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RESEARCH PROTOCOL

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Cohort profile: The PreEclampsia, Angiogenesis, Cardiac dysfunction and Hypertension (PEACH) Study

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Abstract

Background: Hypertensive disorders of pregnancy (HDP) remain a leading cause of maternal morbidity and mortality worldwide, with implications for maternal and neonatal well-being in the short term and for long-term maternal cardiovascular health. Although the mechanisms behind HDP remain incompletely understood, evidence suggests that preeclampsia in particular is a syndrome with more than one distinct subtype.

Objectives: The PEACH (PreEclampsia, Angiogenesis, Cardiac dysfunction, Hypertension) Study was established to identify new HDP subtyping systems reflecting aetiology and prognosis and to find markers of later cardiovascular disease risk associated with preeclampsia.

Population: The PEACH Study recruited pregnant women referred to two Copenhagen-area hospitals with suspected preeclampsia (mean gestational age at enrolment: 36.7 weeks) and a group of frequency-matched pregnant women planning delivery at the same hospitals and healthy when enrolled mid-pregnancy.

Design: Prospective, longitudinal pregnancy cohort.

Methods: Participants underwent repeated third-trimester blood sample collection, longitudinal cardiac function assessments using the USCOM-1A during the third trimester and at 1 year postpartum and collection of placental samples immediately after delivery. Medical information was abstracted from medical records and hospital databases.

Preliminary results: During 2016–2018, we recruited 1149 pregnant women, of whom 1101 were followed to delivery. Among 691 women enrolled with suspected preeclampsia, 310 and 172 developed preeclampsia and gestational hypertension respectively. Among 410 women with healthy pregnancies when enrolled mid-pregnancy,

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37 later developed hypertensive disorders of pregnancy. Of 1089 women still in the cohort 1 year postpartum, 578 (53.1%) participated in the follow-up assessment.

Conclusions: The PEACH Study's rich data from women with and without HDP will enable us to identify new, clinically useful HDP subtypes to aid in decision-making regarding monitoring and treatment. Continued postpartum follow-up will help us develop algorithms to identify women at risk of persistent postpartum cardiac dysfunction and later cardiovascular disease after pregnancies complicated by HDP.

KEYWORDS

cardiovascular risk, cohort study, gestational hypertension, longitudinal study, preeclampsia, prospective study

1 | INTRODUCTION

Preeclampsia is an obstetric syndrome currently defined as new-onset, persistent hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) that debuts in the second half of pregnancy, accompanied by proteinuria or other signs of organ dysfunction.[1] Preeclampsia and gestational hypertension (new-onset hypertension without additional features; together known as hypertensive disorders of pregnancy [HDP]) are common causes of maternal and foetal morbidity and mortality, especially in low- and middle-income countries.[2] Affecting up to 10% of pregnancies,[3] HDP range clinically from asymptomatic disease managed by observation to maternal multi-organ failure mid-pregnancy requiring immediate delivery of an extremely preterm, growth-restricted baby to ensure maternal survival.[4,5] For preeclampsia, the late-onset (debut ≥34 weeks' gestation) form is often perceived as less serious than the early-onset form,[4] but since approximately 80% of preeclampsia presents near term, most women with serious preeclampsia complications had late-onset preeclampsia.[5]

The aetiologies underlying HDP remain unclear, but many processes have been individually associated with their development, including an imbalance in maternal circulating angiogenic factors,[8–10] an exaggerated maternal systemic inflammatory response,[6] impaired maternal cardiac function,[7,8] and placental hypoxia due to inadequate implantation.[9] The preeclampsia syndrome in particular probably encompasses multiple aetiological entities that share signs and symptoms but have yet to be disentangled, which likely explains why current preeclampsia classification systems based predominantly on timing of onset and severity of clinical features have limited prognostic value and utility for research.

The risks to maternal health associated with HDP do not disappear after delivery. In particular, women who have had preeclampsia are at increased risk of cardiovascular disease later in life.[10,11] The underlying mechanisms are poorly understood, but studies have found evidence of substantial cardiac dysfunction in women with preeclampsia, both during pregnancy and a year after delivery.[12–14] The role maternal cardiovascular dysfunction plays in HDP development and associated postpartum outcomes is, however, still unclear.[15]

Synopsis

Study question

The PreEclampsia, Angiogenesis, Cardiac dysfunction, Hypertension (PEACH) Study was established to develop new preeclampsia subtyping systems that reflect aetiology and prognosis and to find markers of increased long-term cardiovascular disease risk in women after hypertensive disorders of pregnancy.

What's already known?

Although several pathological processes have been associated with preeclampsia, the condition's aetiology remains widely debated, likely because preeclampsia is a syndrome consisting of more than one subtype. After pregnancy, there are strong associations between a history of hypertensive disorders of pregnancy and later cardiovascular disease.

What this study adds

The PEACH Study followed 1101 pregnant women, including 337 who developed preeclampsia, through delivery; further follow-up is ongoing. Data include cardiac function measurements, blood and placental samples and detailed clinical data.

The PreEclampsia, Angiogenesis, Cardiac dysfunction and Hypertension (PEACH) Study, a prospective, longitudinal cohort study of 1101 women followed from mid-to-late pregnancy through delivery and beyond, was established to address these gaps in our knowledge. The study has two main aims: (1) to develop a new system for classifying HDP that produces aetiologically and prognostically informative subtypes, revolutionising clinical decision-making in the care of women with HDP and ensuring homogeneous patient groups for research, and (2) to identify antepartum and postpartum markers of increased cardiovascular disease risk in women after HDP.

TABLE 1 Overview of data collected by the PEACH Study

Phase	Enrolment group	Timing and frequency of collection	Data type	Description of collected data
Pregnancy	Both groups	At enrolment	Medical history and symptom recording	Medical history, medication in pregnancy, prenatal vitamins, symptoms of preeclampsia and family history of hypertensive disorders of pregnancy. Source: interview.
		Throughout pregnancy, plus relevant pre-pregnancy data	Demographics, medical history and clinical data	Maternal characteristics (e.g. pre-pregnancy BMI, smoking status, medication use, comorbidities), reproductive history (e.g. parity, pregnancy loss, previous pregnancy complications), pregnancy characteristics (e.g. all blood pressure and urine dipstick measurements, preeclampsia symptoms, indications for non-routine visits, complications). Sources: medical records and in-house databases maintained by the Departments of Obstetrics at the participating hospitals.
		Throughout pregnancy	Ultrasound data	Information on estimated due date and birth defects obtained during the two routine ultrasound scans offered to all pregnant women in Denmark in weeks 11–13 and 19–21, and information on foetal growth and Doppler indices during any additional scans to assess foetal growth. Source: in-house databases maintained by the obstetrical ultrasound clinics at the participating hospitals.
		Throughout pregnancy	Laboratory test data	Information on laboratory tests during pregnancy, including any tests run to aid in the evaluation of preeclampsia. Source: in-house databases maintained by the Departments of Clinical Biochemistry at the participating hospitals.
	Suspected preeclampsia group	At enrolment and up to three times per gestational week, in connection with blood draws already planned as a part of regular clinical monitoring	Blood samples	20 ml whole blood per blood draw: A 9 ml EDTA tube for separation of EDTA-plasma; a 3.5 ml sodium citrate tube for separation of citrate plasma; a 4 ml dry tube for separation of serum; and 2.5 ml in a PAXGene tube (PreAnalytiX Gmbh, Qiagen, Switzerland). All samples centrifuged (excepting PAXGene tubes) and stored at −80°C in the Danish National Biobank (www.danishnationalbiobank.com), Copenhagen, Denmark.
		At enrolment, in case of disease progression or decision to deliver, or biweekly if the woman's condition was stable	Cardiac function measurements	Resting hemodynamic indices including cardiac output, stroke volume, heart rate and systemic vascular resistance, measured using the UltraSound Cardiac Output Monitor 1A (USCOM-1A). Blood pressure, measured using a semi-automated device validated for use in pregnancy (Microlife-VSA). Measurements performed at least twice; in case of ≥5 mmHg between the two measurements in either diastolic or systolic blood pressure, measurements were repeated until this discrepancy was <5 mmHg. The last measurement noted.
	Healthy pregnancy group	In gestational weeks 24, 28, 32, 35–36, 37–38 and 40	Blood samples	Same samples collected as in the suspected preeclampsia group.
		In gestational weeks 28, 35–36, 37–38 and 40	Cardiac function measurements	Same procedure as in the suspected preeclampsia group.

(Continues)

TABLE 1 (Continued)

Phase	Enrolment group	Timing and frequency of collection	Data type	Description of collected data
Delivery	Both groups	Within 2 h of delivery	Placental samples	Four samples per placenta, collected using a systematic uniform random sampling approach[27] (see Figure S1) and stored in RNAlater at -80°C in the Danish National Biobank.
		Delivery + 4 h	Clinical data	Delivery details and offspring characteristics (e.g. birth weight, gestational age at birth). Source: medical records.
Postpartum	Both groups	Up to 3 months postpartum	Clinical data	Postpartum characteristics (e.g. level of care, blood pressure readings, laboratory tests, preeclampsia symptoms, complications, breast feeding, medication, surgical procedures, duration of hospital stay, and follow-up after discharge). Source: medical records.
		One year postpartum	Cardiac function measurements	Same procedure as in pregnancy.
			Clinical data	Postpartum antihypertensive medication, current medication, symptoms of heart failure, and any current (subsequent) pregnancy. Source: interview.

2 | METHODS

The PEACH Study is led by the Department of Epidemiology Research at Statens Serum Institut, Copenhagen, Denmark. The study's recruitment phase occurred in collaboration with the Departments of Obstetrics at Copenhagen University Hospitals Rigshospitalet and Hvidovre Hospital and their associated midwifery clinics. In Denmark, antenatal care is hospital-based and free of charge. In addition to first- and second-trimester ultrasound examinations, standard antenatal care for all pregnant women includes regular visits to hospital midwifery clinics.

2.1 | Eligibility and enrolment

The PEACH Study recruited pregnant women referred to the obstetrics departments of the two participating hospitals for clinical evaluation and blood tests for suspected preeclampsia due to signs or symptoms including elevated blood pressure, headache, visual disturbances, right upper quadrant abdominal pain, chest pain or dyspnoea and clinically significant oedema. Women were screened for eligibility for the study at initial presentation and were eligible to participate if they were between 18 and 45 years of age with a singleton pregnancy of at least 20 weeks' duration. As we aimed to characterise preeclampsia in women without pre-pregnancy hypertension or cardiovascular disease, exclusion criteria included pre-existing chronic hypertension, elevated blood pressure noted before 12 weeks' gestation in the absence of documented white coat hypertension and use of anti-coagulant medications (including low-dose aspirin). Women were also ineligible for inclusion if they were unable to understand spoken and written Danish or had been diagnosed with preeclampsia more than 2 weeks before recruitment, or if the evaluating physician ruled out preeclampsia without ordering blood tests. Eligible women were first approached by hospital staff; those interested in participating received study information from PEACH Study personnel and provided informed consent at the time of enrolment.

The study also recruited a group of healthy pregnant women planning delivery at the same hospitals in the same period, frequency matched to the group of women with suspected preeclampsia on age, parity, body-mass index (BMI) and hospital. These women were invited to participate in the study immediately after attending the routine second-trimester ultrasound examination in gestational weeks 19–21. We used the same inclusion and exclusion criteria and consent procedures with these women as we used for women with suspected preeclampsia.

The minimum number of participants required in each group was determined a priori based on expected differences in serum levels of the anti-angiogenic marker sFlt-1,[16] one of the few validated preeclampsia biomarkers at the time the study was conceived (2014–2015), across groups of women with and without HDP. With 700 women in the suspected preeclampsia group and 350 in the healthy pregnancy group, we expected to have 80% power to detect differences in sFlt-1 of ≥312 pg/mL in pairwise comparisons between women with severe preeclampsia, preeclampsia without severe features and gestational hypertension, and 80% power to detect differences in sFlt-1 levels ≥292 pg/mL when comparing women with HDP to those with normotensive pregnancies.

2.2 | Data collection

Table 1 summarises the different types of data collected by the PEACH Study, which include cardiac function indices, blood and

placental samples and clinical and laboratory data. We assessed cardiac function using the UltraSound Cardiac Output Monitor 1A (USCOM-1A, USCOM Ltd, Sydney, Australia). The device uses continuous-wave Doppler ultrasound to assess aortic flow, from which multiple measurements are derived. The USCOM-1A's cardiac output measurements have been validated against transthoracic echocardiography in the obstetric population with good results, especially when used for repeated assessments in the third trimester of pregnancy.[17,18] Blood pressure was measured using the semiautomatic BP monitor Microlife-VSA, a device identical to the Microlife 3AS1-2 that has been validated for use in pregnancy (see Table 1 for details).[19]

We abstracted extensive clinical data from medical records and obtained obstetric details, obstetrical ultrasound information, and the results of all laboratory tests performed on PEACH participants from in-house hospital databases. We are currently setting up the first wave of laboratory analyses (proteomics analyses) on study blood samples.

2.3 | Follow-up

The study protocol called for repeated study visits during pregnancy (Table 1). For women in the suspected preeclampsia group, we obtained blood samples during venipuncture scheduled by hospital obstetricians for clinical monitoring. Therefore, the timing and frequency of sampling for each woman depended on disease severity and hospital practice. Most women had blood samples collected at enrolment. If the obstetrician ruled out an HDP or if immediate delivery was necessary, no further blood samples were collected; otherwise, additional blood samples were obtained up to three times per week, depending on the timing of clinical follow-up. Planned cardiac function assessments in the suspected preeclampsia group occurred (1) at enrolment, (2) when an HDP was diagnosed or progressed, (3) biweekly between recruitment and delivery and (4) immediately before delivery (before the active stage of labour).

For women in the healthy pregnancy group, we collected blood samples and assessed cardiac function following four routine antenatal midwife visits in gestational weeks 28, 35, 38 and 40, with additional blood sampling in gestational weeks 24 and 32. If a participant in the healthy pregnancy group developed an HDP, she was reconsented and followed according to the protocol for the suspected preeclampsia group for the remainder of pregnancy, allowing us to obtain blood samples and cardiac function measurements more frequently than if no HDP had developed.

After delivery, we obtained placental samples from all participants within 2 h of delivery (Table 1; Figure S1). One year postpartum, all participants were invited to have their blood pressure and cardiac function re-evaluated. Follow-up of maternal blood pressure and kidney function at 5–7 years postpartum is scheduled for 2023, and we plan to assess cardiovascular health and collect blood samples from both mothers and children at 10 years postpartum.

2.4 | Comparison of PEACH Study participants and non-participants

Because potential study participants were primarily approached by hospital personnel, we do not have complete information on the number of women who declined to participate. Instead, we used data from Denmark's nationwide health registers to evaluate the degree to which study participants were representative of the women who delivered singletons at the two participating hospitals in 2016–2018. We compared variable distributions in participants and non-participants using mean differences (continuous variables) and risk ratios estimated using log-linear binomial regression (categorical variables).

2.5 | Ethics approval

The study was approved by the Scientific Ethics Committee of the Capital City Region of Denmark (approval no. H-16017257) and registered with the Danish Data Protection Agency (SSI register no. 20/04529).

3 | PRELIMINARY RESULTS

Between September 2016 and March 2018, 701 women with suspected preeclampsia and 448 healthy pregnant women were enrolled in the study (Figure 1: Flowchart of study participation). Thirty-seven women withdrew their consent before participating in a study visit and one woman was lost to follow-up during pregnancy. After chart review, 10 additional women were deemed ineligible to participate, leaving 1101 in the study cohort.

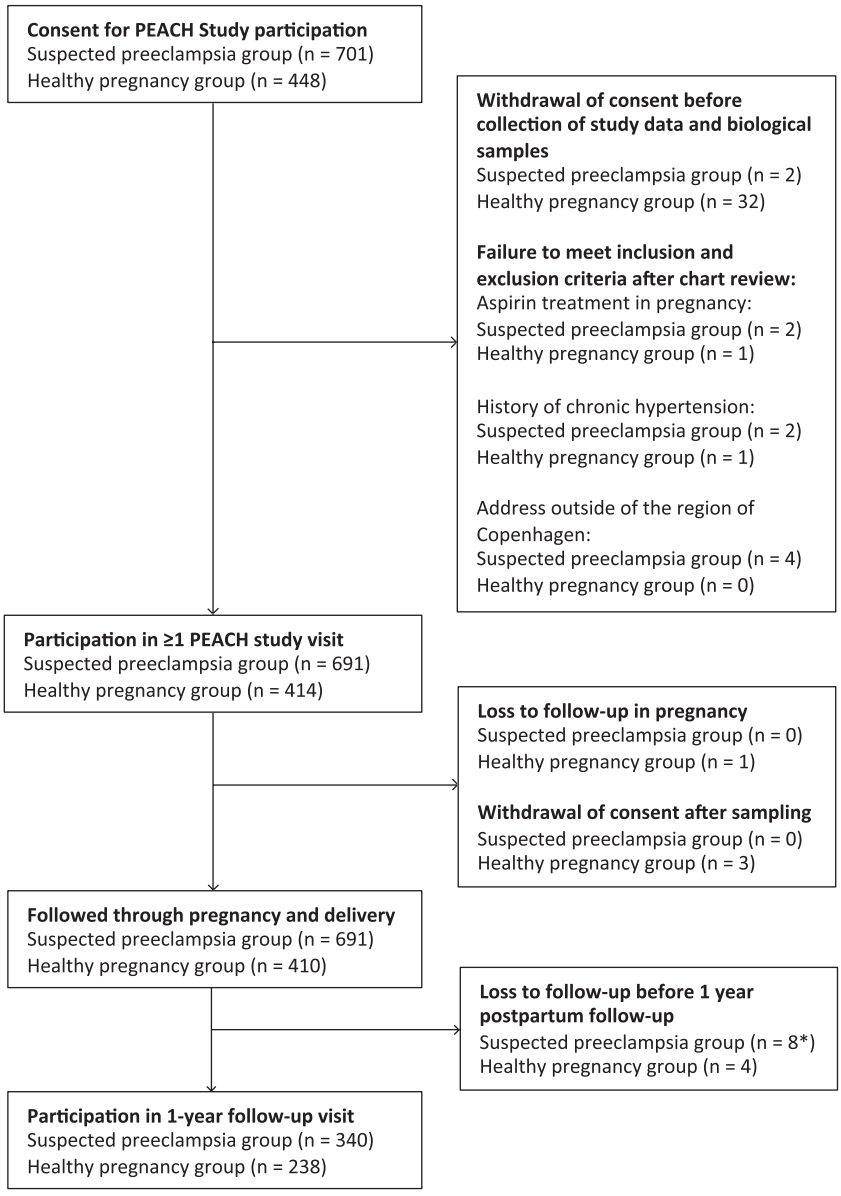
Mean gestational age at enrolment was 36.7 weeks for women in the suspected preeclampsia group and 20.3 weeks for women enrolled with healthy pregnancies. After delivery, we assigned all participants a final HDP diagnosis (if any) using the 2018 diagnostic criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[1] Of 691 participants followed for suspected preeclampsia, 310 fulfilled the criteria for preeclampsia set forth by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018; 173 of these had severe features as defined by the American College of Obstetricians and Gynecologists[20] (see Table S1). An additional 172 women fulfilled the criteria for gestational hypertension, while 209 women did not meet the ISSHP criteria for an HDP. Of the 410 women recruited mid-pregnancy with healthy pregnancies, 37 later fulfilled ISSHP HDP criteria (27 developed preeclampsia, 10 developed gestational hypertension). For women who fulfilled the ISSHP diagnostic criteria, the average time between enrolment and fulfilment of the criteria was 0.14 weeks for women enrolled in the suspected preeclampsia group and 16.9 weeks for women enrolled in the healthy pregnancy group.

Table 2 shows the numbers of samples and measurements by enrolment group and final diagnosis. As expected, women in the

healthy pregnancy group each contributed more blood samples and more cardiac function measurements than women enrolled with suspected preeclampsia. In the suspected preeclampsia group, women with preeclampsia contributed more samples than women with gestational hypertension or no HDP diagnosis, reflecting the intensity of clinical follow-up in the former.

Table S2 compares demographic, obstetric and neonatal characteristics of PEACH Study participants in the two enrolment groups. Despite frequency matching, differences were observed in the distributions of parity and pre-pregnancy BMI between the suspected preeclampsia group and the healthy pregnancy group. Table 3 compares demographic and pre-pregnancy characteristics of PEACH Study participants and non-participating women who delivered singletons at the two participating hospitals in 2016–2018, by HDP diagnosis. Participants and non-participants were generally similar in terms of age, parity, BMI, civil status and smoking status. Women with non-Danish background are underrepresented in the cohort as participants were required to speak and read Danish. Compared with non-participants, socioeconomic variable distributions differed for both participants with preeclampsia and healthy participants; participants appeared to have more education and higher household incomes. Participants with HDP were less likely to have pre-existing diabetes than non-participants, probably because women with diabetes typically receive aspirin prophylaxis, making them ineligible for the study.

Table 4 presents obstetric and neonatal characteristics for participants and non-participants. Among women with HDPs, study participants had lower rates of Caesarean section and were less likely to have long hospital admissions in connection with delivery than non-participants. Participating women with preeclampsia were less likely to deliver preterm and therefore less likely to deliver low birthweight babies. These features suggest that women with severe



*including those we did not contact due to no biological sampling during pregnancy

FIGURE 1 Flowchart of study participation

HDPs, particularly early-onset preeclampsia, are underrepresented in our cohort. Participating women with healthy pregnancies were generally similar to their non-participating counterparts, the exception being that non-HDP pregnancies ending in preterm delivery also appear to be underrepresented in our cohort.

Interestingly, women who were enrolled with suspected preeclampsia but never fulfilled the criteria for an HDP diagnosis differed from non-participants without HDPs in terms of age, BMI and method of conception (Tables 3 and 4). The former were younger (mean age difference −0.73 [95% confidence interval (CI) −1.38, −0.09] years), heavier (mean BMI difference 1.13 [95% CI 0.37, 1.90] kg/m^2) and more likely to have had assisted conceptions than non-participants without HDPs ($RR_{insemination}$ 1.83 [95% CI 1.00, 3.35]; $RR_{IVF/ICSI}$ 1.86 [95% CI 1.16, 2.96]), similar to women with confirmed HDPs. The same differences in age and BMI were observed when comparing these women to those enrolled in the healthy pregnancy group (mean age difference −1.02 [95% CI −1.80, −0.24] years; mean BMI difference 1.17 [95% CI 0.30, 2.04] kg/m^2).

One year postpartum, 12 women (eight from the suspected preeclampsia group and four from the healthy pregnancy group) were lost to follow-up. Consequently, 683 women from the suspected preeclampsia group and 406 women from the healthy pregnancy group were invited to have their blood pressure and cardiac function re-evaluated 1 year postpartum. Of these, 340 (49.8%) and 238 (58.6%), respectively, participated in these evaluations. Women from the suspected preeclampsia group who were not diagnosed with an HDP were less likely to participate in the postpartum visit than women who had preeclampsia (38.3% vs. 57.1%).

4 | COMMENT

4.1 | Principal findings

The PEACH Study is a prospective longitudinal cohort study established to study HDPs and their long-term consequences for maternal health, encompassing 691 women enrolled with suspected HDPs and 410 women without HDPs at enrolment. Information and biological samples already collected from each participating woman include blood samples and cardiac function measurements taken repeatedly through the last half of pregnancy, detailed clinical information, placental samples and postpartum follow-up measurements. These features will enable us to characterise over time biochemical and clinical changes associated with preeclampsia and define new preeclampsia subtypes that reflect underlying aetiology and predict both short- and long-term prognosis.

4.2 | Strengths of the study

Blood samples and cardiac function assessments obtained close to symptom debut in women with suspected preeclampsia will help

TABLE 2 Number of samples for each study participant by recruitment group and final hypertensive disorder of pregnancy diagnosis

	Preeclampsia[b]	Gestational hypertension[b]	Suspected pre-eclampsia group without hypertensive disorders of pregnancy	Healthy pregnancy group without hypertensive disorders of pregnancy
	n = 337	*n* = 182	*n* = 209	*n* = 373
Number of blood samples taken during pregnancy	*n* (%)	*n* (%)	*n* (%)	*n* (%)
0	19 (5.6)	31 (17.0)	48 (23.0)	<5
1	123 (36.5)	83 (45.6)	127 (60.8)	<10
2	83 (24.6)	32 (17.6)	24 (11.5)	15 (4.0)
3	56 (16.6)	20 (11.0)	<10	48 (12.9)
≥4	56 (16.6)	16 (8.8)	<5	297 (79.6)
Number of cardiac function measurements during pregnancy				
0	24 (7.1)	20 (11.0)	29 (13.9)	<5
1	149 (44.2)	87 (47.8)	130 (62.2)	<25
2	90 (26.7)	50 (27.5)	39 (18.7)	71 (19.0)
3	49 (14.5)	19 (10.4)	<15	146 (39.1)
≥4	25 (7.4)	6 (3.3)	<5	134 (35.9)
Placental samples taken after delivery	257 (76.3)	138 (75.8)	143 (68.4)	264 (70.8)
Cardiac function measurement performed 1 year postpartum[a]	190 (57.1)	94 (51.9)	79 (38.3)	215 (58.3)

[a]Out of those invited: 333 women with preeclampsia, 181 with gestational hypertension, 206 from the suspected preeclampsia group without hypertensive disorders of pregnancy and 369 women from the healthy pregnancy group without these disorders.

[b]PEACH participants were assigned a diagnosis of preeclampsia or gestational hypertension if they fulfilled the ISSHP 2018 criteria for the respective conditions (see Table S1), regardless of enrolment group

TABLE 3 Characteristics of PEACH Study participants and non-participants who delivered singletons at participating Copenhagen-area hospitals between September 2016 and June 2018 by final hypertensive disorder of pregnancy diagnosis and recruitment group

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age at delivery (years)							
<25	31 (9.2)	44 (9.0)	10 (5.5)	10 (3.7)	13 (6.2)	20 (5.4)	1172 (6.1)
25–29	101 (30.0)	144 (29.6)	60 (33.0)	75 (27.5)	75 (35.9)	104 (27.9)	5522 (28.8)
30–34	130 (38.6)	176 (36.1)	64 (35.2)	104 (38.1)	87 (41.6)	136 (36.5)	7420 (38.7)
35–39	58 (17.2)	88 (18.1)	39 (21.4)	59 (21.6)	28 (13.4)	91 (24.4)	4030 (21.0)
≥40	17 (5.0)	35 (7.2)	9 (5.0)	25 (9.2)	6 (2.9)	21 (5.6)	1011 (5.3)
Missing	0	0	0	0	0	1 (0.3)	0
Parity							
0	261 (77.5)	366 (75.2)	123 (67.6)	172 (63.0)	112 (53.6)	219 (58.7)	10 376 (54.2)
1	58 (17.2)	91 (18.7)	45 (24.7)	67 (24.5)	79 (37.8)	121 (32.4)	6365 (33.2)
≥2	18 (5.3)	29 (6.0)	14 (7.7)	34 (12.5)	18 (8.6)	32 (8.6)	2365 (12.4)
Missing	0	1 (0.2)	0	0	0	1 (0.3)	49 (0.3)
Pre-pregnancy BMI (kg/m^2)							
<18.5	11 (3.3)	10 (2.1)	7 (3.9)	7 (2.6)	15 (7.2)	14 (3.8)	959 (5.0)
18.5–24.9	160 (47.5)	232 (47.6)	78 (42.9)	122 (44.7)	122 (58.4)	268 (71.9)	12 918 (67.4)
25–29.9	83 (24.6)	112 (23.0)	49 (26.9)	74 (27.1)	46 (22.0)	60 (16.1)	3246 (17.0)
30–34.9	44 (13.1)	59 (12.1)	29 (15.9)	40 (14.7)	17 (8.1)	22 (5.9)	1035 (5.4)
≥35	39 (11.6)	54 (11.1)	19 (10.4)	24 (8.8)	9 (4.3)	7 (1.9)	441 (2.3)
Missing	0	20 (4.1)	0	6 (2.2)	0	2 (0.5)	556 (2.9)
Country of origin[e]							
Denmark	291 (86.4)	367 (75.4)	155 (85.2)	213 (78.0)	173 (82.8)	332 (89.0)	13 681 (71.4)
Other	46 (13.6)	120 (24.6)	27 (14.8)	60 (22.0)	36 (17.2)	40 (10.7)	5474 (28.6)
Missing	0	0	0	0	0	1 (0.3)	0
Highest attained level of education							
Primary school[f]	30 (8.9)	59 (12.1)	8 (4.4)	14 (5.1)	18 (8.6)	13 (3.5)	1591 (8.3)
High school or equiv.[g]	23 (6.8)	55 (11.3)	18 (9.9)	24 (8.8)	19 (9.1)	49 (13.1)	1836 (9.6)
Vocational training	74 (22.0)	78 (16.0)	39 (21.4)	48 (17.6)	35 (16.8)	45 (12.1)	2769 (14.5)
Bachelor's degree	104 (30.9)	150 (30.8)	66 (36.3)	89 (32.6)	74 (35.4)	96 (25.7)	5798 (30.3)
Graduate degree	103 (30.6)	133 (27.3)	49 (26.9)	97 (35.5)	62 (29.7)	168 (45.0)	6839 (35.7)
Missing	3 (0.9)	12 (2.5)	2 (1.2)	1 (0.4)	1 (0.5)	2 (0.5)	322 (1.7)

TABLE 3 (Continued)

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Highest household employment level[h]							
Unemployed	25 (7.4)	62 (12.7)	9 (5.0)	17 (6.3)	18 (8.6)	23 (6.2)	1926 (10.1)
Self-employed	8 (2.4)	22 (4.5)	6 (3.3)	6 (2.2)	5 (2.4)	7 (1.9)	589 (3.1)
Unskilled worker	114 (33.8)	166 (34.1)	61 (33.5)	98 (35.9)	73 (34.9)	100 (26.8)	5838 (30.5)
Skilled worker	69 (20.5)	99 (20.3)	39 (21.4)	49 (18.0)	39 (18.7)	59 (15.8)	3328 (17.4)
Manager or academic worker	116 (34.4)	133 (27.3)	64 (35.2)	97 (35.5)	69 (33.0)	179 (48.0)	7074 (36.9)
Missing	5 (1.4)	5 (1.0)	3 (1.7)	6 (2.2)	5 (2.4)	5 (1.3)	400 (2.1)
Household income[i]							
1st quartile	82 (24.3)	150 (30.8)	36 (19.8)	57 (20.9)	43 (20.6)	61 (16.4)	4989 (26.1)
2nd quartile	98 (29.1)	142 (29.2)	45 (24.7)	79 (28.9)	65 (31.1)	83 (22.3)	4686 (24.5)
3rd quartile	91 (27.0)	132 (27.1)	63 (34.6)	72 (26.4)	55 (26.3)	104 (27.9)	4691 (24.5)
4th quartile	66 (19.6)	63 (12.9)	38 (20.9)	65 (23.8)	46 (22.0)	124 (33.2)	4789 (25.0)
Missing	0	0	0	0	0	1 (0.3)	0
Marital status							
Married/cohabiting	284 (84.3)	393 (80.7)	157 (86.3)	237 (86.8)	178 (85.2)	327 (87.7)	16 015 (83.6)
Single	43 (12.7)	73 (15.0)	19 (10.4)	28 (10.3)	26 (12.4)	34 (9.1)	2395 (12.5)
Multi-family household	7 (2.1)	17 (3.5)	6 (3.3)	7 (2.6)	5 (2.4)	11 (3.0)	650 (3.4)
Missing	3 (0.9)	4 (0.8)	0	1 (0.4)	0	1 (0.3)	95 (0.5)
Smoking status during pregnancy							
Non-smoker	282 (83.7)	413 (84.8)	149 (81.9)	249 (91.2)	176 (84.2)	315 (84.5)	16 626 (86.8)
Quit during pregnancy	14 (4.2)	25 (5.1)	10 (5.5)	11 (4.0)	10 (4.8)	21 (5.6)	800 (4.2)
Smoker	15 (4.5)	20 (4.1)	7 (3.9)	6 (2.2)	13 (6.2)	14 (3.8)	785 (4.1)
Missing	26 (7.7)	29 (6.0)	16 (8.8)	7 (2.6)	10 (4.8)	23 (6.2)	944 (4.9)

(Continues)

TABLE 3 (Continued)

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Pre-pregnancy comorbidity[j]							
Diabetes	6 (1.8)	34 (7.0)	<5	24 (8.8)	<5	<5	311 (1.6)
Cardiovascular disease	5 (1.5)	17 (3.5)	6 (3.3)	10 (3.7)	<5	8 (2.1)	381 (2.0)
Thyroid disease	23 (6.8)	27 (5.5)	14 (7.7)	24 (8.8)	13 (6.2)	12 (3.2)	947 (4.9)
Renal disease	5 (1.5)	8 (1.6)	<5	<5	<5	5 (1.3)	135 (0.7)

Abbreviations: BMI, Body Mass Index; ISSHP, International Society for the Study of Hypertension in Pregnancy; ICD, International Classification of Disease.

[a]PEACH participants were assigned a diagnosis of preeclampsia or gestational hypertension if they fulfilled the ISSHP 2018 criteria for the respective conditions (see Table S1), regardless of enrolment group.

[b]Women with ICD-10 codes O14-O15 (preeclampsia) or O13 or O16 (gestational hypertension), respectively, registered in the Danish National Patient Register. Thus, participants and non-participants differ somewhat in the way their diagnoses were assigned.

[c]Women recruited with suspected preeclampsia but who never fulfilled the ISSHP 2018 criteria for a hypertensive disorder of pregnancy.

[d]Women enrolled into the healthy pregnancy group who remained free of hypertensive disorders of pregnancy as defined by the ISSHP 2018 criteria.

[e]Origin was defined as Danish if at least one parent was a Danish citizen born in Denmark. Otherwise, origin was defined as non-Danish.

[f]10 years of education.

[g]13 years of education or high school diploma.

[h]Employment status of the person in the household with the highest annual income. The unemployed group includes persons unemployed for ≥6 months/year, students, early retirees and other groups outside the labour market. Unskilled work is defined as work not requiring training or without a known degree of specialisation. Skilled work is defined as work requiring vocational training or a 3-year bachelor's degree, while managerial or academic positions require at least a 4-year bachelor's degree.

[i]1st quartile: <329 781 DKK, 2nd quartile: 329 782-472 434.89 DKK, 3rd quartile: 472 435-623 768 DKK, 4th quartile: >623 768 DKK

[j]Pre-pregnancy comorbidities were defined as registration of the following ICD-10 codes (or a corresponding ICD-8 code) in the National Patient Register before pregnancy: diabetes, E10-11 or E13-14; cardiovascular disease, I20-25, I31, I34-37, I39, I42-45, I47-49 or I50; thyroid disease, E03.4-E03.9 or E05; renal disease, N11, N13.0-13.4, 16.2-16.9, N18, N26-28 or Z90.5. Women were also considered to have diabetes if they were registered with ICD-10 codes O24.0, O24.1 or O24.3 during pregnancy.

TABLE 4 Pregnancy, delivery and neonatal characteristics for PEACH Study participants and non-participants who delivered singletons at participating Copenhagen-area hospitals between September 2016 and June 2018 by final hypertensive disorder of pregnancy diagnosis and recruitment group

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Pregnancy characteristics							
Method of conception[e]							
Spontaneous	292 (86.7)	437 (89.7)	155 (88.5)	244 (89.4)	179 (85.7)	336 (90.1)	17 566 (91.7)
Insemination	16 (4.8)	25 (5.1)	10 (5.5)	12 (4.4)	11 (5.3)	18 (4.8)	587 (3.1)
IVF or ICSI	29 (8.6)	25 (5.1)	11 (6.0)	17 (6.2)	19 (9.1)	18 (4.8)	1002 (5.2)
Missing	0	0	0	0	0	1 (0.3)	0
Gestational diabetes[f]							
Yes	13 (3.9)	37 (7.6)	9 (5.0)	11 (4.0)	5 (2.4)	<5	382 (2.0)
No	324 (96.1)	450 (92.4)	173 (95.1)	262 (96.0)	204 (97.6)	368 (98.7)	18 758 (97.9)
Missing	0	0	0	0	0	<5	15 (0.1)
Delivery characteristics							
Induction of labour[g]							
Yes	225 (70.3)	313 (68.0)	116 (67.4)	185 (72.3)	68 (36.7)	87 (25.1)	4496 (25.8)
No	95 (29.7)	147 (32.0)	56 (32.6)	71 (27.7)	117 (63.2)	258 (74.6)	12 962 (74.2)
Missing	0	0	0	0	0	1 (0.3)	0
Mode of delivery							
Vaginal, spontaneous	182 (54.0)	225 (46.2)	129 (70.9)	155 (56.8)	139 (66.5)	270 (72.4)	13 802 (72.1)
Vaginal, vacuum extraction	53 (15.7)	73 (15.0)	18 (9.9)	42 (15.4)	17 (8.1)	38 (10.2)	1546 (8.1)
Caesarean, emergency	85 (25.2)	162 (33.3)	25 (13.7)	59 (21.6)	29 (13.9)	37 (9.9)	2110 (11.0)
Caesarean, non-emergency	17 (5.0)	27 (5.5)	10 (5.5)	17 (6.2)	24 (11.5)	27 (7.2)	1697 (8.9)
Missing	0	0	0	0	0	1 (0.3)	0
Maternal admission to hospital after delivery (days)							
0–2	66 (19.6)	54 (11.1)	69 (37.9)	87 (31.9)	121 (57.9)	244 (65.4)	11 678 (61.0)
3–5	144 (42.7)	206 (42.3)	87 (47.8)	131 (48.0)	74 (35.4)	93 (24.9)	5718 (29.9)
>5	126 (37.4)	226 (46.4)	26 (14.3)	55 (20.2)	10 (4.8)	19 (5.1)	1149 (6.0)
Missing	1 (0.3)	1 (0.2)	0	0	4 (1.9)	17 (4.6)	610 (3.2)

(Continues)

TABLE 4 (Continued)

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Neonatal characteristics							
Gestational age at delivery[h] (weeks)							
<34	15 (4.5)	47 (9.7)	<5	<5	<5	0	306 (1.6)
34–36	30 (8.9)	66 (13.6)	<5	11 (4.0)	9 (4.3)	11 (3.0)	687 (3.6)
37–39	190 (56.4)	255 (52.4)	96 (52.8)	152 (55.7)	91 (43.5)	116 (31.1)	7488 (39.1)
≥40	102 (30.3)	118 (24.2)	83 (45.6)	107 (39.2)	106 (50.7)	245 (65.7)	10 623 (55.5)
Missing	0	1 (0.2)	0	<5	<5	1 (0.3)	51 (0.3)
Birthweight (g)							
<1500	10 (3.0)	30 (6.2)	0	<5	<5	0	149 (0.8)
1500–1999	13 (3.9)	27 (5.5)	0	<5	<5	0	85 (0.4)
2000–2499	27 (8.0)	40 (8.2)	0	11 (4.0)	8 (3.8)	7 (1.9)	405 (2.1)
2500–2999	86 (25.5)	89 (18.3)	14 (7.7)	45 (16.5)	26 (12.4)	39 (10.5)	2118 (11.1)
3000–3499	87 (25.8)	164 (33.7)	65 (35.7)	106 (38.8)	64 (30.6)	112 (30.0)	6522 (34.1)
3500–3999	70 (20.8)	97 (19.9)	79 (43.4)	68 (24.9)	62 (29.7)	139 (37.3)	6756 (35.3)
≥4000	42 (12.5)	36 (7.4)	24 (13.2)	38 (13.9)	40 (19.1)	72 (19.3)	2935 (15.3)
Missing	2 (0.6)	4 (0.8)	0	1 (0.4)	5 (2.4)	4 (1.1)	185 (1.0)
Birthweight for gestational age[i]							
Small for gestational age	101 (30.0)	121 (24.9)	0[j]	36 (13.2)	26 (12.4)	33 (8.9)	2047 (10.7)
Appropriate for gestational age	194 (57.6)	316 (64.9)	161 (88.5)	213 (78.0)	155 (74.2)	307 (82.3)	15 290 (79.8)
Large for gestational age	40 (11.9)	44 (9.0)	20 (11.0)	23 (8.4)	23 (11.0)	29 (7.8)	1582 (8.3)
Missing	2 (0.6)	6 (1.2)	1 (0.6)	1 (0.4)	5 (2.4)	3 (1.1)	236 (1.2)
NICU admission within <24 hours of delivery							
Yes	56 (16.6)	104 (21.4)	14 (7.7)	31 (11.4)	20 (9.6)	24 (6.4)	1169 (6.1)
No	281 (83.4)	383 (78.6)	168 (92.3)	242 (88.6)	189 (90.4)	348 (93.3)	17 986 (93.9)
Missing	0	0	0	0	0	1 (0.3)	0

TABLE 4 (Continued)

	Preeclampsia		Gestational hypertension		No hypertensive disorder of pregnancy		
	PEACH participants[a] (*N* = 337)	Non-participants[b] (*N* = 487)	PEACH participants[a] (*N* = 182)	Non-participants[b] (*N* = 273)	PEACH participants recruited with suspected preeclampsia[c] (*N* = 209)	PEACH participants recruited to healthy group[d] (*N* = 373)	Non-participants (*N* = 19 155)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Respiratory support[k]							
Yes	32 (9.5)	67 (13.8)	8 (4.4)	14 (5.1)	10 (4.8)	14 (3.8)	664 (3.5)
No	305 (90.5)	420 (86.2)	174 (95.6)	259 (94.9)	199 (95.2)	358 (96.0)	18 491 (96.5)
Missing	0	0	0	0	0	1 (0.3)	0
Stillbirth	0	0	0	0	0	0	69 (0.4)
Neonatal mortality[l]	0	6 (1.2)	0	<5	0	0	69 (0.4)

Abbreviations: ICSI, IntraCytoplasmic Sperm Injection; IVF, In Vitro Fertilisation; NICU, Neonatal Intensive Care Unit.

[a]PEACH participants were assigned a diagnosis of preeclampsia or gestational hypertension if they fulfilled the ISSHP 2018 criteria for the respective conditions (see Table S1), regardless of enrolment group.

[b]Women with ICD-10 codes O14-O15 (preeclampsia) or O13 or O16 (gestational hypertension), respectively, registered in the Danish National Patient Register. Thus, participants and non-participants differ somewhat in the way their diagnoses were assigned.

[c]Women recruited with suspected preeclampsia but who never fulfilled the ISSHP 2018 criteria for a hypertensive disorder of pregnancy.

[d]Women enrolled into the healthy pregnancy group who remained free of hypertensive disorders of pregnancy as defined by the ISSHP 2018 criteria.

[e]Information regarding method of assisted reproduction stems from the Danish In Vitro Fertilization Register.

[f]Among women without pre-gestational diabetes.

[g]Among women with intended vaginal delivery.

[h]Based on the expected date of delivery determined by first trimester ultrasound in almost all pregnancies.

[i]Small for gestational age and large for gestational age were defined as birth weight below the 10th and above the 90th centile, respectively, based on growth curves developed by Marsal et al.[28]

[j]According to the ISSHP 2018 criteria, women with gestational hypertension and foetal growth restriction are classified as having preeclampsia, such that the combination of gestational hypertension and a small for gestational age baby was not possible among participants.

[k]Ventilation, intubation, or continuous positive airway pressure (CPAP) treatment of the newborn.

[l]Death of a live-born infant before 28 completed days of life or, for preterm infants, within 28 days of the estimated due date.

us to identify clinically useful markers of impending preeclampsia and assess the importance and effects of pathological processes that may be difficult to disentangle later in disease progression.[21] Repeated follow-up during pregnancy, particularly in women with worsening disease, will permit us to pinpoint changes associated with progression to severe disease.

Because women were recruited with suspected preeclampsia, rather than with confirmed preeclampsia according to a specific definition, our data can be used in the future to examine the impact of changing diagnostic criteria and subtype classifications; furthermore, the degree of detail in our database will accommodate changes in consensus regarding outcome reporting.[22,23] Since we applied limited exclusions, our cohort included a broad range of preeclampsia subtypes, mirroring clinical reality. By retaining data and samples on women in whom preeclampsia was suspected but later ruled out, we can address the common clinical challenge of how to judge preeclampsia risk in women without classical signs of preeclampsia. Finally, continued long-term follow-up of women with well-characterised diagnoses during pregnancy, both in-person and through linkage with Danish national health registers, will provide additional insight into cardiovascular pathology after preeclampsia.

By obtaining blood samples and cardiac function measurements from the healthy pregnancy group first monthly and then biweekly near delivery, we obtained good coverage of the period during which preeclampsia becomes increasingly prevalent. Additionally, our detailed longitudinal data on such a large group of healthy pregnant women provide unique opportunities for studying variation in normal pregnancy.

Although we observed differences between the two enrolment groups in parity and BMI, frequency matching ensured that all categories of age, parity and BMI observed in the suspected preeclampsia group were also represented in the healthy pregnancy group and that both sets of hospital-determined clinical practices were well-represented in both enrolment groups. Follow-up during pregnancy occurred while the women were already visiting the hospital or midwifery clinic for antenatal care, and study blood samples from women in the suspected preeclampsia group were mostly taken in connection with blood draws ordered by their obstetricians. By making participation as easy as possible for both groups, we reduced the risk of selection bias due to differential refusal to participate and improved the likelihood that study results will be generalisable to the broader Danish population. Only one woman was lost to follow-up during pregnancy, thereby further reducing selection bias. The prospective nature of the study and the abstraction of clinical information from medical records eliminated the possibility of recall bias.

4.3 | Limitations of the data

Women with severe forms of preeclampsia, particularly early-onset forms, are underrepresented in our cohort. Early-onset preeclampsia often occurs in high-risk women, many of whom were excluded from our cohort due to pre-pregnancy chronic hypertension or aspirin therapy.[24] Furthermore, such women were often admitted on an emergency basis and we were unable to obtain consent before delivery. Our cohort is therefore best suited to the study of late-onset preeclampsia and cases of suspected preeclampsia where establishing a definite diagnosis is difficult. Because our primary interest was preeclampsia among women without previously recognised hypertension, we excluded women with pre-existing chronic hypertension or related chronic illnesses; consequently, our cohort cannot be used to study super-imposed preeclampsia, and findings based on our cohort, while internally valid, may not be generalisable to women with pre-existing hypertension.

Although our goal was repeated blood sampling during pregnancy, we have only a single set of blood samples for approximately 48% of women in the suspected preeclampsia group. More than half (57%) of the women in this group were enrolled at term; 18% were enrolled at or after their due date. For these women, there was little time for repeated sampling before delivery, particularly because induction of labour is recommended once an HDP diagnosis is confirmed in a term pregnancy.[1] Because we only collected study blood samples in connection with physician-ordered blood draws, we could not collect further samples once an obstetrician ruled out preeclampsia. Blood sample collection from our healthy participants in gestational weeks 24 and 32 required extra hospital visits and was therefore less complete than the four collections scheduled in connection with routine antenatal visits.

The PEACH Study was not designed to study the earliest stages of preeclampsia, particularly the preclinical stages. Only 39% of women were recruited on the day preeclampsia was first suspected, as most women were not immediately referred for clinical work-up. However, we do have a small, well-characterised group of women from the healthy pregnancy group who developed an HDP. Furthermore, we have applied to the biobanks at the participating hospitals to use banked first-trimester serum samples to study early-pregnancy biomarkers in PEACH Study participants.

PEACH participants and non-participants differed with respect to socioeconomic indices, with participants appearing to have somewhat more education, higher-level jobs and higher household incomes. As understanding the Danish language was a prerequisite for participation, participants are also predominantly of Danish ethnicity. Thus, findings based on the PEACH study may not be generalisable to other populations.

Half of the women enrolled in the suspected preeclampsia group and 65% of the women enrolled in the healthy pregnancy group participated in the follow-up visit 1 year postpartum. At 1 year postpartum, employment rates in Danish mothers resemble those of women without children,[25] and women who did not participate in the follow-up visit may simply have been unable to make time for this visit. All participants will be invited to participate in future rounds of follow-up, regardless of attendance at the first postpartum visit.

Cardiac function assessments were performed using the USCOM-1A system. While measurements using this device are non-invasive, fast and well-tolerated,[26] their agreement with transthoracic echocardiography is not perfect, although it is best in the third

trimester, when the majority of our measurements were made.[17] The USCOM device also has very good inter-subject reproducibility,[17] making it ideal for our repeated measurements through pregnancy and 1 year postpartum.

4.4 | Interpretation

The PEACH Study's repeated blood samples obtained during pregnancy and placental samples taken after delivery, along with repeated cardiac function assessments, will allow us to examine the interplay of multiple pathological processes associated with preeclampsia, previously investigated in isolation, in a large group of pregnant women. By combining molecular, genetic, clinical and cardiac profiles in women with and without preeclampsia, we hope to define new preeclampsia subtypes that will allow physicians to triage women presenting with suspected preeclampsia, assess likely prognosis and identify women at greatest risk of persistent postpartum cardiac dysfunction and cardiovascular disease. Continued postpartum follow-up of PEACH participants will provide additional insight into the cardiovascular, nephrological and neurological consequences of the disorder.

5 | CONCLUSION

The PEACH Study's size and prospective design provide a unique opportunity to study the interplay of biological changes associated with preeclampsia and its long-term consequences, and to classify HDPs into clinically meaningful subtypes that also address short- and long-term prognosis.

AUTHOR CONTRIBUTIONS

HAB is the principal investigator, conceiving the PEACH Study, supervising study protocol development and implementation, and obtaining funding. All authors were involved in study design. LGP, FFL and HAB obtained study permissions and ethics approval. LGP and FFL oversaw day-to-day operations and supervised study staff at Hvidovre Hospital and Rigshospitalet, Copenhagen, Denmark. LGP, FFL, MOL, ASA, KH, AT-M, KP, and JAL recruited study participants and collected biological samples. HAB supervised PhD, MPH, and BS students working on the study, with assistance from SB, JW, MM, KMS, and JAL as necessary. KMS oversaw laboratory methods and directed laboratory personnel. LGP, FFL, SB, MOL, and NMS participated in database design, data entry and data management. LGP, SB, and JW conducted the statistical analyses, and LGP wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST

Authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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