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Clinical Factors and Biomarkers During Pregnancy and Risk of Cardiovascular Disease

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IMPORTANCE Cardiovascular disease (CVD) is the leading cause of death among women worldwide. Pregnancy serves as a natural cardiovascular stress test and universal clinical encounter, yet few approaches leverage its insights to inform long-term cardiovascular risk.

OBJECTIVE To determine whether clinical measures and biomarkers obtained during pregnancy may identify women at risk of long-term CVD.

DESIGN, SETTING, AND PARTICIPANTS This was a registry-linked, population-based cohort study of all pregnancies reaching at least 22 weeks between June 2010 and October 2013 in Southern Denmark. Primary analyses were performed in a nested prospective subcohort of Odense Child Cohort participants with available pregnancy biomarker data. Women with preexisting CVD were excluded (n = 114). Follow-up was done through December 31, 2023. Among 38 455 eligible women, 2056 had biomarker data at week 12 or week 29. Analytic subsets with complete data were used for prognostic modeling at week 12 (n = 1379) and week 29 (n = 1389).

EXPOSURES Clinical characteristics, obstetric outcomes, and pregnancy biomarkers including soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor, high-sensitivity cardiac troponin I (hs-cTnI), and N-terminal pro–B-type natriuretic peptide.

MAIN OUTCOMES AND MEASURES Incident maternal CVD, evaluated using Cox proportional hazards models.

RESULTS In the biomarker cohort (median [IQR] age, 30.4 [27.4-33.8] years), 28 women (1.4%) developed CVD during a median (IQR) follow-up of 11.9 (11.2-12.5) years. Maternal age, hypertensive disorders of pregnancy (HDPs), and third-trimester concentrations of hs-cTnI and sFlt-1 were each independently associated with higher long-term CVD risk. A combined model including age and sFlt-1 measured at week 29 improved discrimination for CVD compared with a base model of age alone (ΔAUC, 0.16; 95% CI, 0.02-0.30), whereas a clinical model consisting of age, systolic blood pressure, and non–high-density lipoprotein cholesterol did not. Results were consistent in women without prior hypertension or HDPs and in nulliparous women. CVD incidence and the predictive value of the base model were comparable between the biomarker and the contemporaneous background cohorts (n = 36 274).

CONCLUSIONS AND RELEVANCE These findings support pregnancy as an opportunistic window for sex-specific cardiovascular risk assessment and prevention throughout a woman's life course. Further studies are warranted to validate these findings.

Editorial

Supplemental content

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Cardiovascular disease (CVD) is the leading cause of death among women worldwide, accounting for approximately 30% of mortality.[1] Pregnancy is a unique life stage characterized by routine health care contact and substantial cardiovascular and metabolic stress, during which adverse pregnancy outcomes can uncover long-term CV risk.[2] Within this framework, hypertensive disorders of pregnancy (HDPs) have received the most attention. Large-scale epidemiological studies consistently demonstrate that HDPs are independent predictors of premature cardiovascular events in women, conferring roughly a 2-fold increased relative risk.[3-6] Together, these observations position pregnancy and prenatal care as an opportunistic setting for sex-specific cardiovascular risk assessment.

Evidence to date suggests that the predictive utility of HDPs for future CVD in women is limited at the population level. Accordingly, adding HDP history to conventional cardiovascular risk scores confers only marginal improvements in predicting CVD in middle-aged women, likely because by midlife other risk factors have already emerged and dominate risk estimates.[7-11] On the other hand, existing CV risk models are heavily age dependent and poorly suited to identifying high risk in younger women, who may be biologically vulnerable but clinically overlooked.[11,12] Thus, whether pregnancy can serve as an opportunistic window for CVD risk estimation in young women using conventional or pregnancy-specific biomarkers has yet to be evaluated. We hypothesized that blood-based biomarkers obtained during pregnancy could improve stratification of long-term CV risk in women beyond clinical profiles.

Key Points

Question Are biomarkers measured during pregnancy independently associated with risk of long-term cardiovascular disease (CVD)?

Findings In this cohort study using a population-based registry of 38 455 pregnancies, 2056 women had biomarkers measured during pregnancy, 28 of whom developed CVD over a median follow-up of 11.9 years. Higher third-trimester concentrations of high-sensitivity troponin I and soluble fms-like tyrosine kinase-1 (sFlt-1) were independently associated with subsequent CVD; a combined model including age and sFlt-1 improved risk stratification for CVD compared with age alone, whereas a clinical model did not.

Meaning The findings suggest that pregnancy may provide an opportunistic window for sex-specific cardiovascular risk assessment.

Methods

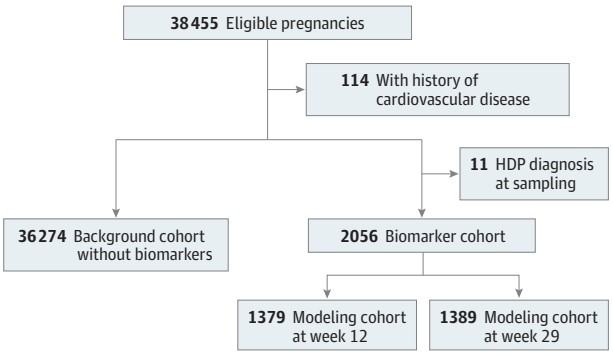
Study Design and Population

This study draws on a population-based, region-wide, longitudinal registry cohort. Primary analyses were conducted in a nested prospective sub cohort of participants from the Odense Child Cohort with pregnancy biomarker data. Eligible participants were women aged 50 years or younger on January 1, 2010, resident in the Region of Southern Denmark at any time between 2010 and 2012, and with a pregnancy reaching at least 22 weeks of gestation between June 2010 and October 2013 (**Figure 1**). The index pregnancy was defined as the first qualifying pregnancy during this period. Exclusion criteria was a history of CVD prior to the index pregnancy (n = 114).

All women were followed up with through December 31, 2023. The primary end point was incident CVD, defined as a composite of stroke (ischemic, transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage), coronary artery disease (myocardial infarction, chronic coronary syndromes, coronary revascularization without myocardial infarction), vascular disease (aortic aneurysm/dissection, peripheral artery disease), atrial fibrillation, and heart failure.

Medical history was assessed from 5 years before the index pregnancy. Obstetric history extended back to 1997, the start of the Danish Medical Birth Registry.

Figure 1. Study Population and Analytic Cohorts



Of 38 455 eligible pregnancies, women with preexisting cardiovascular disease (n = 114) or an HDP diagnosis before sampling (n = 11) were excluded. The background cohort (n = 36 274) had no biomarker or blood pressure data and served as a descriptive comparison group. The biomarker cohort comprised 2056 Odense Child Cohort participants with any biomarker measured at week 12 and/or week 29; modeling cohorts comprised those with complete clinical and biomarker data at week 12 (n = 1379) or week 29 (n = 1389). Of note, completeness at week 12 did not include lipids, NT-proBNP, or hs-cTnI (not assessed at this gestational age).

Among 38 341 eligible women without preexisting CVD, we defined nested cohorts. First, an exploratory biomarker cohort from the Odense Child Cohort included 2056 women with any biomarker measured at gestational week 12 or week 29; women with HDP diagnoses before blood sampling were excluded (n = 11). Second, modeling cohorts were derived from this biomarker cohort and comprised those with complete clinical and biomarker data at week 12 (n = 1379) or week 29 (n = 1389). Because participants could provide samples at both visits, these counts do not sum to the total. Of note, week-12 completeness did not include lipids, N-terminal pro–B-type natriuretic peptide (NT-proBNP), or high-sensitivity cardiac troponin I (hs-cTnI; not assessed at that visit). For context and external validation, women who did not participate in the Odense Child Cohort or who participated but did not donate blood formed a contemporaneous nonbiomarker comparison cohort (n = 36 274), with no overlap with the biomarker cohort.

Data Sources

Registry Data

Data were retrieved from the Danish National Patient Registry, the Danish Medical Birth Registry, and the Danish National Prescription Registry. Diagnoses were adjudicated based on the Danish adaptation of the *International Classification of Diseases, 10th revision*, the Danish version of the Nordic Medico-Statistical Committee classification of surgical procedures, and by medical procedures classified by the Health Care Classification System. Adverse pregnancy outcomes included preterm delivery, stillbirth, fetal growth restriction, and HDPs. Preterm delivery, stillbirth, and fetal growth restriction were assessed from 22 weeks' gestation or later to 14 days postpartum. HDPs, comprising gestational hypertension, preeclampsia, and eclampsia were adjudicated if diagnosed between 22 weeks of gestation or later and 12 weeks postpartum.

Odense Child Cohort

The Odense Child Cohort is a population-based cohort established in the Municipality of Odense, Denmark, enrolling pregnant women and their newborns from January 1, 2010, to December 31, 2012. Detailed aims, design, and cohort profiles have been outlined previously.[13] Briefly, recruitment was based on a confirmed pregnancy before 16 completed weeks of gestation between January 1, 2010, and December 31, 2012, with continuous residence in Odense throughout pregnancy and childbirth. Information on the index pregnancy was collected according to study protocols, and diagnoses of HDPs were retrospectively validated.[13,14] The Danish Society of Obstetrics and Gynecology's criteria (2007-2012) were applied.[14] Long-term outcomes were derived from registry data. All participants gave written informed consent, and the Odense Child Cohort received approval from the Regional Scientific Ethical Committees for Southern Denmark.

Clinical Measures and Biomarker Analyses

Venous blood samples of Odense Child Cohort participants were collected during pregnancy, centrifuged promptly, and stored in aliquots at −80 °C in the institutional biobank until analysis.[13] Gestational age at sampling was determined using routine obstetric data, based on ultrasound measurements in more than 97% of pregnancies and on last menstrual period when ultrasound data were unavailable. Median (IQR) gestational ages at blood sampling were 12.0 (10.3-14.9) and 29.0 (28.4-29.4) weeks, respectively. Detailed information on biomarker assays (NT-proBNP, hs-cTnI, soluble fms-like tyrosine kinase-1 [sFlt-1], and placental growth factor [PlGF]), blood pressure measurements, lipid profiling, and Systematic Coronary Risk Evaluation 2 (SCORE2) calculation is provided in the eMethods in Supplement 1.

Statistical Analyses

Data preparation and statistical analyses were performed using Stata version 18 (StataCorp) and R version 4.5.1 (R Foundation). Continuous variables are reported as medians with IQRs. Categorical variables are presented as counts and percentages.

Concentrations of hs-cTnI, NT-proBNP, sFlt-1, PlGF, and the sFlt-1/PlGF ratio were right-skewed and therefore natural log transformed. All predictors were subsequently standardized to *z* scores, with standardization performed separately for week 12 and week 29 using all women with available measurements at each visit. The same procedure was applied to clinical predictors at the corresponding visit, including systolic blood pressure (SBP), non–high-density lipoprotein (HDL) cholesterol, SCORE2 score, maternal age, and prepregnancy body mass index BMI. *z*-Scored variables were used in all models; therefore, hazard ratios (HRs) and 95% CIs are reported per 1-SD increase.

Association Screening (Biomarker Cohort)

Cause-specific hazards for incident CVD were estimated using Cox proportional hazards models with time since the index birth as the time scale for each predictor. Given the very low mortality (n ≤ 3), competing-risk bias was expected to be negligible. Therefore, death and emigration were treated as censoring events. Adjusted models included age, prepregnancy BMI, occurrence of HDPs in the index pregnancy, and preexisting hypertension. Covariates overlapping with the exposure were omitted from adjustment.

Prognostic Evaluation of Predictive Models (Modeling Cohorts)

Analyses were restricted to the modeling cohorts with complete clinical and biomarker data at week 12 or week 29. Based on the findings from step 1, 7 Cox models were fit: (1) age (base model); (2) age, SBP, and non-HDL cholesterol (clinical model); (3) HDPs; (4) age and HDPs; (5) hs-cTnI; (6) sFlt-1; and (7) age and sFlt-1.

At week 12, model 2 included age and SBP only, as lipids were not measured. For external validation, models 1, 3, and 4 were also fit in the background cohort.

Discrimination was evaluated using the time-dependent area under the receiver operating characteristic curve (AUC) at the median follow-up of 12 years, estimated via inverse probability of censoring weighting with a Cox censoring model. Differences in AUC (ΔAUC) relative to the base model and the clinical model were assessed using Wald contrasts, with 95% CIs derived from influence function–based standard errors.

Sensitivity analyses were performed for both steps, restricting (1) to women without preexisting hypertension or prior HDPs and (2) to nulliparous women. Given the exploratory nature of the analyses, *P* values are not reported.

Results

Baseline Characteristics and Long-Term Outcomes of the Biomarker Cohort

The biomarker cohort comprised 2056 women with a median (IQR) age of 30.4 (27.4-33.8) years and a median (IQR) prepregnancy BMI of 23.4 (21.2-26.4; calculated as weight in kilograms divided by height in meters squared) (**Table 1**). Most participants were of Danish origin (1807 [91.7%]), and 142 (7.2%) were first-generation and 22 (1.1%) second-generation immigrants. The majority were nulliparous (1276 [62.1%]). Adverse pregnancy outcomes occurred in 319 women (15.5%), including fetal growth restriction (97 [4.7%]), preterm delivery (101 [4.9%]), and stillbirth (8 [0.4%]). HDPs were observed in 193

Table 1. Baseline Characteristics and Long-Term Outcomes of the Biomarker Cohort

Characteristic	Biomarker cohort (N = 2056)
Age, median (IQR) y[a]	30.4 (27.4-33.8)
BMI, median (IQR)[a]	23.4 (21.2-26.4)
Ethnicity, No. (%)[a]	
Danish	1807 (91.7)
Immigrant, first generation	142 (7.2)
Immigrant, second generation	22 (1.1)
Education, No. (%)[a]	
None or not coded	≤5[b]
Primary	≤5[b]
Lower secondary	134 (6.5)
Upper secondary	581 (28.3)
Short cycle tertiary	128 (6.2)
Bachelor or equivalent	835 (40.6)
Master or equivalent	349 (17.0)
Doctoral or equivalent	24 (1.2)
Not elsewhere classified	0
Previous births, No. (%)[a]	
0	1276 (62.1)
1	593 (28.8)
2	166 (8.1)
≥3	21 (1.0)
Index pregnancy, No. (%)	
Multiple birth	31 (1.5)
Cesarian section	461 (22.4)
Gestational age at delivery, median (IQR), d	281 (273-287)
Adverse pregnancy outcomes, No. (%)	319 (15.5)
Fetal growth restriction	97 (4.7)
Preterm delivery	101 (4.9)
Stillbirth	8 (0.4)
Hypertensive disorders	193 (9.4)
Medication use, No. (%)	83 (4.0)
Antihypertensives	53 (2.6)
Antidiabetics	28 (1.4)
Statins	≤3[b]
Aspirin	≤3[b]
Long-term follow-up	
Follow-up, median (IQR), y	11.9 (11.2-12.5)
End of follow-up reason, No. (%)	
Emigration	≤70[b]
Death	≤3[b]
End of observation	1989 (96.7)
Cardiovascular disease, No. (%)	
Any	28 (1.4)
Myocardial infarction	0
Chronic coronary syndromes	4 (0.2)
Stroke	14 (0.7)
Aortic aneurysm/dissection	≤3[b]
Peripheral artery disease	≤3[b]
Atrial fibrillation	5 (0.2)
Heart failure	≤3[b]
Medication, No. (%)	
Any	324 (15.8)
Antihypertensives	156 (7.6)
Antidiabetics	157 (7.6)
Statins	34 (1.7)
Antiplatelets	12 (0.6)
Anticoagulation	8 (0.4)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Age, prepregnancy BMI, ethnicity, education, and number of previous births are reported as of the index pregnancy.

[b] Data obscured owing to small numbers.

(9.4%). Over a median (IQR) follow-up of 11.9 (11.2-12.5) years, 28 women (1.4%) developed incident CVD. To evaluate generalizability, we compared women in the biomarker cohort with the broader regional contemporaneous pregnancy population. Baseline characteristics of the index pregnancy and long-term clinical outcomes were largely comparable (eTable 1 in Supplement 1), though HDP prevalence (193 [9.4%] vs 1392 [3.8%]) was more frequent in women in the biomarker cohort.

Association of Clinical Characteristics and Biomarkers With Long-Term CVD

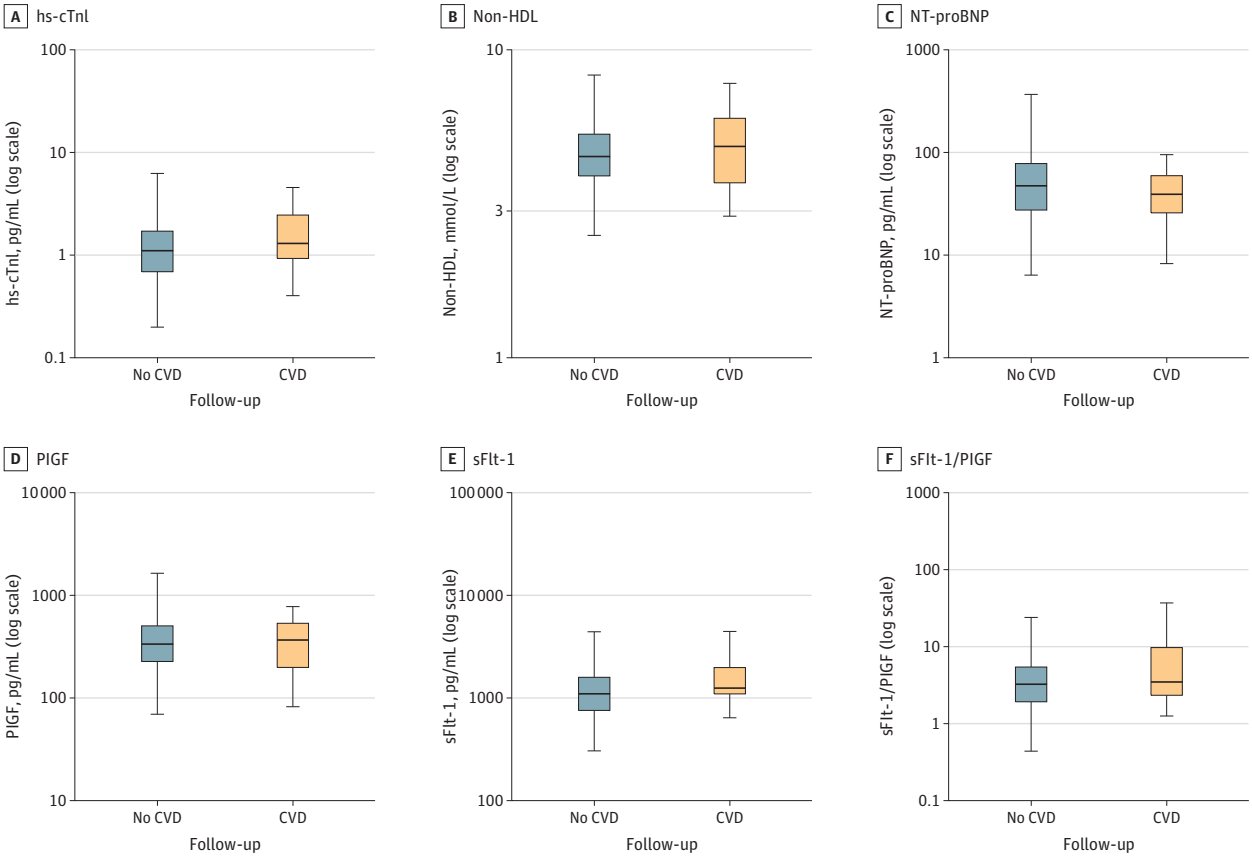
We first assessed associations between adverse pregnancy outcomes and later CVD using a Cox model in which the exposure status was updated upon the occurrence of an adverse pregnancy outcome during any subsequent pregnancy (eMethods in Supplement 1). Adverse pregnancy outcomes or HDPs were each associated with long-term CVD (eFigure 1 in Supplement 1). Adverse pregnancy outcomes were associated with a 76% higher risk of CVD (adjusted HR [aHR], 1.76; 95% CI, 1.38-2.24). For HDPs, the risk was 119% higher (aHR, 2.19; 95% CI, 1.55-3.08). No evidence of heterogeneity in these associations was observed between background and biomarker cohort.

We next examined associations of clinical characteristics and biomarkers with incident CVD in the biomarker cohort, and exposures were restricted to the index pregnancy. Distributions of biomarker concentrations at weeks 12 and 29, stratified by the occurrence of CVD during follow-up, are shown in eFigure 2 in Supplement 1 and **Figure 2**, respectively.

At week 12, neither PlGF, sFlt-1, nor the sFlt-1/PlGF ratio showed an independent association with CVD after adjustment, and SBP lost its crude association once clinical covariates were included (**Table 2**; eTable 2 in Supplement 1).

At week 29, higher concentrations of hs-cTnI and sFlt-1 were each independently associated with increased long-term CVD risk (Table 2). Each 1-SD higher hs-cTnI was associated with a 33% higher risk (aHR, 1.33; 95% CI, 1.10-1.60), and each 1-SD increase sFlt-1 with a 50% higher risk (aHR, 1.50; 95% CI, 1.03-2.18). The sFlt-1/PlGF ratio showed a crude association with incident CVD that was attenuated after adjustment

Figure 2. Distributions of Biomarkers at Week 29



Boxplots show the distribution of biomarker concentrations, stratified by the occurrence of CVD during follow-up (FU), at gestational week 29 on a logarithmic scale. Horizontal lines within boxes indicate median values, boxes represent interquartile ranges (IQR; calculated at Tukey hinges), and whiskers denote the 5th to 95th percentiles. Outliers are not shown. hs-cTnI indicates high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; HDL, high-density lipoprotein cholesterol.

(eTable 2 in Supplement 1). NT-proBNP, PlGF, and lipid measures were not associated with CVD. Among clinical factors, maternal age and HDPs in the index pregnancy remained significantly associated (aHR, 1.50; 95% CI, 1.05-2.15 and aHR, 3.20; 95% CI, 1.29-7.95, respectively), whereas prepregnancy BMI, blood pressure, and SCORE2 score were not significantly associated with incident CVD after adjustment. Sensitivity analyses restricted to women without prior hypertension or HDPs and to nulliparous women yielded similar results (eTables 3 and 4 in Supplement 1).

Integrating Clinical Measures and Biomarkers for Prognostic Modeling

Finally, we evaluated whether integrating biomarkers and clinical measures improved risk discrimination for long-term CVD beyond clinical parameters in the subset with complete data at week 29 (n = 1389) and at week 12 (n = 1379). Baseline characteristics of the week 29 modeling cohort are given in eTable 5 in Supplement 1. Within this cohort, the base model (age) yielded an AUC of 0.60 (95% CI, 0.46 to 0.73), comparable to the background cohort (AUC, 0.58; 95% CI, 0.55 to 0.61) (**Table 3**). Adding HDPs to age showed an AUC of 0.66 (95% CI, 0.53 to 0.79; ΔAUC vs age 0.07; 95% CI, −0.04 to 0.18) in the week 29 modeling cohort, whereas the improvement was evident but almost negligible in the background cohort (AUC, 0.60; 95% CI, 0.57 to 0.63; ΔAUC vs age 0.02; 95% CI, 0.01 to 0.03). Relative to age, the clinical model (age + SBP + non-HDL cholesterol) yielded an AUC of 0.67 (95% CI, 0.54 to 0.80, ΔAUC vs age 0.07; 95% CI, −0.09 to 0.23).

Among biomarker-only models, hs-cTnI showed an AUC of 0.56, (95% CI, 0.44 to 0.68; ΔAUC vs age −0.04; 95% CI, −0.18 to 0.11), while sFlt-1 yielded an AUC of 0.68 (95% CI, 0.56 to 0.80; ΔAUC vs age 0.09; 95% CI, −0.13 to 0.30). The combined model of age and sFlt-1 demonstrated an AUC of 0.75 (95% CI, 0.68 to 0.83), with ΔAUC 0.16 (95% CI, 0.02 to 0.30) compared with age alone. Compared with the clinical model, ΔAUC was 0.09 (95% CI, −0.05 to 0.22).

Results were consistent in sensitivity analyses restricted to women without prior hypertension or HDPs (ΔAUC vs age, 0.15; 95% CI, 0.00-0.30; eTable 6 in Supplement 1) and in nulliparous women (ΔAUC vs age, 0.13; 95% CI, 0.00-0.25; eTable 7 in Supplement 1).

Data from the corresponding week-12 analyses are provided in eTables 8-10 in Supplement 1. Biomarker models were

Table 2. Associations of Clinical Factors and Pregnancy Biomarkers With Long-Term Cardiovascular Disease

Exposure	Individuals, No.[a]	Events, No.[a]	HR (95% CI)[b]
Age	2050	28	1.50 (1.05-2.15)
Prepregnancy BMI	2050	28	0.63 (0.26-1.53)
HDP	2050	28	3.20 (1.29-7.95)
Week 12 measures			
Systolic BP	1393	16	1.35 (0.83-2.20)
Diastolic BP	1393	16	1.16 (0.69-1.92)
PlGF	1549	19	0.77 (0.45-1.30)
sFlt-1	1549	19	1.02 (0.64-1.62)
sFlt-1/PlGF	1549	19	1.26 (0.78-2.04)
Week 29 measures			
Systolic BP	1446	20	0.95 (0.60-1.48)
Diastolic BP	1446	20	1.00 (0.64-1.58)
Total cholesterol	1490	22	1.31 (0.87-1.98)
Non-HDL	1489	22	1.21 (0.80-1.83)
SCORE2 score[c]	1430	20	1.07 (0.74-1.53)
sFlt-1	1501	22	1.50 (1.03-2.18)
PlGF	1501	22	0.92 (0.61-1.38)
sFlt-1/PlGF	1500	22	1.30 (0.94-1.80)
hs-cTnI	1461	20	1.33 (1.10-1.60)
NT-proBNP	1454	19	0.83 (0.53-1.29)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein cholesterol; HDP, hypertensive disorder of pregnancy; HR, hazard ratio; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PlGF, placental growth factor; SCORE2, Systematic Coronary Risk Evaluation 2; sFlt-1, soluble fms-like tyrosine kinase-1; sFlt-1/PlGF, ratio of sFlt-1 to PlGF.

[a] No. and event counts reflect complete cases for each predictor-outcome model. Adjustments were done for age, BMI, preexisting hypertension, and a diagnosis of HDP in the index pregnancy.

[b] HRs and 95% CIs are shown per 1 SD.

[c] SCORE2 is a continuous risk score estimating 10-year risk of fatal and nonfatal cardiovascular disease. Values range from 0% upward, with higher scores indicating greater predicted cardiovascular risk. HRs are shown per 1-SD increase in SCORE2.

Table 3. Model Discrimination for Long-Term Cardiovascular Disease Using Clinical Factors and Third-Trimester Biomarkers

	Cohort, variable (95% CI)				
	Week 29 modeling (No. for each model = 1389; events: n = 18)			Background (No. for each model = 36 274; events: n = 476)	
Model	AUC[a]	ΔAUC vs M1[a]	ΔAUC vs M2[a]	AUC[a]	ΔAUC vs M1[a]
Age (M1)	0.60 (0.46 to 0.73)	NA	NA	0.58 (0.55 to 0.61)	NA
Age + SBP + non-HDL (M2)	0.67 (0.54 to 0.80)	0.07 (−0.09 to 0.23)	NA	NA	NA
HDP	0.59 (0.49 to 0.70)	−0.00 (−0.17 to 0.17)	−0.07 (−0.21 to 0.06)	0.53 (0.52 to 0.55)	−0.05 (−0.08 to −0.02)
Age + HDP	0.66 (0.53 to 0.79)	0.07 (−0.04 to 0.18)	−0.01 (−0.15 to 0.13)	0.60 (0.57 to 0.63)	0.02 (0.01 to 0.03)
hs-cTnI	0.56 (0.44 to 0.68)	−0.04 (−0.18 to 0.11)	−0.11 (−0.25 to 0.03)	NA	NA
sFlt-1	0.68 (0.56 to 0.80)	0.09 (−0.13 to 0.30)	0.01 (−0.16 to 0.19)	NA	NA
Age + sFlt-1	0.75 (0.68 to 0.83)	0.16 (0.02 to 0.30)	0.09 (−0.05 to 0.22)	NA	NA

Abbreviations: AUC, area under the receiver operating characteristic curve; HDL, high-density lipoprotein cholesterol; HDP, hypertensive disorder of pregnancy; hs-cTnI, high-sensitivity cardiac troponin I; NA, not applicable; SBP, systolic blood pressure; sFlt-1, soluble fms-like tyrosine kinase-1.

[a] Time-dependent AUCs for incident cardiovascular disease were estimated at the median follow-up of 12 years.

not fit at week 12 since no biomarker was associated with later CVD at that visit.

Discussion

This cohort study suggests that biomarkers measured during pregnancy can serve as early indicators of long-term maternal CV risk. Over a median 12-year follow-up, third-trimester concentrations of sFlt-1 and hs-cTnI were each independently associated with later CVD. When integrated with age, sFlt-1 improved risk stratification for future CVD beyond age alone, whereas a clinical model including age, SBP, and non-HDL cholesterol did not.

Endothelial dysfunction is a key driver of both CVD and of hypertension during pregnancy, and the endothelial marker

sFlt-1 is known to rise in women with HDPs, especially in preeclampsia. In conjunction with PlGF, sFlt-1 may rule out preeclampsia when clinically suspected.[15] An adverse association between endothelial function and sFlt-1 levels has also been observed in pregnancy not complicated by hypertension.[16] Here, we extend the relevance of third-trimester sFlt-1 levels from obstetric risk stratification to long-term CV risk assessment. Our data align with a small study (n = 64) that reported unfavorable associations of sFlt-1 with surrogate markers of CVD 12 years postpartum.[17] However, another small cohort (n = 117) reported no association of sFlt-1 with clinical CVD, likely reflecting limited statistical power.[18]

Cardiac troponins have been linked to cardiovascular mortality, heart failure, and all-cause mortality in the general population outside pregnancy.[19] However, in young pregnant women, concentrations are low and a substantial fraction of values fall below the limit of detection, even with high-sensitivity assays. In the present study, the median third-trimester hs-cTnI was 1.1 pg/mL, which closely matched levels reported in pregnant US women measured with the same assay.[20] Despite the high proportion of values below the LoD, third-trimester concentrations were independently associated with subsequent CVD when sub-limit of detection values were imputed to the limit of detection. These findings should be interpreted alongside prior observations that hs-cTnI levels can enhance preeclampsia prediction, suggesting gestational levels are associated with both short-term obstetric risk and long-term cardiovascular vulnerability.[21] However, hs-cTnI showed limited discrimination for long-term CVD in this cohort and did not add to the age-sFlt-1 model (ΔAUC, −0.02), which may reflect limited between-individual variation in hs-cTnI and potential information loss from limit of detection–based imputation. Looking ahead, ultra–high-sensitivity assays may expand the measurable range and could further enhance risk discrimination in pregnant populations.

NT-proBNP measured at week 29 was not significantly associated with CVD in our data, although an inverse association between natriuretic peptide levels and both HDPs and incident hypertension 2-7 years postpartum has been reported.[22,23] However, HDPs were associated with lower NT-proBNP 3 years postpartum in another study,[24] suggesting the HDP-heart failure association may not be captured by elevated natriuretic peptides soon after an at-risk pregnancy. Taken together, current evidence indicates that natriuretic peptides may have limited clinical utility for CVD risk stratification in this population.

Maternal age and HDPs were independently associated with long-term CV risk. The incremental improvement of HDPs over age was small in the background cohort but somewhat greater in the modeling cohort, despite a higher HDP prevalence observed in the latter. This difference likely reflects validation against clinical records in the biomarker cohort and the limited sensitivity of registry-based HDP diagnoses, adding evidence that registry-based estimates may underestimate both the prevalence and the population-attributable burden of HDPs for long-term CV risk in women.[14,25,26] However, adding HDPs to the age-sFlt-1 model did not improve its predictive capacity (ΔAUC, 0.00) in our study, suggesting that this model may already capture a substantial proportion of the CV risk information conveyed by HDP history.

A clinical model including age, SBP, and non-HDL cholesterol did not improve stratification for long-term CVD beyond age alone, whereas the age-sFlt-1 model did. Of note, adding either SBP or non-HDL cholesterol to the age–sFlt-1 model did not further improve discrimination (ΔAUC ≤ 0 for both). Although this study was not powered to detect differences between the age-sFlt-1 and the clinical model, these results suggest that sFlt-1 measured during pregnancy may improve discrimination for long-term CVD beyond the traditional clinical risk markers assessed here, which should be addressed in future studies.

Our findings prompt consideration of whether risk stratification should occur during pregnancy or whether these biomarkers exhibit similar associations outside of pregnancy. The answer likely varies by marker. Intriguingly, first-trimester sFlt-1 values were not associated with later CVD, underscoring the importance of timing. Later stages of pregnancy may better capture the cardiovascular stress relevant to long-term cardiovascular health. The observed sFlt-1 pattern is consistent with an evolving anti-angiogenic state that promotes endothelial dysfunction and microvascular injury, potentially predisposing to HDPs and unmasking latent cardiovascular risk. Future studies should clarify whether this association reflects a causal pathway or a shared predisposition to both HDPs and CVD. In contrast, hs-cTnI appears less influenced by pregnancy state: in a representative US sample, third-trimester concentrations were comparable to those in nonpregnant women, and serial changes across trimesters did not predict preeclampsia in previous studies.[20,21] Ultimately, it remains to be determined whether these biomarkers function exclusively within the physiological context of pregnancy or retain predictive value beyond it. Nevertheless, pregnancy represents a unique window to initiate CV risk assessment and prevention in women. The ability of sFlt-1 to inform both short-term obstetric outcomes as well as long-term CVD risk suggests that a single antepartum measurement could yield insights into 2 pivotal stages of women's health. However, to our extent, biomarker assessment during pregnancy should always be viewed in the context of complementing, rather than replacing, postpartum surveillance measures such as blood pressure monitoring, especially in women who experienced adverse pregnancy outcomes.

Strengths and Limitations

Strengths of this study include the unique linkage of a population-based registry with a prospective cohort study, enabling integration of validated pregnancy outcomes, biosamples, and long-term follow-up using a composite CVD end point consistent with prior studies.[4] Sensitivity analyses in women without prior hypertension or HDPs and in nulliparous women confirmed the robustness of our observations. External validation was not feasible because, to our knowledge, no other cohorts currently combine comparable pregnancy biomarker panels with long-term follow-up. Hence, although the incidence of long-term CVD and the predictive performance

of the base model were comparable in the background and week 29 modeling cohorts, the results should be interpreted as exploratory, given the evaluation of multiple biomarkers and models. Other limitations include the relatively small number of CVD events, which reduced statistical power and limited more granular end-point modeling. Data on first-trimester NT-proBNP and hs-cTnI were not available, and generalizability beyond a predominantly Northern European population remains to be established. Additionally, while clarifying the mechanistic roles of these biomarkers may uncover novel targets for early intervention, this study cannot distinguish mechanistic causality from shared predisposition to both HDPs and CVD.

Conclusions

Pregnancy represents a unique opportunity for cardiovascular risk assessment. Pending further validation, pregnancy-derived risk indicators, including circulating biomarkers and clinical profiles, could inform earlier and more targeted preventive strategies across the life course of women.

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