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Prediction model for hypertension in first decade after pre-eclampsia in initially normotensive women

M. C. E. HOOIJSCHUUR[1,2], E. B. N. J. JANSSEN[1,3,4], E. G. MULDER[1], A. A. KROON[3,5], J. M. J. MEIJERS[1], J. J. BRUGTS[6], B. C. T. VAN BUSSEL[7], S. M. J. VAN KUIJK[8], M. E. A. SPAANDERMAN[1] and C. GHOSSEIN-DOHA[1,3,4]

[1]*Department of Obstetrics and Gynecology, Maastricht University Medical Centre and GROW, Maastricht, The Netherlands;* [2]*Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands;* [3]*Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands;* [4]*Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands;* [5]*Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands;* [6]*Department of Cardiology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands;* [7]*Department of Intensive Care Medicine and Public Health Research Institute (CAPHRI), Maastricht University Medical Centre, Maastricht, The Netherlands;* [8]*Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, The Netherlands*

KEYWORDS: cardiovascular disease; cardiovascular risk; hypertension; pre-eclampsia

CONTRIBUTION

What are the novel findings of this work?
Based on five variables, we developed a model with good-to-excellent performance to predict hypertension in the decade following pre-eclampsia in women who were normotensive shortly after delivery.

What are the clinical implications of this work?
Formerly pre-eclamptic women are at high risk for cardiovascular disease, but targeted follow-up incorporating structural cardiac assessment is lacking. After external validation, this model could be used to guide personalized follow-up after pre-eclampsia, with the aim of providing timely diagnosis and treatment of elevated blood pressure to reduce the burden of cardiovascular disease in these women.

ABSTRACT

Objective *To develop a prediction model for the development of hypertension in the decade following pre-eclampsia in women who were normotensive shortly after pregnancy.*

Methods *This was a longitudinal cohort study of formerly pre-eclamptic women attending a university hospital in The Netherlands between 1996 and 2019. We developed a prediction model for incident hypertension using multivariable logistic regression analysis. The model was validated internally using bootstrapping techniques.*

Results *Of 259 women, 185 (71%) were normotensive at the first cardiovascular assessment, at a median of 10 (interquartile range (IQR), 6–24) months after a pre-eclamptic pregnancy, of whom 49 (26%) had developed hypertension by the second visit, at a median of 11 (IQR, 6–14) years postpartum. The prediction model, based on birth-weight centile, mean arterial pressure, total cholesterol, left ventricular mass index and left ventricular ejection fraction, had good-to-excellent discriminative ability, with an area under the receiver-operating-characteristics curve (AUC) of 0.82 (95% CI, 0.75–0.89) and an optimism-corrected AUC of 0.80. The sensitivity and specificity of our model to predict hypertension were 98% and 34%, respectively, and positive and negative predictive values were 35% and 98%, respectively.*

Conclusions *Based on five variables, we developed a good-to-excellent predictive tool to identify incident hypertension following pre-eclampsia in women who were normotensive shortly after pregnancy. After external validation, this model could have considerable clinical utility in tackling the cardiovascular legacy of pre-eclampsia.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

Correspondence to: Ms M. C. E. Hooijschuur, Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, The Netherlands (e-mail: m.c.e.hooijschuur@gmail.com)

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INTRODUCTION

Hypertension is the leading risk factor globally for cardiovascular disease (CVD) morbidity and mortality and is the most substantial and neglected health burden in women[1]. Women with a history of pre-eclampsia (PE) are at increased risk of developing hypertension and related CVD at a relatively young age[2–4].

The cumulative effect of prolonged exposure to high blood pressure results in subclinical low-grade inflammation, endothelial dysfunction and progressively irreversible changes in cardiac and vascular structure and function, increasing continuously the risk of overt clinical cardiovascular events[5,6]. When hypertension is diagnosed before irreversible cardiovascular dysfunction has occurred, blood pressure can be modified by lifestyle adjustment or medication in order to mitigate adverse cardiovascular events[7–12]. Therefore, timely detection of hypertension is of the utmost importance, especially in formerly pre-eclamptic individuals, who are at 2–7-fold increased risk for CVD later in life[3].

Current guidelines recommend counseling and follow-up for CVD risk modification after PE[4], although this is hampered by the lack of prediction tools. Current prediction models for hypertension are not applicable to this relatively young female population, as they are often designed for cohorts dominated by middle-aged men or postmenopausal women. Computed estimates of risk for the diagnosis of hypertension after PE could enable intensified follow-up for those at risk and tempered follow-up for low-risk individuals. To this end, we developed a prediction model for incident hypertension in formerly pre-eclamptic women who were normotensive after giving birth.

METHODS

This was a retrospective longitudinal cohort study conducted at the Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands, between 1996 and December 2019. Since 1996, an extensive cardiovascular assessment at least 6 months postpartum was offered to all women in The Netherlands with a history of PE. Women were referred either by their obstetrician or by their general practitioner. All women who attended the cardiovascular assessment between October 1996 and October 2014 for whom contact details (postal and/or e-mail address) were available were invited for a second cardiovascular assessment. This second assessment was conducted from 2015 onwards as part of the Queen of Hearts study (ClinicalTrials.gov identifier: NCT02347540). For our analysis, we included women attending the second visit who were normotensive at the first visit. The cohort was divided into two groups based on whether or not women developed incident hypertension in the interval between the first and second visit (i.e. a normotensive/normotensive group and a normotensive/hypertensive group). This manuscript was prepared in accordance with the transparent reporting of a multivariable model for individual prognosis or diagnosis (TRIPOD) guideline[13], and the study protocol was approved by the Medical Ethical Committee of the MUMC (METC azM/UM 14-4-118 and 14-2-013).

Outcome and definitions

We defined hypertension as systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg and/or use of antihypertensive medication. These cut-off values are classified as high–normal by the European Society of Cardiology guidelines[14] and as Grade-1 hypertension based on the 2018 guidelines of the American Heart Association[15]. Hypertension at the second visit was the primary outcome. PE and HELLP syndrome were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy[16]. Women with chronic hypertension before pregnancy were excluded. Early-onset PE was defined as PE occurring before 34 weeks' gestation.

Assessment

Clinical

Measurements at both postpartum visits were performed in standardized environmental conditions at a morning clinic according to an identical protocol. Clinical data on obstetric and medical history and use of medication were collected from medical files, discharge letters and by direct patient enquiry. Blood pressure was measured in a sitting position using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846 at first visit, Dinamap V100 at second visit; GE Healthcare, Zipf, Austria), with a cuff size appropriate for arm circumference. Blood pressure was measured as per a predefined standardized protocol at 3-min intervals for a period of 30 min[17]. Median values for SBP, DBP and mean arterial pressure over 11 measurements were reported, and SBP and DBP were used to diagnose hypertension. The operator was blinded to blood pressure values at the first visit when performing measurements at the second visit. Glucose, insulin, total cholesterol, high-density lipoprotein cholesterol and triglyceride levels were obtained from fasting blood samples. Insulin resistance was estimated using the homeostatic model assessment ($HOMA_{IR}$)[18] as glucose (mmol/L) × insulin (mU/L)/22.5. Low-density lipoprotein cholesterol (LDL) level was calculated using the Friedewald equation[19]. Body mass index (BMI) was calculated by dividing body weight in kg by the square of the height in m. Obesity was defined as a BMI ≥ 30 kg/m^2. Body surface area (BSA) was calculated using the formula of Dubois and Dubois[20].

Echocardiography

Cardiac function was evaluated at the first postpartum visit, with the participant in the dorsal recumbent position, using a phased-array echocardiographic Doppler system

(HP Sonos 2000/2500; Hewlett-Packard Company, Palo Alto, CA, USA). Imaging data were analyzed offline using specific software (Excelera; Philips, Eindhoven, The Netherlands). To allow assessment of left ventricular mass (LVM) and relative wall thickness (RWT), we measured left ventricular end-diastolic diameter (LVEDd (mm)), left ventricular end-systolic diameter (mm), and the end-diastolic thickness of both the interventricular septum (mm) and the posterior wall (PWT (mm)) on two-dimensional echocardiography. The Devereux formula was used to estimate LVM both as an absolute figure (g) and indexed for BSA (LVMi, g/m^2)[21]. RWT was calculated as follows: $RWT = (PWT \times 2)/LVEDd$. The heart rate (HR (bpm)) was obtained by taking the reciprocal of the mean of five consecutive RR intervals on the electrocardiogram multiplied by 60 s. We estimated the mean aortic velocity time integral (VTI) by averaging the outer edge tracing of continuous-wave Doppler recordings of aortic flow at the level of the aortic valve.

Stroke volume (SV (mL)) was calculated as the product of VTI and the cross-sectional area at the level of the aortic annulus in the parasternal long-axis view. Cardiac output (CO (L/min)) was obtained by multiplying SV by HR, and cardiac index ($L/min/m^2$) by dividing CO by BSA. Left ventricular end-diastolic volume (EDV (mL)) and end-systolic volume (ESV (mL)) were estimated using the Teichholz formula[22]. Left ventricular ejection fraction (LVEF (%)) was calculated as $(EDV - ESV)/EDV \times 100\%$. Total peripheral vascular resistance ($dynes \times s/cm^5$) was obtained by $80 \times$ mean arterial pressure (mmHg)/CO.

By measuring the transmitral flow pattern on pulsed-wave Doppler echocardiography in the apical four-chamber view, we derived the early diastole (E)/atrial contraction (A) ratio, which provides a crude estimate for diastolic function and corresponds with the ratio of peak mitral flow velocity during early diastole and that during atrial contraction. The pulsed-wave Doppler sample volume (5 mm) was positioned carefully at the tip of the mitral valve leaflets. The sweep rate was set at 50 mm/s[23,24].

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) and R version 3.6.1 (R Foundation for Statistical Computing Platform, Vienna, Austria). Baseline characteristics are expressed as median (interquartile range (IQR)) or mean ± SD for continuous variables and *n* (%) for categorical variables. The Mann–Whitney *U*-test was employed for comparison of quantitative variables. Cross-tabulation significance levels were based on Pearson's χ-square test or Fisher's exact test for categorical variables; two-sided *P*-value of < 0.05 was considered to indicate statistical significance.

We used univariable logistic regression analysis to estimate the association between single predictors and the primary outcome (incident hypertension), quantified as odds ratios (OR) with 95% CIs. Only parameters recorded at the first visit were included. For the initial model, we selected parameters with a *P* of < 0.10, and the final prediction model was developed with multivariable logistic regression using backward stepwise selection. All potential predictors that contributed to the model based on Akaike's information criterion were incorporated into the final model. Variance inflation factor was used to exclude collinearity. We also aimed to develop an additional model that would be applicable in primary care (i.e. increasing accessibility by reducing the number of parameters that require additional tests).

To derive a prediction model, we used the regression coefficients, including the model intercept, to formulate a prediction formula. We computed the predicted probabilities and assessed measures of discrimination and calibration. Discrimination describes a model's ability to distinguish those who develop the outcome from those who do not. We used classification tables to evaluate the accuracy of risk stratification according to the adjusted score. Discriminative ability was quantified as the area under the receiver-operating-characteristics curve (AUC), and was interpreted as non-informative (< 0.5), poor (0.5 to < 0.6), moderate (0.6 to < 0.7), good (0.7 to < 0.8), good-to-excellent (0.8 to < 0.9) or excellent (≥ 0.9)[25]. For the internal calibration plot, we split the study cohort into quintiles based on the predicted probability of incident hypertension. This plot compares the mean predicted probability in each quintile with the proportion positive for the outcome. Ideally, all points are situated on the 45° reference line. A point above this line indicates underestimation of the risk and a point below the line indicates overestimation.

The model was validated internally using bootstrapping. The bootstrap routine yields a shrinkage factor between 0 and 1 that is used to penalize (i.e. shrink towards 0) the regression coefficients. This step ensures fewer extreme predictions when applied to new participants to counteract the effect of overfitting (i.e. the phenomenon that a model works better on the data that were used to develop it compared with data outside the development cohort). Subsequently, the model intercept was re-estimated to make sure that the average predicted probability of the penalized model was exactly equal to the observed frequency of hypertension. In addition, the bootstrap routine yields a measure of optimism, which is the expected difference in discriminative ability of the model between the development cohort and future patients.

RESULTS

Baseline characteristics

From 1996 until 2014, 1200 women with a history of PE underwent postpartum cardiovascular assessment at the MUMC (Figure 1). From January 2015 until December 2019, 823 (69%) of those women were invited for a second visit, of whom 259 (31%) consented to participate. Cardiovascular and metabolic characteristics

of the women who responded to the invitation compared with those who did not are presented in Table S1. The study sample consisted mainly of white women from Northern Europe, with the exception of five women (with South-American, Asian, African, Asian/Northern European and African/Northern European ancestry). The first visit took place at a median of 10 (IQR, 6–24) months postpartum. At this evaluation, 74 (29%) women were considered hypertensive, of whom 45 had SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg and 29 were using antihypertensive medication. The characteristics of these women are presented in Table S2. For our analysis, 185 (71%) women who were normotensive at the first visit were included. These women attended a second visit at a median of 11 (IQR, 6–14) years after their first evaluation. Of the 185 initially normotensive women, 136 (74%) remained normotensive and 49 (26%) developed hypertension during this period, of whom 40 had SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg and nine were taking antihypertensive medication (Figure 1).

Women who remained normotensive *vs* women who became hypertensive

The baseline characteristics of the women who were normotensive at the initial visit are presented in Table 1, according to whether they subsequently developed incident hypertension. Women with incident hypertension had their second visit 4 years later compared with those who remained normotensive. At the initial visit, there were no differences in age or BMI between the groups. At the second visit, women with incident hypertension were on average 4 years older and had higher BMI compared with women who remained normotensive. With respect to the index pregnancy, the incidence of early-onset PE and concomitant HELLP syndrome was comparable between groups, although women with incident hypertension delivered on average 22 days earlier an infant with lower birth-weight centile compared to those who remained normotensive.

Women with incident hypertension had higher blood pressure, total cholesterol and LDL at the first evaluation compared with women who remained normotensive (Table 1). At the second assessment, women with incident hypertension had a higher HR and pulse pressure in addition to higher blood pressure. At first evaluation, cardiac parameters were comparable between groups, with the exception of higher LVM and LVMi in women with incident hypertension (Table 2).

Prediction model derivation and performance

The association between single variables and incident hypertension, quantified as ORs with 95% CIs, and the number of missing variables imputed are presented in Table 3. Univariable logistic regression analysis showed that incident hypertension was associated with gestational age at delivery and birth-weight centile of the neonate in

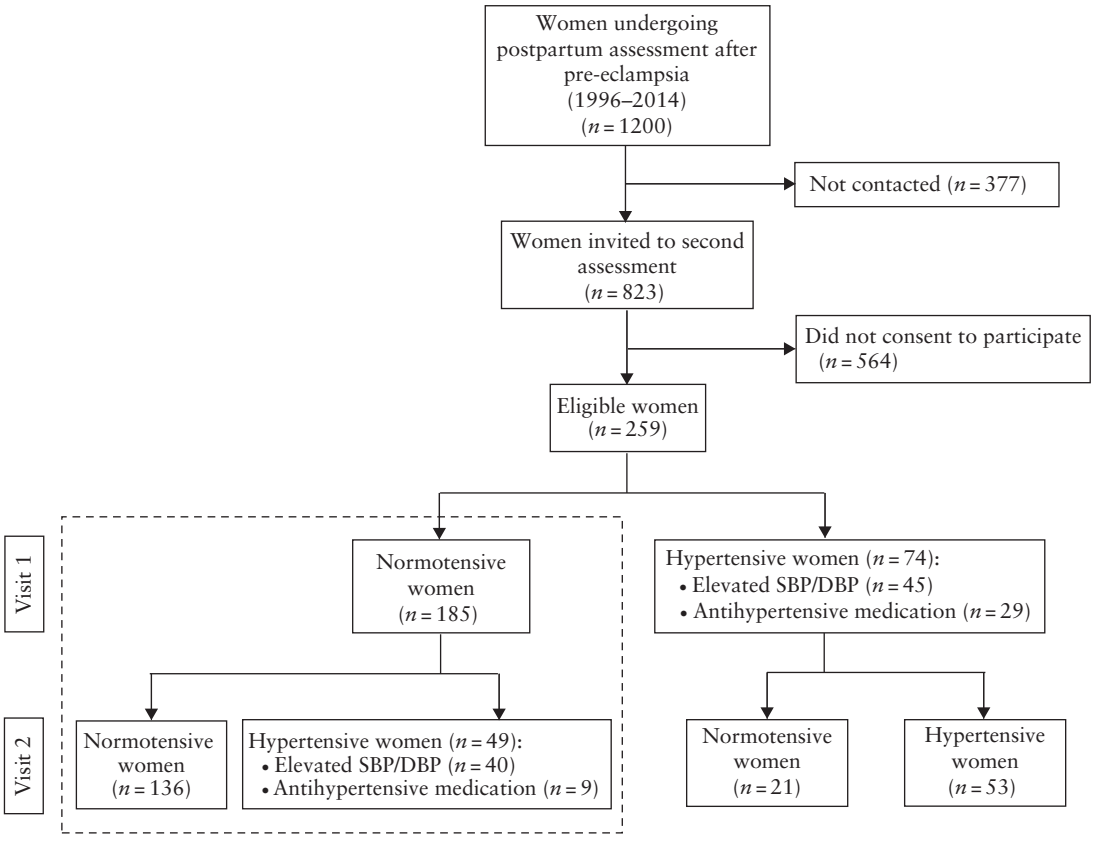

Figure 1 Flowchart summarizing enrolment of study participants and classification according to blood pressure. Dashed box indicates study population. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 1 Baseline characteristics and cardiovascular and cardiometabolic parameters in 185 formerly pre-eclamptic (PE) women, according to blood pressure status at second cardiovascular assessment

Characteristic	*Total* (n = *185*)	*Normotensive* (n = *136*)	*Hypertensive* (n = *49*)	P*
Interval from delivery to first visit (months)	9 (6–22)	10 (6–21)	8 (7–27)	0.914
Interval from first to second visit (years)	11 (6–14)	9 (5–13)	13 (9–16)	< 0.001
Interval from delivery to second visit (years)	12 (7–15)	11 (7–14)	14 (10–19)	< 0.001
Age (years)				
First visit	31.8 ± 4.4	31.5 ± 4.0	32.5 ± 5.4	0.316
Second visit	42.0 ± 6.4	40.9 ± 5.8	44.9 ± 7.1	< 0.001
Body mass index (kg/m^2)				
First visit	23.1 (21.4–26.0)	23.1 (21.2–25.9)	23.4 (21.6–26.9)	0.607
Second visit	24.7 (22.6–27.1)	24.4 (22.2–26.8)	26.0 (23.2–28.7)	0.012
Obese				
First visit	20 (10.8)	14 (10.3)	6 (12.2)	0.706
Second visit	21 (11.4)	12 (8.8)	9 (18.4)	0.071
Index pregnancy				
GA at delivery (weeks)	34.7 (31.7–36.6)	35.4 (32.6–37.0)	32.3 (28.0–35.0)	< 0.001
Primiparous	158 (85.4)	118 (86.8)	40 (81.6)	0.383
Birth-weight centile (%)	20.0 (9.0–47.0)	25.0 (10.0–49.5)	12.0 (7.0–31.0)	0.012
Early-onset PE	107 (57.8)	75 (55.1)	32 (65.3)	0.217
HELLP syndrome	143 (77.3)	109 (80.1)	34 (69.4)	0.123
Recurrent PE and/or HELLP syndrome†	32 (17.3)	20 (14.7)	12 (24.5)	0.128
SBP (mmHg)				
First visit	110 (107–116)	109 (105–113)	117 (110–122)	< 0.001
Second visit	113 (106–123)	111 (105–115)	131 (122–136)	< 0.001
DBP (mmHg)				
First visit	70 (65–73)	68 (65–72)	73 (70–76)	< 0.001
Second visit	71 (67–77)	70 (66–73)	81 (77–85)	< 0.001
MAP (mmHg)				
First visit	84 (81–89)	83 (79–87)	90 (84–93)	< 0.001
Second visit	87 (83–95)	85 (81–88)	100 (96–106)	< 0.001
Pulse pressure (mmHg)				
First visit	42 (37–47)	41 (37–47)	43 (38–48)	0.099
Second visit	42 (38–49)	41 (36–46)	48 (41–57)	< 0.001
Heart rate (bpm)				
First visit	69 (64–76)	68 (63–75)	70 (66–78)	0.338
Second visit	66 (60–73)	65 (60–72)	69 (63–79)	0.004
Total cholesterol (mmol/L)‡	4.7 (4.1–5.4)	4.5 (4.1–5.3)	5.0 (4.4–5.6)	0.012
HDL (mmol/L)‡	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.5)	0.540
LDL (mmol/L)‡	2.8 (2.4–3.5)	2.8 (2.3–3.4)	3.1 (2.6–3.6)	0.032
Triglycerides (mmol/L)‡	0.81 (0.62–1.15)	0.78 (0.59–1.07)	0.84 (0.67–1.33)	0.098
Glucose (mmol/L)‡	5.1 (4.8–5.4)	5.0 (4.8–5.3)	5.1 (4.8–5.5)	0.190
Insulin (mU/L)‡	8.1 (5.5–12.0)	7.4 (5.2–11.5)	8.5 (6.5–13.0)	0.216
$HOMA_{IR}$‡	1.80 (1.20–2.64)	1.70 (1.15–2.59)	1.89 (1.33–2.77)	0.208
HbA1c (%)‡	5.3 (5.0–5.5)	5.3 (5.0–5.5)	5.3 (4.9–5.5)	0.575

Data are given as median (interquartile range), mean ± SD or *n* (%). *Normotensive *vs* hypertensive. †Recorded at second visit. ‡Recorded at first visit. DBP, diastolic blood pressure; GA, gestational age; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 2 Cardiac geometry and function in 185 formerly pre-eclamptic women at first cardiovascular assessment, according to blood pressure status at second assessment

Parameter	*Total* (n = *185*)	*Normotensive* (n = *136*)	*Hypertensive* (n = *49*)	P*
LAD (mm)	35 (32–37)	34 (32–37)	35 (33–38)	0.168
CO (L/min)	4.9 (4.2–5.6)	4.8 (4.2–5.5)	5.2 (4.5–5.9)	0.112
CI (L/min/m^2)	2.8 (2.5–3.1)	2.7 (2.5–3.1)	2.9 (2.5–3.2)	0.171
TPVR (dynes×s/cm^5)	1364 (1200–1559)	1363 (1215–1549)	1367 (1187–1647)	0.685
E/A ratio	1.4 (1.3–1.7)	1.5 (1.3–1.7)	1.4 (1.2–1.7)	0.247
LVEF (%)	64 (61–67)	64 (61–67)	65 (63–68)	0.062
LVM (g)	130 (115–150)	128 (112–150)	139 (125–151)	0.018
LVM index (g/m^2)	74 (65–83)	73 (63–81)	77 (72–85)	0.009
RWT	0.33 (0.30–0.36)	0.32 (0.30–0.35)	0.33 (0.32–0.36)	0.050

Data are given as median (interquartile range). *Normotensive *vs* hypertensive. CI, cardiac index; CO, cardiac output; E/A ratio, ratio of peak mitral early to late diastolic flow velocity; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; RWT, relative wall thickness; TPVR, total peripheral vascular resistance.

the index pregnancy, and with the following variables measured at the first visit: mean arterial pressure, total cholesterol, LDL, LVM, LVMi, LVEF and RWT. After multivariable logistic regression with stepwise backward selection, the final model included birth-weight centile of the neonate in the index pregnancy, mean arterial pressure, total cholesterol, LVMi and LVEF. (Gestational age at delivery was not included in the final model because of its collinearity with birth-weight centile.)

The Hosmer–Lemeshow goodness-of-fit test yielded a *P*-value of 0.4116. The outcome of the model was the individual risk estimate, which ranged from 0% to 98% in our population. The AUC of the model was 0.82 (95% CI, 0.75–0.89) (Figure 2). The quintile internal calibration curve showed adequate risk estimation across the entire range of predictions (Figure 3).

Considering the significant time interval between the first and second visits, we further adjusted our model for the study design by including time between visits. Performance was comparable (AUC, 0.85 (95% CI, 0.79–0.91); Hosmer–Lemeshow goodness-of-fit test, $P = 0.838$) with that of the original model. Moreover, additional models were developed that require fewer tests and might therefore increase applicability, including a model without echocardiographic and laboratory

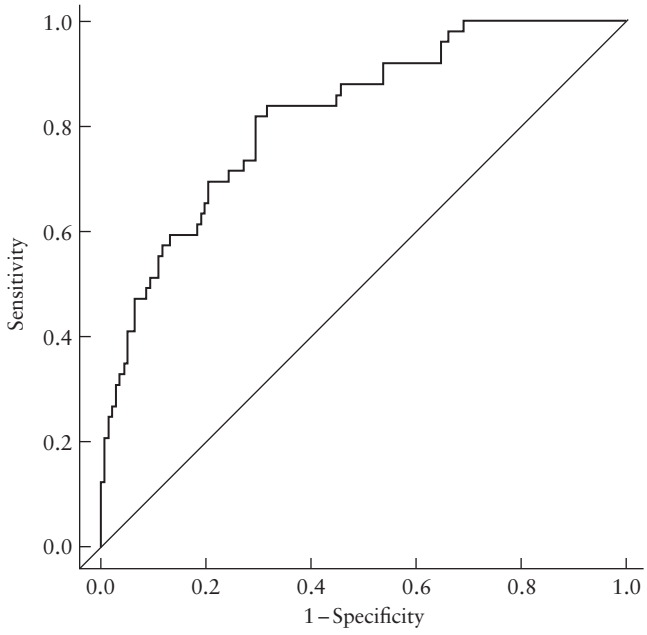

Figure 2 Receiver-operating-characteristics curve for prediction of incident hypertension using multivariable logistic regression model. Area under curve, 0.82 (95% CI, 0.75–0.89).

Table 3 Logistic regression coefficients (β) and odds ratios (OR) to estimate risk of developing hypertension

Variable	*Missing variables (n)*	*Univariable analysis*			*Multivariable analysis* β*
		β	*OR (95% CI)*	P	
Clinical					
Age (in years)	0	0.051	1.05 (0.98–1.13)	0.171	—
BMI (in kg/m^2)	0	0.025	1.03 (0.94–1.11)	0.552	—
Early-onset PE	0	0.426	1.53 (0.78–3.07)	0.219	—
HELLP syndrome	0	−0.577	0.56 (0.27–1.19)	0.126	—
GA at delivery (in weeks)	0	−0.026	0.98 (0.96–0.99)	< 0.001	—
Birth-weight centile (in %)	0	−0.014	0.99 (0.97–1.00)	0.070	−0.003
Metabolic					
MAP (in mmHg)	0	0.174	1.19 (1.12–1.28)	< 0.001	0.176
Heart rate (in bpm)	2	0.009	1.01 (0.98–1.04)	0.576	—
Total cholesterol (in mmol/L)	1	0.439	1.55 (1.07–2.27)	0.021	0.390
HDL (in mmol/L)	1	−0.274	0.76 (0.27–2.03)	0.591	—
LDL (in mmol/L)	2	0.499	1.65 (1.07–2.56)	0.024	—
Triglycerides (in mmol/L)	1	0.160	1.17 (0.87–1.69)	0.292	—
Glucose (in mmol/L)	4	0.439	1.55 (0.79–3.07)	0.202	—
Insulin (in mU/L)	9	0.042	1.04 (0.98–1.11)	0.159	—
$HOMA_{IR}$	11	0.177	1.19 (0.94–1.51)	0.140	—
HbA1c (in %)	9	−0.207	0.81 (0.37–1.78)	0.604	—
Echocardiographic					
LVM (in g)	1	0.017	1.02 (1.00–1.03)	0.024	—
LVMi (in g/m^2)	1	0.036	1.04 (1.01–1.07)	0.016	0.044
E/A ratio	3	−0.626	0.53 (0.18–1.47)	0.239	—
CO (in L/min)	2	0.168	1.18 (0.86–1.63)	0.301	—
CI (in L/min/m^2)	2	0.319	1.38 (0.75–2.49)	0.292	—
TPVR (in dynes × s/cm^5)	2	0.001	1.00 (1.00–1.00)	0.349	—
LVEF (in %)	9	0.084	1.09 (1.00–1.19)	0.052	0.113
RWT	1	0.010	1.01 (1.00–1.02)	0.026	—

*Regression coefficients adjusted for shrinkage factor and re-estimated intercept (−28.521). BMI, body mass index; CI, cardiac index; CO, cardiac output; E/A ratio, ratio of peak mitral early to late diastolic flow velocity; GA, gestational age; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment insulin resistance; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, LVM index; MAP, mean arterial pressure; PE, pre-eclampsia; RWT, relative wall thickness; TPVR, total peripheral vascular resistance.

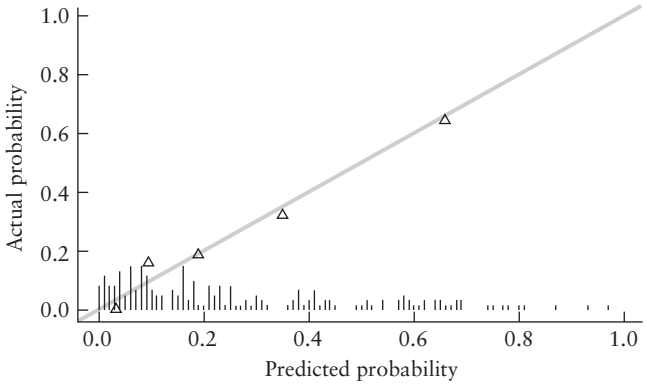

Figure 3 Internal calibration curve showing predicted and observed probabilities of incident hypertension. Patients are grouped in quintiles according to predicted probability. △, quintile mean; ——, perfect calibration.

parameters and a model without echocardiographic parameters. The predictive performance of both models was only slightly reduced, but calibration was less accurate (Figures S1 and S2).

Internal validation

Internal validation yielded a shrinkage factor of 0.87, by which the regression coefficients were multiplied to adjust for overfitting in another population. Subsequently, the model intercept was re-estimated. The optimism in the estimation of the AUC was 0.024. Therefore, the expected discriminative performance in future patients, expressed as AUC, is 0.82 – 0.02 = 0.80.

Final prediction model

The risk of incident hypertension in the 10 years following a pregnancy complicated by PE can be calculated according to the formula: $1/(1+\exp^{-\text{linear predictor}})$, in which the linear predictor = −28.521 − (0.003 × birth-weight centile (%)) + (0.176 × mean arterial pressure (mmHg)) + (0.390 × fasting total cholesterol (mmol/L)) + (0.044 × LVMi (g/m^2)) + (0.113 × LVEF (%)).

Aiming to detect all women with a 10% risk of developing hypertension in the decade following pregnancy complicated by PE, the current model has a specificity of 34% (95% CI, 26–42%) and a sensitivity of 98% (95% CI, 94–100%) (Table S3). Moreover, positive and negative predictive values are 35% (95% CI, 27–43%) and 98% (95% CI, 96–100%), respectively.

DISCUSSION

In this longitudinal follow-up study, we developed a good-to-excellent performing diagnostic prediction model for incident hypertension after PE in women that were normotensive shortly after delivery. The final model includes birth-weight centile, mean arterial pressure, total cholesterol, LVMi and LVEF.

In recent decades, a relationship between PE and incident hypertension has been firmly established[3,23]. As such, pregnancy outcome represents a unique indicator of risk for subsequent hypertension. Nevertheless, despite widespread awareness in the medical community, regular blood-pressure checks have not been implemented into the aftercare of PE pregnancy. The exact reasons are unclear, but may relate to the large variability in CVD risk after PE. Personalized follow-up, including application of the prediction model developed herein, could be used to temper or intensify aftercare. As the prediction model has high sensitivity, it offers an opportunity to distinguish high- from low-risk women and to optimize the use of healthcare resources.

Untreated hypertension, even before 40 years of age, is a strong but modifiable risk factor for CVD[26]. Every increment in SBP of 20 mmHg or DBP of 10 mmHg from a blood pressure of 115/75 mmHg upwards results in roughly double the risk of vascular mortality[27]. In women, CVD risk is associated with elevations from lower SBP ranges compared with men; for example, the risk of myocardial infarction for women with SBP of 110–119 mmHg was shown to be comparable to that for men with SBP ≥ 160 mmHg[28].

Prolonged exposure to elevated blood pressure accelerates vascular aging; structural and functional changes of the vascular wall seen in young people with hypertension are comparable to those in older normotensive individuals[6,8,9,29]. These changes are reversible if blood pressure is normalized, but extend eventually towards hypertension-related end-organ damage[9,30].

Lowering blood pressure reduces the risk of cardiovascular events. For every 10-mmHg decrease in SBP, the risk for coronary heart disease, stroke, heart failure and all-cause mortality declines by 17%, 27%, 28% and 13%, respectively[31,32]. Moreover, the likelihood of successful CVD risk reduction relates to the duration of treatment, treatment intensity and the period of elevated blood pressure (i.e. prolonged blood pressure lowering results in a greater reduction in cardiovascular events)[33]. These findings underscore the value of early detection and treatment of hypertension. Treating traditional cardiovascular risk factors in formerly pre-eclamptic women is likely to reduce their elevated CVD risk, as their future risk for CVD is substantially higher when more risk factors are present. Forceful treatment of elevated blood pressure is of the utmost importance, as hypertension seems to explain most of the excess CVD risk after PE[34,35]. However, current guidelines for initiating treatment for hypertension are based on the predicted 10-year risk for CVD, which is often low in formerly pre-eclamptic women because of their young age. However, the actual lifetime risk in these young women is likely to be underestimated, because currently available CVD risk calculators do not include female-specific characteristics, such as PE, which are considered major risk factors for CVD[4]. Therefore, current practice could be resulting in insufficient treatment. Our risk-assessment tool is one of the first to be applied in this specific high-risk female population.

In the first years after the PE pregnancy, LVM was higher in women who would go on to develop incident hypertension within the next decade. Elevated LVM is indicative of increased afterload, and predicts cardiovascular events even below the cut-off value for left ventricular hypertrophy[36–38]. Reduction in LVM, as a result of the treatment of hypertension and with it, lowering of cardiac pressure load, is associated with a considerable reduction in cardiovascular events[37,39]. Moreover, in formerly pre-eclamptic women, early treatment with angiotensin-converting-enzyme inhibitors after pregnancy improved left ventricular remodeling (LVM, RWT) and diastolic function 6 months postpartum[40]. These findings indicate that early detection and treatment could, at least partly, lead to regression of cardiac abnormalities, resulting in improved cardiovascular outcome after PE.

In line with others[41], 21/74 (28%) of the women in our study population were considered hypertensive at first evaluation but recovered before the second visit. A possible explanation could be that regression from hypertension to normal blood pressure after pregnancy takes longer than the interval between delivery and the first visit. These women were not included in our study as they were assigned to the hypertensive subgroup. From a clinical point of view, the diagnosis of hypertension meant that these women were already under surveillance and therefore receiving care.

There are some limitations of this study that need to be addressed. First, different devices were used to measure blood pressure at the first and second visits. However, the rest of the study was conducted in the same hospital with similar conditions and protocol, meaning that the overall risk of measurement bias was low. Secondly, our model includes two echocardiographic parameters, which could make the model less applicable in low-resource settings. Third, women who did not respond to our invitation for the second visit showed a slightly worse cardiovascular risk profile at the first visit compared with the responders, which might have led to underestimation of the number of women with hypertension at the first visit. However, this is unlikely to have influenced the validity of the prediction model because women with hypertension at the first visit were excluded. Moreover, the current prediction model was developed without a fixed time interval between the first and second visits. Such an interval should be incorporated when the model is validated externally. Finally, our cohort included a large proportion of high-risk PE pregnancies (i.e. those with early-onset PE or HELLP syndrome). Therefore, external validation in women with term PE is warranted to test the generalizability of the model.

In conclusion, we have developed a good-to-excellent model for the prediction of incident hypertension in the decade following PE in women who were normotensive shortly after delivery. After external validation, this model could be used to guide personalized follow-up after hypertensive pregnancy, with the aim of providing timely diagnosis and treatment of elevated blood pressure to reduce the overall burden of CVD.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Baseline characteristics and cardiovascular and cardiometabolic parameters in 823 women with history of pre-eclampsia, according to whether or not they responded to invitation for second cardiovascular assessment

Table S2 Baseline characteristics and cardiovascular and cardiometabolic parameters in 259 women with history of pre-eclampsia who attended two cardiovascular assessments, according to blood pressure status at first visit

Table S3 Sensitivity, specificity and negative and positive predictive values for multivariable logistic regression model (after internal validation) to predict incident hypertension

Figure S1 Receiver-operating-characteristics curve and internal calibration curve for Additional Model 1, which includes as variables only birth-weight centile and mean arterial pressure.

Figure S2 Receiver-operating-characteristics curve and internal calibration curve for Additional Model 2, which includes as variables only birth-weight centile, mean arterial pressure and fasting total cholesterol.