BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055534
Article Type:	Original research
Date Submitted by the Author:	15-Jul-2021
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Keywords:	Maternal medicine < OBSTETRICS, Hypertension < CARDIOLOGY, EPIDEMIOLOGY

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Levels of cardiovascular biomarkers, blood pressure, and their correlations in women with previous preeclamptic pregnancy within seven-year postpartum

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Word count: 2,923 words

Keywords: blood pressure, cardiovascular disease, high-sensitivity C-reactive protein, hypertension, microalbuminuria, postpartum, preeclampsia

ABSTRACT (250 words)

Objective: To assess the levels of cardiovascular biomarkers and their relation to blood pressure measured within seven years postpartum in women with previous preeclamptic pregnancies, compared with women with previous normotensive pregnancies

Design: Cross-sectional study.

Setting: Two tertiary hospitals in the southern regions of Thailand.

Participants: Women with preeclamptic and normotensive pregnancies in the past seven years were enrolled from October 1, 2020 to April 30, 2021. Eligible women were interviewed, examined for body mass index (BMI) and blood pressure, and donated morning spot urine and blood samples.

Primary outcome measures: Serum high-sensitivity C-reactive protein (hs-CRP), creatinine, fasting blood glucose (FBS), glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, urine microalbumin/creatinine ratio (UACR) and sodium were measured. Group differences in biomarkers were tested using unpaired t-test, Wilcoxon rank sum test, or Chi-square test. Pearson's correlation coefficients of biomarkers and blood pressure were calculated.

Results: From 206 women included in analysis, 88 had preeclamptic pregnancies and 118 had normotensive pregnancies. Compared with women with previous normotensive pregnancies, women with previous preeclamptic pregnancies had significantly increased rates of hypertension (31.8% vs. 7.6%), obesity (55.7% vs. 40.7%), in addition to higher serum levels of FBS, HbA1c, LDL cholesterol, creatinine, and UACR. Correlation coefficients of BMI, serum creatinine, and UACR with blood pressure ranged from 0.27 to 0.31.

Conclusion: The risk of hypertension after a preeclamptic pregnancy was increased. Blood pressure measurement combined with BMI, serum creatinine, and UACR screening, at least once during seven years postpartum, is suggested for early detection of cardiovascular risk.

Strengths and limitations of this study

- This study comprehensively assessed blood pressure and their correlations to cardiovascular biomarkers and behavioral measures, during different periods following preeclamptic pregnancies.
- Two tertiary hospitals in the southern regions of Thailand, where preeclampsia is common, were selected to recruit participants with heterogeneous religious and social backgrounds.
- Measuring blood pressure and biomarkers at different periods after delivery in a cross-sectional in design might not be similar to the findings from individual longitudinal changes.
- Although age- and parity-matched approach was used for inclusion criteria, lower participation rate in women with previous preeclamptic pregnancies than those with normotensive pregnancies may introduce the selection bias.

INTRODUCTION

Preeclampsia is a common hypertensive disorder in pregnancy (HDP), classically diagnosed by hypertension plus proteinuria in pregnancy,[1] affecting about 3% of pregnancies worldwide.[2] The registered incidence of preeclampsia was 1% in 2014 with a higher rate in central and southern regions of Thailand.[3] The pathogenesis of preeclampsia remains unclear; however, it is likely to be related to abnormal placentation and placenta function, endothelial injury, and systemic inflammation.[4,5] Preeclampsia is highly associated with increased maternal and fetal morbidity and mortality,[6] and has been one of the most common, direct obstetric causes of maternal death for many decades, especially in low- and middle-income countries.[7]

Although placental delivery usually resolves the acute clinical signs of preeclampsia, the health risks to pregnant women persist long after delivery.[4] Several studies have demonstrated that women with previous preeclampsia are at increased risk of future hypertension, cardiovascular diseases (CVDs), diabetes mellitus, and renal diseases.[8–10] These non-communicable diseases represent a global burden, particularly high systolic blood pressure, which is the largest contributor to all-causes of deaths in females.[11] The mechanisms linking preeclampsia and future CVDs are currently unknown, and both share common risk factors as well as new or persistent endothelial injury after preeclampsia are proposed.[12,13]

Some studies have demonstrated that women with preeclamptic pregnancies have elevated biomarkers of endothelial injury, and inflammation several years after delivery including microalbuminuria[14] and high-sensitivity C-reactive protein (hs-CRP),[15] respectively. Both biomarkers have also been associated with increased risk of CVDs.[16,17] The association between preeclampsia and cardiovascular diseases may result from common metabolic risk factors such as insulin resistance, obesity, and dyslipidemia.[18,19] Likewise,

behavioral risk factors including, high sodium intake, a sedentary lifestyle, and sleep disturbances, are related to high blood pressure in pregnant women[20–22] as well as the general population.[23–25] Nonetheless, only a few studies have investigated these behavioral risk factors in the postpartum period. In regards to the postpartum period, breastfeeding is another protective factor against hypertension and CVDs.[26,27]

To date, there are several studies concerning the levels of cardiovascular biomarkers after pregnancies complicated by preeclampsia.[14,15,18,28–32] However, most studies were cross-sectional in design, with limited postpartum periods and specific time points. We identified few previous studies evaluating correlations between blood pressure and biomarkers.[30,33] Comprehensive assessment of postpartum blood pressure, cardiovascular biomarkers, and behavioral measures in the years following delivery can be useful, as this is a time in life where chronic hypertension may first present after previous pregnancy complications such as preeclampsia.[34] Hence, this study aimed to assess the levels of cardiovascular biomarkers, and their relation to blood pressure and behavior risk factors, measured within seven years postpartum in women with previous preeclamptic pregnancies, as compared with women with previous normotensive pregnancies.

MATERIALS AND METHODS

Study design and setting

A cross-sectional study was conducted in the southern regions of Thailand, where preeclampsia is common.[3] Two tertiary hospitals from Songkhla and Narathiwat provinces were selected to recruit participants with heterogeneous religious and social backgrounds. Each hospital has in total approximately 4,000 deliveries a year and is responsible for providing care to women with preeclampsia in either the Songkhla or Narathiwat provinces.

Sample size calculation

Due to the lack of previous studies, an assumed correlation coefficient between biomarkers and blood pressure of 0.5 was used to calculate the required sample size. With a type I error of 5% and type II error of 20%, the required sample size was 29 women from each period of postpartum year slots (< 2 years, 2-4 years, and > 4 years, since last delivery).

Study participants

Delivery records of women who gave birth in the two study hospitals from January 1, 2014 to June 30, 2020, were screened for eligibility. Women were eligible if they were at least 18 years old, not currently pregnant, and lived in the same province as the study hospital. Those who were non-Thai, unable to be contacted, or had communication barriers, were excluded. According to their most recent pregnancy, women with previous preeclamptic pregnancies were 1:1 matched with women with previous normotensive pregnancies, using maternal age (± 5 years), parity (either primipara or multipara), and duration since last delivery (± 2 months). Eligible women were informed by phone, and invited to participate in the study. Women were enrolled from October 1, 2020 to April 30, 2021.

Exposure assessment

Preeclampsia was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg after 20 weeks of gestation, accompanied by proteinuria.[1] Proteinuria was defined as ≥ 300 mg/24 h, protein to creatinine ratio ≥ 0.3, or a dipstick reading of 2+. According to the most recent pregnancy, the diagnosis recorded in delivery records was used to define women across all severity forms of preeclampsia (with or without severe features, superimposed preeclampsia, or eclampsia). Controls were women without neither diagnosis of preeclampsia, gestational hypertension, nor chronic hypertension during their most recent pregnancy.

Data collection

Eligible women who agreed to participate were asked to visit the outpatient department of the study hospital after fasting overnight. At the study visit, a trained research assistant interviewed the women for demographic and obstetric information, physical activity, and sleep quality. Morning spot urine and blood samples were collected from the participants. Physical activity was evaluated using the Thai version of the Global Physical Activity Questionnaire (GPAQ).[35] Total physical activity including activity for work, during transport, and leisure time was described using metabolic equivalent of task (MET)-minutes per week. The World Health Organization (WHO) recommendations on physical activity for health ≥ 600 MET-minutes per week were used. Sleep quality was assessed using the Thai version of the Pittsburgh Sleep Quality Index (PSQI).[36] A global score, ranging from 0 to 21, was the sum of seven components assessing each sleep problem. Higher score indicated worse sleep quality, and a global score > 5 indicated poor sleep quality.

Body weight was measured after all heavy clothing was removed. Body mass index (BMI) was derived from weight in kilograms, divided by the square of the height in meters. The BMI cut-off points for Asian populations of 23-24.9 kg/m^2 for being overweight, and ≥ 25 kg/m^2 for obesity were used.[37] SBP and DBP were measured using an automatic cuff-oscillometric device (HEM-7300; Omron Healthcare, Kyoto, Japan) in mmHg, after women had rested for at least 15 minutes. Three consecutive blood pressure measurements were taken, and their average was used. Current diagnosis of hypertension was defined as blood pressure at study visit ≥ 140/90 mmHg, self-reported hypertension or currently under antihypertensive treatment.

Laboratory methods

The biomarkers assessed in this study included: serum high-sensitivity C-reactive protein (hs-CRP; particle enhanced immunoturbidimetric method), creatinine (creatinine in urine and

serum measured by enzymatic colorimetric method), fasting blood glucose (FBS; enzymatic hexokinase method), glycated hemoglobin (HbA1c; capillary electrophoresis method), low-density lipoprotein (LDL) cholesterol (homogeneous enzymatic colorimetric method), urine microalbumin/creatinine ratio (UACR; urine microalbumin measured by immunoturbidimetric method), urine sodium (indirect ion selective electrodes method), and urine sodium/creatinine ratio. Most biomarkers were measured using a Cobas 6000 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany), except the HbA1c was measured using a Capillarys 3 Tera (Sebia, France), at the clinical chemistry laboratory (Songklanagarind Hospital, Prince of Songkla University, Thailand).

Statistical analysis

Demographic and obstetrics information of participants were descriptively presented. Differences in demographic and obstetrics information, physical and behavioral measures, and biomarkers between women with previous preeclamptic pregnancies and normotensive pregnancies were tested. For continuous data, an unpaired t-test or Wilcoxon rank sum test was used as appropriate. For categorical data, a Chi-square test was used. Due to skewed distribution, blood pressure and biomarkers between women with previous preeclamptic pregnancies and previous normotensive pregnancies at different periods since last delivery (< 2 years, 2-4 years, and > 4 years) were compared using a Wilcoxon test, with Holm-Bonferroni adjustment for multiple comparisons. The correlations between biomarkers and blood pressure were calculated using Pearson's correlation coefficient. All data were analyzed using R version 4.0.4.

Patients and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination results of this study.

RESULTS

A total of 1,337, eligible women were identified from delivery records of the two study hospitals. Of these, 219 did not have a registered phone number in the hospital database, 581 were unable to be contacted, and two were deceased. We invited 537 women to participate in the study, of which 211 agreed to enroll into the study. Medical records of all enrolled women were reviewed in more detail, and five were not preeclampsia; resulting in 206 women included in analyses (88 women with previous preeclamptic pregnancies and 118 women with previous normotensive pregnancies) (Supplementary Figure 1).

The demographic and obstetrics information of participating women are presented in Table 1. Women with previous preeclamptic pregnancies were significantly older (mean ± SD in age: 36.0 ± 5.9 vs. 34.1 ± 6.5) compared with women with previous normotensive pregnancies. Family history of hypertension (63.6% vs. 42.4%) and CVDs (26.1% vs. 10.2%) was more commonly reported in women with previous preeclamptic pregnancies. The proportion of women reporting family history of HDP was not different between the groups, whereas women with previous preeclampsia more often had family history of CVD than that of the controls (23% vs. 12%, Table 1). Time since the last delivery varied from 0.7 to 7 years, for the total study group. Median time since delivery was similar for both previous preeclamptic (2.2 years, IQR 1.5-4.5) and previous normotensive (2.0 years, IQR 1.5-4.1) pregnancy groups. At their last delivery, the group of women with preeclamptic pregnancies were older, had higher pre-pregnancy BMI, higher rates of being overweight and obesity, had a higher prevalence of preterm birth as well as low infant birth weight.

At the postpartum study visit, women with previous preeclamptic pregnancies had higher SBP, DBP, and BMI as compared to controls (Table 2). More women with preeclamptic pregnancies were obese and diagnosed with hypertension, compared with women with normotensive pregnancies. Both study groups had similar high rates of

insufficient physical activity (~50%), and poor sleep quality (~71%). No statistically significant difference in lactation duration was found between the two groups (median lactation time of six and eight months). Figure 2 shows the SBP and DBP in women with previous preeclamptic pregnancies and normotensive pregnancies stratified by periods of postpartum duration. Median SBPs in women with previous preeclamptic pregnancies were significantly higher than women with previous normotensive pregnancies at any investigated time point postpartum (< 2, 2-4, and > 4 years postpartum; Figure 1A). Significant differences in DBPs between women with previous preeclamptic pregnancies and normotensive pregnancies were detected only at > 4 years postpartum investigation (Figure 1B).

Levels of FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR were significantly higher in women with previous preeclamptic pregnancies (Table 3). There were no significant differences in levels of hs-CRP, urine sodium and sodium/creatinine ratio between the two study groups. As shown in Table 4, most clinical measures and biomarkers were weakly correlated with SBP and DBP ($r < 0.30$). Fair correlations between BMI and UACR and DBP, and serum creatinine and SBP ($r = 0.31$) were found, and the correlations for two study groups are presented in Supplementary Table 1. Serum creatinine in women with previous preeclamptic pregnancies was significantly higher at < 2 years postpartum than in the control group (Figure 2A). Women with previous preeclamptic pregnancies also had a significantly elevated UACR (Figure 2B) and BMI (Figure 2C) measured at > 4 years postpartum, compared with women with previous normotensive pregnancies.

DISCUSSION

Women with previous preeclamptic pregnancies not only had increased blood pressure and risk of hypertension at postpartum follow-up, but also elevated BMI, FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR levels compared with women with previous normotensive pregnancies. We found no significant differences in hs-CRP nor in behavioral factors (lactation duration, total physical activity, sleep quality, and sodium intake). However, fair correlations between BMI, serum creatinine, and UACR and blood pressure were observed.

The group of women with previous preeclamptic pregnancies had consistently elevated blood pressure already from the first year of postpartum, when compared to controls. This finding was consistent with various studies conducted in Canada, the United Kingdom, Norway and the United States, with follow-up durations ranging from six weeks to one year postpartum.[30,33,38,39] The increased risk of hypertension in women with previous preeclamptic pregnancies in our study is also supported by a systematic review from 2007 including 13 studies mostly conducted in Western, not Asian countries.[8] Although the risk of hypertension after preeclampsia was relatively consistent in this review, the pathophysiology and mechanisms may vary across ethnicity and postpartum durations.

Two previous systematic reviews found similar results as ours, after a preeclamptic pregnancy, namely higher BMI, FBS, and LDL cholesterol as compared to controls.[40,41] Our finding of a small, but significant elevation in HbA1c was not replicated in these aforementioned reviews. Inconsistent HbA1c findings might result from different population characteristics, with a variation in insulin resistance and obesity rates.[42] Our group of women with previous preeclamptic pregnancies had elevated levels of biomarkers related to kidney function (serum creatinine and UACR), which was not replicated in a systematic review.[43] Although a previous study suggested that proteinuria after preeclampsia might

take up to two years to normalize, data related to creatinine levels after preeclampsia is lacking.[44] Detection of microalbuminuria after preeclampsia was hypothesized, due to endothelial injury in the kidney,[45] which is also an important factor in the pathophysiology of preeclampsia.[4,5] Whether our group of previous preeclamptic women had abnormal kidney function also prior to their preeclamptic pregnancy, is however not known.

Our finding of unaltered hs-CRP in women with previous preeclamptic pregnancies was similar to the findings of two studies that followed-up women with preeclampsia and HDP at one year postpartum.[38,39] However, a significant association between HDP and higher CRP levels was shown when the follow-up duration was up to 20 years postpartum in previous studies.[29,46] This is suggestive that increased inflammation (measured as elevated hs-CRP) may develop over time after preeclampsia, and possibly linked to other evidences of metabolic dysregulation.

In our study, a slightly longer lactation duration was found in women with previous normotensive pregnancies compared to previous preeclamptic pregnancies, but this difference was not statistically significant. In normal pregnancy, two cohort studies have reported lower blood pressure during lactation at one- or five-month postpartum.[47,48] Sodium intake, reflected by spot urine sodium/creatinine ratio, did not differ between women with previous preeclamptic and normotensive pregnancies, and only correlated weakly with postpartum blood pressure, which was in line with a previous study from ≥ 8 months postpartum.[49] This is also consistent with blood pressure not necessarily being affected by levels of sodium intake, but by intrinsic salt sensitivity in preeclampsia.[50,51]

Our participating women had moderate rates of physical activity, with no difference in median values between the two study groups. A previous study reported a higher percentage (62%) of women meeting the recommendations on physical activity at three and six months after preeclampsia;[52] however, this study used a different questionnaire for physical

activity. Seventy percent of women in our study experienced poor sleep quality, regardless of their preeclamptic status during pregnancy. The prevalence of poor sleep quality was higher than previously reported at two months postpartum.[53] Women participating in our study might have underlying sleep problems, leading to worsening of sleep disruption normally occurring during the postpartum period.[54]

Only three of the investigated biomarkers were fairly correlated with blood pressure: BMI, serum creatinine, and UACR. Elevated BMI has previously been shown to represent a risk factor for incident hypertension during the postpartum period.[55] In the general population, a correlation between blood pressure, creatinine and microalbuminuria is already known.[56,57] We suggest that these biomarkers could be useful for early detection of high blood pressure, and subsequently guide lifestyle modification in postpartum women with previous preeclampsia.

To date, there are few studies focusing on blood pressure levels and cardiovascular biomarkers after preeclampsia in Asia, as most studies have been conducted in Europe and North America. Our study comprehensively examined blood pressure and their correlations to cardiovascular biomarkers and behavioral measures, during different periods following delivery. Another advantage of our study is that detailed information on the diagnosis of preeclampsia was checked from medical records using prespecified criteria; thus, preventing misclassification of the study exposure.

There were a few limitations in our study. Firstly, our study was cross-sectional in design at different periods after delivery, and might not truly represent individual longitudinal changes in blood pressure and biomarkers. Secondly, our study had a low participation rate; especially in women with previous preeclamptic pregnancies. Finally, our study took place at two tertiary hospitals that provided health care for people in only urban and suburban areas; hence, women living within the same district as the study hospitals were more likely to

participate in the study. This might have affected the external validity of our study, as women who did not participate in the study might have different socioeconomic status and disease severity.

In conclusion, women with previous preeclamptic pregnancies had more often hypertension, as well as higher levels of BMI, FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR within seven-year of postpartum. Our findings suggest that women with previous preeclamptic pregnancies should have their blood pressure checked at least once during the first years after delivery. Measurements of BMI, serum creatinine, and UACR could provide additional benefit in targeting women at high risk of hypertension. Further research on optimal follow-up content and timing after preeclamptic pregnancies, in order to optimize early intervention and reduce the risk for long-term CVDs, is still required.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

Ethics approval

This study was approved by the Institute Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC.62-135-18-1), and approval to conduct the study was obtained by the hospital directors. All enrolled women provided written consent to participate in the study.

ACKNOWLEDGEMENTS

We would like to acknowledge the hard work of the research assistants in data collection, and the help of the medical technologists in laboratory measurements. We would also like to

extend our gratitude to the healthcare providers of the study hospitals for their cordial support, and all participants that took part in the study.

CONTRIBUTORS

JS, TL, and ACS participated in study design and planning. PR contributed to study planning and data collection. WS supervised specimen's collection and laboratory measurements. JS collected and analyzed the data. JS and TL involved in data interpretation and manuscript writing. All authors reviewed the draft and approved the final version of the manuscript.

FUNDING

This study was part of the first author's thesis, for partial fulfillment of the requirements for a Ph.D. degree in Epidemiology, at Prince of Songkla University, Thailand, which was supported by the Royal Golden Jubilee Ph.D. Program–RGJ (PHD/0183/2561). This study was part of the PIH-GDM project funded by a TSRI Research Career Development Grand–RSA (RSA6180009), and the Targeted Research Grants Program of the Faculty of Medicine, Prince of Songkla University, Thailand. The funding agencies had no involvement in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

COMPETING INTERESTS

None declared.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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Supplementary Table 1 Pearson's correlation coefficients of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with clinical measures and biomarkers for the two study groups

Table 1 Demographic and obstetrics information of participating women (N = 206)

Characteristics	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Age at the last delivery (years), mean (SD)	33.0 (5.6)	31.2 (6.5)	0.037
Age at postpartum study visit (years), mean (SD)	36.0 (5.9)	34.1 (6.5)	0.029
Religion			0.119
Buddhism	44 (50.0)	45 (38.1)	
Islam	44 (50.0)	73 (61.9)	
Education			0.732
Less than Bachelor's degree	35 (39.8)	43 (36.4)	
Bachelor's degree or higher	53 (60.2)	75 (63.6)	
Monthly family income (USD), median (IQR)	1000 (483,1667)	833 (500,1208)	0.249
Medical history			
Pre-existing hypertension	7 (8.0)	0 (0.0)	0.002
Diabetes mellitus	5 (5.7)	2 (1.7)	0.14
Dyslipidemia	2 (2.3)	1 (0.8)	0.577
Family history			
Family history of hypertension	56 (63.6)	50 (42.4)	0.002
Family history of cardiovascular disease	23 (26.1)	12 (10.2)	0.005
Family history of HDP	7 (8.0)	4 (3.4)	0.211
Pre-pregnancy BMI, median (IQR)	23.5 (20.6,27.0)	21.8 (19.5,25.2)	0.02
Pre-pregnancy BMI categories			0.019
Normal (BMI < 23 kg/m^2)	38 (43.2)	73 (61.9)	
Overweight (BMI 23-24.9 kg/m^2)	19 (21.6)	13 (11.0)	
Obesity (BMI ≥ 25 kg/m^2)	31 (35.2)	32 (27.1)	
Characteristics of most recent pregnancy			
Parity (primipara)	41 (46.6)	46 (39.0)	0.342
Gestational diabetes	11 (12.5)	12 (10.2)	0.763
Twin pregnancy	3 (3.4)	0 (0.0)	0.076
Preterm birth (< 37 weeks of gestation)	37 (42.0)	12 (10.2)	< 0.001
Low infant birth weight (< 2500 g)	39 (44.3)	17 (14.4)	< 0.001
Postpartum duration (years)			0.544
< 2	41 (46.6)	58 (49.2)	
2-4	18 (20.5)	29 (24.6)	
> 4	29 (33.0)	31 (26.3)	

Data are reported as n (%) unless stated otherwise
BMI: body mass index; HDP: hypertensive disorder in pregnancy; IQR: interquartile range

Table 2 Physical and behavioral measures at postpartum study visit for the two study groups (N = 206)

Measures	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Systolic blood pressure (mmHg), median (IQR)	121.2 (112.8,135.5)	112.0 (102.8,119.3)	< 0.001
Diastolic blood pressure (mmHg), median (IQR)	82.5 (74.3,90.8)	70.8 (64.4,80.0)	< 0.001
Current diagnosis of hypertension	28 (31.8)	9 (7.6)	< 0.001
BMI, median (IQR)	26.0 (22.3,29.6)	23.5 (20.8,27.7)	0.017
BMI categories			0.038
Normal (BMI < 23 kg/m^2)	25 (28.4)	54 (45.8)	
Overweight (BMI 23-24.9 kg/m^2)	14 (15.9)	16 (13.6)	
Obesity (BMI ≥ 25 kg/m^2)	49 (55.7)	48 (40.7)	
Lactation duration (months), median (IQR)	6.0 (3.0,14.8)	8.0 (3.0,12.5)	0.678
Insufficient physical activity	45 (51.1)	57 (48.3)	0.794
Sleep quality			0.854
Good (PSQI global score ≤ 5)	26 (29.9)	31 (27.7)	
Poor (PSQI global score > 5)	61 (70.1)	81 (72.3)	

Data are reported as n (%) unless stated otherwise

Abbreviations: BMI, body mass index; IQR, interquartile range; MET, metabolic equivalent of task, PSQI, Pittsburgh Sleep Quality Index

Table 3 Comparison of biomarkers at postpartum study visit for the two study groups (N = 206)

Biomarkers	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Serum FBS (mg/dL), median (IQR)	86.5 (82.1,92.7)	82.8 (76.4,88.8)	< 0.001
Serum HbA1c (%), median (IQR)	5.5 (5.3,5.7)	5.2 (5.1,5.5)	< 0.001
Serum LDL cholesterol (mg/dL), mean (SD)	140.4 (36.4)	129.8 (33.1)	0.03
Serum creatinine (mg/dL), median (IQR)	0.7 (0.6,0.8)	0.6 (0.6,0.7)	< 0.001
Serum hs-CRP (mg/L), median (IQR)	2.3 (0.9,4.2)	1.7 (0.6,3.7)	0.171
UACR (mg/g Cr), median (IQR)	7.3 (4.5,23.8)	4.9 (3.3,8.1)	< 0.001
Urine sodium (mmol/L), mean (SD)	144.8 (57.8)	151.1 (58.3)	0.437
Urine sodium/creatinine ratio, median (IQR)	13.7 (8.7,20.0)	16.8 (10.0,21.0)	0.301

Abbreviations: Cr, creatinine; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; UACR, urine microalbumin/creatinine ratio

Table 4 Pearson's correlation coefficients of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with clinical measures and biomarkers for the total study group (N = 206)

Variables	Correlation coefficient (r)	
	SBP	DBP
Pre-pregnancy BMI	0.23[b]	0.25[c]
BMI	0.28[c]	0.31[c]
Lactation duration	0.02	-0.03
Total physical activity	0.03	0.01
PSQI global score	0.05	0.10
Serum FBS	0.10	0.12
Serum HbA1c	0.15[a]	0.16[a]
Serum LDL cholesterol	0.12	0.13
Serum creatinine	0.31[c]	0.28[c]
Serum hs-CRP	0.01	0.07
UACR	0.27[c]	0.31[c]
Urine sodium	-0.06	-0.07
Urine sodium/creatinine ratio	-0.05	-0.11

[a] P-value < 0.05; [b] P-value < 0.01; [c] P-value < 0.001

Abbreviations: BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; UACR, urine microalbumin/creatinine ratio

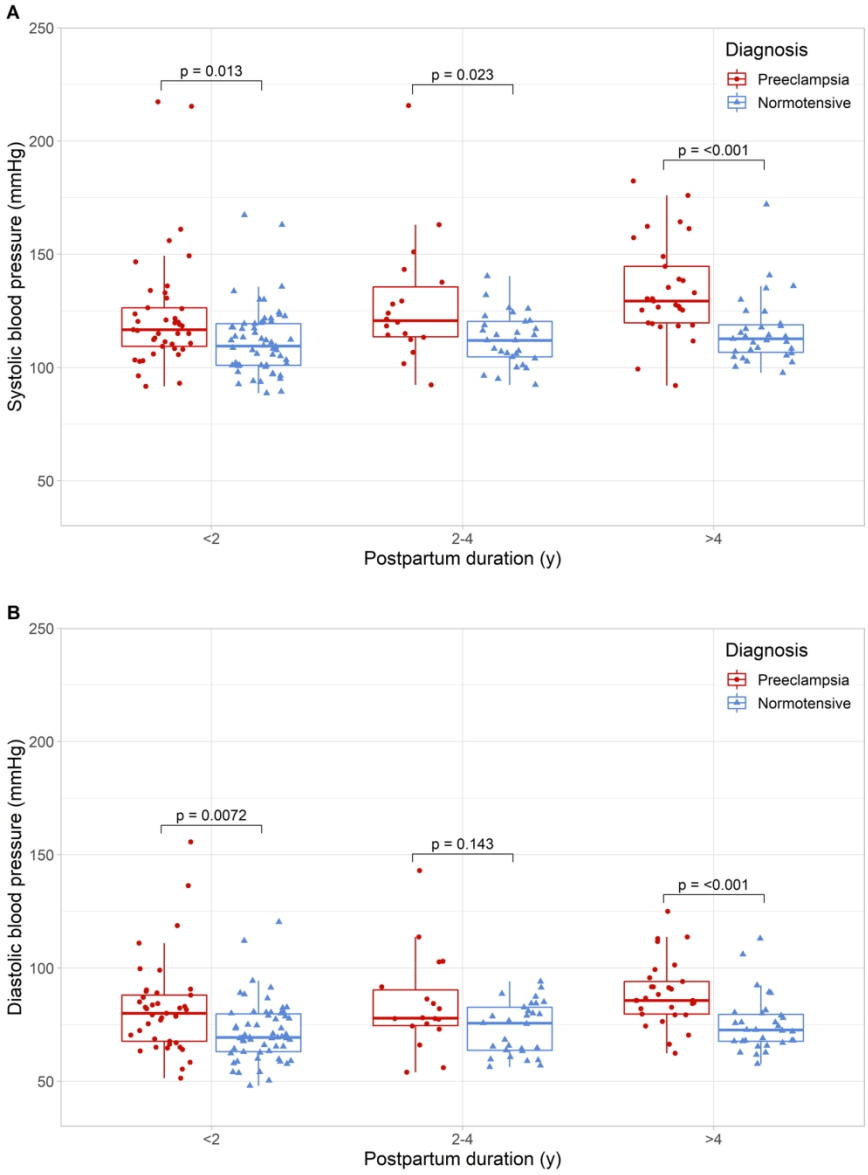

Figure 1 Boxplot of systolic blood pressure (A) and diastolic blood pressure (B) for the two study groups (N = 206) at < 2 years, 2-4 years, and > 4 years postpartum

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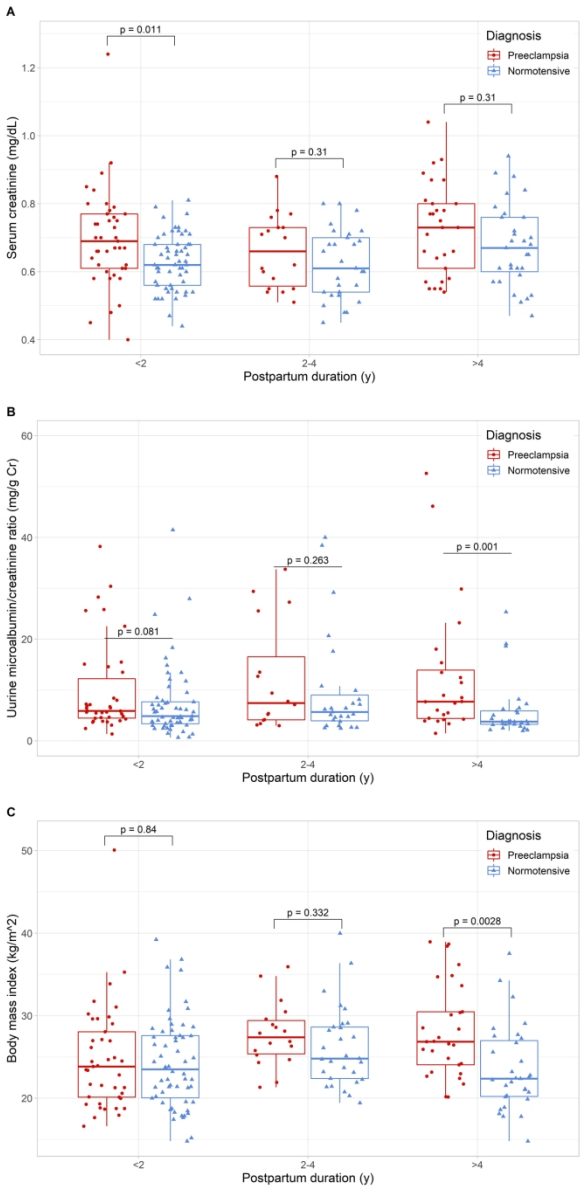

Figure 2 Boxplot of creatinine (A), urine microalbumin/creatinine ratio (B), and BMI (C) for the two study groups (N = 206) at < 2 years, 2-4 years, and > 4 years postpartum
*15 outliers in figure 3B were removed for better visualization

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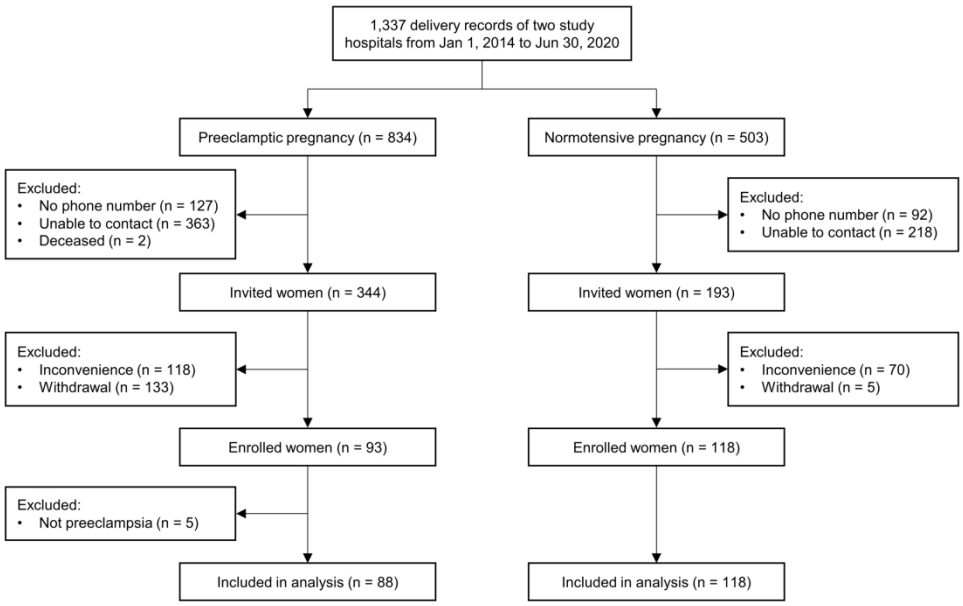

218x139mm (300 x 300 DPI)

Supplementary Table 1 Pearson's correlation coefficients of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with clinical measures and biomarkers for the two study groups

	Correlation coefficient (r)			
	Previous preeclamptic pregnancy (n = 88)		**Previous normotensive pregnancy (n = 118)**	
Variables	**SBP**	**DBP**	**SBP**	**DBP**
Pre-pregnancy BMI	0.26[a]	0.20	0.16	0.25[b]
BMI	0.30[b]	0.27[a]	0.22[a]	0.31[b]
Lactation duration	-0.10	-0.15	0.16	0.08
Total physical activity	-0.01	0.00	0.15	0.11
PSQI global score	0.14	0.22	-0.01	0.02
Serum FBS	0.06	0.07	0.10	0.11
Serum HbA1c	0.06	0.06	0.20[a]	0.22[a]
Serum LDL cholesterol	0.07	0.07	0.10	0.13
Serum creatinine	0.39[c]	0.38[c]	0.07	0.03
Serum hs-CRP	0.06	0.00	0.00	0.14
UACR	0.24[a]	0.31[b]	0.31[b]	0.30[b]
Urine sodium	-0.06	-0.02	-0.02	-0.07
Urine sodium/creatinine ratio	0.00	-0.05	-0.06	-0.13

[a] P-value < 0.05; [b] P-value < 0.01; [c] P-value < 0.001

Abbreviations: BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; UACR, urine microalbumin/creatinine ratio

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10 and Tables 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-4
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figures 2-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Levels of blood pressure, cardiovascular biomarkers, and their correlations in women with previous preeclamptic pregnancy within seven-year postpartum: a cross-sectional study in Thailand

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055534.R1
Article Type:	Original research
Date Submitted by the Author:	09-Mar-2022
Complete List of Authors:	Sukmanee, Jarawee; Prince of Songkla University - Hat Yai Campus, Epidemiology Unit Rothmanee, Penkae; Naradhiwas Rajanagarindra Hospital, Division of Obstetrics and Gynecology Sriwimol, Wilaiwan ; Prince of Songkla University, Department Pathology Staff, Annetine; Oslo University Hospital Liabsuetrakul, Tippawan; Prince of Songkla University, Department of Epidemiology, Faculty of Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Obstetrics and gynaecology, Global health
Keywords:	Maternal medicine < OBSTETRICS, Hypertension < CARDIOLOGY, EPIDEMIOLOGY

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Levels of blood pressure, cardiovascular biomarkers, and their correlations in women with previous preeclamptic pregnancy within seven-year postpartum: a cross-sectional study in Thailand

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Word count: 3,200 words

Keywords: blood pressure, cardiovascular disease, high-sensitivity C-reactive protein, hypertension, microalbuminuria, postpartum, preeclampsia

ABSTRACT (296 words)

Objective: To assess the levels of blood pressure, cardiovascular biomarkers, and their correlations measured within seven years postpartum in women with previous preeclamptic pregnancies, compared with women with previous normotensive pregnancies.

Design: Cross-sectional study.

Setting: Two tertiary hospitals in the southern regions of Thailand.

Participants: Women with preeclamptic and normotensive pregnancies in the past seven years were enrolled from October 1, 2020 to April 30, 2021. Eligible women were interviewed, examined for body mass index (BMI) and blood pressure, and donated morning spot urine and blood samples.

Primary outcome measures: Serum high-sensitivity C-reactive protein (hs-CRP), creatinine, fasting blood glucose (FBS), glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, urine microalbumin/creatinine ratio (UACR) and sodium were measured. Group differences in biomarkers were tested using unpaired t-test, Wilcoxon rank sum test, or Chi-square test. Levels of blood pressure and biomarkers between the two study groups at <2 years, 2-4 years, and >4 years were also compared. The correlations between blood pressure and biomarkers were analyzed using Pearson's correlation and partial correlation methods.

Results: From 206 women included in analysis, 88 had preeclamptic pregnancies and 118 had normotensive pregnancies. Compared with women with previous normotensive pregnancies, women with previous preeclamptic pregnancies had significantly increased rates of hypertension (31.8% vs. 7.6%, p <0.001) and obesity (55.7% vs. 40.7%, p=0.038) as well as higher serum levels of FBS (p <0.001), HbA1c (p <0.001), LDL cholesterol (p=0.03), creatinine (p <0.001), and UACR (p <0.001). Correlation coefficients of BMI, serum creatinine, and UACR with blood pressure ranged from 0.27 to 0.31.

Conclusion: The risk of hypertension after a preeclamptic pregnancy was increased. Blood pressure measurement combined with BMI, serum creatinine, and UACR screening, at least once during seven years postpartum, is suggested for early detection of cardiovascular risk.

Strengths and limitations of this study

- Two tertiary hospitals in the southern regions of Thailand, where preeclampsia is common, were selected to recruit participants with heterogeneous religious and social backgrounds.
- This study comprehensively assessed blood pressure and their correlations to cardiovascular biomarkers and behavioral measures, during different periods following preeclamptic pregnancies.
- This was cross-sectional in design at different periods after delivery, and might not truly reflect individual longitudinal changes in blood pressure and biomarkers.
- The findings might not represent women with previous preeclamptic pregnancies since this study took place at two tertiary hospitals located in urban area and suffered from a low participation rate.

INTRODUCTION

Preeclampsia is a common hypertensive disorder in pregnancy (HDP), classically diagnosed by hypertension plus proteinuria in pregnancy,[1] affecting about 3% of pregnancies worldwide.[2] The registered incidence of preeclampsia was 1% in 2014 with a higher rate in central and southern regions of Thailand.[3] The pathogenesis of preeclampsia remains unclear; however, it is likely to be related to abnormal placentation and placenta function, endothelial injury, and systemic inflammation.[4,5] Preeclampsia is highly associated with increased maternal and fetal morbidity and mortality,[6] and has been one of the most common, direct obstetric causes of maternal death for many decades, especially in low- and middle-income countries.[7]

Although placental delivery usually resolves the acute clinical signs of preeclampsia, the health risks to pregnant women persist long after delivery.[4] Several studies have demonstrated that women with previous preeclampsia are at increased risk of future hypertension, cardiovascular diseases (CVDs), diabetes mellitus, and renal diseases.[8–10] These non-communicable diseases represent a global burden, particularly high systolic blood pressure, which is the largest contributor to all-causes of deaths in females.[11] The mechanisms linking preeclampsia and future CVDs are currently unknown, and both share common risk factors or pathways related to inflammation, vascular remodeling, angiogenesis, apoptosis, hemostasis, and renin-angiotensin-aldosterone system as well as new or persistent endothelial injury after preeclampsia are proposed.[12–14]

Some studies have demonstrated that women with preeclamptic pregnancies have elevated biomarkers of endothelial injury, and inflammation several years after delivery including microalbuminuria[15] and high-sensitivity C-reactive protein (hs-CRP),[16] respectively. Both biomarkers have also been associated with increased risk of CVDs.[17,18] The association between preeclampsia and cardiovascular diseases may result from common

metabolic risk factors such as insulin resistance, obesity, and dyslipidemia.[19,20] Likewise, behavioral risk factors including, high sodium intake, a sedentary lifestyle, and sleep disturbances, are related to high blood pressure in pregnant women[21–23] as well as the general population.[24–26] Nonetheless, only a few studies have investigated these behavioral risk factors in the postpartum period. In regards to the postpartum period, breastfeeding is another protective factor against hypertension and CVDs.[27,28]

To date, there are several studies concerning the levels of cardiovascular biomarkers after pregnancies complicated by preeclampsia.[15,16,19,29–33] However, most studies were cross-sectional in design, with limited postpartum periods and specific time points. We identified few previous studies evaluating correlations between blood pressure and biomarkers.[31,34] Comprehensive assessment of postpartum blood pressure, cardiovascular biomarkers, and behavioral measures in the years following delivery can be useful, as this is a time in life where chronic hypertension may first present after previous pregnancy complications such as preeclampsia.[35] Hence, this study aimed to assess the levels of blood pressure, cardiovascular biomarkers, and their correlations measured within seven years postpartum in women with previous preeclamptic pregnancies, compared with women with previous normotensive pregnancies.

MATERIALS AND METHODS

Study design and setting

A cross-sectional study was conducted in the southern regions of Thailand, where preeclampsia is common.[3] Two tertiary hospitals from Songkhla and Narathiwat provinces were selected to recruit participants with heterogeneous religious and social backgrounds. Each hospital has in total approximately 4,000 deliveries a year and is responsible for providing care to women with preeclampsia in either the Songkhla or Narathiwat provinces.

Sample size calculation

Due to the lack of previous studies, an assumed correlation coefficient between biomarkers and blood pressure of 0.5 was used to calculate the required sample size. With a type I error of 5% and type II error of 20%, the required sample size was 29 women from each period of postpartum year slots (<2 years, 2-4 years, and >4 years, since last delivery).

Study participants

Delivery records of women who gave birth in the two study hospitals from January 1, 2014 to June 30, 2020, were screened for eligibility. Women were eligible if they were at least 18 years old, not currently pregnant, and lived in the same province as the study hospital. Those who were non-Thai, unable to be contacted, or had communication barriers, were excluded. According to their most recent pregnancy, women with previous preeclamptic pregnancies were 1:1 matched with women with previous normotensive pregnancies, using maternal age (± 5 years), parity (either primipara or multipara), and duration since last delivery (± 2 months). Eligible women were informed by phone, and invited to participate in the study. Women were enrolled from October 1, 2020 to April 30, 2021.

Exposure assessment

Preeclampsia was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg after 20 weeks of gestation, accompanied by proteinuria.[1] Proteinuria was defined as ≥300 mg/24 h, protein to creatinine ratio ≥0.3, or a dipstick reading of 2+. According to the most recent pregnancy, the diagnosis recorded in delivery records was used to define women across all severity forms of preeclampsia (with or without severe features, superimposed preeclampsia, or eclampsia). Controls were women without neither diagnosis of preeclampsia, gestational hypertension, nor chronic hypertension during their most recent pregnancy.

Data collection

Eligible women who agreed to participate were asked to visit the outpatient department of the study hospital after fasting overnight. At the study visit, a trained research assistant interviewed the women for demographic and obstetric information, physical activity, and sleep quality. Morning spot urine and blood samples were collected from all participants after fasting overnight for 12 hours, then refrigerated and transported in cold storage to the clinical chemistry laboratory unit for analysis of biomarkers within the same day. Physical activity was evaluated using the Thai version of the Global Physical Activity Questionnaire (GPAQ).[36] Total physical activity including activity for work, during transport, and leisure time was described using metabolic equivalent of task (MET)-minutes per week. The World Health Organization (WHO) recommendations on physical activity for health ≥ 600 MET-minutes per week were used. Sleep quality was assessed using the Thai version of the Pittsburgh Sleep Quality Index (PSQI).[37] A global score, ranging from 0 to 21, was the sum of seven components assessing each sleep problem. Higher score indicated worse sleep quality, and a global score >5 indicated poor sleep quality.

Body weight was measured after all heavy clothing was removed. Body mass index (BMI) was derived from weight in kilograms, divided by the square of the height in meters. The BMI cut-off points for Asian populations of 23-24.9 kg/m^2 for being overweight, and ≥25 kg/m^2 for obesity were used.[38] SBP and DBP were measured using an automatic cuff-oscillometric device (HEM-7300; Omron Healthcare, Kyoto, Japan) in mmHg, after women had rested for at least 15 minutes. Three consecutive blood pressure measurements were taken, and their average was used. Current diagnosis of hypertension was defined as blood pressure at study visit ≥140/90 mmHg, self-reported hypertension or currently under antihypertensive treatment.

Laboratory methods

The biomarkers assessed in this study included: serum high-sensitivity C-reactive protein (hs-CRP; particle enhanced immunoturbidimetric method), creatinine (creatinine in urine and serum measured by enzymatic colorimetric method), fasting blood glucose (FBS; enzymatic hexokinase method), glycated hemoglobin (HbA1c; capillary electrophoresis method), low-density lipoprotein (LDL) cholesterol (homogeneous enzymatic colorimetric method), urine microalbumin/creatinine ratio (UACR; urine microalbumin measured by immunoturbidimetric method), urine sodium (indirect ion selective electrodes method), and urine sodium/creatinine ratio. Most biomarkers were measured using a Cobas 6000 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany), except the HbA1c was measured using a Capillarys 3 Tera (Sebia, France), at the clinical chemistry laboratory (Songklanagarind Hospital, Prince of Songkla University, Thailand).

Statistical analysis

Demographic and obstetrics information of participants were descriptively presented. Differences in demographic and obstetrics information, physical and behavioral measures, and biomarkers between women with previous preeclamptic pregnancies and normotensive pregnancies were tested. For continuous data, an unpaired t-test or Wilcoxon rank sum test was used as appropriate. For categorical data, a Chi-square test was used. Due to skewed distribution, blood pressure and biomarkers between women with previous preeclamptic pregnancies and previous normotensive pregnancies at different periods since last delivery (<2 years, 2-4 years, and >4 years) were compared using a Wilcoxon test, with Holm-Bonferroni adjustment for multiple comparisons. The correlations between biomarkers and blood pressure were calculated using Pearson's correlation method and the partial correlation analysis controlling with age at postpartum study visit and pre-existing hypertension. The correlations between blood pressure and preeclampsia were also analyzed by controlling age

at postpartum study visit, pre-existing hypertension, BMI, and renal function (serum creatinine and UACR). Factors associated with hypertension at postpartum study visit were analyzed using multivariate logistic regression after excluding women with pre-existing hypertension. All data were analyzed using R version 4.0.4 (R Core Team 2021, Vienna, Austria).

Ethics approval

This study was approved by the Institute Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC.62-135-18-1), and approval to conduct the study was obtained by the hospital directors. All enrolled women provided written consent to participate in the study.

Patients and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination results of this study.

RESULTS

A total of 1,337, eligible women were identified from delivery records of the two study hospitals. Of these, 219 did not have a registered phone number in the hospital database, 581 were unable to be contacted, and two were deceased. We invited 537 women to participate in the study, of which 211 agreed to enroll into the study. Medical records of all enrolled women were reviewed in more detail, and five were not preeclampsia; resulting in 206 women included in analyses (88 women with previous preeclamptic pregnancies and 118 women with previous normotensive pregnancies) (Supplementary Figure 1).

The demographic and obstetrics information of participating women are presented in Table 1. Women with previous preeclamptic pregnancies were significantly older (mean ± SD in age: 36.0 ± 5.9 vs. 34.1 ± 6.5) compared with women with previous normotensive pregnancies. Family history of hypertension (63.6% vs. 42.4%) and CVDs (26.1% vs. 10.2%) was more commonly reported in women with previous preeclamptic pregnancies. The

proportion of women reporting family history of HDP was not different between the groups. Time since the last delivery varied from 0.7 to 7 years, for the total study group. Median time since delivery was similar for both previous preeclamptic (2.2 years, IQR 1.5-4.5) and previous normotensive (2.0 years, IQR 1.5-4.1) pregnancy groups. At their last delivery, the group of women with preeclamptic pregnancies were older, had higher pre-pregnancy BMI, higher rates of being overweight and obesity, had a higher prevalence of preterm birth as well as low infant birth weight.

At the postpartum study visit, women with previous preeclamptic pregnancies had significantly higher SBP ($p < 0.001$), DBP ($p < 0.001$), and BMI ($p=0.017$) as compared to controls (Table 2). More women with preeclamptic pregnancies were obese and diagnosed with hypertension, compared with women with normotensive pregnancies ($p=0.038$ and $p<0.001$, respectively). Both study groups had similarly high rates of insufficient physical activity (~50%), and poor sleep quality (~71%). No statistically significant difference in lactation duration was found between the two groups (median lactation time of six and eight months). Figure 1 shows the SBP and DBP in women with previous preeclamptic pregnancies and normotensive pregnancies stratified by periods of postpartum duration. Median SBPs in women with previous preeclamptic pregnancies were significantly higher than women with previous normotensive pregnancies at any investigated time point postpartum (< 2, 2-4, and > 4 years postpartum; $p=0.013$, 0.014, and <0.001, respectively) in Figure 1A. Significant differences in DBPs between women with previous preeclamptic pregnancies and normotensive pregnancies were detected at <2 years postpartum investigation ($p=0.007$) and >4 years postpartum investigation ($p< 0.001$) in Figure 1B.

Levels of FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR were significantly higher in women with previous preeclamptic pregnancies (all; $p < 0.001$ except LDL cholesterol; $p=0.03$; Table 3). There were no significant differences in levels of hs-CRP

(p=0.171), urine sodium (p=0.437) and sodium/creatinine ratio (p=0.301) between the two study groups. As shown in Table 4, weak correlations between pre-pregnancy BMI, postpartum BMI, serum creatinine and UACR with both SBP and DBP in Pearson's and partial correlation methods. The correlations for all biomarkers in total and two study groups are presented in Supplementary Table 1. A history of preeclampsia was significantly correlated with SBP and DBP (both, r=0.35) and lower correlations were shown (both, r=0.22) after adjusting for age, pre-existing hypertension, postpartum BMI, serum creatinine, and UACR. Final model of multivariate logistic regression assessing factors associated with hypertension at postpartum study visit is shown in Supplementary Table 2. Women with previous preeclamptic pregnancies had higher odds of having hypertension at postpartum study visit when compared to normotensive pregnancies (adjusted OR=4.32, 95% CI 1.57-11.84). Serum creatinine in women with previous preeclamptic pregnancies was significantly higher at <2 years postpartum than in the control group (p=0.011; Figure 2A). Women with previous preeclamptic pregnancies also had a significantly elevated UACR (p=0.001; Figure 2B) and BMI (p=0.003; Figure 2C) measured at >4 years postpartum, compared with women with previous normotensive pregnancies.

DISCUSSION

Women with previous preeclamptic pregnancies not only had increased blood pressure and risk of hypertension at postpartum follow-up, but also elevated BMI, FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR levels compared with women with previous normotensive pregnancies. We found no significant differences in hs-CRP nor in behavioral factors (lactation duration, total physical activity, sleep quality, and sodium intake). However, fair correlations between BMI, serum creatinine, and UACR and blood pressure were observed.

The group of women with previous preeclamptic pregnancies had consistently elevated blood pressure already from the first year of postpartum, when compared to controls. This finding was consistent with various studies conducted in Canada, the United Kingdom, Norway and the United States, with follow-up durations ranging from six weeks to one year postpartum.[31,34,39,40] The increased risk of hypertension in women with previous preeclamptic pregnancies in our study is also supported by a systematic review from 2007 including 13 studies mostly conducted in Western, not Asian countries.[8] Although the risk of hypertension after preeclampsia was relatively consistent in this review, the pathophysiology and mechanisms may vary across ethnicity and postpartum durations.

Two previous systematic reviews found similar results as ours, after a preeclamptic pregnancy, namely higher BMI, FBS, and LDL cholesterol as compared to controls.[41,42] Our finding of a small, but significant elevation in HbA1c was not replicated in these aforementioned reviews. Inconsistent HbA1c findings might result from different population characteristics, with a variation in insulin resistance and obesity rates.[43] Our group of women with previous preeclamptic pregnancies had elevated levels of biomarkers related to kidney function (serum creatinine and UACR), which was not replicated in a systematic review.[44] Although a previous study suggested that proteinuria after preeclampsia might take up to two years to normalize, data related to creatinine levels after preeclampsia is lacking.[45] Detection of microalbuminuria after preeclampsia was hypothesized, due to endothelial injury in the kidney,[46] which is also an important factor in the pathophysiology of preeclampsia.[4,5] Whether our group of previous preeclamptic women had abnormal kidney function also prior to their preeclamptic pregnancy, is however not known.

Our finding of unaltered hs-CRP in women with previous preeclamptic pregnancies was similar to the findings of two studies that followed-up women with preeclampsia and HDP at one year postpartum.[39,40] However, a significant association between HDP and

higher CRP levels was shown when the follow-up duration was up to 20 years postpartum in previous studies.[30,47] This is suggestive that increased inflammation (measured as elevated hs-CRP) may develop over time after preeclampsia, and possibly linked to other evidences of metabolic dysregulation.

In our study, a slightly longer lactation duration was found in women with previous normotensive pregnancies compared to previous preeclamptic pregnancies, but this difference was not statistically significant. In normal pregnancy, two cohort studies have reported lower blood pressure during lactation at one- or five-month postpartum.[48,49] Sodium intake, reflected by spot urine sodium/creatinine ratio, did not differ between women with previous preeclamptic and normotensive pregnancies, and only correlated weakly with postpartum blood pressure, which was in line with a previous study from ≥ 8 months postpartum.[50] This is also consistent with blood pressure not necessarily being affected by levels of sodium intake, but by intrinsic salt sensitivity in preeclampsia.[51,52]

Our participating women had moderate rates of physical activity, with no difference in median values between the two study groups. A previous study reported a higher percentage (62%) of women meeting the recommendations on physical activity at three and six months after preeclampsia;[53] however, this study used a different questionnaire for physical activity. Seventy percent of women in our study experienced poor sleep quality, regardless of their preeclamptic status during pregnancy. The prevalence of poor sleep quality was higher than previously reported at two months postpartum.[54] Women participating in our study might have underlying sleep problems, leading to worsening of sleep disruption normally occurring during the postpartum period.[55]

Only three of the investigated biomarkers were fairly correlated with blood pressure: BMI, serum creatinine, and UACR. Elevated BMI has previously been shown to represent a risk factor for incident hypertension during the postpartum period.[56] In the general

population, a correlation between blood pressure, creatinine and microalbuminuria is already known.[57,58] We suggest that these biomarkers could be useful for early detection of high blood pressure, and subsequently guide lifestyle modification in postpartum women with previous preeclampsia.

To date, there are few studies focusing on blood pressure levels and cardiovascular biomarkers after preeclampsia in Asia, as most studies have been conducted in Europe and North America. Our study comprehensively examined blood pressure and their correlations to cardiovascular biomarkers and behavioral measures, during different periods following delivery. Another advantage of our study is that detailed information on the diagnosis of preeclampsia was checked from medical records using prespecified criteria; thus, preventing misclassification of the study exposure.

There were some limitations in our study. Firstly, our study was cross-sectional in design at different periods after delivery, and might not truly represent individual longitudinal changes in blood pressure and biomarkers. Secondly, our study suffered from a low participation rate, especially in women with previous preeclamptic pregnancies. Third, seven women in previous preeclamptic pregnancy had pre-existing hypertension and continued anti-hypertensive medication when participating in our study which may affect blood pressure and their correlation with the studied biomarkers. However, the same findings were identified when the subgroup analysis excluding these women was explored. Finally, our study took place at two tertiary hospitals that provided health care for people in only urban and suburban areas; hence, women living within the same district as the study hospitals were more likely to participate in the study. This might have affected the external validity of our study, as women who did not participate in the study might have different socioeconomic status and disease severity.

In conclusion, women with previous preeclamptic pregnancies had more often hypertension, as well as higher levels of BMI, FBS, HbA1c, LDL cholesterol, serum creatinine, and UACR within seven-year of postpartum. Our findings suggest that women with previous preeclamptic pregnancies should have their blood pressure checked at least once during the first years after delivery. Measurements of BMI, serum creatinine, and UACR could provide additional benefit in targeting women at high risk of hypertension and offering them an early consultation about future cardiovascular risk and lifestyle intervention as well as risk monitoring strategies. Further research on optimal follow-up content and timing after preeclamptic pregnancies, in order to optimize early intervention and reduce the risk for long-term CVDs, is still required.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

ACKNOWLEDGEMENTS

We would like to acknowledge the hard work of the research assistants in data collection, and the help of the medical technologists in laboratory measurements. We would also like to extend our gratitude to the healthcare providers of the study hospitals for their cordial support, and all participants that took part in the study.

FOOTNOTES

Contributors: JS, TL, and ACS participated in study design and planning. PR contributed to study planning and data collection. WS supervised specimen's collection and laboratory measurements. JS collected and analyzed the data. JS and TL involved in data interpretation

and manuscript writing. All authors reviewed the draft and approved the final version of the manuscript.

Funding: This study was part of the first author's thesis, for partial fulfillment of the requirements for a Ph.D. degree in Epidemiology, at Prince of Songkla University, Thailand, which was supported by the Royal Golden Jubilee Ph.D. Program–RGJ (PHD/0183/2561). This study was part of the PIH-GDM project funded by a TSRI Research Career Development Grand–RSA (RSA6180009), and the Targeted Research Grants Program of the Faculty of Medicine, Prince of Songkla University, Thailand. The funding agencies had no involvement in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: None declared.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Provenance and peer review: Not commissioned; externally peer reviewed.

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566 **Table 1** Demographic and obstetrics information of participating women (N = 206)

Characteristics	**Previous preeclamptic pregnancy (n = 88)**	**Previous normotensive pregnancy (n = 118)**	**P-value**
Age at the last delivery (years), mean (SD)	33.0 (5.6)	31.2 (6.5)	0.037
Age at postpartum study visit (years), mean (SD)	36.0 (5.9)	34.1 (6.5)	0.029
Religion			0.119
Buddhism	44 (50.0)	45 (38.1)	
Islam	44 (50.0)	73 (61.9)	
Education			0.732
Less than Bachelor's degree	35 (39.8)	43 (36.4)	
Bachelor's degree or higher	53 (60.2)	75 (63.6)	
Monthly family income (USD), median (IQR)	1000 (483,1667)	833 (500,1208)	0.249
Medical history			
Pre-existing hypertension	7 (8.0)	0 (0.0)	0.002
Diabetes mellitus	5 (5.7)	2 (1.7)	0.14
Dyslipidemia	2 (2.3)	1 (0.8)	0.577
Family history			
Family history of hypertension	56 (63.6)	50 (42.4)	0.002
Family history of cardiovascular disease	23 (26.1)	12 (10.2)	0.005
Family history of HDP	7 (8.0)	4 (3.4)	0.211
Pre-pregnancy BMI, median (IQR)	23.5 (20.6,27.0)	21.8 (19.5,25.2)	0.02

Characteristics	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Pre-pregnancy BMI categories			0.019
Normal (BMI <23 kg/m^2)	38 (43.2)	73 (61.9)	
Overweight (BMI 23-24.9 kg/m^2)	19 (21.6)	13 (11.0)	
Obesity (BMI ≥25 kg/m^2)	31 (35.2)	32 (27.1)	
Characteristics of most recent pregnancy			
Parity (primipara)	41 (46.6)	46 (39.0)	0.342
Gestational diabetes	11 (12.5)	12 (10.2)	0.763
Twin pregnancy	3 (3.4)	0 (0.0)	0.076
Preterm birth (<37 weeks of gestation)	37 (42.0)	12 (10.2)	<0.001
Low infant birth weight (<2500 g)	39 (44.3)	17 (14.4)	<0.001
Postpartum duration (years)			0.544
< 2	41 (46.6)	58 (49.2)	
2-4	18 (20.5)	29 (24.6)	
> 4	29 (33.0)	31 (26.3)	

Data are reported as n (%) unless stated otherwise

Abbreviations: BMI, body mass index; HDP, hypertensive disorder in pregnancy; IQR, interquartile range

Table 2 Physical and behavioral measures at postpartum study visit for the two study groups (N = 206)

Measures	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Systolic blood pressure (mmHg), median (IQR)	121.2 (112.8,135.5)	112.0 (102.8,119.3)	<0.001
Diastolic blood pressure (mmHg), median (IQR)	82.5 (74.3,90.8)	70.8 (64.4,80.0)	<0.001
Current diagnosis of hypertension	28 (31.8)	9 (7.6)	<0.001
BMI, median (IQR)	26.0 (22.3,29.6)	23.5 (20.8,27.7)	0.017
BMI categories			0.038
Normal (BMI <23 kg/m^2)	25 (28.4)	54 (45.8)	
Overweight (BMI 23-24.9 kg/m^2)	14 (15.9)	16 (13.6)	
Obesity (BMI ≥25 kg/m^2)	49 (55.7)	48 (40.7)	
Lactation duration (months), median (IQR)	6.0 (3.0,14.8)	8.0 (3.0,12.5)	0.678
Insufficient physical activity	45 (51.1)	57 (48.3)	0.794
Sleep quality			0.854
Good (PSQI global score ≤5)	26 (29.9)	31 (27.7)	
Poor (PSQI global score >5)	61 (70.1)	81 (72.3)	

Data are reported as n (%) unless stated otherwise

Abbreviations: BMI, body mass index; IQR, interquartile range; MET, metabolic equivalent of task, PSQI, Pittsburgh Sleep Quality Index

Table 3 Comparison of biomarkers at postpartum study visit for the two study groups (N = 206)

Biomarkers	Previous preeclamptic pregnancy (n = 88)	Previous normotensive pregnancy (n = 118)	P-value
Serum FBS (mg/dL), median (IQR)	86.5 (82.1,92.7)	82.8 (76.4,88.8)	< 0.001
Serum HbA1c (%), median (IQR)	5.5 (5.3,5.7)	5.2 (5.1,5.5)	< 0.001
Serum LDL cholesterol (mg/dL), mean (SD)	140.4 (36.4)	129.8 (33.1)	0.03
Serum creatinine (mg/dL), median (IQR)	0.7 (0.6,0.8)	0.6 (0.6,0.7)	< 0.001
Serum hs-CRP (mg/L), median (IQR)	2.3 (0.9,4.2)	1.7 (0.6,3.7)	0.171
UACR (mg/g Cr), median (IQR)	7.3 (4.5,23.8)	4.9 (3.3,8.1)	< 0.001
Urine sodium (mmol/L), mean (SD)	144.8 (57.8)	151.1 (58.3)	0.437
Urine sodium/creatinine ratio, median (IQR)	13.7 (8.7,20.0)	16.8 (10.0,21.0)	0.301

Abbreviations: Cr, creatinine; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; UACR, urine microalbumin/creatinine ratio

Table 4 Pearson's correlation and partial correlation coefficients of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with clinical measures, and biomarkers for the total study group (N = 206)

Variables†	Correlation coefficient (r)		Partial correlation coefficients (r)*	
	SBP	DBP	SBP	DBP
Pre-pregnancy BMI	0.23[b]	0.25[c]	0.21[b]	0.22[b]
BMI	0.28[c]	0.31[c]	0.28[c]	0.31[c]
Serum HbA1c	0.15[a]	0.16[a]	0.18[b]	0.22[b]
Serum creatinine	0.31[c]	0.28[c]	0.25[c]	0.21[b]
UACR	0.27[c]	0.31[c]	0.22[b]	0.20[b]

†Only variables with significant correlation coefficients shown: [a] P-value < 0.05; [b] P-value < 0.01; [c] P-value < 0.001. Full results presented in Supplementary Table 1

*Partial correlation coefficients adjusted by age at the postpartum study visit and pre-existing hypertension

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; UACR, urine microalbumin/creatinine ratio

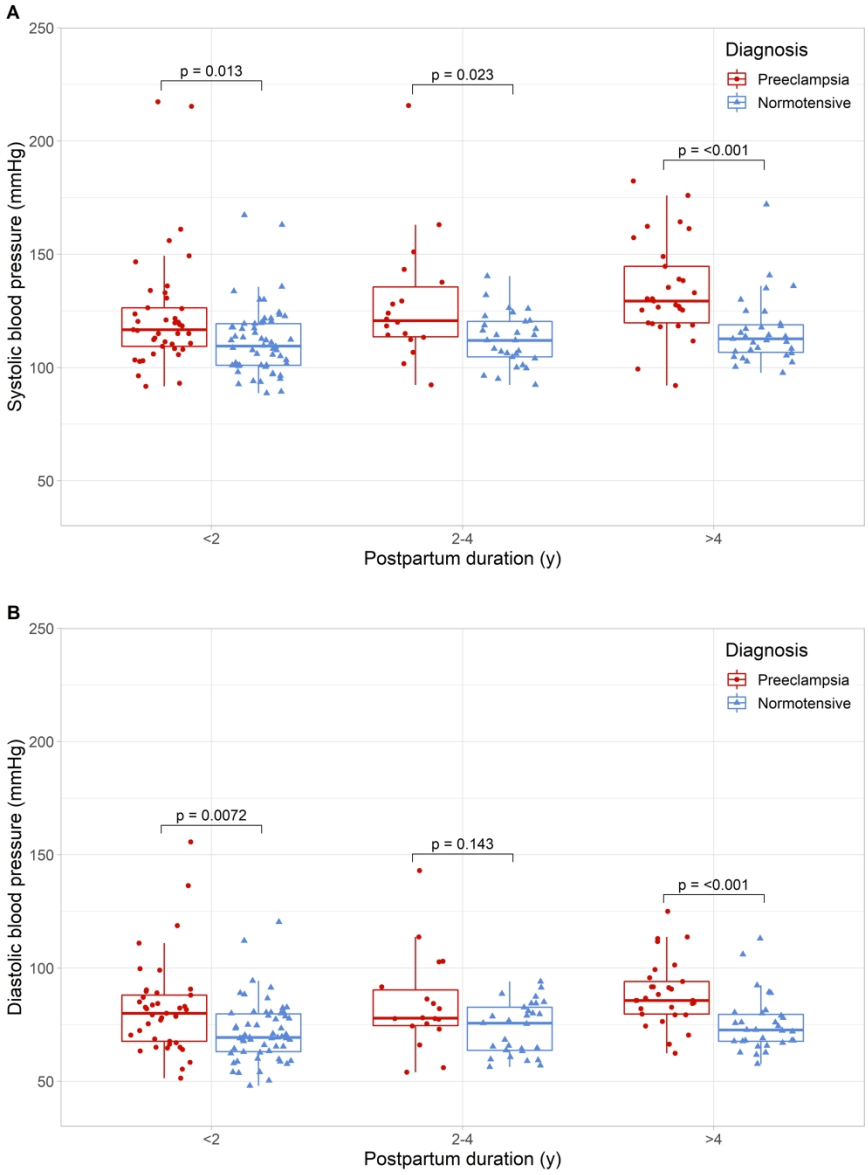


Figure 1 Boxplot of systolic blood pressure (A) and diastolic blood pressure (B) for the two study groups (N = 206) at <2 years, 2-4 years, and >4 years postpartum visits

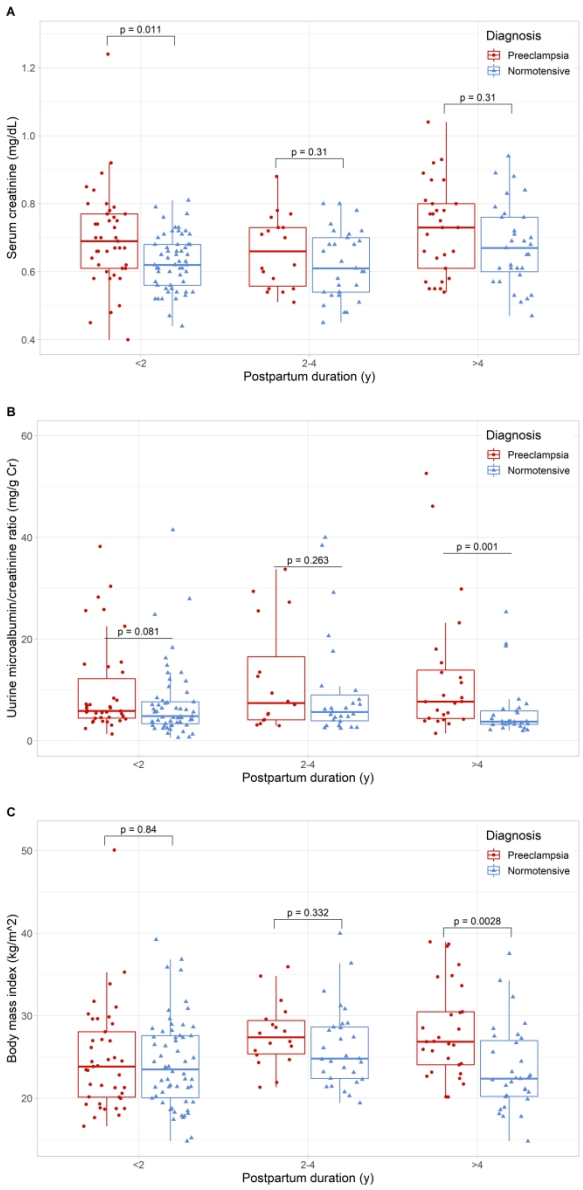
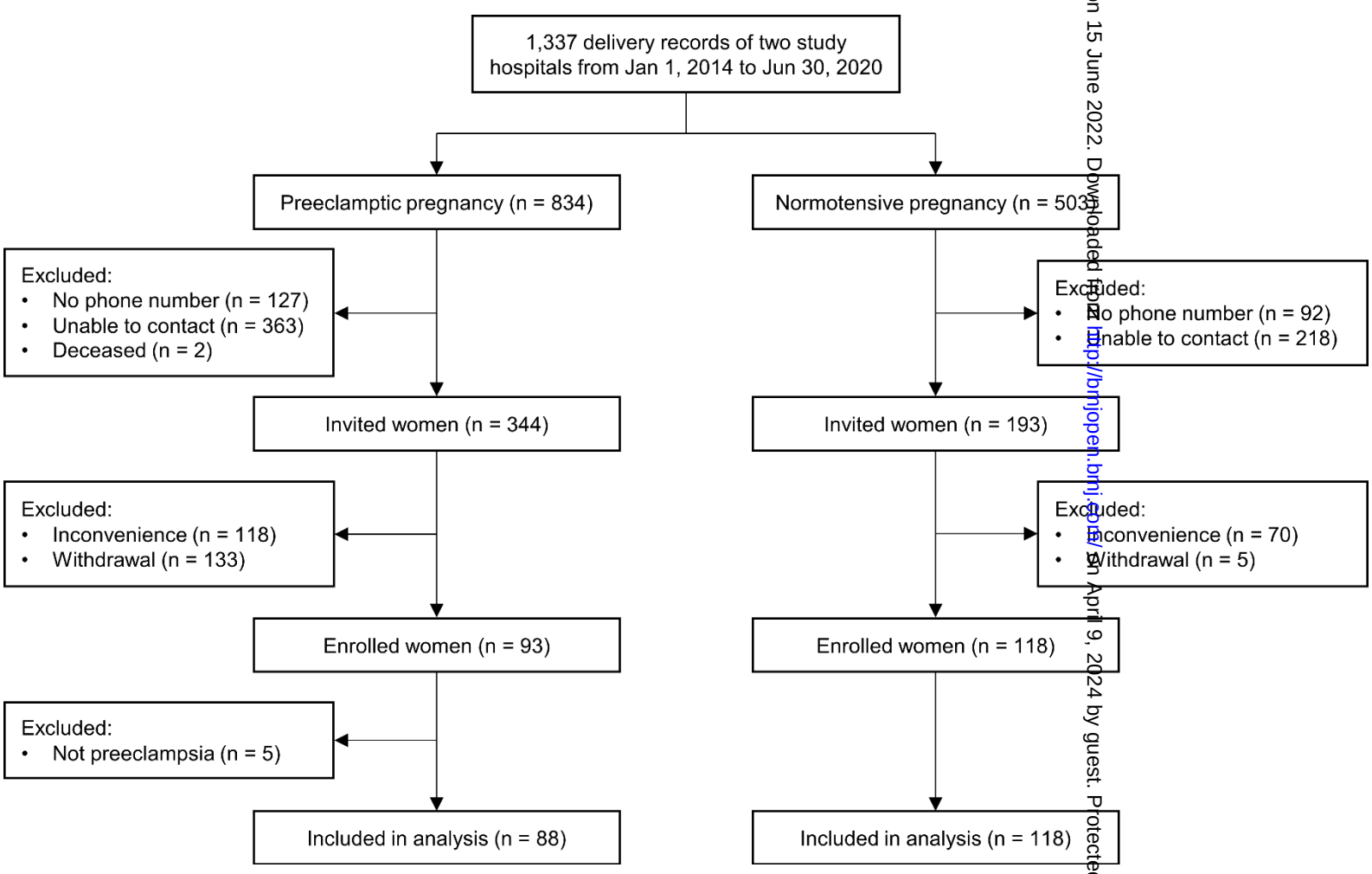


Figure 2 Boxplot of creatinine (A), urine microalbumin/creatinine ratio (B), and BMI (C) for the two study groups (N = 206) at <2 years, 2-4 years, and >4 years postpartumvisits*15 outliers in Figure 2B were removed for better visualization

121x250mm (600 x 600 DPI)

Supplementary Figure 1 Study flow chart



Supplementary Table 1 Pearson's correlation coefficients of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with clinical measures and biomarkers for the total and two study groups

	Correlation coefficient (r)					
	Total study group (N = 206)		**Previous preeclamptic pregnancy (n = 88)**		**Previous normotensive pregnancy (n = 118)**	
Variables	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
Pre-pregnancy BMI	0.23[b]	0.25[c]	0.26[a]	0.20	0.16	0.25[b]
BMI	0.28[c]	0.31[c]	0.30[b]	0.27[a]	0.22[a]	0.31[b]
Lactation duration	0.02	-0.03	-0.10	-0.15	0.16	0.08
Total physical activity	0.03	0.01	-0.01	0.00	0.15	0.11
PSQI global score	0.05	0.10	0.14	0.22	-0.01	0.02
Serum FBS	0.10	0.12	0.06	0.07	0.10	0.11
Serum HbA1c	0.15[a]	0.16[a]	0.06	0.06	0.20[a]	0.22[a]
Serum LDL cholesterol	0.12	0.13	0.07	0.07	0.10	0.13
Serum creatinine	0.31[c]	0.28[c]	0.39[c]	0.38[c]	0.07	0.03

Serum hs-CRP	0.01	0.07	0.06	0.00	0.00	0.14
UACR	0.27[c]	0.31[c]	0.24[a]	0.31[b]	0.31[b]	0.30[b]
Urine sodium	-0.06	-0.07	-0.06	-0.02	0.02	-0.07
Urine sodium/creatinine ratio	-0.05	-0.11	0.00	-0.05	0.06	-0.13

[a] P-value < 0.05; [b] P-value < 0.01; [c] P-value < 0.001

Abbreviations: BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; UACR, urine microalbumin/creatinine ratio

Supplementary Table 2 Final model of factors associated with hypertension at postpartum study visit in women without preexisting hypertension (N = 199)

Variables	Crude OR (95% CI)	Adj. OR (95% CI)	P(Wald's test)	P(LR-test)
Previous pregnancy: ref=Normotensive				
Preeclampsia	4.52 (1.95,10.44)	4.32 (1.57,11.84)	0.005	0.003
Age at postpartum study visit	1.11 (1.04,1.19)	1.10 (1.02,1.20)	0.016	0.012
Religion: ref=Buddhism				
Islam	1.97 (0.86,4.53)	2.88 (1.01,8.16)	0.047	0.039
UACR	1.85 (1.40,2.46)	1.91 (1.34,2.73)	<0.001	<0.001

Best fitted model with AIC 138.6; adjusted for serum LDL cholesterol, serum creatinine and urine sodium

Abbreviations: LDL, low-density lipoprotein; UACR, urine microalbumin/creatinine ratio

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10 and Tables 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-4 , Supplementary Table 1 and Supplementary Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figures 1-2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.