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ORIGINAL RESEARCH

Prediction of Pregnancy-Related Cardiovascular Outcomes Using Electrocardiogram-Based Deep Learning Estimation of Cardiorespiratory Fitness

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ABSTRACT

BACKGROUND Peak oxygen consumption (peak VO_2), the gold standard measure of cardiorespiratory fitness, may identify women at high risk for pregnancy-related cardiovascular (CV) complications, but ascertainment is not widely scalable. We previously developed and validated a deep learning model to estimate peak VO_2 from the resting 12-lead electrocardiogram (ECG).

OBJECTIVES The purpose of this study was to examine the association of deep learning ECG-predicted peak VO_2 with incident pregnancy-related CV complications.

METHODS We evaluated ECG-estimated peak VO_2 among individuals with a clinical 12-lead ECG from 1 year before pregnancy to 13 weeks of gestation in a multi-institutional electronic health record pregnancy cohort. Multivariable-adjusted mixed-effects logistic regression models examined associations between ECG-estimated peak VO_2 with pregnancy-related CV complications up to 1 year postpartum (severe hypertensive disorders of pregnancy, major adverse cardiac events, and maternal death).

RESULTS Among 3,650 pregnancies from 3,437 women (mean age at delivery 33 ± 6 years), median ECG-estimated VO_2 was 27.0 mL/kg/min (IQR: 21.9-31.2), and 723 (20%; 95% CI: 19%-21%) experienced a pregnancy-related CV complication over a median follow-up time of 1.7 years (IQR: 1.6-1.8 years). Lower ECG-estimated peak VO_2 was associated with a higher complication risk (adjusted OR: 1.09 per 1-metabolic equivalent lower fitness; 95% CI: 1.03-1.17; $P < 0.01$). Women in the lowest quartile of ECG-estimated peak VO_2 had 61% greater odds of CV complications than the highest quartile (OR: 1.61; 95% CI: 1.13-2.30; $P = 0.008$).

CONCLUSIONS Lower ECG-estimated cardiorespiratory fitness was associated with a higher risk of pregnancy-related CV complications, supporting artificial intelligence-enabled ECG analysis as a scalable tool for antepartum risk stratification of pregnancy-related CV complications. (JACC Adv. 2026;5:102764) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CPT = Current Procedural Terminology

CV = cardiovascular

CVD = cardiovascular disease

DBP = diastolic blood pressure

DM = diabetes mellitus

ECG = electrocardiogram

HDP = hypertensive disorders of pregnancy

HF = heart failure

HTN = hypertension

ICD = International Classification of Diseases

MACE = major adverse cardiovascular events

MI = myocardial infarction

MET = metabolic equivalent

SBP = systolic blood pressure

The United States has the highest maternal mortality of all industrialized countries, with an estimated maternal mortality rate of 22.3 per 100,000 births.[1] While maternal mortality has declined worldwide over the past 2 decades, maternal deaths in the United States are rising, particularly among non-Hispanic Black women.[2,3] A recent maternal report from the Centers of Disease Control found that over 80% of pregnancy-related deaths were preventable.[4] Cardiovascular (CV) conditions, including hypertensive disorders of pregnancy (HDP), cardiomyopathy, and valvular disease, are among the leading causes of maternal mortality, accounting for nearly 32% of pregnancy-related deaths.[5,6] Recent analyses established that failure to identify women at high risk for developing serious cardiac events during pregnancy is an important driver of preventable pregnancy-related death.[7,8] Early assessment of patient-specific risks of pregnancy-related CV complications has the potential to significantly reduce maternal morbidity and mortality because it enables more frequent monitoring, additional diagnostic testing, and targeted interventions, but present screening tools are limited to crude markers or require costly diagnostic tests.

Assessment of maximal oxygen consumption at peak exercise (peak VO_2), an integrative gold standard measurement of cardiorespiratory fitness, has been shown to predict adverse outcomes in many populations, including pregnant women, and may help to identify women at elevated risk for CV complications during pregnancy.[9-11] However, broad access to peak VO_2 with exercise testing is limited due to prohibitive cost and need for specialized equipment and expert interpretation.[12] Among nonpregnant individuals, we previously trained and validated Deep electrocardiogram (ECG)-VO_2, a deep learning model that accurately estimates cardiorespiratory fitness (as measured by peak VO_2) using the resting 12-lead ECG, and demonstrated that lower ECG-estimated cardiorespiratory fitness is associated with future CV events, including myocardial infarction (MI), atrial fibrillation, heart failure (HF), and overall mortality, in an ambulatory care sample (37% women, mean age 46 ± 20 years).[13,14] We now apply Deep ECG-VO_2 to a multi-institutional electronic health record pregnancy cohort comprising >56,000 pregnancies to examine the prognostic value of ECG-estimated peak VO_2 for pregnancy-related CV complications occurring from 13 weeks' gestation through 1 year postpartum (**Central Illustration**). We hypothesize that ECG-estimated peak VO_2 will be significantly associated with incident pregnancy-related CV complications during this prespecified assessment window.

STUDY SAMPLE

PADME (Predictive Analysis with Deep Learning Models for Maternal Endpoints) is an electronic health record cohort of 56,833 pregnancies among 38,996 individuals who delivered within the Mass General Brigham multi-institutional health care system from 2001 to 2019.[15] Candidate pregnancies were identified from a validated primary care electronic health record cohort (Community Care Cohort Project, C3PO) of 520,868 individuals receiving longitudinal primary care between 2001 and 2019. This cohort selection process and study design have been shown to reduce selection bias and data missingness and enable longitudinal tracking of pregnancy-related CV complications.[15] The PADME study protocol was approved by the Mass General Brigham Institutional Review Board and adheres to the principles of the Declaration of Helsinki.

We included all pregnancy episodes with at least one 12-lead ECG performed within 1 year prior to conception (start of pregnancy) through 13 weeks of gestation. Each pregnancy episode was assigned 1 ECG (ECG assignment is further detailed in the Supplemental Methods and Supplemental Figure 1). Of note, when multiple ECGs were available for a given pregnancy, we selected the ECG closest to 13 weeks' gestation to harmonize exposure timing across pregnancies.

From this starting sample of 3,957 pregnancies (among 3,718 individuals) with qualifying ECGs, we excluded those with missing body mass index (BMI) and systolic blood pressure (SBP) data (n = 307), yielding a final sample of 3,650 pregnancies (among 3,437 individuals).

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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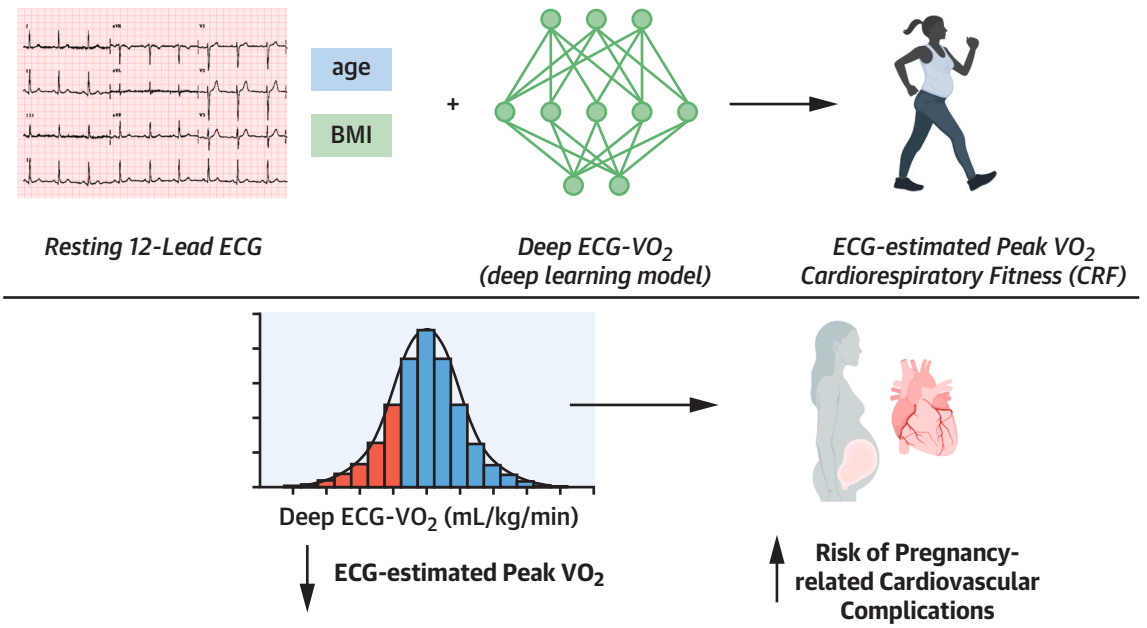
CENTRAL ILLUSTRATION **Deep Learning Estimated Cardiorespiratory Fitness From the 12-Lead Electrocardiogram Is Associated With Pregnancy-Related Cardiovascular Complications**



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Peak VO_2 was estimated using deep electrocardiogram-VO_2 a deep learning model incorporating resting 12-lead electrocardiogram features along with age and body mass index. Lower electrocardiogram-estimated peak VO_2 is associated with a greater risk of incident pregnancy-related cardiovascular complications. Each 1-U decrease in metabolic equivalent unit (MET = 3.5 mL/kg/min) corresponds to a ~10% heightened risk of a pregnancy-related cardiovascular complication. BMI = body mass index; ECG = electrocardiogram.

ESTIMATION OF PEAK VO_2 FROM THE 12-LEAD ELECTROCARDIOGRAM

Deep ECG-VO_2 model is a deep learning model that utilizes a pretraining approach, dubbed Patient Contrastive Learning of Representations, which creates numerical (latent) representations of ECG waveforms that accentuate the differences between ECGs from different individuals while highlighting similarities within ECGs. This model was previously trained and validated on individuals who underwent clinical cardiopulmonary exercise testing at Massachusetts General Hospital from 2011 to 2017.[14] Deep ECG-VO_2 incorporates patient age, sex, BMI, and a deep learning-based representation of the resting 12-lead ECG to provide an estimate of peak VO_2 with favorable accuracy against gold standard cardiopulmonary exercise testing (mean error ~6 mL/kg/min) compared to linear models or standard reference equations. We applied Deep ECG-VO_2 on all ECG tracings from our study sample (details summarized in Supplemental Methods). No participants from the original Deep ECG VO_2 training set were used in this analysis.

BASELINE CLINICAL COVARIATES

Clinical covariates, including demographic data, pregnancy characteristics, vital signs, comorbidities, smoking status, and prevalent cardiovascular disease (CVD), were assessed from 1 year preceding the start of the pregnancy episode (gestational age 0) to the end of the first trimester of pregnancy (gestational age 13 weeks), except for smoking status, which was assessed as smoking any time prior to delivery. Maternal age was defined at delivery. Gestation type, including single and multiple gestation, was ascertained using International Classification of Diseases (ICD) or Current Procedural Terminology (CPT) codes.[15] Gravidity and parity were ascertained from

clinical notes using regular expressions, as previously described.[15] Prevalent comorbidities, including diabetes mellitus (DM) and hyperlipidemia, were ascertained based on the presence of at least one ICD, CPT, and/or electronic health record-specific diagnosis code corresponding to the relevant disease.[15] Hypertension (HTN) treatment was assessed as antihypertensive medication use beginning 1 year prior to the start of the pregnancy episode (gestational age 0) to the end of the first trimester. Smoking status was ascertained from formal smoking questionnaire data documented in the electronic health record. Prevalent CVD was defined as clinically diagnosed CVD documented in the electronic health record prior to or at the index pregnancy/ECG (eg, venous thromboembolism, cerebrovascular disease/transient ischemic attack, HF/cardiomyopathy, arrhythmias, or prior MI).[15] Missingness was present for several baseline covariates, including BMI, SBP, smoking status, alcohol use, parity, and gravidity, and is summarized in the **Table 1** legend.

BMI and SBP data were extracted from clinical encounters. Due to significant missingness (>40%) of baseline vital signs in the electronic health record, a natural language processing algorithm and manual review were used to recover BMI and SBP data from unstructured notes.[15] For pregnancies with multiple BMI and SBP recordings, we selected the BMI and SBP value most proximal to 13 weeks of gestation. Primary analyses were restricted to pregnancies with available BMI and SBP after this recovery process.

PREGNANCY-RELATED CARDIOVASCULAR COMPLICATIONS

Pregnancy-related CV complications were defined as the composite of severe HDP, major adverse CV events (MACE), and maternal death, as assessed from the end of the first trimester (gestational age 13 weeks) to 1 year postpartum. Severe HDP included preeclampsia with and without severe features, eclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome, and was ascertained by previously validated code sets after 20 weeks' gestation with positive predictive value ≥85%.[15] MACE included MI, HF including peripartum cardiomyopathy, vascular dissection, thromboembolism (venous, pulmonary, and systemic), cerebrovascular disease (transient ischemic attack, hemorrhagic, and ischemic cerebrovascular accident), ventricular and atrial arrythmias, and cardiac arrest.[15] Clinical definitions for MI, HF, and stroke were defined codes using previously validated code sets with positive predictive value ≥85%, while remaining MACE events were defined using previously published ICD-9, ICD-10, or CPT code groupings.[1,2] Maternal death was ascertained from the Social Security Death Index or Mass General Brigham internal documentation of death, with cause of death manually adjudicated by a physician reviewer.

STATISTICAL ANALYSIS

The distribution of ECG-estimated peak VO_2 was first winsorized to limit leverage of outliers on analyses, setting the minimum VO_2 as 5 mL/kg/min and maximum as 60 mL/kg/min (24 patients had VO_2 <5 mL/kg/min and 0 patients had VO_2 >60 mL/kg/min before winsorizing to 5 and 60, respectively). Baseline characteristics were tabulated across the total sample, according to ECG-estimated VO_2 quartile, and above and below VO_2 of 14 mL/kg/min (moderate/high vs low fitness) and compared using *t*-tests, chi-squared tests, or Wilcoxon rank sum tests, as appropriate. In primary analyses, we examined the association of ECG-estimated peak VO_2 with incident pregnancy-related CV complications using mixed-effects logistic regression models with a random intercept per patient to account for within-individual correlation across repeated pregnancies and covariates modeled as fixed effects, consistent with standard analytic practice in obstetrics cohort studies.[3,4] Models were first adjusted for maternal age at delivery, and then further adjusted for SBP, HTN medications, DM, and gestation type (singleton or multiple gestation). Covariates were ascertained during the baseline period, defined as 1 year before pregnancy through 13 weeks' gestation. Because prepregnancy BMI is used in the derivation of ECG-estimated VO_2, prepregnancy BMI was not included as a covariate in the primary model, but we fit an exploratory model with additional adjustment for prepregnancy BMI.

In secondary analyses, we examined the association of ECG-estimated peak VO_2 with incident HDP and MACE, separately. We also examined the association of ECG-estimated peak VO_2 dichotomized into low (VO_2 ≤14 mL/kg/min) vs moderate/high fitness (>14 mL/kg/min) with incident pregnancy-related CV complications. We performed additional subgroup analyses by race/ethnicity (White vs non-White), maternal age (≥35 years vs <35 years), prevalent CVD, and obesity status (prepregnancy BMI ≥30 kg/m^2 vs BMI <30 kg/m^2) and tested interaction terms to assess heterogeneity of effect between subgroups.

Finally, we performed sensitivity analyses restricting to first pregnancies available in PADME, pregnancies with ECGs performed within the first

TABLE 1 Baseline Clinical Characteristics

	Overall (N = 3,650)	Q1 (n = 913)	Q2 (n = 912)	Q3 (n = 912)	Q4 (n = 913)	*P* Value
Median peak VO_2 (mL/kg/min)	27.0 (21.9, 31.2)	17.9 (14.4, 20.2)	24.6 (23.4, 25.9)	29.1 (28.0, 30.0)	33.9 (32.4, 36.2)	<0.001
Clinical characteristics						
Maternal age at ECG, y	32 (6)	32 (6)	32 (6)	32 (6)	31 (6)	<0.001
Maternal age at delivery, y	33 (6)	34 (6)	33 (6)	33 (6)	32 (6)	<0.001
Body mass index, kg/m^2	27.3 (6.6)	34.5 (6.9)	27.7 (4.7)	24.8 (3.7)	22.2 (2.8)	<0.001
Obesity (BMI ≥30 kg/m^2), n (%)	1,024 (28%)	668 (73%)	258 (28%)	83 (9%)	15 (2%)	<0.001
Systolic BP, mm Hg	113 (13)	118 (14)	114 (13)	111 (12)	110 (11)	<0.001
Diastolic BP, mm Hg[a]	67 (9)	72 (10)	70 (9)	68 (9)	67 (8)	<0.001
Hypertension treatment, n (%)	351 (10%)	155 (17%)	90 (10%)	60 (7%)	46 (5%)	<0.001
DM, n (%)	254 (7%)	137 (15%)	63 (7%)	32 (4%)	22 (2%)	<0.001
Hyperlipidemia, n (%)	540 (15%)	200 (22%)	123 (14%)	109 (12%)	108 (12%)	<0.001
Hypertension, n (%)	660 (18%)	296 (32%)	171 (19%)	106 (12%)	87 (10%)	<0.001
Smoking, n (%)	118 (3%)	36 (4%)	24 (3%)	21 (2%)	37 (4%)	0.09
Alcohol use, n (%)	327 (9%)	82 (9%)	77 (8%)	74 (8%)	94 (10%)	<0.001
Prevalent CVD, n (%)	496 (14%)	151 (17%)	118 (13%)	120 (13%)	107 (12%)	0.02
Pregnancy characteristics						
Gravidity, n[a]	2.8 (1.9)	3.2 (2.0)	3.0 (2.0)	2.7 (1.7)	2.4 (1.6)	<0.001
Parity, n[a]	2.4 (1.3)	2.7 (1.5)	2.4 (1.3)	2.3 (1.2)	2.1 (1.0)	<0.001
Singleton pregnancy, n (%)	3,449 (95%)	858 (94%)	862 (95%)	856 (94%)	873 (96%)	0.33
Nulliparous, n (%)[a]	831 (27%)	181 (22%)	208 (26%)	212 (28%)	230 (31%)	0.001
Incident pregnancy-related cardiovascular complications						
Antepartum and postpartum						
Composite outcome, n (%)	723 (20%)	246 (27%)	181 (20%)	160 (18%)	136 (15%)	<0.001
Severe HDP, n (%)	421 (12%)	170 (19%)	105 (12%)	74 (8%)	72 (8%)	<0.001
MACE, n (%)	358 (10%)	102 (11%)	87 (10%)	99 (11%)	70 (8%)	0.049
Maternal death, n (%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)	0.57
Antepartum						
Composite outcome, n (%)	577 (16%)	197 (22%)	140 (15%)	127 (14%)	113 (12%)	<0.001
Severe HDP, n (%)	344 (9%)	138 (15%)	86 (9%)	58 (6%)	62 (7%)	<0.001
MACE, n (%)	262 (7%)	71 (8%)	62 (7%)	75 (8%)	54 (6%)	0.14
Maternal death, n (%)	0	0	0	0	0	-
Postpartum						
Composite outcome, n (%)	146 (4%)	49 (5%)	41 (5%)	33 (3%)	23 (3%)	<0.001
Severe HDP, n (%)	77 (2%)	32 (4%)	19 (2%)	16 (2%)	10 (1%)	<0.001
MACE, n (%)	96 (3%)	31 (3%)	25 (3%)	24 (3%)	16 (2%)	0.14
Maternal death, n (%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)	0.57

Results are displayed as mean (SD) or n (%), unless otherwise noted. [a]Gravidity, parity, and primiparous data available for 3,138 pregnancies. DBP available for 2,566 pregnancies. Smoking data available for 2,265 pregnancies. Alcohol use data available for 808 pregnancies. The remaining covariates are available for all 3,650 pregnancies.

BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; DM = diabetes mellitus; CVD = cardiovascular disease; ECG = electrocardiogram; HDP = hypertensive disorders of pregnancy; MACE = major adverse cardiovascular events.

trimester (from start of pregnancy up to 13 weeks of gestation), and pregnancies among nulliparous women.

Two-sided *P* values <0.05 were considered statistically significant. Statistical analyses were performed using R Version 4.4.0.

RESULTS

We ascertained ECG-estimated peak VO_2 for 3,650 pregnancies from 3,437 individuals (mean maternal age at delivery 33 ± 6 years; 1933/3,650 [53%] non-Hispanic White). Median ECG-estimated VO_2 was 27.0 mL/kg/min (IQR: 21.9-31.2 mL/kg/min) (Supplemental Figure 2), with 208/3,650 (6%) pregnancies with low estimated cardiorespiratory fitness as defined as VO_2 ≤14 mL/kg/min. Median follow-up time from start of pregnancy (estimated date of conception) was 1.7 years (IQR: 1.6-1.8 years). Baseline characteristics stratified by ECG-estimated VO_2 quartile are displayed in **Table 1** (comparisons with the original Deep ECG-VO_2 cohort are displayed in

TABLE 2 Clinical Indications for ECG Testing

ECG Indication	N	%
Ischemic and structural heart disease	915	32%
Cardiac arrhythmias and conduction	770	27%
General symptoms and wellness	513	18%
Vascular and circulatory disorders	172	6%
Neurological and cerebrovascular	146	5%
Others/unspecified	122	4.2%
Respiratory conditions	89	3.1%
Gastrointestinal and abdominal	41	1.4%
Musculoskeletal and trauma	38	1.3%
Metabolic and endocrine	25	0.9%
Congenital heart defects	22	0.8%
Mental health and behavioral	21	0.7%
Infectious and systemic inflammatory	17	0.6%
Hematologic and coagulation	7	0.2%

Data on clinical indications for ECG testing were available for n = 2,898 ECGs. Abbreviation as in Table 1.

Supplemental Table 1). Clinical indications for ECG testing are summarized in **Table 2**.

Compared with individuals in the highest ECG-VO_2 quartile, women in the lowest quartile had significantly greater burden of CV comorbidities (obesity: 668/913 [73%] vs 15/913 [2%], HTN: 296/913 [32%] vs 87/913 [10%], DM: 137/913 [15%] vs 22/913 [2%], and hyperlipidemia: 200/913 [22%] vs 108/913 [12%], $P < 0.001$) and prevalent CVD (151/913 [17%] vs 107/913 [12%], $P = 0.019$), although 164/913 (18%) of women in the lowest ECG-VO_2 quartile had no traditional CV risk factors. Maternal age, gestation type, gravidity, and parity were similar across VO_2 quartiles. Similarly, women with low ECG-estimated cardiorespiratory fitness (VO_2 ≤14 mL/kg/min) had greater prevalence of cardiac comorbidities and prevalent CVD compared with women with moderate/high cardiorespiratory fitness (VO_2 >14 mL/kg/min) (Supplemental Table 2).

TABLE 3 Association of ECG-Estimated VO_2 With Incident Pregnancy-Related Cardiovascular Complications

		Age-Adjusted		Multivariable-Adjusted	
Outcomes	n/N	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Incident pregnancy-related CV complications	723/3,650	1.21 (1.13-1.30)	<0.001	1.09 (1.03-1.17)	<0.01
Severe HDP	421/3,650	1.27 (1.17-1.38)	<0.001	1.11 (1.04-1.18)	0.002
MACE	358/3,650	1.08 (0.99-1.18)	0.09	1.06 (0.97-1.17)	0.21

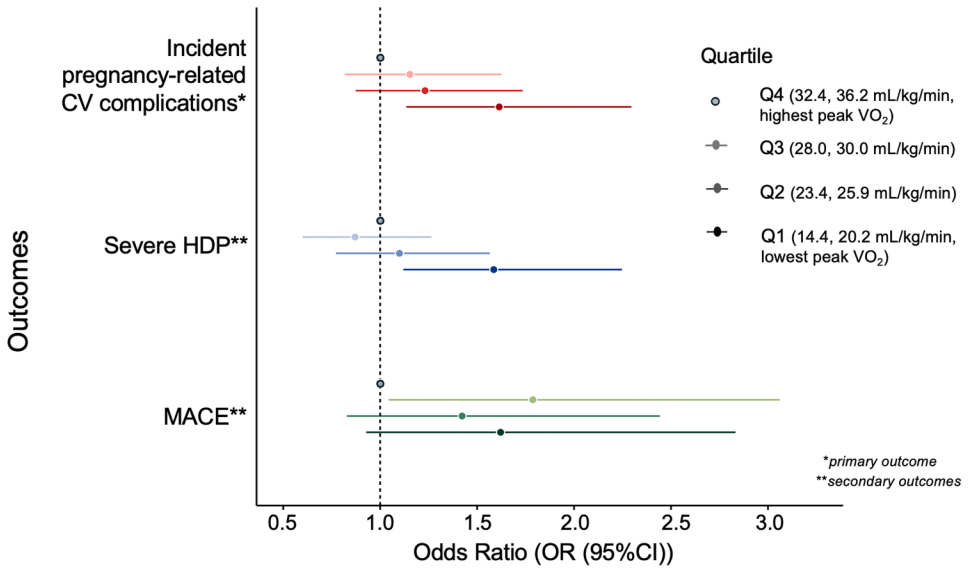
OR represents odds of outcome per 1-U decrease in metabolic equivalent unit (MET = 3.5 mL/kg/min). Age-adjusted model is adjusted for maternal age at delivery. Multivariable model is further adjusted for systolic blood pressure, hypertension medication use, diabetes, and gestation type (fixed effects) with a random intercept for each participant.
CV = cardiovascular; other abbreviations as in Table 1.

Among 3,650 pregnancies, 723 (20%; 95% CI: 19%-21%) developed incident pregnancy-related CV complications between 13 weeks of gestation to 1 year postpartum, including 421/3,650 (12%; 95% CI: 10%-13%) severe HDP, 358/3,650 (10%; 95% CI: 9%-11%) MACE, and 2/3,650 (0.05%; 95% CI: 0.01%-0.20%) maternal deaths.

ASSOCIATION OF ECG-ESTIMATED PEAK VO_2 WITH INCIDENT PREGNANCY-RELATED CV COMPLICATIONS. We examined the association of ECG-estimated peak VO_2 with incident pregnancy-related CV complications. In both age- and multivariable-adjusted analyses, ECG-estimated VO_2 was associated with pregnancy-related CV complications (multivariable-adjusted OR_{adj} per 1-U lower metabolic equivalent [MET = 3.5 mL/kg/min] 1.09; 95% CI: 1.03-1.17; $P < 0.01$) (**Table 3**). Specifically, compared with individuals in the highest ECG-estimated peak VO_2 quartile, women in the lowest quartile had >60% higher odds of developing a pregnancy-related CV complication during pregnancy (OR_{adj} 1.61; 95% CI: 1.13-2.30; $P = 0.008$) (**Figure 1**). Notably, results were attenuated when further adjusting for BMI in exploratory multivariable-adjusted analyses (OR: 1.35; 95% CI: 0.86-2.10; $P = 0.19$) (Supplemental Table 3). Additional exploratory analyses further adjusting for smoking status demonstrated similar directional trends with primary analyses, but associations were attenuated and no longer statistically significant (Supplemental Table 4). Sensitivity analyses restricting to first pregnancies available in PADME and to pregnancies with ECGs performed within the first trimester of pregnancy showed results consistent with our primary analyses (Supplemental Tables 5 and 6). Finally, as HDP is also a risk factor for pregnancy-related CV complication, we performed sensitivity analyses restricting to pregnancies among nulliparous women (Supplemental Table 7) and excluding pregnancies with prevalent HDP among multiparous women (Supplemental Table 8), with similar results to our primary analyses.

In secondary analyses, we examined the association of ECG-estimated peak VO_2 with severe HDP and MACE outcomes separately (**Table 3**). We found that ECG-estimated VO_2 was significantly associated with future risk of severe HDP in both age- and multivariable-adjusted analyses (multivariable-adjusted OR_{adj} 1.11 per 1-U lower MET, 95% CI: 1.04-1.18; $P = 0.002$). Similarly, women in the lowest ECG-VO_2 quartile had significantly greater odds of developing severe HDP vs women in the highest quartile (OR_{adj} 1.59; 95% CI: 1.12-2.25; $P = 0.009$, **Figure 1**).

FIGURE 1 Association of Electrocardiogram-Estimated VO_2 Quartiles With Incident Pregnancy-Related Cardiovascular Complications



OR represents odds of developing pregnancy-related cardiovascular complication compared with electrocardiogram-estimated peak VO_2 quartile 4 (highest estimated peak VO_2 quartile, reference). Model is adjusted for maternal age at delivery, systolic blood pressure, hypertension medication use, diabetes, and gestation type. CV = cardiovascular; HDP = hypertensive disorder of pregnancy; MACE = major adverse cardiovascular event.

ECG-estimated peak VO_2 was not significantly associated with incident MACE (OR_{adj} 1.06 per 1-U lower MET; 95% CI: 0.97-1.17; $P = 0.21$) (Table 3).

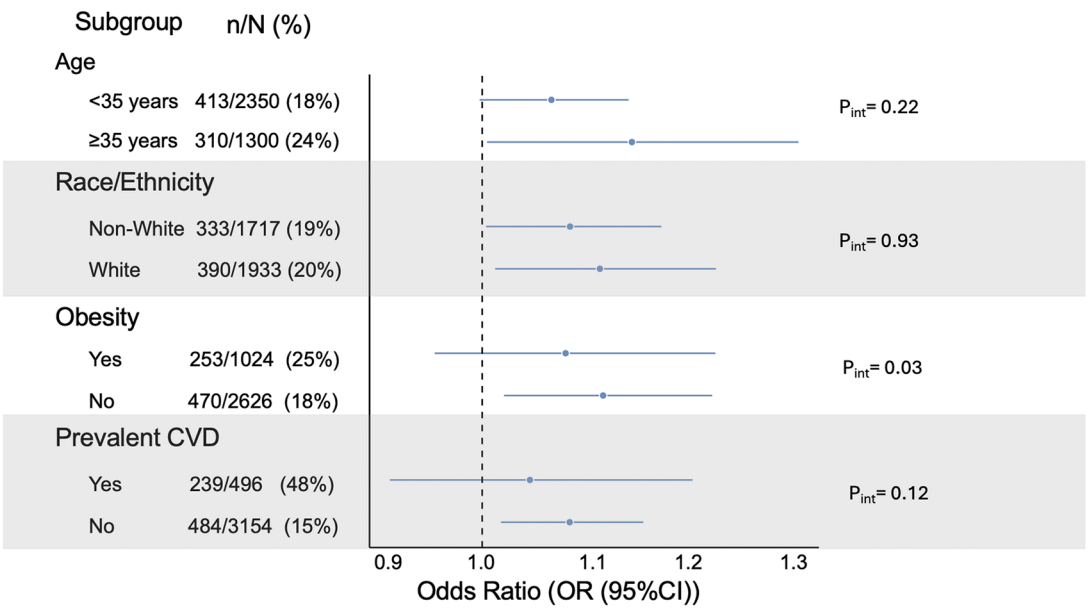
When examining the association of ECG-estimated cardiorespiratory fitness with incident pregnancy-related CV complications using a clinically significant cutoff of peak VO_2 ≤14 mL/kg/min, risk of incident pregnancy-related CV complications was higher among low (ECG-VO_2 ≤14 mL/kg/min) vs moderate-to-high cardiorespiratory fitness (ECG-VO_2 >14 mL/kg/min), although the association was not statistically significant (OR_{adj} 1.39; 95% CI: 0.86-2.25; $P = 0.17$) (Supplemental Figure 3).

SUBGROUP ANALYSES. We examined the prognostic value of ECG-VO_2 for incident pregnancy-related CV complications in key subgroups including race/ethnicity, maternal age (≥35 vs <35 years of age), obesity status (BMI <30 vs ≥30 kg/m^2), and prevalent CVD (Figure 2, Supplemental Table 9). We found that the associations of ECG-estimated peak VO_2 with incident pregnancy-related CV complications were comparable for race/ethnicity, maternal age, and prevalent CVD subgroups. Notably, heterogeneity of effect was observed for obesity status, with ECG-estimated peak VO_2 more associated with incident pregnancy-related CV complications among women without obesity vs with obesity (OR_{adj} per 1-U lower MET 1.13; 95% CI: 1.02-1.24 in women without obesity vs OR_{adj} 1.09; 95% CI: 0.95-1.24 in women with obesity, $P_{int} = 0.03$) (Figure 2).

DISCUSSION

Among 3,650 pregnancies in a contemporary electronic health record-based pregnancy cohort, we demonstrate that cardiorespiratory fitness estimated using deep learning-enabled analysis of the 12-lead ECG before the second trimester is associated with future pregnancy-related CV complications. Our findings are 3-fold. First, lower ECG-derived peak VO_2 is associated with a higher risk of developing a composite of pregnancy-related CV complications, including severe HDP, MACE, and maternal death, although the magnitude of effect was attenuated after adjustment for BMI. Second, women with lower ECG-derived peak VO_2 had greater burden of cardiometabolic disease, including higher BMI and greater prevalence of obesity, HTN, DM, and hyperlipidemia, although nearly 20% of women with low

FIGURE 2 Subgroup Analyses (Maternal Age, Race/Rthnicity, Obesity, and Prevalent Cardiovascular Disease)



OR represents odds of incident pregnancy-related cardiovascular complication per 1-U decrease in metabolic equivalent unit (MET = 3.5 mL/kg/min). Model is adjusted for maternal age at delivery, systolic blood pressure, hypertension medications, diabetes, and gestation type. CVD = cardiovascular disease.

ECG-estimated peak VO_2 were free of any traditional CV risk factors. Finally, ECG-estimated VO_2 was similarly associated with incident pregnancy-related CV complications among women in key subgroups, including race/ethnicity, maternal age, obesity status, and prevalent CVD. Taken together, artificial intelligence-enabled analysis of ECGs performed early in antepartum care may enable efficient and scalable risk prognostication for identifying pregnancies at high risk for developing CV complications.

One of the key barriers to reducing preventable pregnancy-related deaths is failure to identify high-risk women early in pregnancy.[8] Currently available risk stratification tools for pregnancy-related CV complications are limited to individuals with preexisting CVD and/or require extensive disease-specific information or imaging data that are not routinely captured in obstetric populations.[16-19] Furthermore, current guidance for selecting patients for low-dose aspirin for preeclampsia prevention relies on risk factor-based criteria (eg, prior preeclampsia, chronic HTN, multifetal gestation, etc) and does not incorporate direct physiologic measures of CV reserve.[20,21] In this context, ECG-VO_2 could serve as a scalable, low-burden complement to existing risk frameworks by providing an early-pregnancy estimate of cardiorespiratory fitness from a routinely available test for individuals both with and without preexisting CVD and those who do not meet traditional high-risk criteria.

Cardiorespiratory fitness, as quantified by cardiopulmonary exercise testing-derived peak VO_2, has been shown to predict CV outcomes in pregnant populations.[9-11] For example, in a prospective study of 43 women, lower cardiorespiratory fitness measured by cycle-ergometer cardiopulmonary exercise testing was associated with a greater risk of HDP.[22] Similarly, among 33 pregnant women with congenital heart disease who underwent cardiopulmonary exercise testing prior to delivery, lower peak VO_2 was independently associated with adverse maternal events, including HF, sustained arrythmias, cardiac arrest, stroke, and maternal death.[11] By contrast, in a large population-based cohort with prepregnancy treadmill testing, cardiorespiratory fitness was not independently associated with adverse birth outcomes, highlighting that observed associations may depend on outcome definition, timing of fitness assessment, and covariate adjustment.[23] Despite these data, routine ascertainment of

peak VO_2 is not feasible for broad pregnancy risk stratification due to limited availability, significant cost, and the need for expert interpretation.[24,25] Although exercise testing has been shown to be safe in pregnancy, there is reticence among providers to refer pregnant patients for exercise testing because of perceived maternal-fetal safety concerns.[23,26,27] To circumvent these challenges, our group previously developed Deep ECG-VO_2, a deep learning model that can accurately estimate peak VO_2 from the resting 12-lead ECG. In the present study, lower ECG-estimated VO_2 is associated with pregnancy-related CV complications, including severe HDP, MACE, and maternal death, with women in the lowest quartile of ECG-estimated peak VO_2 experiencing >60% greater odds of developing a CV complication during pregnancy compared with those in the highest quartile. We hypothesize that this association reflects reduced integrated CV reserve and cardiometabolic health, which may predispose to maladaptive hemodynamic adaptation and endothelial/vascular dysfunction during pregnancy, pathways that are closely linked to severe HDP. Consistent with this, the observed association between lower ECG-predicted VO_2 and pregnancy-related CV complications was most pronounced for severe HDP, with no significant association seen for incident MACE. However, it is important to acknowledge that incident MACE events were rare (n = 358), limiting power to precisely evaluate relationships with MACE. Whether cardiorespiratory fitness during pregnancy is more tightly linked to HDP-related vascular and hemodynamic physiology rather than more cardiac-centric MACE events warrants further investigation in larger prospective pregnancy cohorts. Finally, women with lower ECG-estimated VO_2 had greater burden of cardiometabolic risk, including higher BMI and higher prevalence of obesity, HTN, DM, and hyperlipidemia. Furthermore, inclusion of BMI in multivariable models attenuated the primary associations between ECG-VO_2 and pregnancy-related CV complications, underscoring the close relationship between estimated fitness and adiposity-related risk and supporting ECG-estimated cardiorespiratory fitness as a single integrated measure of underlying cardiometabolic health. Notably, nearly 20% of individuals in the lowest ECG-VO_2 quartile had no documented traditional CV risk factors. This may reflect true heterogeneity in cardiorespiratory fitness among younger women, as supported by cardiopulmonary exercise testing reference standards showing wide distributions of peak VO_2 in women of reproductive age, or clinical selection as ECGs in our sample were often obtained for cardiopulmonary symptoms that may indicate reduced functional capacity even in the absence of documented comorbidity.[28] Although prospective pregnancy cohorts with systematic ECG ascertainment will be important to clarify this phenotype, these findings suggest that ECG-VO_2 may capture additional physiologic vulnerability beyond routinely ascertained cardiometabolic comorbidity.

Currently, routine 12-lead ECG testing is not recommended during antenatal care and is largely performed in women presenting with cardiopulmonary symptoms or among women with a history of existing CVD or prior pregnancy-related CV complication. We contend that integration of Deep ECG-VO_2 into routine antenatal screening could further refine risk assessment of CV risk among healthy individuals without symptoms. Indeed, we showed in sensitivity analyses that ECG-estimated VO_2 is an accurate prognosticator of pregnancy-related CV risk even among individuals without prior complications during pregnancy. A key window of opportunity to integrate widespread ECG testing into antepartum care is during first trimester prenatal screening. We therefore examined the prognostic value of Deep ECG-VO_2 for pregnancy-related CV complications during the first trimester and found that ECG-estimated peak VO_2 is similarly associated with incident CV complications during pregnancy in sensitivity analyses restricted to pregnancies with ECGs performed within the first trimester only.

Finally, we found that Deep ECG-VO_2 provides prognostic value for pregnancy-related CV complications in key vulnerable subgroups, including women of non-White race and without prevalent CVD. In the United States, non-White women experience substantially higher rates of maternal mortality than White women, with rates of maternal death 3 to 4 times higher among Black women vs White women, emphasizing the need for risk stratification tools with generalizability across diverse populations.[3,29] We demonstrate that ECG-estimated VO_2 was associated with pregnancy-related CV complications among both non-White women and White women, highlighting generalizability as a key strength of our model. We similarly found that ECG-estimated cardiorespiratory fitness was associated with pregnancy-related CV complications among women without prevalent CVD and without obesity. Identifying women without traditional risk factors like obesity may discern masked risk for adverse CV

events during pregnancy. Furthermore, while studies consistently demonstrate that women with established CVD are at highest risk of developing CV-related complications during pregnancy, most maternal morbidity and mortality occur among patients without established diagnoses of CVD.[16-19] The ability of ECG-estimated VO_2 to accurately capture risk among women without prevalent CVD is an important strength as women without prevalent CVD are less likely to be screened and/or closely monitored for the development of pregnancy-related CV complications. Taken together, identification of pregnant individuals at higher risk for CV complications using ECG-VO_2 may enable more targeted prevention approaches, including more frequent monitoring, enhanced access to multidisciplinary care, and provision of preventive therapies (eg, low-dose aspirin for preeclampsia prophylaxis).[7,30] Potential downstream actions could include earlier and/or more frequent maternal-fetal medicine and cardio-obstetrics follow-up, closer surveillance of blood pressure and cardiopulmonary symptoms, and lower thresholds for additional evaluation when clinically indicated (eg, natriuretic peptides, echocardiography, or ambulatory rhythm monitoring for dyspnea, edema, or palpitations).

STUDY LIMITATIONS. Our study has several limitations worth noting. First, Deep ECG-VO_2 was derived and validated in fitter men and nonpregnant women, and to date had not been extrapolated to pregnant populations. Second, peak VO_2 was estimated from ECGs obtained for clinical indications, which may introduce selection bias and result in potentially higher event rates in our sample. Compared with the parent PADME pregnancy electronic health record cohort from which our analysis sample was drawn, our sample demonstrated a higher burden of CV comorbidities and greater prevalence of existing CVD, highlighting the need for prospective validation of Deep ECG-VO_2 among pregnant individuals using protocolized ECGs. Notably, availability of prospective pregnancy cohorts with systematic ECG ascertainment is limited, precluding our ability to include an unselected healthy control population. Third, missing data were present for several baseline covariates. Although missingness for most variables examined was not associated with the primary outcome, missingness in parity and gravidity was associated with the outcome, suggesting that pregnancies with incomplete obstetric history data may have differed systematically from those with complete data. Fourth, we examined ECGs prior to 13 weeks' gestation to standardize exposure assessment and to capture risk information before the onset of many pregnancy-related complications. Because CV reserve is progressively stressed through pregnancy and underlying disease may become symptomatic in the late second trimester, future work should reevaluate whether serial ECG-VO_2 assessment and/or later-pregnancy ECG-VO_2 measurements may provide additional prognostic value beyond early pregnancy alone. Fifth, longitudinal postpartum blood pressure trajectories were not systematically available for incorporation in our primary analyses. Furthermore, because persistent postpartum HTN characterized by elevated diastolic blood pressure may be more prevalent after HDP than isolated SBP elevation, future studies with standardized blood pressure ascertainment across pregnancy and the postpartum period are needed to determine whether incorporating diastolic blood pressure (DBP)-based definitions and postpartum BP trajectories improves performance and clinical utility of ECG-VO_2-informed risk stratification. Finally, our sample comprised individuals from a single geographical location who predominantly received their obstetrical care in tertiary and quaternary settings, limiting generalizability to diverse populations, particularly as many deliveries occur in community or low-risk settings.

CONCLUSIONS

In a contemporary pregnancy electronic health record sample, we show that lower estimated cardiorespiratory fitness from a validated deep learning model based on the resting 12-lead ECG is associated with higher risk of pregnancy-related CV complications, including severe HDP, MACE, and maternal death. Integration of 12-lead ECG testing into routine antepartum care may identify women with silent risk and enhance early prevention efforts to ameliorate the burden of adverse CV outcomes in pregnant women.

DATA SHARING Mass General Brigham data contain protected health information and cannot be shared publicly.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Cardiorespiratory fitness estimated from the resting 12-lead ECG, derived from a validated deep learning model, is associated with incident pregnancy-related CV complications and may help identify high-risk patients preconception or early in pregnancy.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Cardiorespiratory fitness is an established marker of CV reserve and adverse outcomes. This study extends its prognostic relevance to pregnancy-related CV complications using a scalable, ECG-based surrogate.

TRANSLATIONAL OUTLOOK: Integration Deep-ECG VO_2 into antepartum care may help identify women are at highest risk of developing pregnancy-related CV complications and support targeted surveillance and preventive strategies.

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APPENDIX For supplemental tables and Methods section, please see the online version of this paper.