Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 30 (2022) 68–81

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Postnatal cardiovascular morbidity following preterm pre-eclampsia: An observational study

Laura Ormesher [a,b,*], Suzanne Higson [c], Matthew Luckie [c], Stephen A. Roberts [d], Heather Glossop [b], Andrew Trafford [e], Elizabeth Cottrell [a], Edward D. Johnstone [a,b], Jenny E. Myers [a,b]

[a] Maternal and Fetal Health Research Centre, Division of Developmental Biology and Medicine, University of Manchester, UK
[b] Saint Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, UK
[c] Manchester Heart Centre, Manchester University NHS Foundation Trust, Manchester, UK
[d] Centre for Biostatistics, University of Manchester, UK
[e] Division of Cardiovascular Sciences, University of Manchester, UK

ARTICLE INFO

Keywords:
Pre-eclampsia
Postpartum
Echocardiography
Left ventricular remodelling
Diastolic dysfunction

ABSTRACT

Objective: To explore the nature of postnatal cardiovascular morbidity following pregnancies complicated by preterm pre-eclampsia and investigate associations between pregnancy characteristics and maternal postnatal cardiovascular function.

Study design: This was an observational sub-study of a single-centre feasibility randomised double-blind placebo-controlled trial (https://www.clinicaltrials.gov; NCT03466333), involving women with preterm pre-eclampsia, delivering before 37 weeks. Eligible women underwent echocardiography, arteriography and blood pressure monitoring within three days of birth, six weeks and six months postpartum. Correlations between pregnancy and cardiovascular characteristics were assessed using Spearman's correlation.

Main Outcome Measures: The prevalence of cardiovascular dysfunction and remodelling six months following preterm pre-eclampsia.

Results: Forty-four women completed the study. At six months, 27 (61 %) had diastolic dysfunction, 33 (75 %) had raised total vascular resistance (TVR) and 18 (41 %) had left ventricular remodelling. Sixteen (46 %) women had *de novo* hypertension by six months and only two (5 %) women had a completely normal echocardiogram. Echocardiography did not change significantly from six weeks to six months. Earlier gestation at delivery and lower birthweight centile were associated with worse six-month diastolic dysfunction (E/E': rho = -0.39, p = 0.001 & rho = -0.42, p = 0.005) and TVR (rho = -0.34, p = 0.02 & rho = -0.37, p = 0.01).

Conclusions: Preterm pre-eclampsia is associated with persistent cardiovascular morbidity-six months postpartum in the majority of women. These cardiovascular changes have significant implications for long-term cardiovascular health. The graded severity of diastolic dysfunction and TVR with worsening pre-eclampsia phenotype suggests a dose–effect. However, the mechanistic link remains uncertain.

1. Introduction

Pre-eclampsia complicates 3–5 % of pregnancies [1] and is associated with significant perinatal and maternal morbidity and mortality [2]. There is abundant observational data linking pre-eclampsia with postnatal maternal cardiovascular dysfunction [3–6] and long-term cardiovascular risk [7–17]. This association is independent of mutual risk factors, including age, obesity and pre-existing hypertension [8]. Future cardiovascular risk in women with pre-eclampsia is graded in terms of severity and recurrence of pre-eclampsia; i.e. presence of severe features [8,10,12,16,18,19], prematurity [7,11,15,17], fetal growth restriction (FGR) [14,19] or pre-eclampsia recurrence [13,16] are associated with particularly increased cardiovascular risk in epidemiological studies. Compared with normotensive term pregnancies, preterm

* Corresponding author at: Maternal and Fetal Health Research Centre, St Mary's Hospital, Manchester University NHS Foundation Trust, Oxford Road, Manchester M13 9WL, UK.
E-mail address: laura.ormesher@manchester.ac.uk (L. Ormesher).

https://doi.org/10.1016/j.preghy.2022.08.007
Received 10 March 2022; Received in revised form 10 August 2022; Accepted 11 August 2022
Available online 17 August 2022

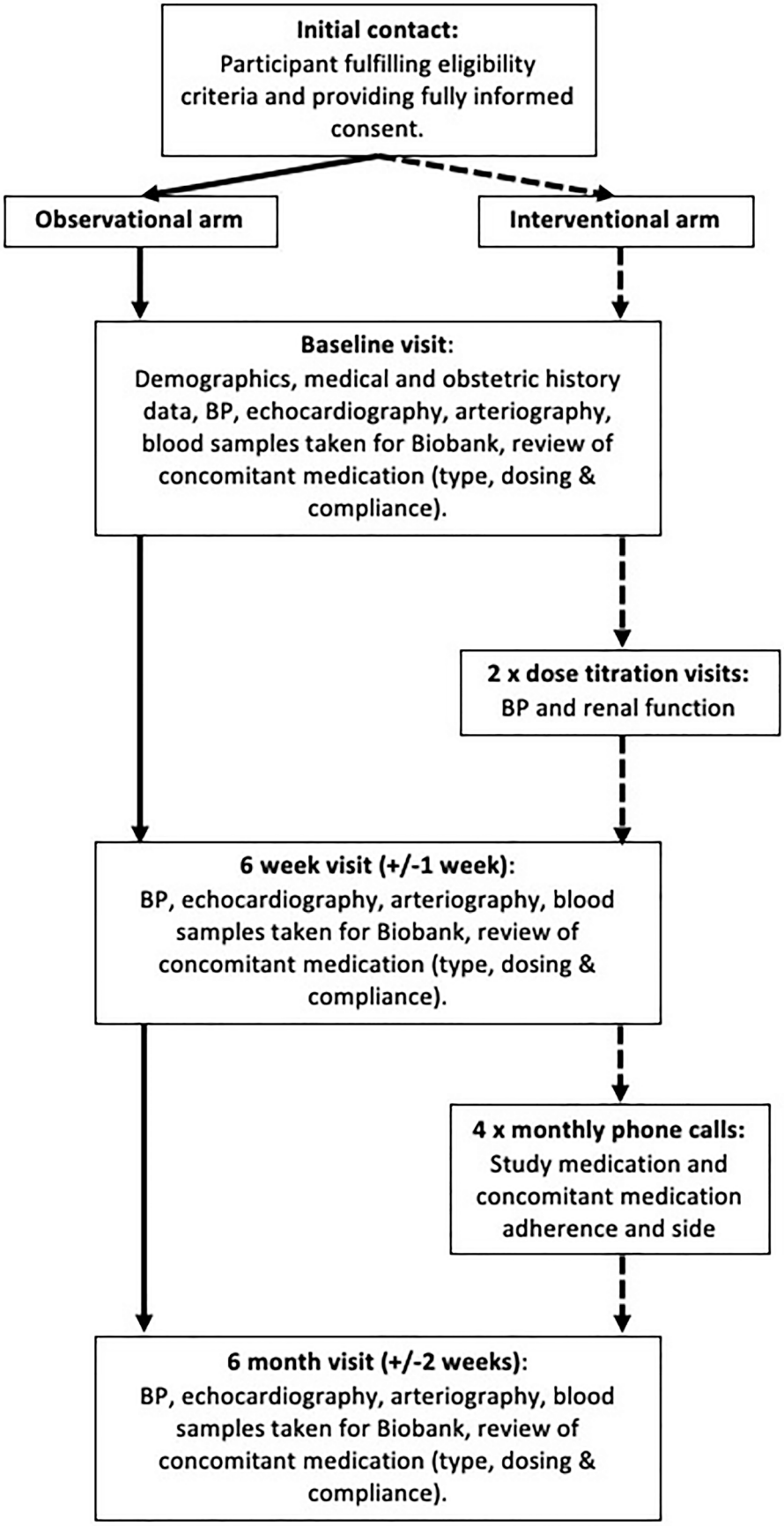

Fig. 1. Study schematic.

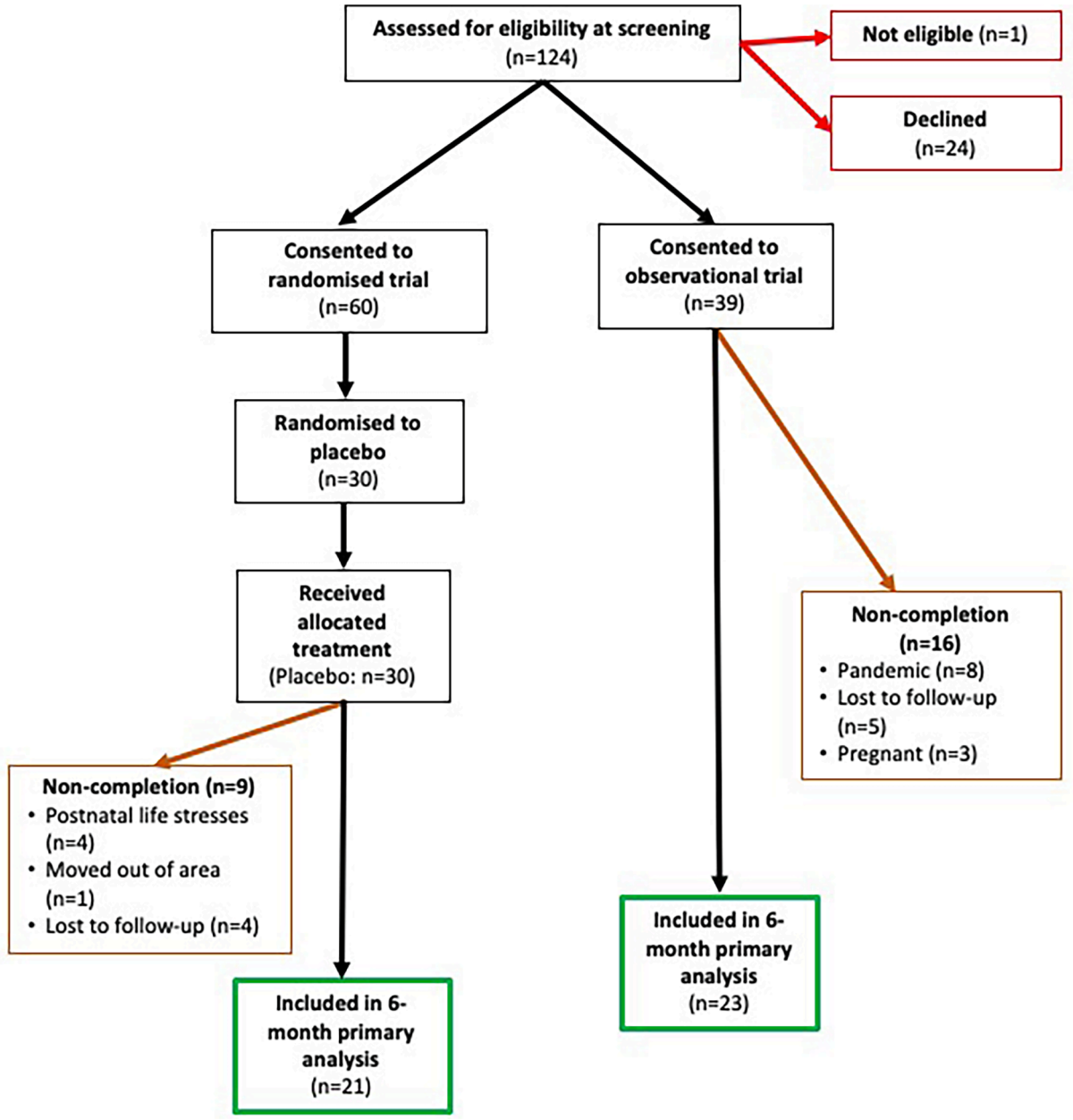

Fig. 2. Consort diagram.

pre-eclampsia is associated with two- to eightfold and three- to eightfold risks of cardiovascular events [7,8,15,17] and deaths [7,11,14], respectively.

This study focuses on women with preterm pre-eclampsia, requiring delivery before 37 weeks' gestation. Preterm pre-eclampsia affects 0.6–0.8 % of pregnancies in the United Kingdom (UK) [20]. The aim of this study was to explore the nature of postnatal cardiovascular dysfunction and remodelling following pregnancies complicated by preterm pre-eclampsia and identify any associations between pregnancy characteristics and cardiovascular function at six months. This could aid appropriate counselling for affected women and potentially identify subgroups who could benefit from intervention targeted in the postnatal period.

2. Methods

2.1. Study design

This was a sub-study of PICk-UP (Postnatal enalapril to Improve Cardiovascular fUnction following preterm Pre-eclampsia), which was a single-centre feasibility randomised double-blind placebo-controlled trial (RCT), carried out at St Mary's Hospital, Manchester, UK [21]. Eligible women who declined participation in the interventional trial or were recruited following completion of recruitment to the interventional trial were invited to participate in the observational study. Data for this report were combined from the observational study and the placebo arm of the RCT. PICk-UP was funded by the Medical Research Council (MRC) and prospectively registered at clinicaltrials.gov (NCT03466333).

2.2. Inclusion and exclusion criteria

Postnatal women with preterm pre-eclampsia (requiring delivery

Table 1
Baseline characteristics.

		Interventional trial (placebo arm; n = 30)	Observational trial (n = 39)	Total cohort (n = 69)
Age at enrolment		30.9 (6.6)	31.7 (6.5)	31.34 (6.47)
Ethnicity	**White**	17 (57 %)	18 (46 %)	35 (51 %)
	Black	4 (13 %)	6 (15 %)	10 (14 %)
	Asian	9 (30 %)	11 (28 %)	20 (29 %)
	Other	0 (0 %)	4 (10 %)	4 (6 %)
Booking BMI		29.4 (7.5)	28.3 (7.6)	28.8 (7.5)
Smoker in pregnancy		4 (13 %)	4 (10 %)	8 (12 %)
Pre-existing hypertension*		6 (20 %)	6 (15 %)	12 (17 %)
Pre-existing renal disease		0 (0 %)	2 (5 %)	2 (3 %)
Booking sBP		116 (14)	115 (14)	116 (14)
Booking dBP		74 (11)	71 (11)	72 (11)
Diabetes		2 (7 %)	2 (5 %)	4 (6 %)
Previous venous thromboembolism		1 (3 %)	0 (0 %)	1 (1 %)
Primiparity		15 (50 %)	22 (56 %)	37 (54 %)
No known pre-eclampsia risk factors†		19 (63 %)	25 (64 %)	44 (64 %)
Multiparous with no known risk factors		3/15 (20 %)	8/17 (47 %)	11/32 (34 %)
Multiparous with previous pre-eclampsia		5/15 (33 %)	7/17 (41 %)	12/32 (38 %)

Frequencies: N (%).
Continuous data: mean (standard deviation).
*Diagnosed before or during the first 20 weeks of pregnancy.
†Risk factors including hypertension, renal disease, diabetes, antiphospholipid syndrome, systemic lupus erythematous, age > 40, BMI > 30 kg/m^2 or previous preeclampsia(38).
BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure.

before 37 weeks) were consented to take part in the studies within 3 days of delivery. Pre-eclampsia was defined as new or worsening hypertension with proteinuria and/or evidence of organ dysfunction and/or placental dysfunction, as per the International Society of the Study of Hypertension in Pregnancy (ISSHP) guidelines [22]. Abnormal angiogenic markers (sFlt:PLGF > 85) in combination with new/worsening hypertension were also included in the definition [23]. Women had to be able to give informed consent and be aged ≥ 18 years. Women with known cardiac disease were excluded. In the interventional trial, additional exclusion criteria included current use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers or contraindication to ACE inhibitors, due to potential randomisation to enalapril.

2.3. Study procedures

Women underwent research visits at baseline (within three days of delivery), six weeks and six months postpartum, as illustrated in Fig. 1. Cardiovascular investigations included peripheral blood pressure (BP; Alere Microlife BP monitors, Cheshire, UK); echocardiography (VIVID S70, GE Healthcare, UK) to assess haemodynamics, left ventricular remodelling and function; arteriography to assess arterial stiffness and venepuncture for cardiovascular and placental biomarkers (including high sensitivity troponin [HScTnT], *N*-terminal pro-brain natriuretic peptide [NTproBNP], placental growth factor [PlGF] and soluble fms-like tyrosine kinase-1 [sFlt]). All study procedures have been described in detail previously [21]. Women were not aware of findings at baseline as the echocardiograms were analysed post-hoc in batches.

2.4. Aims

The primary aim was to describe the natural history of maternal postnatal cardiovascular dysfunction following preterm pre-eclampsia, using longitudinal data from three postnatal timepoints. Secondary aims included correlation of i) pregnancy and pre-eclampsia phenotypes, ii) maternal characteristics and iii) biomarkers with maternal cardiovascular phenotype at six months postpartum. Additionally, we aimed to assess the correlation between the above factors and change in maternal cardiovascular parameters over time.

2.5. Echocardiography-defined classifications

Abnormal echocardiography values were pre-defined, as per the main RCT [21]. Systolic dysfunction was determined using a combination of Simpson's BiPlane measurement of the left ventricle (left ventricular ejection fraction [LVEF] < 55 %) [24], 2-dimensional speckle-tracking (global longitudinal strain [GLS] > -18 %) [25] and tissue Doppler at the mitral annulus (S' <0.064 m/s) [24]. Diastolic dysfunction was defined using the British Society of Echocardiography (BSE) clinical flow chart [26], using discrete cut-offs for pulse wave Doppler measures (E/A and deceleration time) and age-adjusted reference ranges for tissue Doppler (E') and left atrial volume. Given the relatively young age of this cohort, inclusion of criteria using age-adjusted reference ranges was considered most suitable. Concentric left ventricular remodelling was defined by relative wall thickness (RWT) > 0.42 and hypertrophy was defined as left ventricular mass index (LVMi) > 95 g/m^2 [27]. Raised total vascular resistance (TVR) was defined as > 1200 dyne.s^{-1}cm^{-5} [28].

2.6. Statistical analysis

All statistical analyses were performed using Stata v14.2. Continuous variables were presented as mean (standard deviation) and median (interquartile range), as appropriate. Categorical variables were presented as counts (percentage). Continuous variables were compared between timepoints and groups using paired *t*-test, following log-transformation where required. Correlations between pregnancy / maternal characteristics and 6-month postnatal maternal cardiovascular parameters were assessed using Spearman's correlations. Correlations between baseline placental biomarkers and cardiovascular parameters were assessed using a linear regression model with number of days postpartum as a covariate. No adjustment was made for multiple testing. Intermodality agreement was assessed using intraclass correlation coefficients (ICC) and linear regression analyses. This was an exploratory study with no prior data to inform the correlation between baseline and six-month cardiovascular parameters and therefore no *a priori* sample size calculation was possible.

Table 2
Pregnancy outcomes.

Perinatal outcomes		
Gestation at delivery (weeks + days (days))*		35 + 0 (20)
Gestation at PE diagnosis (weeks + days (days))*		34 + 0 (26)
Infant sex	**Male** 41 (53 %)	**Female** 37 (47 %)
Multiple pregnancy		8 (12 %)
	Singleton pregnancies (61 pregnancies)	**Multiple pregnancies (8 pregnancies; 17 infants)**
Birthweight centile*	2.9 (24.1)	21.6 (24.4)
Birthweight centile < 10th	40/61 (66 %)	7/17 (41 %)
Birthweight centile < 3rd	31/61 (51 %)	3/17 (18 %)
Delivery < 34 weeks	20/61 (33 %)	7/17 (41 %)
NICU admission (days)*	7 (21)	5 (9)
Respiratory distress syndrome	15/58 (26 %)	7/17 (41 %)
Interventricular haemorrhage	3/58 (5 %)	0/17 (0 %)
Seizure	1/58 (1 %)	0/17 (0 %)
NEC	4/58 (6 %)	0/17 (0 %)
Adverse perinatal outcome†	19/61 (31 %)	7/17 (41 %)
Stillbirth	3/61 (5 %)	0/17 (0 %)
NND	2/61 (3 %)	0/17 (0 %)
Maternal outcomes		
Maximum systolic blood pressure		164 (12)
Maximum diastolic blood pressure		106 (9)
Eclampsia / HELLP syndrome		0 (0 %)
Abruption		1 (2 %)
Maternal death		0 (0 %)
Gestational diabetes		5 (7 %)
Pre-eclampsia with severe features‡		53 (77 %)
Spontaneous preterm birth		5 (7 %)
Antenatal steroids for lung maturity		47 (68 %)

Frequencies: N(%).
Continuous data: mean (standard deviation).
*Median (interquartile range).
Maternal outcomes were determined at the time of randomisation.
†Composite adverse perinatal outcome: respiratory distress syndrome / intraventricular haemorrhage / necrotising enterocolitis / stillbirth / neonatal death.
‡Definition of pre-eclampsia with severe features: maximum blood pressure > 160/110 mmHg / progressive deterioration in alanine aminotransferase / creatinine / platelets.
PE, pre-eclampsia; C-section, Caesarean section; NICU, neonatal intensive care; RDS, respiratory distress syndrome; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NND, neonatal death; HELLP, haemolysis, elevated liver enzymes, and a low platelet count.

3. Results

Forty women were recruited to the observational study and 30 were recruited to the placebo arm of the PICk-UP trial between September 2018 and February 2020. One woman was excluded from the observational study, due to inaccurate pre-eclampsia diagnosis. Follow-up for the observational study was affected by the Covid-19 global pandemic which prevented four of the six-week and eight of the six-month follow-up visits. Forty-four women completed the study at six months (Fig. 2).

3.1. Baseline characteristics

Cohort baseline characteristics are summarised in Table 1. Twenty (29 %) women had an underlying medical condition, including hypertension, renal disease, diabetes, previous thromboembolism and anti-phospholipid syndrome.

Table 2 summarises the pregnancy outcomes of the cohort. The majority of women were delivered due to maternal indications (n = 37, 54 %).

Table 3
Prevalence of cardiovascular and echocardiographic abnormalities at baseline (within 3 days of delivery), 6 weeks and 6 months postpartum.

	Baseline (n = 69)	6 weeks (n = 50)	6 months (n = 44)
Raised TVR (>1200)	34 (49 %)	45 (90 %)	33 (75 %)
Systolic dysfunction	14 (20 %)	13 (26 %)	3 (7 %)
Diastolic dysfunction	58 (84 %)	21 (42 %)	27 (61 %)
No remodelling	13 (19 %)	25 (50 %)	26 (59 %)
Concentric remodelling	33 (48 %)	20 (40 %)	16 (36 %)
Concentric hypertrophy	22 (32 %)	5 (10 %)	1 (2 %)
Eccentric hypertrophy	1 (1 %)	0 (0 %)	1 (2 %)
Requiring antihypertensives	53 (77 %)	19 (38 %)	15 (34 %)
Requiring antihypertensives or BP > 140/90 mmHg	58 (84 %)	24 (48 %)	25 (57 %)
Requiring antihypertensives or BP > 140/90 mmHg in the absence of pre-existing hypertension	46/57 (81 %)	15/41 (37 %)	16/35 (46 %)

Frequencies: N (%).
Diastolic dysfunction defined using British Society of Echocardiography guideline flow chart26.
TVR, total vascular resistance; BP, blood pressure.

3.2. Change in cardiovascular parameters over time

At six months, diastolic and systolic dysfunction affected 61 % and 7 % of women, respectively (Table 3). When using age-adjusted reference ranges for all diastolic functional measures [26] including E/A and deceleration time, diastolic dysfunction affected 32 (73 %) women. Prevalence of diastolic dysfunction is significantly impacted by the classification used. For example, the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging guideline does not use age-adjusted reference ranges, in contrast with BSE [26,29]. For this reason, prevalence of diastolic dysfunction using the different definitions is summarised in Supplementary Table 1. TVR was raised in 75 % and 41 % of women had persistent left ventricular remodelling at six months (Table 3). Of those with no pre-existing hypertension (diagnosed before or during the first half of pregnancy), 16/35 (46 %) had a diagnosis of hypertension, defined by clinic BP $\geq$ 140/90 [30] and/or need for antihypertensives, at six months.

There was considerable overlap in echocardiography abnormalities and only 2 (5 %) women had a completely normal echocardiogram at six months (Fig. 3).

The majority of echocardiography parameters significantly improved from baseline to six weeks; however there was no significant change in any echocardiography parameter from six weeks to six months (Table 4). Regression analyses demonstrated no correlation between study completion and baseline or 6-month cardiovascular phenotype.

Six (8 %) women had raised HScTnT (16–18 ng/L) or NTproBNP (468–1259 pg/mL) at baseline. Both cardiac biomarkers had normalised by six weeks postpartum. The change in placental and cardiovascular biomarker levels over time is summarised in Table 5. Baseline placental biomarkers were significantly influenced by the number of days postpartum (PlGF: linear regression coefficient −21.5 pg/mL/day (95 % CI −38.6 - −4.5), p = 0.01 and sFlt: linear regression coefficient −1145.6 pg/mL/day (95 % CI –1717.8 - −573.4), p < 0.001).

Table 6 summarises the change in BP and arterial stiffness over time. Central and peripheral sBP declined from baseline to six months postpartum; however, there was no significant change in dBP.

3.3. Relationship between pre-eclampsia and cardiovascular phenotypes

The presence of pre-existing hypertension (n = 12) did not influence systolic or diastolic function at six months (GLS: −19.96 (2.34) versus −20.88 (1.55), p = 0.16; E/E': 7.93 (1.13) versus 7.43 (1.59), p = 0.38). However, women with pre-existing hypertension had worse left ventricular remodelling (LVMi: 81.91 (21.24) versus 63.06 (10.70), p =

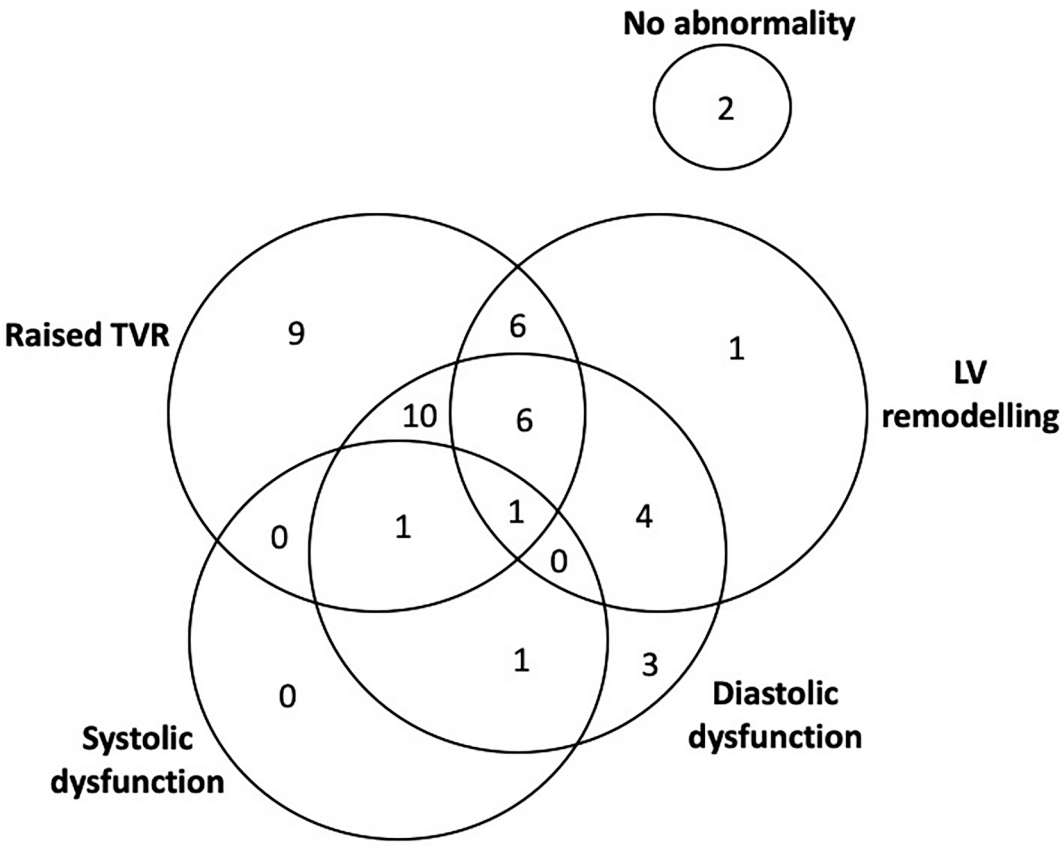

Fig. 3. Venn diagram of 6-month echocardiographic abnormalities.

0.001) and higher TVR (2034 (795) versus 1567 (323), p = 0.009) at six months, compared to those without (Fig. 4). Despite this, prevalence of cardiovascular morbidity at 6 months remained high in those without pre-existing hypertension: 25/35 (71 %) had diastolic dysfunction, 2/35 (6 %) had systolic dysfunction, 11/35 (31 %) had left ventricular remodelling and 26/35 (74 %) had raised TVR. Pre-eclampsia with severe features, as defined by the National Institute for Health and Care Excellence (NICE) [31] was not significantly associated with any six-month echocardiography parameter (Fig. 4). Only two women with a multifetal pregnancy completed the study at 6 months. For this reason, there was insufficient power to investigate the relationship between multifetal pregnancy and maternal cardiovascular phenotype. Exploratory analyses (Spearman's correlation) demonstrated no correlation between BMI and 6-month cardiovascular phenotype. On the other hand, blood pressure correlated with diastolic function and left ventricular remodelling, but not systolic function (Supplementary Fig. 1).

Earlier gestations at pre-eclampsia diagnosis and delivery were associated with worse diastolic dysfunction (E/E': rho = -0.34, p = 0.03 and rho = -0.39, p = 0.001, respectively) and TVR (rho = -0.42, p = 0.004 and rho = -0.34, p = 0.02, respectively) at six months (Fig. 5).

Prolonged pre-eclampsia duration (up to 48 days) was associated with increased TVR, but not E/E' at six months (rho = 0.36, p = 0.02 and rho = 0.20, p = 0.20, respectively; Supplementary Fig. 2). On the other hand, prolonged pre-eclampsia duration was associated with reduced improvement in remodelling and a trend toward reduced improvement in diastolic dysfunction from baseline to six months (LVMi: rho = -0.33, p = 0.03; E/E': rho = -0.27, p = 0.08). Lower birthweight centile was also associated with worse diastolic dysfunction and TVR at six months (E/E': rho = -0.42, p = 0.005 and TVR: rho = -0.37, p = 0.01; Fig. 4). There was no correlation between birthweight centile, gestation at diagnosis or delivery, and LV remodelling (LVMi and RWT) or systolic function (LVEF, GLS and S').

3.4. Relationship between biomarkers and cardiovascular phenotype

There were no significant associations between baseline PlGF, sFlt or sFlt:PlGF and six-week or six-month echocardiography measures. Some baseline biomarkers showed borderline significant associations with early postnatal echocardiography measures; however none persisted beyond the six-week visit (Supplementary Fig. 3).

3.5. Intermodality correlations

There was good to excellent agreement between Alere Microlife and TensioClinic arteriography in the measurement of sBP (ICC 0.87 (95 % CI 0.83 – 0.91)) and dBP (ICC 0.92 (95 % CI 0.89 – 0.95). Although there was a significant linear relationship between E/A (measured by pulse wave Doppler at the mitral inlet) and E/A strain rate (measured using speckle-tracking software; coefficient: 1.48 (95 % CI 1.15–1.81, p < 0.001, Supplementary Fig. 3), absolute values showed poor agreement (ICC 0.56 (95 % CI 0.40–0.68). In terms of different echocardiographic measures of systolic dysfunction, LVEF correlated with GLS (coefficient: −0.82 (95 % CI −1.07 - −0.56), p < 0.001, Fig. 6).

4. Discussion

4.1. Main findings

In this prospective longitudinal study, we demonstrated a high prevalence of persistent cardiovascular abnormalities at six months postpartum, following preterm pre-eclampsia. Only two women (5 %) had a completely normal echocardiogram at six months, with the majority of abnormalities attributable to raised TVR, diastolic dysfunction and left ventricular remodelling. In those who were not known to be hypertensive before 20 weeks' gestation, nearly half (46 %) had *de novo*

Table 4
Change in postnatal echocardiography measures over time.

	Baseline (n = 69)	6 weeks (n = 50)	6 months (n = 44)	Mean difference between timepoints (95 % C.I.)		
				Baseline to 6 weeks	Baseline to 6 months	6 weeks to 6 months
TVR (dyne.s^{-1}cm^{-5})	1427 (382)	1749 (424)	1662 (486)	322* (175–469)	235* (72–397)	87 (-274–99))
HR (bpm)	85.3 (13.7)	75.3 (11.7)	78.2 (12.3)	−10.0* (-14.8 - −5.3)	−7.2* (-12.2 - −2.1)	2.9 (-2.1–7.8)
SV (mL)	73.9 (16.1)	63.1 (12.8)	64.8 (13.3)	−10.8* (-16.3 - −5.4)	−9.1* (-14.8 - −3.3)	1.7 (-3.6–7.1)
CO (L/minute)	6.3 (1.6)	4.7 (1.0)	5.0 (1.1)	−1.6* (-2.1 - −1.5)	−1.2* (-1.8 - −6.9)	3.2 (-1.2–7.6)
LVEF (%)	63 (5)	62 (4)	62 (3)	−1.1 (-2.7–0.5)	−1.0 (-2.5–0.6)	0.1 (-1.3–1.5)
Myocardial strain and strain rate						
LV basal strain (%)	−15.7 (3.3)	−16.3 (2.2)	−17.0 (2.5)	−0.6 (-1.7–0.4)	−1.3* (-2.5 - −0.2)	−0.7 (-1.6–0.3)
LV mid strain (%)	−18.8 (2.3)	−19.1 (1.8)	−19.7 (1.9)	−0.2 (-1.0–0.6)	−0.9* (-1.7 - −0.1)	−0.7 (-1.4–0.1)
LV apical strain (%)	−25.3 (3.8)	−24.5 (3.0)	−25.3 (2.6)	0.8 (-0.5–2.1)	0.1 (-1.2–1.4)	−0.8 (-1.9–0.4)
GLS (%)	−19.9 (2.4)	−20.0 (2.2)	−20.7 (1.8)	0.0 (-0.9–0.8)	−0.8 (-1.6–0.1)	−0.7 (-1.6–0.1)
E/A strain rate	2.19 (0.72)	2.38 (0.68)	2.21 (0.73)	0.19 (-0.07–0.46)	0.03 (-0.25–0.30)	−0.17 (-0.46–0.12)
Mitral inflow						
E deceleration time (ms)	192 (32)	197 (29)	189 (34)	4.9 (-6.8–16.5)	−3.7 (-16.5–9.2)	−8.5 (-21.6–4.6)
E/A ratio	1.22 (0.28)	1.3 (0.27)	1.24 (0.28)	0.12* (0.02–0.22)	0.03 (-0.08–0.13)	−0.09 (-0.20–0.02)
Mitral annular motion						
Septal peak S' velocity (m/s)	0.09 (0.02)	0.08 (0.01)	0.08 (0.01)	−0.01 (-0.02–0.00)	−0.01 (-0.02–0.00)	0.00 (0.00–0.00)
Lateral peak S' velocity (m/s)	0.10 (0.02)	0.09 (0.02)	0.09 (0.02)	0.00 (-0.01–0.00)	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)
E/E' ratio	8.71 (2.00)	7.37 (1.68)	7.53 (1.51)	−1.35* (-2.04 - −0.66)	−1.19* (-1.89 - −0.49)	0.16 (-0.40–0.81)
Tricuspid valve						
TR Vmax (cm/s)	0.98 (1.17)	0.58 (0.95)	0.55 (0.97)	−0.40* (-0.80–0.00)	−0.43* (-0.85 - −0.01)	−0.03 (-0.42–0.36)
Cardiac morphology						
LVIDd (cm)	4.49 (0.45)	4.32 (0.48)	4.30 (0.42)	−0.17 (-0.34–0.00)	−0.18* (-0.35 - −0.01)	−0.02 (-0.20–0.17)
PWd (cm)	1.12 (0.19)	0.94 (0.19)	0.89 (0.17)	−0.18* (-0.25 - −0.11)	−0.23* (-0.30 - −0.16)	−0.05 (-0.13–0.02)
SWd (cm)	1.01 (0.18)	0.88 (0.17)	0.8 (0.16)	−0.12* (-0.19 - −0.06)	−0.13* (-0.19 - −0.06)	0.00 (-0.07–0.07)
LVM (g)	172.02 (48.50)	132.40 (46.79)	125.33 (39.32)	−39.62* (-57.20 - –22.04)	−46.69* (-63.96 - −29.43)	−7.07 (-24.91–10.77)
LVMi (g/m^2)	89.58 (18.65)	70.39 (18.73)	66.92 (15.28)	−19.19* (-26.06 - −12.32)	–22.67* (-29.33 - −16.01)	−3.47 (-10.54–3.59)
RWT	0.50 (0.10)	0.44 (0.10)	0.41 (0.09)	−0.06* (-0.10 - −0.03)	−0.09* (-0.12 - −0.05)	−0.02 (-0.06–0.02)
LAV (mL)	47.3 (14.4)	39.7 (11.3)	38.9 (10.5)	−7.7* (-12.6 - −2.8)	−8.4* (-13.5 - −3.4)	−0.8 (-5.3–3.8)
LAVi (mL/m^2)	24.7 (6.3)	21.2 (4.7)	20.9 (4.7)	−3.5* (-5.6 - −1.4)	−3.7* (-5.9 - −1.5)	−0.3 (-2.2–1.7)

Mean (standard deviation).
Variables were compared between time-points using paired *t*-test.
*P value < 0.05.
C.I., confidence interval; HR, heart rate; SV, stroke volume; CO, cardiac output; LVEF, left ventricular ejection fraction; LV, left ventricular; GLS; global longitudinal strain; TVR, total vascular resistance; LVIDd, LV internal diameter in diastole; PWd, posterior wall diameter in diastole; SWd, septal wall diameter in diastole; LVM, left ventricular mass; LVMi, LVM indexed to body surface area; RWT, relative wall thickness; LAV left atrial volume; LAVi, LAV indexed to body surface area; TR Vmax, tricuspid regurgitation maximum velocity.

Table 5
Change in postnatal placental and cardiovascular biomarkers over time.

Biomarker	Baseline (n = 69)	6 weeks (n = 50)	6 months (n = 44)	Difference in log-transformed biomarkers between timepoints (95 % C.I.)		
				Baseline to 6 weeks	Baseline to 6 months	6 weeks to 6 months
sFlt (pg/mL)	1432 (1753)	88 (17)	80 (14)	−2.92* (-3.16 - −2.67)	−2.99* (-3.25–2.73)	−0.07* (-0.13 - −0.02)
PlGF (pg/mL)	22 (20)	10 (3)	10 (4)	−1.06* (-1.28 - −0.83)	−1.02* (-1.25 - −0.78)	0.04 (-0.07–0.15)
sFlt:PlGF	57 (46)	10 (4)	8 (3)	−1.86* (-2.09 - −1.63)	−1.97* (-2.21 - −1.74)	−0.11 (-0.23–0.00)
HScTnT* (ng/L)	5 (6)	<3 (1)	<3 (0)	−0.61* (-0.83 - −0.39)	−0.68* (-0.90 - −0.46)	−0.06 (-0.23–0.10)
NTproBNP (pg/mL)	64 (161)	25.5 (26)	30 (36)	−0.89* (-1.28 - −0.51)	−0.85* (-1.28 - −0.43)	0.04 (-0.29–0.37)

Continuous data: median (interquartile range).
Log-transformed variables were compared between time-points using paired *t*-test.
*P value < 0.05.
C.I., confidence interval; sFlt, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; HScTnT, high-sensitivity cardiac Troponin T; NTproBNP, *N*-terminal pro-brain natriuretic peptide.

hypertension at six months postpartum.

Correlations between pre-eclampsia and cardiovascular phenotypes were investigated in order to explore a potential causal relationship between the two. None of the standard metrics defining maternal disease severity [32] correlated significantly with six-month postpartum cardiovascular phenotype. On the other hand, other markers of severity (including lower birthweight centile and earlier gestation at diagnosis / delivery) were associated with worse diastolic dysfunction (E/E') and TVR at six months. Longer duration of pre-eclampsia prior to delivery was also associated with higher six-month TVR, indicating a potential dose–effect.

Table 6
Change in postnatal blood pressure and arterial stiffness over time.

	Baseline (n = 69)	6 weeks (n = 50)	6 months (n = 44)	Mean difference between timepoints (95 % C.I.)		
				Baseline to 6 weeks	Baseline to 6 months	6 week to 6 months
Arteriography						
Pulse wave velocity	8.3 (1.8)	7.4 (1.5)	7.6 (1.8)	−0.9* (-1.6 - −0.2)	−0.8 (-1.5–0.0)	0.2 (-0.6–0.9)
Heart rate (bpm)	86.4 (16.1)	80.6 (13.6)	84.4 (14.0)	−5.8 (-11.8–0.2)	−1.9 (-8.1–4.3)	3.9 (-2.1–9.9)
Systolic blood pressure (mmHg)	137.6 (9.8)	125.1 (11.5)	132.1 (17.41)	−12.5 (-16.7 - −8.3)	−5.5* (-10.9–0.0)	7.0* (0.6–13.4)
Diastolic blood pressure (mmHg)	83.4 (8.8)	78.4 (10.6)	81.8 (13.6)	−5.0* (-8.9 - −1.2)	−1.7 (-6.1–2.8)	3.3 (-2.0–8.6)
Augmentation index (aortic)	24.2 (15.1)	23.1 (12.0)	21.9 (12.2)	−1.1 (-6.7–4.4)	−2.4 (-8.0–3.3)	−1.2 (-6.5–4.1)
Augmentation index (brachial)	–23.4 (28.8)	−28.8 (23.8)	−30.9 (24.2)	−5.4 (-16.1–5.3)	−7.6 (-18.5–3.4)	−2.2 (-12.6–8.3)
Central systolic blood pressure (mmHg)	132.6 (12.5)	119.5 (13.3)	125.8 (21.0)	−13.2* (-18.2 - −8.0)	−6.7 (-13.4–0.0)	6.4 (-1.2–13.9)
Alere Microlife						
Systolic blood pressure (mmHg)	135.4 (9.0)	126.4 (10.9)	127.9 (13.7)	−8.9* (-12.6 - −5.3)	−7.5* (-11.7 - −3.2)	1.5 (-3.6–6.5)
Diastolic blood pressure (mmHg)	90.1 (7.6)	84.6 (9.4)	86.7 (12.2)	−5.5 (-8.6 - −2.4)	−3.4 (-7.1–0.3)	2.1 (-2.4–6.5)
Mean arterial pressure (mmHg)	105.2 (7.4)	98.6 (9.5)	100.4 (12.4)	−6.6 (-97 - −3.6)	−4.8 (-8.4 - −1.1)	1.9 (-2.6–6.4)

Continuous data: mean (standard deviation).
Variables were compared between time-points using paired *t*-test.
*P value < 0.05.
C.I., confidence interval; bpm, beats per minute; mmHg, millimetres of mercury.

4.2. Strengths and limitations

To our knowledge, this is the largest longitudinal dataset describing postnatal cardiovascular structure and function following preterm pre-eclampsia. This study describes a multi-ethnic cohort with a predominantly severe pre-eclampsia phenotype. This study comprises data from women who participated in the PICk-UP study, which required a pre-eclampsia diagnosis for inclusion. As a result, a significant limitation of the study is a lack of control group for comparison. To compensate for this, age-adjusted reference ranges were used and a six-month follow-up period chosen, by which time maternal haemodynamics and cardiac parameters should have returned to the non-pregnant state [33–35]. Another limitation is the modest sample size, which was exacerbated by non-completion due to the concurrent pandemic. As this was a descriptive, exploratory study without pre-stated hypotheses, adjustment was not made for multiple testing. Statistical significance should therefore be interpreted as suggestive rather than definitive. Due to the lack of pre-pregnancy echocardiography data, it is not possible to confirm direction of causality between pre-eclampsia and cardiovascular dysfunction. Additionally, the three-day window for the baseline visit potentially limited our ability to relate baseline placental biomarkers with six-month cardiovascular outcomes, given the rapid decline in sFlt and PlGF in the first 48 h postpartum [36].

4.3. Interpretation

In the absence of any cardioprotective intervention, women with preterm pre-eclampsia have a high prevalence of cardiovascular abnormalities at six months postpartum. This is consistent with previous studies [4,5,37]. Diastolic dysfunction, as defined by the BSE [26], affected 61 % women, compared with 8 % two years following a normotensive pregnancy [4]. These findings have significant implications for long-term cardiovascular risk [38–40]. Ladeiras-Lopes et al.'s *meta*-analysis [38] demonstrated a 3.53-fold increase in cardiovascular events or death associated with a diagnosis of diastolic dysfunction within 11 years. Diastolic dysfunction precedes and independently predicts left ventricular remodelling following myocardial infarction [41,42]. It is therefore likely that the prevalence of adverse remodelling will increase over time, despite already affecting 41 % of the cohort. Remodelling is an independent predictor of cardiovascular events (hazard ratio 1.70 (95 % CI 1.34–2.16) within 10 years) [43] and overt hypertension [4,44], which is the leading modifiable risk factor for all-cause mortality [45]. Hypertension frequently requires lifelong therapy [46], thereby constituting an important outcome to clinicians and patients alike. Hypertension affected 57 % of the total cohort at six months, comparable with McCarthy et al.'s [37] findings of 71 % (95 % CI 42–74 % versus 66–76 %, $p = 0.06$).

The association between pre-eclampsia phenotype (birthweight centile and gestation at diagnosis/delivery) and diastolic function, suggests a potential dose–effect. Although the lack of pre-pregnancy echocardiography data limits our ability to confirm direction of causation, the lack of relationship between pre-pregnancy cardiovascular risk factors (including hypertension) and postnatal diastolic dysfunction points away from pre-eclampsia being solely a consequence of cardiovascular dysfunction. On the other hand, there was an association between remodelling and pre-existing hypertension, highlighting the possibility that women with pre-existing hypertension had some degree of pre-pregnancy cardiovascular changes. One could speculate that if pre-eclampsia is a cause of cardiovascular dysfunction, duration of exposure should correlate with severity of cardiovascular dysfunction; this was only observed for TVR in this cohort. This could be attributable to insufficient power or inaccurate timing of pre-eclampsia diagnosis.

Preterm pre-eclampsia is a heterogenous condition defined by clinical manifestations of endothelial dysfunction (proteinuria and hypertension) [22] and likely comprises more than one pathological process [47,48]. It is therefore plausible that direction of causality differs between subclasses of pre-eclampsia. This is supported by the inconsistencies observed in the correlations between maternal/pregnancy characteristics and six-month echocardiography parameters in this cohort.

The mechanism by which pre-eclampsia might be a cause of cardiovascular dysfunction is not known. In Shahul et al.'s [49] prospective

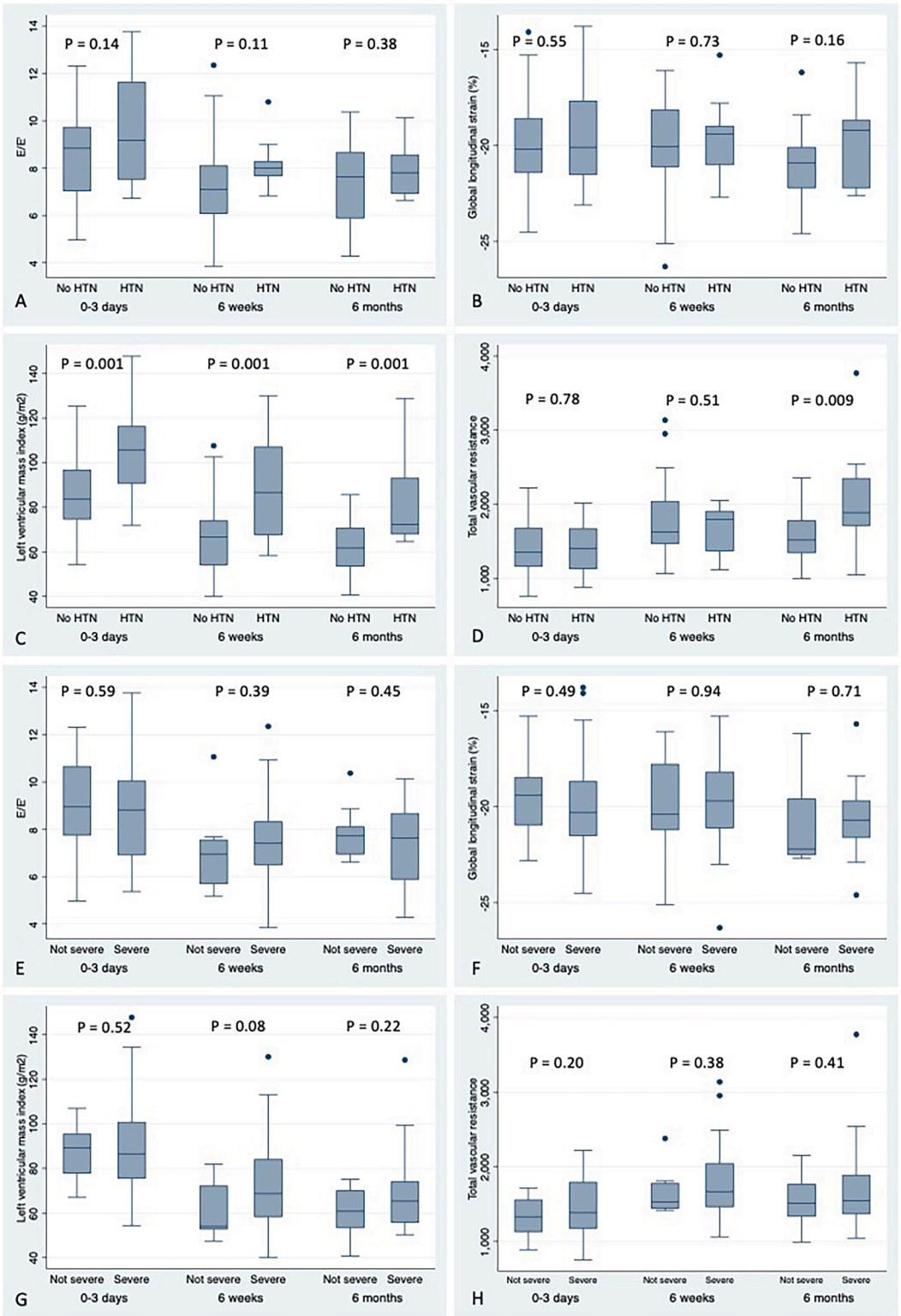

Fig. 4. Influence of pre-existing hypertension and pre-eclampsia severity on change in echocardiography over time. Box plots demonstrating the influence of pre-existing hypertension on **A.** E/E'; **B.** global longitudinal strain; **C.** left ventricular mass index; **D.** total vascular resistance; and the influence of severe features of pre-eclampsia on **E.** E/E'; **F.** global longitudinal strain; **G.** left ventricular mass index; **H.** total vascular resistance. The line represents median; the box includes 25th to 75th percentile; the whiskers extend to the upper and lower adjacent values and the dots represent outliers. P values are derived using paired *t*-test, comparing the two groups at different time-points. Data are pooled from the placebo and observational arms of the study. Definition of pre-eclampsia with severe features: maximum BP $\geq$ 160/110 mmHg / alanine aminotransferase $>$ 100U/L / creatinine $>$ 100 μmol/L / platelets $<$ 100x10^9/L. HTN, pre-existing hypertension diagnosed $<$ 20 weeks' gestation; E/E', early diastolic filling to early diastolic mitral annular velocity ratio; BP, blood pressure.

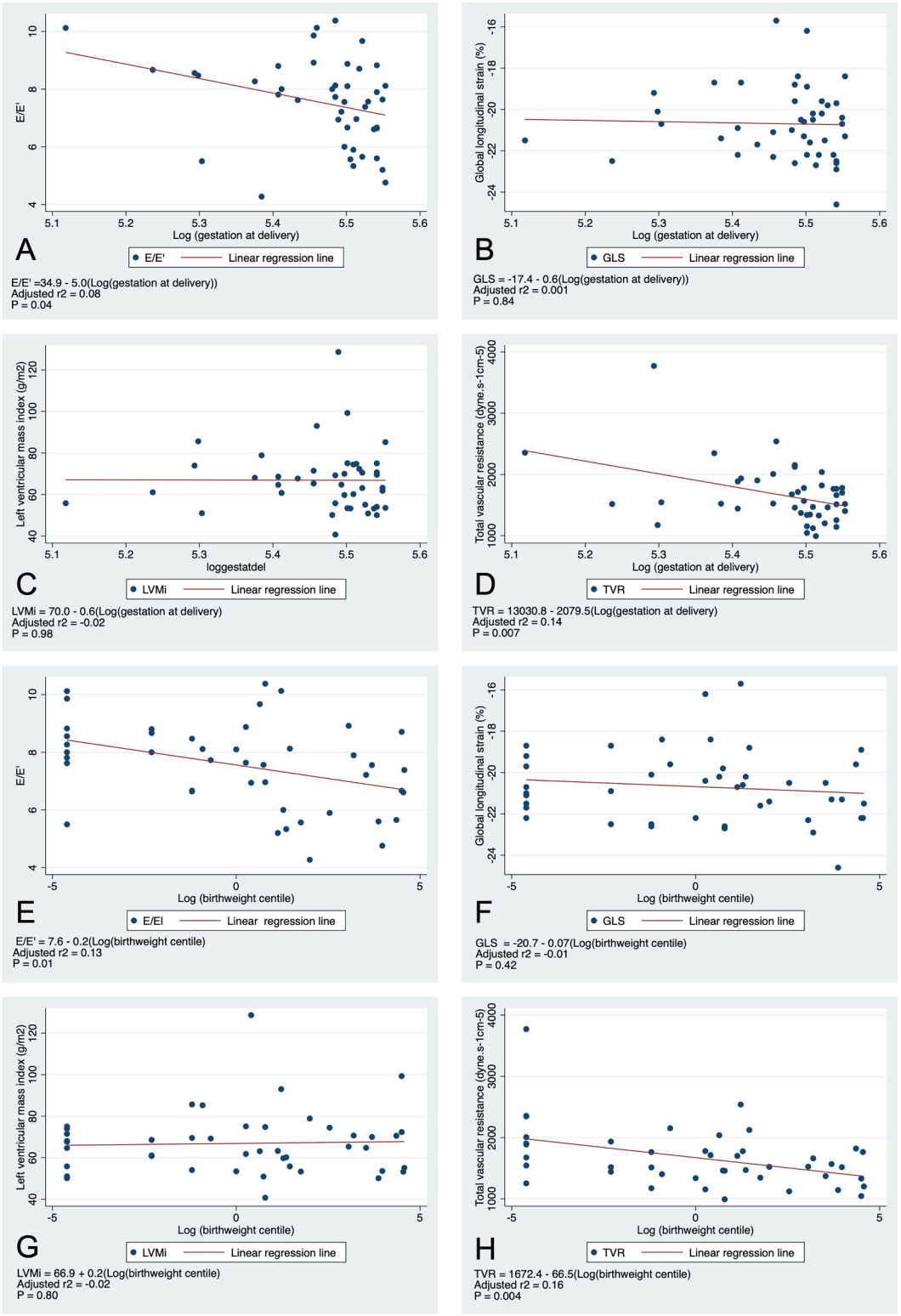

Fig. 5. Relationship between gestation at delivery / birthweight centile and cardiovascular function and remodelling six months postpartum. Scatter plots illustrating the relationship between gestation at delivery and A. E/E'; B. global longitudinal strain; C. left ventricular mass index; D. total vascular resistance; and birthweight centile and E. E/E'; F. global longitudinal strain; G. left ventricular mass index; H. total vascular resistance. Dots represent individual women; linear regression lines were added to aid interpretation. Data are pooled from the placebo and observational arms of the study. E/E', early diastolic filling to early diastolic mitral annular velocity ratio; GLS, global longitudinal strain, LVMi, left ventricular mass index; TVR, total vascular resistance.

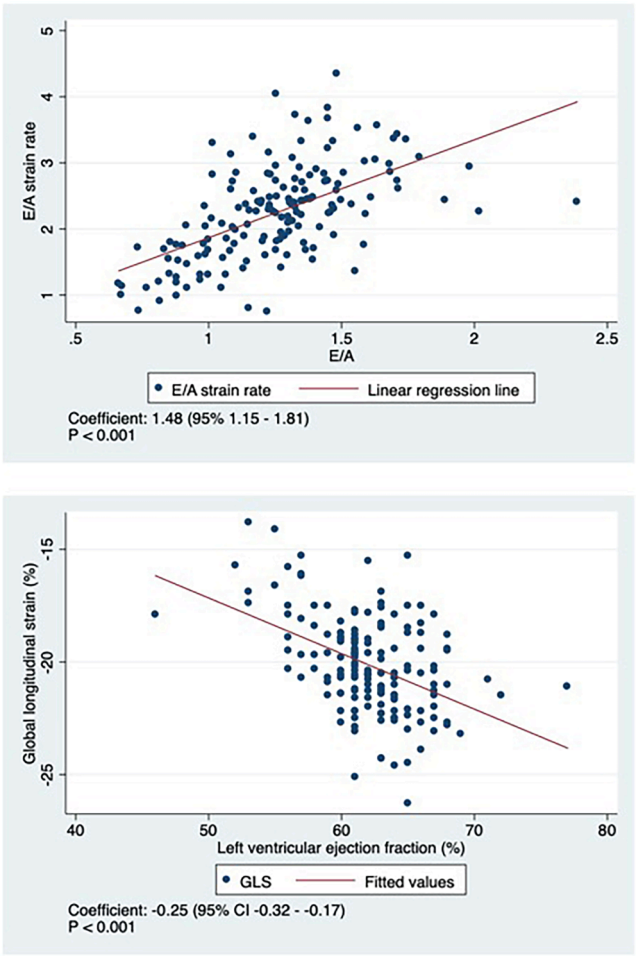

Fig. 6. Correlations of cardiac function between modalities. Scatter plot of **A.** pulse wave Doppler-derived E/A and speckle tracking-derived E/A strain rate ratio; and **B.** left ventricular ejection fraction and global longitudinal strain. E/A, early to late diastolic filling ratio; LVEF, left ventricular ejection fraction; GLS, global logintudinal strain.

study of hypertensive disorders of pregnancy, third trimester sFlt levels independently correlated with GLS. This correlation persisted after adjusting for age and other medical confounders [49], demonstrating a plausible aetiological role of sFlt in pre-eclampsia-related cardiovascular dysfunction. Previous studies have reported an inverse relationship between sFlt levels and both gestation at delivery and birthweight centile [50,51]. Both of these pregnancy outcomes were associated with worse diastolic dysfunction in our cohort, supporting a potential role of sFlt in the development of cardiovascular dysfunction. However, in our cohort an association between baseline postnatal sFlt and six-month cardiovascular parameters was not demonstrated. This could represent divergent mechanistic pathways in different subclasses of pre-eclampsia, absence of causality or limitations of our data (due to variable postnatal timing and insufficient sample size).

The absence of relationship between baseline HScTnT/NTproBNP and six-month cardiovascular parameters suggests that early postnatal cardiovascular biomarkers are unlikely to be effective in identifying women at particular risk of persistent cardiovascular morbidity. In order to relate our findings to long-term cardiovascular function, participants have been invited to be followed up two to five years postpartum. However, given the moderate overall sample size (n = 99, including the enalapril, placebo and observational arms), correlation of early postnatal cardiovascular dysfunction with long-term cardiovascular events will not be possible with this cohort alone. Our findings justify larger prospective cohort and/or intervention studies to investigate the significance and define the mechanisms of postnatal cardiovascular dysfunction following preterm pre-eclampsia.

This study clearly demonstrates that women with preterm pre-eclampsia will benefit from appropriate counselling, lifestyle changes and therapeutic interventions to improve cardiovascular function, remodelling and long-term risk. The intention for future pregnancy needs to be considered in the design of future interventions. Cardioprotective therapies need to either be safe in pregnancy or have short-term efficacy, to allow conception following treatment cessation. The interventional arm of PICk-UP [21] demonstrated an improvement in diastolic function and remodelling with six months' treatment with enalapril compared with placebo. Further work is needed to determine whether six months' treatment is sufficient to confer long-term reduction in cardiovascular risk.

5. Conclusion

Preterm pre-eclampsia is associated with persistent diastolic dysfunction, left ventricular remodelling and hypertension at six months postpartum. These have significant implications to long-term cardiovascular health. The graded severity of diastolic dysfunction with worsening prematurity and FGR suggests a dose–effect. However, the mechanism linking pre-eclampsia and cardiovascular dysfunction remains uncertain and requires further investigation.

6. Contribution to authorship

LO carried out the study, with assistance from HG and SH, supervised by JM. All authors were responsible for writing / reviewing the paper. LO was responsible for data analysis, supervised by SR.

7. Details of ethics approval

Study approvals were received from the local Research Ethics Committee (18/NW/0253), Health Research Authority and Medicines and Healthcare products Regulatory Agency.

Funding

This study was funded by the MRC (MR/R001693/1). Roche Diagnostics Limited kindly donated Elecsys® sFlt-1 and PlGF test kits (for use on a cobas e 601 instrument); however they had no involvement in the design and conduct of the trial or analysis and interpretation of trial results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to acknowledge the following contributions: the MRC (MR/R001693/1) for funding this research, the research midwives and assistants (Clare Waters, Christine Hughes and Jess Morecroft), clinical research fellows (Lynne Warrander and Alice Dempsey), Raianne Wallworth who processed blood samples, Pankaj Gupta and Prashanth Patel from the University Hospitals of Leicester Pathology Services, who carried out the urinary HP LC-MS/MS; Gillian Tranter from Trafford General Hospital who measured sFlt:PlGF levels; protocol reviewers (Lucy Chappell, Basky Thilaganathan and Paul Leeson); the Manchester University NHS Foundation Trust Sponsor, and the independent Trial Steering Committee (Bernadette Brennan, Lynne Webster, Fergus McCarthy, Jamie Kitt, Rose McGarty and Stephen Roberts).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2022.08.007.

References

[1] S. Hernández-Díaz, S. Toh, S. Cnattingius, Risk of pre-eclampsia in first and subsequent pregnancies: Prospective cohort study, BMJ 339 (7711) (2009) 34, https://doi.org/10.1136/bmj.b2255.

[2] Knight M, Nair M, Tuffnell D, ShakespeareJ, Kenyon S KJ (Eds.)onbehalfo. M-U. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. *Oxford Natl Perinat Epidemiol Unit, Univ Oxford 2017*.

[3] C.S. Evans, L. Gooch, D. Flotta, D. Lykins, R.W. Powers, D. Landsittel, J.M. Roberts, S.G. Shroff, Cardiovascular system during the postpartum state in women with a history of preeclampsia, Hypertension 58 (1) (2011) 57–62.

[4] K. Melchiorre, G.R. Sutherland, M. Liberati, B. Thilaganathan, Preeclampsia is associated with persistent postpartum cardiovascular impairment, Hypertension 58 (4) (2011) 709–715, https://doi.org/10.1161/HYPERTENSIONAHA.111.176537.

[5] P. Soma-Pillay, M.C. Louw, A.O. Adeyemo, J. Makin, R.C. Pattinson, Cardiac diastolic function after recovery from pre-eclampsia, Cardiovasc J. Afr. 29 (1) (2018) 26–31.

[6] S. Vaddamani, A. Keepanasseril, A.A. Pillai, B. Kumar, Maternal cardiovascular dysfunction in women with early onset preeclampsia and late onset preeclampsia: A cross-sectional study, Pregnancy Hypertens. 10 (2017) 247–250, https://doi.org/10.1016/j.preghy.2017.10.010.

[7] L.J. Leon, F.P. McCarthy, K. Direk, A. Gonzalez-Izquierdo, D. Prieto-Merino, J. P. Casas, L. Chappell, Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: A CALIBER study, Circulation 140 (13) (2019) 1050–1060.

[8] L. Bellamy, J.P. Casas, A.D. Hingorani, D.J. Williams, Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis, Br. Med. J. 335 (7627) (2007) 974–977, https://doi.org/10.1136/bmj.39335.385301.BE.

[9] R. Wu, T. Wang, R. Gu, D. Xing, C. Ye, Y. Chen, X. Liu, L. Chen, Hypertensive disorders of pregnancy and risk of cardiovascular disease-related morbidity and mortality: A systematic review and meta-analysis, Cardiology. 145 (10) (2020) 633–647.

[10] S.D. McDonald, A. Malinowski, Q. Zhou, S. Yusuf, P.J. Devereaux, Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses, Am. Heart J. 156 (5) (2008) 918–930, https://doi.org/10.1016/j.ahj.2008.06.042.

[11] H.U. Irgens, L. Reisæter, L.M. Irgens, R.T. Lie, Long term mortality of mothers and fathers after pre-eclampsia: Population based cohort study, Br. Med. J. 323 (7323) (2001) 1213–1217, https://doi.org/10.1136/bmj.323.7323.1213.

[12] S.M. Grandi, K.B. Filion, S. Yoon, H.T. Ayele, C.M. Doyle, J.A. Hutcheon, G. N. Smith, G.C. Gore, J.G. Ray, K. Nerenberg, R.W. Platt, Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis, Circulation 139 (8) (2019) 1069–1079.

[13] N. Auger, W.D. Fraser, M. Schnitzer, L. Leduc, J. Healy-Profitós, G. Paradis, Recurrent pre-eclampsia and subsequent cardiovascular risk, Heart 103 (3) (2017) 235–243, https://doi.org/10.1136/heartjnl-2016-309671.

[14] H.K.R. Riise, G. Sulo, G.S. Tell, J. Igland, O. Nygård, S.E. Vollset, A.-C. Iversen, R. Austgulen, A.K. Daltveit, Incident coronary heart disease after Preeclampsia: Role of reduced fetal growth, preterm delivery, and parity, J. Am. Heart Assoc. 6 (3) (2017), e004158, https://doi.org/10.1161/JAHA.116.004158.

[15] C. Arnott, M. Nelson, M. Alfaro Ramirez, J. Hyett, M. Gale, A. Henry, D. S. Celermajer, L. Taylor, M. Woodward, Maternal cardiovascular risk after hypertensive disorder of pregnancy, Heart 106 (24) (2020) 1927–1933.

[16] A.K. Wikström, B. Haglund, M. Olovsson, S.N. Lindeberg, The risk of maternal ischaemic heart disease after gestational hypertensive disease, BJOG An. Int. J. Obstet. Gynaecol. 112 (11) (2005) 1486–1491, https://doi.org/10.1111/j.1471-0528.2005.00733.x.

[17] G.C.S. Smith, J.P. Pell, D. Walsh, Pregnancy complications and maternal risk of ischaemic heart disease: A retrospective cohort study of 129 290 births, Lancet 357 (9273) (2001) 2002–2006, https://doi.org/10.1016/S0140-6736(00)05112-6.

[18] J.A. Lykke, J. Langhoff-Roos, B.M. Sibai, E.F. Funai, E.W. Triche, M.J. Paidas, Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother, Hypertension 53 (6) (2009) 944–951, https://doi.org/10.1161/HYPERTENSIONAHA.109.130765.

[19] J.A. Lykke, J. Langhoff-Roos, C.J. Lockwood, E.W. Triche, M.J. Paidas, Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery, Paediatr. Perinat. Epidemiol. 24 (4) (2010) 323–330, https://doi.org/10.1111/j.1365-3016.2010.01120.x.

[20] D.L. Rolnik, D. Wright, L.C.Y. Poon, A. Syngelaki, N. O'Gorman, C. de Paco Matallana, R. Akolekar, S. Cicero, D. Janga, M. Singh, F.S. Molina, N. Persico, J. C. Jani, W. Plasencia, G. Papaioannou, K. Tenenbaum-Gavish, K.H. Nicolaides, ASPRE trial: performance of screening for preterm pre-eclampsia, Ultrasound Obstet. Gynecol. 50 (4) (2017) 492–495.

[21] L. Ormesher, S. Higson, M. Luckie, S.A. Roberts, H. Glossop, A. Trafford, E. Cottrell, E.D. Johnstone, J.E. Myers, Postnatal enalapril to improve cardiovascular function following preterm preeclampsia (PICk-UP): A randomized double-blind placebo-controlled feasibility trial, Hypertension 76 (6) (2020) 1828–1837.

[22] M.A. Brown, L.A. Magee, L.C. Kenny, et al., The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice, Pregnancy Hypertens. 13 (2018) 291–310, https://doi.org/10.1016/j.preghy.2018.05.004.

[23] PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio) | Diagnostic guidance | NICE. 2016.

[24] A. Harkness, L. Ring, D.X. Augustine, D. Oxborough, S. Robinson, V. Sharma, Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography, Echo Res. Pract. 7 (1) (2020) G1–G18, https://doi.org/10.1530/ERP-19-0050.

[25] H. Yang, L. Wright, T. Negishi, K. Negishi, J. Liu, T.H. Marwick, Research to practice: assessment of left ventricular global longitudinal strain for surveillance of cancer chemotherapeutic-related cardiac dysfunction, JACC Cardiovasc Imaging. 11 (8) (2018) 1196–1201, https://doi.org/10.1016/j.jcmg.2018.07.005.

[26] T. Matthew, R. Steeds, R. Jones, et al., A guideline protocol for the echocardiographic assessment of diastolic function – A protocol of the british society of echocardiography, Echo Res. Pract. (2013) 5–6.

[27] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.-U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015) 1–39.e14.

[28] E. Timokhina, T. Kuzmina, A. Strizhakov, E. Pitskhelauri, I. Ignatko, V. Belousova, Maternal cardiac function after normal delivery, preeclampsia, and eclampsia: A prospective study, J. Pregnancy. 2019 (2019) 9795765, https://doi.org/10.1155/2019/9795765.

[29] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, et al., Recommendations for the evaluation of leftventricular diastolic function by echocardiography: an update from the american society ofechocardiography and the european associationof cardiovascular imaging, J. Am. Soc. Echocardiogr. 29 (2016) 277–314.

[30] Hypertension in adults: diagnosis and management [NG136] | Guidance and guidelines | NICE. *2019*.

[31] Hypertension in pregnancy: diagnosis and management [NG133] | Guidance and guidelines | NICE. 2019.

[32] National Institute for Health and Clinical Excellenc, Hypertension in pregnancy: diagnosis and management. 2011 (August 2010).

[33] M. Sanghavi, J.D. Rutherford, Cardiovascular physiology of pregnancy, Circulation 130 (12) (2014) 1003–1008, https://doi.org/10.1161/CIRCULATIONAHA.114.009029.

[34] O. Savu, R. Jurcuţ, S. Giuşcă, T. van Mieghem, I. Gussi, B.A. Popescu, C. Ginghină, F. Rademakers, J. Deprest, J.-U. Voigt, Morphological and functional adaptation of the maternal heart during pregnancy, Circ. Cardiovasc Imaging. 5 (3) (2012) 289–297.

[35] S.C. Robson, W. Dunlop, S. Hunter, Haemodynamic changes during the early puerperium, Br. Med. J. (Clin. Res. Ed). 294 (6579) (1987) 1065, https://doi.org/10.1136/bmj.294.6579.1065.

[36] L. Saleh, A.H. van den Meiracker, R. Geensen, A. Kaya, J.E. Roeters van Lennep, J. J. Duvekot, K. Verdonk, E.A.P. Steegers, H. Russcher, A.H.J. Danser, W. Visser, Soluble fms-like tyrosine kinase-1 and placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia, Ultrasound Obstet. Gynecol. 51 (6) (2018) 751–757.

[37] F.P. McCarthy, J. O'Driscoll, P. Seed, A. Brockbank, A. Cox, C. Gill, M. Green, M. Marber, L. Poston, A. Placzek, A. Shennan, J. Sparkes, P. Leeson, B. Thilaganathan, L.C. Chappell, Planned delivery to improve postpartum cardiac function in women with preterm pre-eclampsia: the PHOEBE mechanisms of action study within the PHOENIX RCT, Effic. Mech. Eval. 8 (12) (2021) 1–28.

[38] R. Ladeiras-Lopes, M. Araújo, F. Sampaio, A. Leite-Moreira, R. Fontes-Carvalho, The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis, Rev. Port Cardiol. (English Ed. 38 (11) (2019) 789–804, https://doi.org/10.1016/j.repce.2019.03.012.

[39] D. Modin, S.R. Biering-Sørensen, R. Mogelvang, N. Landler, J.S. Jensen, T. Biering-Sørensen, Prognostic value of echocardiography in hypertensive versus nonhypertensive participants from the general population, Hypertension 71 (4) (2018) 742–751, https://doi.org/10.1161/HYPERTENSIONAHA.117.10674.

[40] J. Medina-Lezama, O. Narvaez-Guerra, K. Herrera-Enriquez, O.L. Morey-Vargas, J. F. Bolaños-Salazar, J.P. Abugattas, H. Zea-Diaz, J.L. Chirinos-Revilla, J. G. Fernandez-Sivincha, V. Delgado-Lazo, D.A. Chirinos, R.R. Townsend, J. A. Chirinos, Hemodynamic patterns identified by impedance cardiography predict mortality in the general population: The PREVENCION study, J. Am. Heart Assoc. 7 (18) (2018), https://doi.org/10.1161/JAHA.118.009259.

[41] F.A. Flachskampf, Raised diastolic pressure as an early predictor of left ventricular remodeling after infarction: should echocardiography or natriuretic peptides be used for assessment? Rev. Española Cardiol. (English Ed. 63 (9) (2010) 1009–1012, https://doi.org/10.1016/s1885-5857(10)70202-4.

[42] J. López Haldón, M.F. Quero, F. Mancha, et al., Value of NT-ProBNP level and echocardiographic parameters in st-segment elevation myocardial infarction treated by primary angioplasty: Relationships between these variables and their usefulness as predictors of ventricular remodeling, Rev. Esp. Cardiol. 63 (9) (2010) 1019–1027, https://doi.org/10.1016/S0300-8932(10)70223-2.

[43] S.D. Pierdomenico, M. Di Nicola, A.M. Pierdomenico, D. Lapenna, F. Cuccurullo, Cardiovascular risk in subjects with left ventricular concentric remodeling at

baseline examination: A meta-analysis, J. Hum. Hypertens. 25 (10) (2011) 585–591, https://doi.org/10.1038/jhh.2011.24.

[44] S. Kenchaiah, M.A. Pfeffer, Cardiac remodeling in systemic hypertension, Med. Clin. North Am. 88 (1) (2004) 115–130, https://doi.org/10.1016/S0025-7125(03)00168-8.

[45] J.D. Stanaway, A. Afshin, E. Gakidou, S.S. Lim, D. Abate, K.H. Abate, C. Abbafati, N. Abbasi, H. Abbastabar, F. Abd-Allah, J. Abdela, A. Abdelalim, I. Abdollahpour, R.S. Abdulkader, M. Abebe, Z. Abebe, S.F. Abera, O.Z. Abil, H.N. Abraha, A. R. Abrham, L.J. Abu-Raddad, N.ME. Abu-Rmeileh, M.M.K. Accrombessi, D. Acharya, P. Acharya, A.A. Adamu, A.A. Adane, O.M. Adebayo, R.A. Adedoyin, V. Adekanmbi, Z. Ademi, O.O. Adetokunboh, M.G. Adib, A. Admasie, J.C. Adsuar, K.A. Afanvi, M. Afarideh, G. Agarwal, A. Aggarwal, S.A. Aghayan, A. Agrawal, S. Agrawal, A. Ahmadi, M. Ahmadi, H. Ahmadieh, M.B. Ahmed, A.N. Aichour, I. Aichour, M.T.E. Aichour, M.E. Akbari, T. Akinyemiju, N. Akseer, Z. Al-Aly, A. Al-Eyadhy, H.M. Al-Mekhlafi, F. Alahdab, K. Alam, S. Alam, T. Alam, A. Alashi, S. M. Alavian, K.A. Alene, K. Ali, S.M. Ali, M. Alijanzadeh, R. Alizadeh-Navaei, S. M. Aljunid, A. Alkerwi, F. Alla, U. Alsharif, K. Altirkawi, N. Alvis-Guzman, A. T. Amare, W. Ammar, N.H. Anber, J.A. Anderson, C.L. Andrei, S. Androudi, M. D. Animut, M. Anjomshoa, M.G. Ansha, J.M. Antó, C.A.T. Antonio, P. Anwari, L. T. Appiah, S.C.Y. Appiah, J. Arabloo, O. Aremu, J. Ärnlöv, A.l. Artaman, K. K. Aryal, H. Asayesh, Z. Ataro, M. Ausloos, E.F.G.A. Avokpaho, A. Awasthi, B. P. Ayala Quintanilla, R. Ayer, T.B. Ayuk, P.S. Azzopardi, A. Babazadeh, H. Badali, A. Badawi, K. Balakrishnan, A.G. Bali, K. Ball, S.H. Ballew, M. Banach, J.A. M. Banoub, A. Barac, S.L. Barker-Collo, T.W. Bärnighausen, L.H. Barrero, S. Basu, B.T. Baune, S. Bazargan-Hejazi, N. Bedi, E. Beghi, M. Behzadifar, M. Behzadifar, Y. Béjot, B.B. Bekele, E.T. Bekru, E. Belay, Y.A. Belay, M.L. Bell, A.K. Bello, D. A. Bennett, I.M. Bensenor, G. Bergeron, A. Berhane, E. Bernabe, R.S. Bernstein, M. Beuran, T. Beyranvand, N. Bhala, A. Bhalla, S. Bhattarai, Z.A. Bhutta, B. Biadgo, A. Bijani, B. Bikbov, V. Bilano, N. Bililign, M.S. Bin Sayeed, D. Bisanzio, T. Biswas, T. Bjørge, B.F. Blacker, A. Bleyer, R. Borschmann, I.R. Bou-Orm, S. Boufous, R. Bourne, O.J. Brady, M. Brauer, A. Brazinova, N.J.K. Breitborde, H. Brenner, A. N. Briko, G. Britton, T. Brugha, R. Buchbinder, R.T. Burnett, R. Busse, Z.A. Butt, L. E. Cahill, L. Cahuana-Hurtado, I.R. Campos-Nonato, R. Cárdenas, G. Carreras, J. J. Carrero, F. Carvalho, C.A. Castañeda-Orjuela, J. Castillo Rivas, F. Castro, F. Catalá-López, K. Causey, K.M. Cercy, E. Cerin, Y. Chaiah, H.-Y. Chang, J.-C. Chang, K.-L. Chang, F.J. Charlson, A. Chattopadhyay, V.K. Chattu, M.L. Chee, C.-Y. Cheng, A. Chew, P.-C. Chiang, O. Chimed-Ochir, K.L. Chin, A. Chitheer, J.-Y. Choi, R. Chowdhury, H. Christensen, D.J. Christopher, S.-C. Chung, F. M. Cicuttini, M. Cirillo, A.J. Cohen, D. Collado-Mateo, C. Cooper, O.R. Cooper, J. Coresh, L. Cornaby, P.A. Cortesi, M. Cortinovis, M. Costa, E. Cousin, M.H. Criqui, E.A. Cromwell, D.K. Cundiff, A.K. Daba, B.A. Dachew, A.F. Dadi, A.A. M. Damasceno, L. Dandona, R. Dandona, S.C. Darby, P.I. Dargan, A. Daryani, R. Das Gupta, J. Das Neves, T.T. Dasa, A.P. Dash, D.V. Davitoiu, K. Davletov, V. De la Cruz-Góngora, F.P. De La Hoz, D. De Leo, J.-W. De Neve, L. Degenhardt, S. Deiparine, R.P. Dellavalle, G.T. Demoz, E. Denova-Gutiérrez, K. Deribe, N. Dervenis, A. Deshpande, D.C. Des Jarlais, G.A. Dessie, G.A. Deveber, S. Dey, S. D. Dharmaratne, M. Dhimal, M.T. Dinberu, E.L. Ding, H.D. Diro, S. Djalalinia, H. P. Do, K. Dokova, D.T. Doku, K.E. Doyle, T.R. Driscoll, M. Dubey, E. Dubljanin, E. E. Duken, B.B. Duncan, A.R. Duraes, N. Ebert, H. Ebrahimi, S. Ebrahimpour, D. Edvardsson, A. Effiong, A.E. Eggen, C. El Bcheraoui, Z. El-Khatib, I.R. Elyazar, A. Enayati, A.Y. Endries, B. Er, H.E. Erskine, S. Eskandarieh, A. Esteghamati, K. Estep, H. Fakhim, M. Faramarzi, M. Fareed, T.A. Farid, C.S.E.s. Farinha, A. Farioli, A. Faro, M.S. Farvid, M.H. Farzaei, B. Fatima, K.A. Fay, A.A. Fazaeli, V. L. Feigin, A.B. Feigl, S.-M. Fereshtehnejad, E. Fernandes, J.C. Fernandes, G. Ferrara, A.J. Ferrari, M.L. Ferreira, I. Filip, J.D. Finger, F. Fischer, N.A. Foigt, K. J. Foreman, T. Fukumoto, N. Fullman, T. Fürst, J.M. Furtado, N.D. Futran, S. Gall, S. Gallus, A. Gamkrelidze, M. Ganji, A.L. Garcia-Basteiro, W.M. Gardner, A. K. Gebre, A.T. Gebremedhin, T.G. Gebremichael, T.F. Gelano, J.M. Geleijnse, Y.C. D. Geramo, P.W. Gething, K.E. Gezae, R. Ghadimi, K. Ghadiri, K. Ghasemi Falavarjani, M. Ghasemi-Kasman, M. Ghimire, R. Ghosh, A.G. Ghoshal, S. Giampaoli, P.S. Gill, T.K. Gill, R.F. Gillum, I.A. Ginawi, G. Giussani, E. V. Gnedovskaya, W.W. Godwin, S. Goli, H. Gómez-Dantés, P.N. Gona, S. V. Gopalani, A.C. Goulart, A. Grada, M.E. Grams, G. Grosso, H.C. Gugnani, Y. Guo, R. Gupta, R. Gupta, T. Gupta, R.A. Gutiérrez, D.S. Gutiérrez-Torres, J.A. Haagsma, T.D. Habtewold, V. Hachinski, N. Hafezi-Nejad, T.B. Hagos, T.T. Hailegiyorgis, G. B. Hailu, A. Haj-Mirzaian, A. Haj-Mirzaian, R.R. Hamadeh, S. Hamidi, A.J. Handal, G.J. Hankey, Y. Hao, H.L. Harb, S. Harikrishnan, J.M. Haro, H. Hassankhani, H. Y. Hassen, R. Havmoeller, C.N. Hawley, S.I. Hay, A. Hedayatizadeh-Omran, B. Heibati, B. Heidari, M. Heidari, D. Hendrie, A. Henok, I. Heredia-Pi, C. Herteliu, F. Heydarpour, S. Heydarpour, D.T. Hibstu, T.B. Higazi, E.H. Hilawe, H.W. Hoek, H.J. Hoffman, M.K. Hole, E. Homaie Rad, P. Hoogar, H.D. Hosgood, S.M. Hosseini, M. Hosseinzadeh, M. Hostiuc, S. Hostiuc, D.G. Hoy, M. Hsairi, T. Hsiao, G. Hu, H. Hu, J.J. Huang, M.A. Hussen, C.K. Huynh, K.M. Iburg, N. Ikeda, O.S. Ilesanmi, U. Iqbal, S.S.N. Irvani, C.M.S. Irvine, S.M.S. Islam, F. Islami, M.D. Jackson, K. H. Jacobsen, L. Jahangiry, N. Jahanmehr, S.K. Jain, M. Jakovljevic, S.L. James, S. K. Jassal, A.U. Jayatilleke, P. Jeemon, R.P. Jha, V. Jha, J.S. Ji, J.B. Jonas, J. Jonnagaddala, Z. Jorjoran Shushtari, A. Joshi, J.J. Jozwiak, M. Jürisson, Z. Kabir, A. Kahsay, R. Kalani, T. Kanchan, S. Kant, C. Kar, M. Karami, B. Karami Matin, A. Karch, C. Karema, N. Karimi, S.M. Karimi, A. Kasaeian, D.H. Kassa, G. M. Kassa, T.D. Kassa, N.J. Kassebaum, S.V. Katikireddi, A. Kaul, N. Kawakami, Z. Kazemi, A.K. Karyani, A.T. Kefale, P.N. Keiyoro, G.R. Kemp, A.P. Kengne, A. Keren, C.N. Kesavachandran, Y.S. Khader, B. Khafaei, M.A. Khafaie, A. Khajavi, N. Khalid, I.A. Khalil, G. Khan, M.S. Khan, M.A. Khan, Y.-H. Khang, M.M. Khater, M. Khazaei, H. Khazaie, A.T. Khoja, A. Khosravi, M.H. Khosravi, A.A. Kiadaliri, D. N. Kiirithio, C.-I. Kim, D. Kim, Y.-E. Kim, Y.J. Kim, R.W. Kimokoti, Y. Kinfu, A. Kisa, K. Kissimova-Skarbek, M. Kivimäki, L.D. Knibbs, A.K.S. Knudsen, S. Kochhar, Y. Kokubo, T. Kolola, J.A. Kopec, S. Kosen, P.A. Koul, A.i. Koyanagi, M. A. Kravchenko, K. Krishan, K.J. Krohn, H. Kromhout, B. Kuate Defo, B. Kucuk Bicer, G.A. Kumar, M. Kumar, I. Kuzin, H.H. Kyu, C. Lachat, D.P. Lad, S.D. Lad, A. Lafranconi, R. Lalloo, T. Lallukka, F.H. Lami, J.J. Lang, V.C. Lansingh, S. L. Larson, A. Latifi, J.V. Lazarus, P.H. Lee, J. Leigh, M. Leili, C.T. Leshargie, J. Leung, M. Levi, S. Lewycka, S. Li, Y. Li, J. Liang, X. Liang, Y.u. Liao, M.L. Liben, L.-L. Lim, S. Linn, S. Liu, R. Lodha, G. Logroscino, A.D. Lopez, S. Lorkowski, P. A. Lotufo, R. Lozano, T.C.D. Lucas, R. Lunevicius, S. Ma, E.R.K. Macarayan, Í. E. Machado, F. Madotto, H.T. Mai, M. Majdan, R. Majdzadeh, A. Majeed, R. Malekzadeh, D.C. Malta, A.A. Mamun, A.-L. Manda, H. Manguerra, M. A. Mansournia, L.G. Mantovani, J.C. Maravilla, W. Marcenes, A. Marks, R. V. Martin, S.C.O. Martins, F.R. Martins-Melo, W. März, M.B. Marzan, B. B. Massenburg, M.R. Mathur, P. Mathur, K. Matsushita, P.K. Maulik, M. Mazidi, C. McAlinden, J.J. McGrath, M. McKee, R. Mehrotra, K.M. Mehta, V. Mehta, T. Meier, F.A. Mekonnen, Y.A. Melaku, A. Melese, M. Melku, P.T.N. Memiah, Z. A. Memish, W. Mendoza, D.T. Mengistu, G.A. Mensah, G.B.M. Mensink, S. T. Mereta, A. Meretoja, T.J. Meretoja, T. Mestrovic, H.B. Mezgebe, B. Miazgowski, T. Miazgowski, A.I. Millear, T.R. Miller, M.K. Miller-Petrie, G.K. Mini, M. Miraresfin, A. Mirica, E.M. Mirrakhimov, A.T. Misganaw, H. Mitiku, B. Moazen, B. Mohajer, K. A. Mohammad, M. Mohammadi, N. Mohammadifard, M. Mohammadnia-Afrouzi, S. Mohammed, F. Mohebi, A.H. Mokdad, M. Molokhia, F. Momeniha, L. Monasta, Y. Moodley, G. Moradi, M. Moradi-Lakeh, M. Moradinazar, P. Moraga, L. Morawska, J. Morgado-Da-Costa, S.D. Morrison, M.M. Moschos, S. Mouodi, S. M. Mousavi, D. Mozaffarian, K.B. Mruts, A.A. Muche, K.F. Muchie, U.O. Mueller, O. S. Muhammed, S. Mukhopadhyay, K. Muller, K.I. Musa, G. Mustafa, A.F. Nabhan, M. Naghavi, A. Naheed, A. Nahvijou, G. Naik, N. Naik, F. Najafi, V. Nangia, J. R. Nansseu, B.R. Nascimento, B. Neal, N. Neamati, I. Negoi, R.I. Negoi, S. Neupane, C.R.J. Newton, J.W. Ngunjiri, A.Q. Nguyen, G. Nguyen, H.T. Nguyen, H.L. T. Nguyen, H.T. Nguyen, M. Nguyen, N.B. Nguyen, E. Nichols, J. Nie, D.N. A. Ningrum, Y.L. Nirayo, N. Nishi, M.R. Nixon, M. Nojomi, S. Nomura, O. F. Norheim, M. Noroozi, B.o. Norrving, J.J. Noubiap, H.R. Nouri, M. Nourollahpour Shiadeh, M.R. Nowroozi, E.O. Nsoesie, P.S. Nyasulu, C.M. Obermeyer, C.M. Odell, R. Ofori-Asenso, F.A. Ogbo, I.-H. Oh, O. Oladimeji, A.T. Olagunju, T.O. Olagunju, P.R. Olivares, H.E. Olsen, B.O. Olusanya, J.O. Olusanya, K.L. Ong, S.K. Ong, E. Oren, H.M. Orpana, A. Ortiz, E. Ota, S.S. Otstavnov, S. Øverland, M.O. Owolabi, M. P a, R. Pacella, A.P. Pakhare, A.H. Pakpour, A. Pana, S. Panda-Jonas, E.-K. Park, C.D.H. Parry, H. Parsian, S. Patel, S. Pati, S.T. Patil, A. Patle, G.C. Patton, D. Paudel, K.R. Paulson, W.C. Paz Ballesteros, N. Pearce, A. Pereira, D.M. Pereira, N. Perico, K. Pesudovs, M. Petzold, H.Q. Pham, M.R. Phillips, J.D. Pillay, M. A. Piradov, M. Pirsaheb, T. Pischon, F. Pishgar, O. Plana-Ripoll, D. Plass, S. Polinder, K.R. Polkinghorne, M.J. Postma, R. Poulton, A. Pourshams, H. Poustchi, D. Prabhakaran, S. Prakash, N. Prasad, C.A. Purcell, M.B. Purwar, M. Qorbani, A. Radfar, A. Rafay, A. Rafiei, F. Rahim, Z. Rahimi, A. Rahimi-Movaghar, V. Rahimi-Movaghar, M. Rahman, M.H.u. Rahman, M.A. Rahman, R. K. Rai, F. Rajati, S. Rajsic, S.B. Raju, U. Ram, C.L. Ranabhat, P. Ranjan, G.K. Rath, D.L. Rawaf, S. Rawaf, K.S. Reddy, C.D. Rehm, J. Rehm, R.C. Reiner, M.B. Reitsma, G. Remuzzi, A.M.N. Renzaho, S. Resnikoff, L.M. Reynales-Shigematsu, S. Rezaei, A. L.P. Ribeiro, J.A. Rivera, K.T. Roba, S. Rodríguez-Ramírez, L. Roever, Y. Román, L. Ronfani, G. Roshandel, A. Rostami, G.A. Roth, D. Rothenbacher, A. Roy, E. Rubagotti, L. Rushton, C. Sabanayagam, P.S. Sachdev, B. Saddik, E. Sadeghi, S. Saeedi Moghaddam, H. Safari, Y. Safari, R. Safari-Faramani, M. Safdarian, S. Safi, S. Safiri, R. Sagar, A. Sahebkar, M.A. Sahraian, H.S. Sajadi, N. Salam, P. Salamati, Z. Saleem, Y. Salimi, H. Salimzadeh, J.A. Salomon, D.D. Salvi, I. Salz, A.M. Samy, J. Sanabria, M.D. Sanchez-Niño, T.G. Sánchez-Pimienta, T. Sanders, Y. Sang, D.F. Santomauro, I.S. Santos, J.V. Santos, M.M. Santric Milicevic, B.P. Sao Jose, M. Sardana, A.R. Sarker, R. Sarmiento-Suárez, N. Sarrafzadegan, B. Sartorius, S. Sarvi, B. Sathian, M. Satpathy, A.R. Sawant, M. Sawhney, M. Saylan, M. Sayyah, E. Schaeffner, M.I. Schmidt, I.J.C. Schneider, B. Schöttker, A.E. Schutte, D. C. Schwebel, F. Schwendicke, J.G. Scott, S. Seedat, M. Sekerija, S.G. Sepanlou, M. L. Serre, E. Serván-Mori, S. Seyedmousavi, H. Shabaninejad, G. Shaddick, A. Shafieesabet, M. Shahbazi, A.A. Shaheen, M.A. Shaikh, T. Shamah Levy, M. Shams-Beyranvand, M. Shamsi, H. Sharafi, K. Sharafi, M. Sharif, M. Sharif-Alhoseini, H. Sharifi, J. Sharma, M. Sharma, R. Sharma, J. She, A. Sheikh, P. Shi, K. Shibuya, M.S. Shiferaw, M. Shigematsu, M.-J. Shin, R. Shiri, R. Shirkoohi, I. Shiue, F. Shokraneh, H. Shoman, M.G. Shrime, M.S. Shupler, S.i. Si, S. Siabani, A. M. Sibai, T.J. Siddiqi, I.D. Sigfusdottir, R. Sigurvinsdottir, D.A.S. Silva, J.P. Silva, D. G.A. Silveira, J.A. Singh, N.P. Singh, V. Singh, D.N. Sinha, E. Skiadaresi, V. Skirbekk, D.L. Smith, M. Smith, B.H. Sobaih, S. Sobhani, R. Somayaji, M. Soofi, R.J.D. Sorensen, J.B. Soriano, I.N. Soyiri, A. Spinelli, L.A. Sposato, C. T. Sreeramareddy, V. Srinivasan, V.I. Starodubov, N. Steckling, D.J. Stein, M. B. Stein, G. Stevanovic, L. Stockfelt, M.A. Stokes, L. Sturua, M.L. Subart, A. Sudaryanto, M.B. Sufiyan, G. Sulo, B.F. Sunguya, P.J. Sur, B.L. Sykes, C.E. I. Szoeke, R. Tabarés-Seisdedos, T. Tabuchi, S.K. Tadakamadla, K. Takahashi, N. Tandon, S.G. Tassew, M. Tavakkoli, N. Taveira, A. Tehrani-Banihashemi, T. G. Tekalign, S.W. Tekelemedhin, M.G. Tekle, H. Temesgen, M.-H. Temsah, O. Temsah, A.S. Terkawi, B. Tessema, M. Teweldemedhin, K.R. Thankappan, A. Theis, S. Thirunavukkarasu, H.J. Thomas, M.L. Thomas, N. Thomas, G. D. Thurston, B. Tilahun, T. Tillmann, Q.G. To, M. Tobollik, M. Tonelli, R. Topor-Madry, A.E. Torre, M. Tortajada-Girbés, M. Touvier, M.R. Tovani-Palone, J. A. Towbin, B.X. Tran, K.B. Tran, T.C. Truelsen, N.T. Truong, A.G. Tsadik, L. Tudor Car, E.M. Tuzcu, H.D. Tymeson, S. Tyrovolas, K.N. Ukwaja, I. Ullah, R.L. Updike, M.S. Usman, O.A. Uthman, M. Vaduganathan, A. Vaezi, P.R. Valdez, A. Van Donkelaar, E. Varavikova, S. Varughese, T.J. Vasankari, V. Venkateswaran, N. Venketasubramanian, S. Villafaina, F.S. Violante, S.K. Vladimirov, V. Vlassov, S. E. Vollset, T. Vos, K. Vosoughi, G.T. Vu, I.S. Vujcic, F.S. Wagnew, Y. Waheed, S. G. Waller, J.L. Walson, Y. Wang, Y. Wang, Y.-P. Wang, E. Weiderpass, R.

G. Weintraub, F. Weldegebreal, A. Werdecker, A.A. Werkneh, J.J. West, R. Westerman, H.A. Whiteford, J. Widecka, T. Wijeratne, A.S. Winkler, A.B. Wiyeh, C.S. Wiysonge, C.D.A. Wolfe, T.Y. Wong, S. Wu, D. Xavier, G. Xu, S. Yadgir, A. Yadollahpour, S.H. Yahyazadeh Jabbari, T. Yamada, L.L. Yan, Y. Yano, M. Yaseri, Y.J. Yasin, A. Yeshaneh, E.M. Yimer, P. Yip, E. Yisma, N. Yonemoto, S.-J. Yoon, M. Yotebieng, M.Z. Younis, M. Yousefifard, C. Yu, Z. Zaidi, S.B. Zaman, M. Zamani, L. Zavala-Arciniega, A.L. Zhang, H. Zhang, K. Zhang, M. Zhou, S.R. M. Zimsen, S. Zodpey, C.J.L. Murray, Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018) 1923–1994.

[46] M.R. Nelson, C.M. Reid, H. Krum, P. Ryan, L.M.H. Wing, J.J. McNeil, Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the Second Australian National Blood Pressure Study (ANBP2), Am. J. Hypertens. 16 (1) (2003) 39–45, https://doi.org/10.1016/S0895-7061(02)03143-6.

[47] Leavey K, Bainbridge SA, Cox BJ. Large Scale Aggregate Microarray Analysis Reveals Three Distinct Molecular Subclasses of Human Preeclampsia. Gleicher N, ed. *PLoS One*. 2015;10(2):e0116508. doi:10.1371/journal.pone.0116508.

[48] K. Leavey, S.J. Benton, D. Grynspan, J.C. Kingdom, S.A. Bainbridge, B.J. Cox, Unsupervised placental gene expression profiling identifies clinically relevant subclasses of human preeclampsia, Hypertension 68 (1) (2016) 137–147, https://doi.org/10.1161/HYPERTENSIONAHA.116.07293.

[49] S. Shahul, D. Medvedofsky, J.B. Wenger, J. Nizamuddin, S.M. Brown, S. Bajracharya, S. Salahuddin, R. Thadhani, A. Mueller, A. Tung, R.M. Lang, Z. Arany, D. Talmor, S.A. Karumanchi, S. Rana, Circulating antiangiogenic factors and myocardial dysfunction in hypertensive disorders of pregnancy, Hypertension 67 (6) (2016) 1273–1280.

[50] S. Rana, W.T. Schnettler, C. Powe, J. Wenger, S. Salahuddin, A.S. Cerdeira, S. Verlohren, F.H. Perschel, Z. Arany, K.-H. Lim, R. Thadhani, S.A. Karumanchi, Clinical characterization and outcomes of preeclampsia with normal angiogenic profile, Hypertens Pregnancy. 32 (2) (2013) 189–201.

[51] X. Bian, A. Biswas, X. Huang, K.J. Lee, T.-T. Li, H. Masuyama, A. Ohkuchi, J. S. Park, S. Saito, K.H. Tan, T. Yamamoto, A. Dietl, S. Grill, W.D.J. Verhagen-Kamerbeek, J.-Y. Shim, M. Hund, Short-term prediction of adverse outcomes using the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio in asian women with suspected preeclampsia, Hypertension 74 (1) (2019) 164–172.