; thus 124 women present with BP-PRS >95th percentile as opposed to 125 women with BP-PRS ≤5th percentile. *P* values were calculated with the χ^2 test. BP-PRS indicates polygenic risk score for blood pressure; and PE, preeclampsia.

with BP-PRS. This highlights the intricate nature of preeclampsia subtypes and the need for further research. Additionally, although LBP-PRS is associated with lower risk for preeclampsia, the background of the disease is complex and heterogenic in nature, and due to this, the use of BP-PRS as a predictive factor in these women cannot be justified.

Early-onset preeclampsia,^{9,10} preeclampsia with severe features,¹¹ and recurrent preeclampsia^{12–14} are subtypes strongly related to chronic hypertension and future CVD risk.³³ In preeclampsia, and probably these subtypes in particular, there seems to also be pre-pregnancy endothelial dysfunction^{34,35} influencing women's increased risk for future CVD. In our study, HBP-PRS was associated with an increased risk for recurrent preeclampsia and preeclampsia with severe features. Thus, women with HBP-PRS might be in increased risk for a future CVD as well. In our study, the difference in BP values between women with HBP-PRS compared with others was already seen in the first antenatal visit. This might imply that these women have constantly higher BP values than those with LBP-PRS. Obviously, this might be one explanation for these women's higher risk for CVD although preeclampsia-related vascular changes and other factors are involved. The role of BP-PRS in identifying women at higher risk for cardiometabolic complications could be a target for further investigation.

A major strength of this study is the precise BP data covering the whole pregnancy and BP measurements performed by medical professionals. In the FINNPEC data, preeclampsia diagnoses were retrospectively confirmed by a study nurse and physician to improve reliability of the diagnoses. The genetic data of the cohort are comprehensive, and investigation focusing on PRS allows for exploring large amounts of genetic information. Our case-control cohort is not matched, and only multiple pregnancies and women under the age of 18 years were excluded from the FINNPEC cohort. Consequently, our cohort represents the general obstetric population.

Additionally, a few limitations should be acknowledged. The FINNPEC cohort was recruited from the Finnish university hospitals. Due to this, the cohort might represent women with more severe symptoms or earlier disease than the general obstetric population. On the other hand, the most severe cases might not be recruited due to urgent deliveries after hospital referral. We used BP-PRS in our analyses; however, genetic variants other than BP-related ones may affect the onset of the disease. Furthermore, the hypertensive control group in our study was relatively small, impairing the power of our data. The study population was genetically mainly Finnish; thus our results cannot be directly generalized to other ethnicities. Finally, the effect of antihypertensive medications on BP could not be evaluated in our data, leading to a possible

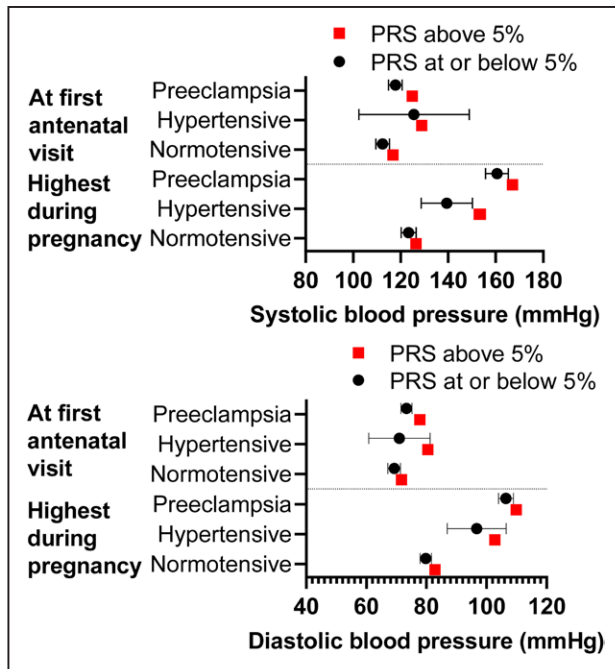


Figure 2. Systolic and diastolic blood pressure (BP) values at the first antenatal visit and highest BP values during pregnancy presented in women with low (≤ 5 th percentile) polygenic risk score (PRS) for systolic BP and women with higher BP-PRS across the 3 study groups (1514 women with preeclampsia, 219 hypertensive and 764 normotensive control women).

Data are presented as means with 95% CI. Detailed data on BP values can be found in [Table S2](#).

underestimation of maximum BP values and BP changes in the preeclampsia and hypertensive control groups.

PERSPECTIVES

This study demonstrated that women with HBP-PRS are more likely to develop preeclampsia and display higher BP values during pregnancy. Additionally, LBP-PRS is associated with a decreased risk for preeclampsia. Moreover, women with HBP-PRS are affected more often by preeclampsia with severe features and recurrent preeclampsia. In clinical practice, identifying women with higher risk for preeclampsia would offer new insights for early diagnosis and more efficient management. Additionally, women with hypertensive pregnancy complications are more likely to develop CVD in the future.^{10,36–38} Identifying women with the highest risk for these complications would offer an opportunity to affect the risk factors for preeclampsia, which would also be beneficial regarding future CVD risk. The role of BP-PRS in the prediction of preeclampsia is an important target for future research. To our knowledge, few studies have investigated PRS and predisposition to hypertensive disorders of pregnancy. The results of a previous study have been convergent with our findings.¹⁶ Further research to confirm these results is needed. Combining maternal,

paternal, and offspring PRS and their relationship to pregnancy outcomes, as well as associations between CVD-PRS and preeclampsia, provides interesting subjects for future research.

ARTICLE INFORMATION

Received January 10, 2022; accepted June 7, 2022.

Affiliations

Department of Obstetrics and Gynecology, Tampere University Hospital, Finland (A.K., E.T., H.L.). Center for Child, Adolescent, and Maternal Health, Faculty of Medicine and Health Technology (A.K., E.T., J.T., H.L.) and Faculty of Social Sciences (H.H.), Tampere University, Finland. Computational Medicine, Faculty of Medicine (J.T.), Center for Life Course Health Research, Faculty of Medicine (J.T.), Biocenter Oulu (J.T.), and PEDEGO Research Unit, Medical Research Center Oulu, Oulu University Hospital (E.K., A.P.), University of Oulu, Finland. Institute for Molecular Medicine Finland, Helsinki Institute of Life Science (S. Ruotsalainen, S. Ripatti, K.K., H.L.), Department of Public Health, Clinicum, Faculty of Medicine (S. Ripatti), Department of Food and Nutrition (T.J.), and Folkhälsan Research Center and Stem Cells and Metabolism Research Program (J.K.), University of Helsinki, Finland. Broad Institute of MIT and Harvard, Cambridge, MA (S. Ripatti). Medical and Clinical Genetics (T.J., H.L.), Obstetrics and Gynaecology (S.H.), and Children's Hospital (E.K.), University of Helsinki and Helsinki University Hospital, Finland. Public Health Promotion Unit (E.K.) and Department of Government Services (A.P.), National Institute for Health and Welfare, Helsinki, Finland. Department of Clinical and Molecular Medicine, Norwegian University of Health and Technology, Trondheim, Norway (E.K.). Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden (J.K.). Department of Clinical Genetics, Kuopio University Hospital, Finland (T.S.).

Acknowledgments

We appreciate the expert technical assistance of Eija Kortelainen and late Susanna Mehtälä and contribution of the members and assisting personnel of the FINNPEC study group (Finnish Genetics of Pre-Eclampsia). In addition, we thank Prof Teemu Niiranen for his valuable comments on the manuscript.

Sources of Funding

The FINNPEC study (Finnish Genetics of Pre-Eclampsia) was supported by the Jane and Aatos Erkko Foundation, Juho Vainio Foundation, Päivikki and Sakari Sohlberg Foundation, Academy of Finland, research funds of the University of Helsinki, government special state subsidy for the health sciences for the Hospital District of Helsinki and Uusimaa, Finska Läkaresällskapet, Liv och Hälsa Foundation, NovoNordisk Foundation, Finnish Foundation for Pediatric Research, Emil Aaltonen Foundation, Sigrid Juselius Foundation, and the Finnish Foundation for Laboratory Medicine.

Disclosures

None.

REFERENCES

- American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol.* 2020;135:e237–e260. doi: 10.1097/AOG.0000000000003892
- Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2011;25:391–403. doi: 10.1016/j.bpobgyn.2011.01.006
- Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. *Curr Opin Obstet Gynecol.* 2013;25:124–132. doi: 10.1097/GCO.0b013e328335e0ef5
- Riise HKR, Sulo G, Tell GS, Iglund J, Egeland G, Nygard O, Selmer R, Iversen AC, Daltveit AK. Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors. *Int J Cardiol.* 2019;282:81–87. doi: 10.1016/j.ijcard.2019.01.097
- Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol.* 1989;161:1200–1204. doi: 10.1016/0002-9378(89)90665-0
- Lisowska M, Pietrucha T, Sakowicz A. Preeclampsia and related cardiovascular risk: common genetic background. *Curr Hypertens Rep.* 2018;20:71. doi: 10.1007/s11906-018-0869-8

7. Correa PJ, Palmeiro Y, Soto MJ, Ugarte C, Illanes SE. Etiopathogenesis, prediction, and prevention of preeclampsia. *Hypertens Pregnancy*. 2016;35:280–294. doi: 10.1080/10641955.2016.1181180
8. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertens*. 2013;3:44–47. doi: 10.1016/j.preghy.2012.11.001
9. Dall'Asta A, D'Antonio F, Saccone G, Buca D, Mastantuoni E, Liberati M, Flacco ME, Frusca T, Ghi T. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2021;57:698–709. doi: 10.1002/uog.22107
10. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974. doi: 10.1136/bmj.39335.385301.BE
11. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analysis. *Am Heart J*. 2008;156:918–930. doi: 10.1016/j.ahj.2008.06.042
12. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, Vogelvang TE, Lely AT, Franx A, van Rijn BB. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. *BJOG*. 2018;125:1642–1654. doi: 10.1111/1471-0528.15394
13. Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profitós J, Paradis G. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart*. 2017;103:235–243. doi: 10.1136/heartjnl-2016-309671
14. Honigberg MC, Riise HKR, Daltveit AK, Tell GS, Sulo G, Igland J, Klungsøyr K, Scott NS, Wood MJ, Natarajan P, et al. Heart failure in women with hypertensive disorders of pregnancy: insights from the Cardiovascular Disease in Norway Project. *Hypertension*. 2020;76:1506–1513. doi: 10.1161/HYPERTENSIONAHA.120.15654
15. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*. 2005;330:565. doi: 10.1136/bmj.38380.674340.E0
16. Steinthorsdottir V, McGinnis R, Williams NO, Stefansdottir L, Thorleifsson G, Shooter S, Fadista J, Sigurdsson JK, Auro KM, Berezina G, et al; FINNPEC Consortium; GOPEC Consortium. Genetic predisposition to hypertension is associated with preeclampsia in European and Central Asian women. *Nat Commun*. 2020;11:5976. doi: 10.1038/s41467-020-19733-6
17. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, et al; Million Veteran Program. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50:1412–1425. doi: 10.1038/s41588-018-0205-x
18. Sung YJ, Winkler TW, de Las Fuentes L, Bentley AR, Brown MR, Kraja AT, Schwander K, Ntalla I, Guo X, Franceschini N, et al; CHARGE Neurology Working Group; COGENT-Kidney Consortium; GIANT Consortium; Lifelines Cohort Study. A large-scale multi-ancestry genome-wide study accounting for smoking behavior identifies multiple significant loci for blood pressure. *Am J Hum Genet*. 2018;102:375–400. doi: 10.1016/j.ajhg.2018.01.015
19. Feitosa MF, Kraja AT, Chasman DI, Sung YJ, Winkler TW, Ntalla I, Guo X, Franceschini N, Cheng CY, Sim X, et al; InterAct Consortium. Novel genetic associations for blood pressure identified via gene-alcohol interaction in up to 570K individuals across multiple ancestries. *PLoS One*. 2018;13:e0198166. doi: 10.1371/journal.pone.0198166
20. McGinnis R, Steinthorsdottir V, Williams NO, Thorleifsson G, Shooter S, Hjartardottir S, Bumpstead S, Stefansdottir L, Hildyard L, Sigurdsson JK, et al; FINNPEC Consortium; GOPEC Consortium. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet*. 2017;49:1255–1260. doi: 10.1038/ng.3895
21. Apicella C, Ruano CSM, Méhats C, Miralles F, Vaiman D. The role of epigenetics in placental development and the etiology of preeclampsia. *Int J Mol Sci*. 2019;20:E2837. doi: 10.3390/ijms20112837
22. Kamrani A, Alipourfard I, Ahmadi-Khiavi H, Yousefi M, Rostamzadeh D, Izadi M, Ahmadi M. The role of epigenetic changes in preeclampsia. *Biofactors*. 2019;45:712–724. doi: 10.1002/biof.1542
23. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med*. 2020;12:44. doi: 10.1186/s13073-020-00742-5
24. Igo RP Jr, Kinzy TG, Cooke Bailey JN. Genetic risk scores. *Curr Protoc Hum Genet*. 2019;104:e95. doi: 10.1002/cphg.95
25. Jääskeläinen T, Heinonen S, Kajantie E, Kere J, Kivinen K, Pouta A, Laivuori H; FINNPEC Study Group. Cohort profile: the Finnish Genetics of Pre-Eclampsia Consortium (FINNPEC). *BMJ Open*. 2016;6:e013148. doi: 10.1136/bmjopen-2016-013148
26. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–575. doi: 10.1086/519795
27. Loh PR, Danecek P, Palamara PF, Fuchsberger C, A Reshef Y, K Finucane H, Schoenherr S, Forer L, McCarthy S, Abecasis GR, et al. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat Genet*. 2016;48:1443–1448. doi: 10.1038/ng.3679
28. Browning BL, Browning SR. Genotype imputation with millions of reference samples. *Am J Hum Genet*. 2016;98:116–126. doi: 10.1016/j.ajhg.2015.11.020
29. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun*. 2019;10:1776. doi: 10.1038/s41467-019-09718-5
30. Consortium 1000 Genomes Project, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, et al. A global reference for human genetic variation. *Nature*. 2015;526:68–74. doi: 10.1038/nature15393
31. Collister JA, Liu X, Clifton L. Calculating polygenic risk scores (PRS) in UK Biobank: a practical guide for epidemiologists. *Front Genet*. 2022;13:818574. doi: 10.3389/fgene.2022.818574
32. Ogge G, Chaiworapongsa T, Romero R, Hussein Y, Kusanovic JP, Yeo L, Kim CJ, Hassan SS. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. *J Perinat Med*. 2011;39:641–652. doi: 10.1515/jpm.2011.098
33. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213–1217. doi: 10.1136/bmj.323.7323.1213
34. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672–683. doi: 10.1056/NEJMoa031884
35. Cindrova-Davies T, Sanders DA, Burton GJ, Charnock-Jones DS. Soluble FLT1 sensitizes endothelial cells to inflammatory cytokines by antagonizing VEGF receptor-mediated signalling. *Cardiovasc Res*. 2011;89:671–679. doi: 10.1093/cvr/cvq346
36. Benschop L, Duvekot JJ, Roeters van Lennep JE. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. *Heart*. 2019;105:1273–1278. doi: 10.1136/heartjnl-2018-313453
37. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1–19. doi: 10.1007/s10654-013-9762-6
38. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53:944–951. doi: 10.1161/HYPERTENSIONAHA.109.130765