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Multiple Prior Live Births Are Associated With Cardiac Remodeling and Heart Failure Risk in Women

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ABSTRACT

Objective: Greater parity has been associated with cardiovascular disease risk. We sought to find whether the effects on cardiac remodeling and heart failure risk are clear.

Methods: We examined the association of number of live births with echocardiographic measures of cardiac structure and function in participants of the Framingham Heart Study (FHS) using multivariable linear regression. We next examined the association of parity with incident heart failure with preserved (HFpEF) or reduced (HFrEF) ejection fraction using a Fine-Gray subdistribution hazards model in a pooled analysis of n = 12,635 participants in the FHS, the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and Prevention of Renal and Vascular Endstage Disease. Secondary analyses included major cardiovascular disease, myocardia infarction and stroke.

Results: Among n = 3931 FHS participants (mean age 48 $\pm$ 13 years), higher numbers of live births were associated with worse left ventricular fractional shortening (multivariable β -1.11 (0.31); $P = 0.0005$ in $\geq$ 5 live births vs nulliparous women) and worse cardiac mechanics, including global circumferential strain and longitudinal and radial dyssynchrony ($P < 0.01$ for all comparing $\geq$ 5 live births vs nulliparity). When examining HF subtypes, women with $\geq$ 5 live births were at higher risk of developing future HFrEF compared with nulliparous women (HR 1.93, 95% CI 1.19−3.12; $P = 0.008$); by contrast, a lower risk of HFpEF was observed (HR 0.58, 95% CI 0.37−0.91; $P = 0.02$).

Conclusions: Greater numbers of live births are associated with worse cardiac structure and function. There was no association with overall HF, but a higher number of live births was associated with greater risk for incident HFrEF. (*J Cardiac Fail 2023;00:1−11*)

Key Words: Pregnancy, echocardiography, heart failure.

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Brief Lay Summary

Among 3931 participants in the Framingham Heart Study, there was an association of greater number of live births with lower cardiac function among women. In a larger group of patients across 4 cohorts (with a total of 12,635 participants), more live births were associated with a higher risk of developing heart failure with lower cardiac function as compared with patients who had never experienced a live birth.

Introduction

Pregnancy presents a window of opportunity to identify those who may be at greater long-term cardiovascular risk, both because this is a unique time period when women are strongly engaged in medical care and because adverse pregnancy outcomes (including hypertensive disorders of pregnancy, preterm delivery, delivery of small-for-gestational-age infants, and gestational diabetes) are associated with increased risk of future cardiovascular disease.[1,2] However, it remains incompletely understood whether and how pregnancy itself may have adverse cardiovascular consequences that are persistent rather than temporary. Prior observational studies suggest that even when combined with other reproductive risk factors, parity additionally contributes to future cardiovascular disease (CVD) risk profiles and is associated with risk of future coronary artery disease, atrial fibrillation (AF) and hospitalizations for myocardial infarction (MI).[3-6] However, mechanistic explanations for these associations are poorly understood. In this context, we sought to determine whether (1) an increasing number of live births is associated with structural or functional cardiovascular remodeling in women as assessed by echocardiography and (2) whether an increasing number of live births is associated with major cardiovascular outcomes by leveraging a large multicohort collaboration with pooled, harmonized individual-level data.

Methods

Study Sample

We examined the association of number of live births and subclinical cardiovascular disease in a retrospective analysis of women enrolled in the Framingham Heart Study (FHS) who attended the FHS Offspring examination 6 (1995−1998) or the third-generation examination 1 (2002−2005) and for whom data regarding number of live births were available. Details of the cohorts have been published previously.[7,8] In brief, the FHS Offspring cohort was recruited in 1971 and included adult children and spouses of the original FHS participants. The third-generation cohort included grandchildren of the original cohort. Of 4059 eligible women, we excluded individuals with prevalent heart failure (HF) (n = 14), prevalent MI (n = 25), prevalent stroke (n = 16), prevalent AF (n = 23), advanced kidney disease (estimated glomerular filtration rate less than 30 mL/min/1.73m^2; n = 15), missing clinical covariates (n = 29), and missing parity data (n = 6), leaving 3931 individuals for analysis. All participants provided informed consent, and the study was approved by the appropriate institutional review board.

We next examined the association of live births with future risk of CVD, including MI, HF (by subtype) and CVD in a multicohort collaboration that included participants who attended the FHS Offspring examination 6, the Cardiovascular Health Study (CHS) 1989−1990; 1992−1993 for the African-American cohort), the Multi-Ethnic Study of Atherosclerosis (MESA) 2000−2002), and the Prevention of Renal and Vascular Endstage Disease (PREVEND) 1997−1998) baseline examinations. Individual-level data were harmonized and pooled from the 4 cohorts, as previously described.[9] Individuals of male sex (n = 13,546) and those with prevalent HF (n = 174), MI (n = 369), stroke (n = 144), missing covariates (n = 367), or missing live-birth data (1663) were excluded. The total sample size was 12,635, including FHS (n = 3937), CHS (n = 2927), MESA (n = 3567), and PREVEND (n = 2204). Cohort-specific details have been published previously.[9] In brief, MESA recruited a diverse population of asymptomatic participants, excluding those with known clinical CVD, prior cardiovascular procedures or current AF.[10] CHS recruited older adults (> 65 years of age) between 1989 and 1990 with risk factors for coronary disease and stroke; an African-American cohort was recruited between 1992 and 1993.[11] PREVEND included participants of the city of Groningen, The Netherlands, between 1997 and 1998.[12] All cohorts followed participants longitudinally for incident cardiovascular events, as outlined previously.[9]

Clinical Assessment

Comprehensive medical histories, including anthropometrics, assessment of resting blood pressure and fasting blood work were obtained for all participants. Live-birth histories were assessed by self-report. Body mass indexes (BMIs) were calculated as weight divided by height squared and expressed as kg/m^2. Diabetes mellitus (DM) was defined as a fasting glucose level $\geq$ 126 mg/dL, random glucose $\geq$ 200 mg/dL or the use of hypoglycemic medications. Blood pressure (BP) was calculated as the average of 2 seated measurements.

Echocardiography

Participants in FHS underwent standard 2-dimensional transthoracic echocardiography using an HP

Sonos 5500 ultrasound machine (Phillips Medical Systems; Andover, MA) as previously described.[13] Digital echocardiographic data were analyzed offline according to standardized techniques by readers blinded to clinical data. Speckle-tracking-based analyses of left ventricular (LV) function were additionally performed at the 8th examination (years 2005−2008) (2D Cardiac Performance Analysis, version 1.1; Tomtec Imaging Systems; Unterschleissheim, Germany) with interobserver intraclass correlation coefficients $\geq$ 0.84 for all global strain measurements.[14] Primary measures included left atrial dimension, fractional shortening, LV mass, global longitudinal strain, and global circumferential strain, with secondary measures of global radial strain (short-axis view and apical views) and longitudinal and radial synchrony.

Coronary Artery Calcium and Noninvasive Arterial Stiffness Assessment

Coronary artery calcification (CAC) data were obtained from participants who also attended examination 7 (n = 1612; 1998−2001). Imaging was obtained using an 8-slice multidetector computed tomography scanner (LightSpeed Ultra; General Electric, Fairfield, CT) using standard protocols.[15] Scans were interpreted independently by experienced readers on offline workstations (Aquarius; TeraRecon, Acton, MA) and defined as calcification involving the coronary arteries. In addition, carotid-femoral pulse wave velocity (PWV) was calculated using tonometry waveforms in 3219 participants, as previously described in detail.[16] Briefly, after resting for ~5 minutes in the supine position, brachial systolic and diastolic blood pressures were obtained by a semiautomatic auscultatory device. Using a custom tonometer (Cardiovascular Engineering, Norwood, MA), arterial tonometry with simultaneous electrocardiogram was obtained from the right side of the body for the brachial, radial, femoral, and carotid arteries. Transit distances were measured from the suprasternal notch to each pulse-recording site. For analyses, both CAC and PWV were inverse-transformed due to skewed distributions, similar to previous studies.[16,17]

Clinical Outcomes

Participants in each cohort were followed longitudinally for the development of the following cardiovascular endpoints: overall HF, HF by subtype (see below), major CVD, MI, and stroke. Major CVD was inclusive of MI, stroke, HF, coronary insufficiency, and peripheral arterial disease. Follow-up time was censored at 15 years. Study investigators, consisting of a 3-physician panel, adjudicated outcomes using established protocols after reviewing all hospital and outpatient medical records. Overall, HF was ascertained by signs and symptoms as previously described.[9] Incident HF events were categorized as heart failure with reduced ejection fraction (HFrEF) (LV ejection fraction $<$ 50%), heart failure with preserved ejection fraction (HFpEF) (LV ejection fraction $\geq$ 50%) or unclassified (LV ejection fraction was unavailable at or around time of presentation due to HF), as determined by review of the medical records.

Statistical Analysis

Baseline characteristics of FHS participants are displayed by number of live births, with individuals who experienced $\geq$ 5 live births grouped together. The primary cross-sectional analyses evaluated the association of number of live births and measures of cardiac structure and function using multivariable linear regression. Models were initially adjusted for age and then further adjusted for heart rate (HR), systolic blood pressure (SBP), history of antihypertensive therapy, BMI, total cholesterol, high density lipoprotein, smoking status, and DM. Reported regression coefficients represent difference as compared to women without histories of live births (referent group, referred to throughout the manuscript as nulliparous). We examined effect sizes for each group of live births compared with the nulliparous group as referent. We also considered live births as a continuous variable and examined *P* for trend across increasing number of live births.

In secondary analyses, we examined the association of number of live births and overall HF as well as HF subtypes. We additionally examined incident cardiovascular events, specifically MI, stroke and CVD. Participant-level data were harmonized across cohorts and pooled together. Because the maximum category of live births that could be reported in PREVEND was $\geq$ 3, main analyses included FHS, CHS and MESA, with secondary analyses including PREVEND with recategorization of maximum number of live births as $\geq$ 3. The association of number of live births with overall HF and CVD were assessed using Cox proportional hazards regression models, adjusting for age and then further adjusting for BMI, SBP, total cholesterol, high-density lipoprotein, DM, and smoking history. Data were then further adjusted for race and highest level of education completed. For HF subtypes, we fitted a Fine-Gray subdistribution hazards model to account for multiple competing risks. The Lunn-McNeil method was also used to test whether parity was associated with differential risk for HFrEF vs HFpEF. The proportionality of hazards assumption was met. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). For FHS analyses, a Bonferroni-corrected *P*

value threshold of less than 0.05/5 (= 0.01) for primary echocardiographic traits was considered for statistical significance. For remaining secondary analyses, a $P < 0.05$ was considered statistically significant.

Results

The clinical characteristics of FHS participants (n = 3931) by number of live births are reported in Table 1. In the overall sample, the average participant age was 48 ± 13 years, with older ages in groups with greater number of live births. Of the total cohort, 15% were receiving hypertension therapy, 4% had DM, and 16% were current smokers.

Greater Number of Live Births Is Associated With Lower Fractional Shortening

Among FHS participants, we examined the association of number of live births and measures of cardiac structure and function using both age-adjusted and multivariable linear regression models (Table 2). After multivariable adjustment, we observed lower fractional shortening with higher mean number of live births (Fig. 1). Specifically, women who experienced ≥ 3 live births demonstrated significantly lower LV fractional shortening when compared to nulliparous women (Table 2). In addition, myocardial strain imaging was measured as a marker of tissue deformation. Global circumferential strain was worse for increasing numbers of births after multivariable adjustment (Table 2). However, global longitudinal strain and radial strain did not demonstrate a meaningful trend across parity groups. Last, measures of myocardial synchrony were worse with increasing numbers of live births. Specifically, both longitudinal and radial dyssynchrony was greater in women with ≥ 3 live births compared with nulliparous women, although neither synchrony measure showed a significant P for trend across increasing number of live births ($P > 0.10$ for both). These findings persisted even after adjusting for highest level of education completed (Supplementary Table 1).

Measures of left atrial diameter did not differ significantly across categories of live births as compared to nulliparous women in either age-adjusted or multivariable-adjusted models (Table 2).

Coronary Artery Calcification and Carotid-Femoral Pulse Wave Velocity

CAC and PWV did not differ across categories of live births as compared to nulliparous women after multivariable adjustment (Table 2).

The Association of Number of Live Births and Incident Cardiovascular Events

Baseline characteristics of participants included in the multicohort analysis are reported by individual cohort and in aggregate (Supplementary Table 2). The mean age was highest for CHS (72 ± 5 years) and lowest for FHS (49 ± 13 years). Baseline characteristics varied by cohort. The prevalence of hypertension and diabetes was greatest in participants of CHS and MESA as compared with FHS and PREVEND. Nulliparity was slightly higher in participants of FHS (21%) as compared with PREVEND, CHS and MESA (19%, 19% and 18%, respectively).

Over 12.5 (11.4−14.1) years of follow-up, 832 HF events, 2046 major CVD events, 582 MIs, and 703 stroke events occurred. Among participants of FHS,

Table 1. Baseline Characteristics: Framingham Heart Study Participants

Characteristic	Number of Live Births						Total
	0 n = 833	1 n = 495	2 n = 1025	3 n = 838	4 n = 426	≥ 5 n = 314	n = 3931
Clinical Characteristics							
Age, years	41 (14)	46 (12)	49 (11)	51 (12)	54 (12)	56 (12)	48 (13)
Systolic blood pressure, mmHg	115 (16)	118 (18)	119 (18)	121(19)	123 (19)	125 (20)	119 (18)
Heart rate, beats per minute	64 (11)	65 (10)	64 (9)	64 (10)	64 (9)	65 (10)	64 (10)
Body mass index, kg/m^2	25.9 (6)	26.6 (6.3)	26.6 (5.9)	26.6 (5.7)	27.3 (5.6)	27.4 (5.8)	26.6 (5.9)
Hypertension treatment, n (%)	87 (10)	59 (12)	151 (15)	136 (16)	87 (20)	64 (20)	584 (15)
Diabetes mellitus, n (%)	24 (3)	24 (5)	42 (4)	38 (5)	31 (7)	23 (7)	182 (4)
Current smoker, n (%)	123 (15)	94 (19)	164 (16)	112 (13)	85 (20)	49 (16)	627 (16)
Education, n (%)							
Did not complete high school	10 (1)	15 (3)	19 (2)	17 (2)	14 (3)	15 (5)	90 (2)
High school graduate	107 (13)	89 (18)	223 (22)	211 (25)	120 (29)	93 (30)	843 (22)
Some college	192 (23)	149 (30)	355 (35)	293 (35)	152 (36)	113 (36)	1254 (32)
College graduate or above	517 (63)	238 (48)	423 (41)	312 (37)	132 (32)	89 (29)	1711 (44)
Laboratory Measures							
Total cholesterol, mg/dL	191 (39)	195 (39)	196 (37)	200 (37)	205 (37)	204 (39)	197 (38)
Triglycerides, mg/dL	105 (76)	112 (73)	110 (65)	115 (73)	129 (87)	122 (71)	113 (74)
High density lipoprotein, mg/dL	61 (16)	61 (18)	60 (18)	59 (16)	58 (16)	57 (16)	60 (16)

Note: For continuous variables, mean with standard deviation was reported.

Table 2. Association of Live Births With Measures of Cardiac Structure and Function

Measure	Live births	Age-Adjusted		MV-Adjusted	
		β (SE)	*P* value	β (SE)	*P* value
LV fractional shortening	1	−0.43 (0.25)	0.09	−0.36 (0.25)	0.16
	2	−0.49 (0.21)	0.02	−0.38 (0.21)	0.07
	3	−0.76 (0.23)	0.0008	−0.65 (0.23)	0.004
	4	−0.91 (0.28)	0.001	−0.82 (0.28)	0.004
	≥ 5	−1.25 (0.32)	<0.0001	−1.11 (0.31)	0.0005
LA diameter	1	0.03 (0.02)	0.21	0.03 (0.02)	0.18
	2	−0.01 (0.02)	0.75	−0.00 (0.02)	0.79
	3	0.02 (0.02)	0.42	0.02 (0.02)	0.20
	4	0.06 (0.03)	0.02	0.04 (0.02)	0.06
	≥ 5	−0.00 (0.03)	0.91	−0.01 (0.02)	0.59
LV mass	1	−1.36 (1.65)	0.41	−2.13 (1.42)	0.14
	2	−1.30 (1.38)	0.34	−1.37(1.19)	0.25
	3	−1.13 (1.46)	0.44	−0.85(1.27)	0.50
	4	1.57 (1.82)	0.39	0.60 (1.58)	0.70
	≥ 5	2.10 (2.04)	0.30	1.36 (1.77)	0.44
Global longitudinal strain	1	0.03 (0.18)	0.87	0.01 (0.18)	0.93
	2	0.16 (0.15)	0.31	0.18 (0.15)	0.23
	3	0.15 (0.16)	0.36	0.17 (0.16)	0.30
	4	0.05 (0.20)	0.81	−0.02 (0.20)	0.93
	≥ 5	0.45 (0.23)	0.05	0.42 (0.22)	0.06
Global circumferential strain	1	0.44 (0.30)	0.14	0.39 (0.30)	0.19
	2	0.35 (0.25)	0.16	0.27 (0.25)	0.28
	3	0.73 (0.27)	0.006	0.65 (0.27)	0.01
	4	0.94 (0.33)	0.005	0.90 (0.33)	0.007
	≥ 5	1.12 (0.38)	0.003	1.01 (0.40)	0.007
Radial strain (short axis)	1	1.20 (1.04)	0.25	1.30 (1.04)	0.21
	2	1.61 (0.88)	0.07	1.77 (0.88)	0.04
	3	2.33 (0.93)	0.01	2.56 (0.93)	0.006
	4	0.26 (1.16)	0.82	0.50 (1.16)	0.66
	≥ 5	1.88 (1.32)	0.15	2.19 (1.32)	0.10
Radial strain (apical)	1	−0.97 (0.43)	0.02	−0.91 (0.43)	0.03
	2	−0.65 (0.36)	0.07	−0.58 (0.36)	0.11
	3	−1.04 (0.38)	0.006	−0.95 (0.38)	0.01
	4	−0.78 (0.47)	0.10	−0.67 (0.47)	0.15
	≥ 5	−1.46 (0.53)	0.006	−1.30 (0.53)	0.01
Radial synchrony	1	6.21 (2.86)	0.03	6.07 (2.86)	0.03
	2	2.26 (2.41)	0.35	2.22 (2.42)	0.36
	3	6.55 (2.55)	0.01	6.56 (2.55)	0.01
	4	9.25 (3.15)	0.003	9.19 (3.17)	0.004
	≥ 5	10.80 (3.56)	0.002	10.64 (3.57)	0.003
Longitudinal synchrony	1	2.51 (2.05)	0.22	2.67 (2.04)	0.19
	2	0.23 (1.73)	0.89	0.82 (1.72)	0.63
	3	2.89 (1.83)	0.11	3.59 (1.82)	0.05
	4	6.47 (2.26)	0.004	6.76 (2.26)	0.003
	≥ 5	8.35 (2.55)	0.001	8.87 (2.54)	0.0005
CAC	1	0.22 (0.16)	0.16	0.18 (0.16)	0.25
	2	0.03 (0.13)	0.83	0.01 (0.13)	0.93
	3	−0.02 (0.13)	0.88	−0.01 (0.13)	0.90
	4	0.21 (0.16)	0.20	0.15 (0.16)	0.35
	≥ 5	−0.04 (0.17)	0.80	−0.08 (0.17)	0.62
Pulse wave velocity	1	−0.02 (0.01)	0.05	−0.01 (0.01)	0.25
	2	−0.04 (0.00)	<0.0001	−0.02 (0.01)	0.004
	3	−0.02 (0.01)	0.01	−0.01 (0.01)	0.19
	4	−0.03 (0.01)	0.02	−0.02 (0.01)	0.05
	≥ 5	−0.03 (0.01)	0.05	−0.02 (0.01)	0.08

Note: Beta estimates represent difference as compared to nulliparous women (referent group). The multivariable model adjusted for age, heart rate, systolic blood pressure, history of antihypertensive therapy, body mass index, total cholesterol, high-density lipoprotein, smoking status, and diabetes mellitus.

CAC, coronary artery calcification; LA, left atrium; LV, left ventricular; MV multivariable.

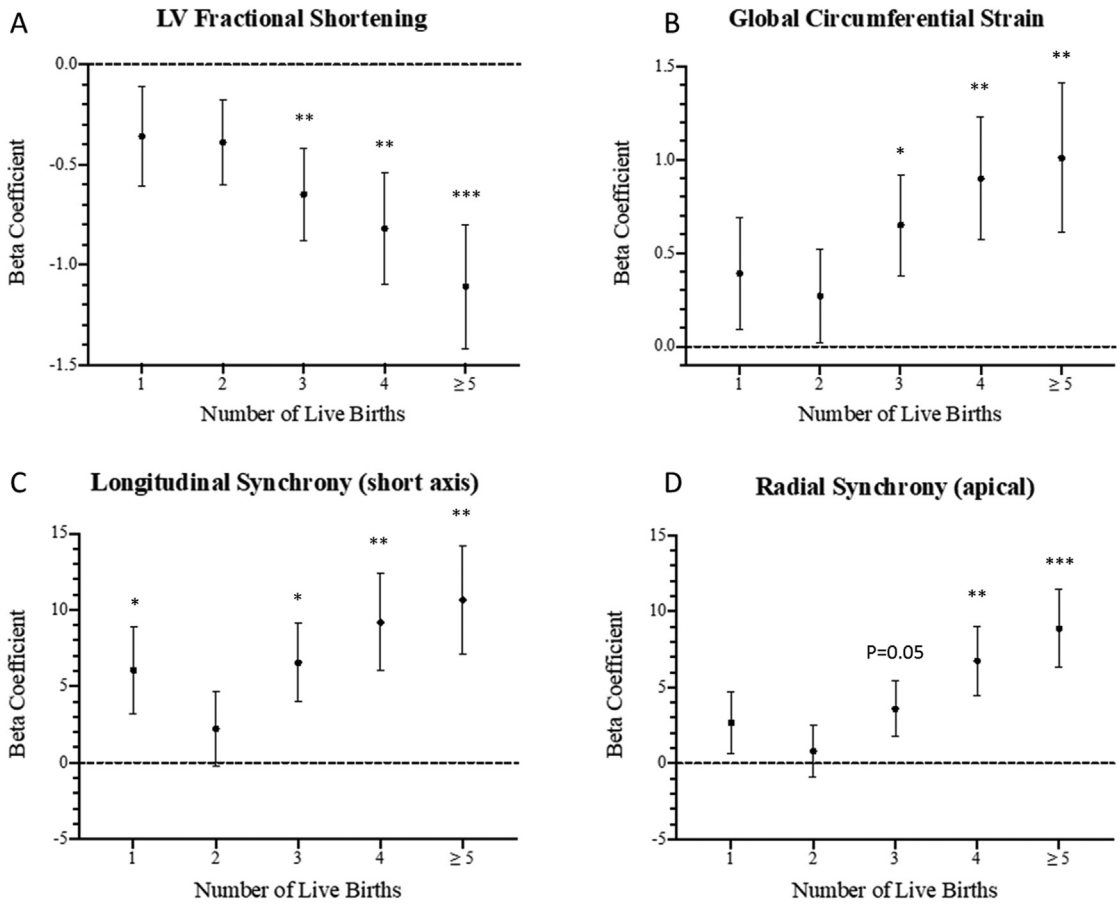


Fig. 1. Echocardiographic assessment by parity. Regression coefficients ($\beta \pm$ SE) represent difference compared to nulliparity. *$P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

CHS, and MESA, the number of live births was not associated with risk of future overall HF or major CVD (Table 3), nor with any of the components of major CVD examined, including MI and stroke (data, therefore, not shown). Similar results emerged with the inclusion of PREVEND (Supplementary Table 3). Also, no significant difference in major CVD risk was observed in individual cohorts by parity (Supplementary Table 4), with the exception of CHS, in which those with $\geq$ 5 live births demonstrated higher rates of major CVD as compared to those without histories of live birth.

Parity Is Associated With Higher Risk of HFrEF and Lower Risk of HFpEF

Of 832 overall HF events, 225 were classified as HFrEF and 298 as HFpEF; 309 events could not be classified by subtype. Although no differences in risk of overall HF by number of live births were observed, when accounting for multiple competing risks (death, other HF subtype, unclassified HF) in Fine-Gray subdistribution hazards models, greater numbers of live births were associated with increased risk of HFrEF as compared to those without histories of live births. Specifically, women with $\geq$ 5 live births had a nearly 2-fold increased risk of future HFrEF compared with nulliparous women; multivariable-adjusted HR 1.93 (95% CI 1.19−3.12; $P = 0.008$ for $\geq$ 5 live births).

By contrast, women with $\geq$ 4 live births experienced significantly less HFpEF as compared with those without histories of live births: multivariable-adjusted HR 0.58 (95% CI 0.36−0.92; $P = 0.02$) for 4 live births; HR 0.58 (95% CI 0.37−0.91; $P = 0.02$) for $\geq$ 5 live births.

We then used the Lunn-McNeil method to test whether the association of number of live births was different for HFrEF vs HFpEF (Table 4). With the exception of 2 live births, all parity categories demonstrated a differential risk of HFrEF vs HFpEF as compared with nulliparity.

In cause-specific Cox models additionally accounting for race and differences in highest level of education completed, similar findings were observed, with suggestion of higher risk of HFrEF (HR 1.87 (95% CI 1.14−3.06); $P = 0.01$ for $\geq$ 5 live births vs nulliparity (Supplementary Table 5). Further,

Table 3. Cardiovascular outcomes by number of live births

Live Births	Events (n)	Age adjusted HR (95% CI)	*P* value	MV adjusted HR (95% CI)	*P* value
Overall Heart Failure					
0	153	Referent		Referent	
1	151	1.14 (0.91−1.43)	0.25	1.16 (0.93−1.45)	0.19
2	202	0.89 (0.72−1.10)	0.28	0.92 (0.74−1.14)	0.44
3	148	1.01 (0.80−1.26)	0.96	1.02 (0.81−1.28)	0.86
4	77	0.87 (0.66−1.15)	0.34	0.91 (0.69−1.20)	0.51
≥ 5	101	1.17 (0.91−1.50)	0.23	0.99 (0.76−1.27)	0.92
HFrEF					
0	32	Referent		Referent	
1	38	1.45 (0.91−2.33)	0.12	1.50 (0.93−2.40)	0.09
2	51	1.18 (0.76−1.84)	0.46	1.20 (0.77−1.88)	0.42
3	45	1.59 (1.01−2.51)	0.05	1.62 (1.02−2.56)	0.04
4	21	1.27 (0.73−2.20)	0.39	1.29 (0.75−2.25)	0.36
≥ 5	38	2.20 (1.37−3.56)	0.001	1.93 (1.19−3.12)	0.008
HFpEF					
0	70	Referent		Referent	
1	43	0.75 (0.51−1.10)	0.14	0.74 (0.50−1.08)	0.12
2	77	0.79 (0.57−1.09)	0.15	0.80 (0.57−1.11)	0.18
3	54	0.82 (0.57−1.17)	0.27	0.81 (0.57−1.17)	0.27
4	24	0.59 (0.37−0.95)	0.03	0.58 (0.36−0.92)	0.02
≥ 5	30	0.69 (0.44−1.06)	0.09	0.58 (0.37−0.91)	0.02
Major CVD					
0	353	Referent		Referent	
1	318	1.02 (0.88−1.19)	0.78	1.03 (0.89−1.20)	0.69
2	542	0.99 (0.87−1.13)	0.89	1.00 (0.88−1.15)	0.97
3	357	0.92 (0.79−1.07)	0.28	0.94 (0.81−1.09)	0.43
4	223	1.01 (0.85−1.19)	0.95	1.03 (0.87−1.22)	0.72
≥ 5	253	1.22 (1.03−1.44)	0.02	1.07 (0.91−1.26)	0.43

Note: Outcomes reported represent data across cohorts, excluding PREVEND. HR are for Cox cause-specific hazards model with the exception of HF subtypes, where Fine-Gray models were used to account for multiple competing risks.

CVD, cardiovascular disease, inclusive of myocardial infarction, stroke, heart failure, coronary insufficiency, and peripheral arterial disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

exploratory analyses adjusting for prevalent MI did not substantively alter results (data not shown).

When including PREVEND, women with ≥ 3 live births were grouped together in accordance with data capture in this cohort. In these secondary analyses (Supplementary Table 3), there was no significant difference across categories of live births (as compared with nulliparity) with respect to overall HF or major CVD. After multivariable adjustment, women with ≥ 3 live births were at significantly lower risk of HFpEF (β 0.73 [0.54−0.98]; $P = 0.04$), whereas association of ≥3 live births with HFrEF was no longer statistically significant (HR 1.41 (0.98−2.03), $p = 0.07$).

Discussion

We studied the association of number of live births with cardiac structure and function in a rigorously phenotyped community-based sample of women and further examined the association of parity with incident cardiovascular events in a

Table 4. Differential risk of HFrEF vs HFpEF by number of live births

Live Births	MV adjusted HR (95% CI)	*P* value	MV adjusted HR (95% CI)	*P* value	**LM *P* value
	HFrEF		HFpEF		
1	1.50 (0.93−2.40)	0.09	0.74 (0.50−1.08)	0.12	0.03
2	1.20 (0.77−1.88)	0.42	0.80 (0.57−1.11)	0.18	0.15
3	1.62 (1.02−2.56)	0.04	0.81 (0.57−1.17)	0.27	0.02
4	1.29 (0.75−2.25)	0.36	0.58 (0.36−0.92)	0.02	0.03
≥ 5	1.93 (1.19−3.12)	0.008	0.58 (0.37−0.91)	0.02	0.0004

Note: Multivariable (MV) adjusted hazard ratios for heart failure with reduced ejection fraction (HFrEF) vs heart failure with preserved ejection fraction (HFpEF) when accounting for multiple competing risks in Fine-Gray subdistribution hazard models are displayed. The Lunn-McNeill method was also used to determine whether the association of number of live births was different for HFrEF vs HFpEF.

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LM, Lunn-McNeil method.

**P* value for Fine-Gray subdistribution hazard models.

***LM, *P* value represents the *P* value for the Lunn-McNeil method.

pooled analysis across 4 longitudinal cohorts. Our findings are as follows. First, greater numbers of live births were associated with lower measures of LV systolic function. Importantly, this finding was further associated with impaired cardiac mechanics. Specifically, greater numbers of live births were associated with worse global circumferential strain as well as worse myocardial dyssynchrony (Visual Abstract). This decrement in systolic function and cardiac mechanics appeared to be a graded effect across number of live births, with $\geq$ 3 live births showing significant differences compared with nulliparous women. Based on these primary findings, we examined the association of number of live births with incident cardiovascular events in secondary analyses. Of note, parity was not associated with major CVD or overall HF. However, when examining HF subtypes, we found that a greater number of live births was associated with risk of future HFrEF but not HFpEF. Specifically, women with $\geq$ 5 live births had a nearly 2-fold increased risk of future HFrEF compared with nulliparous women. Taken together, these findings suggest that a greater number of live births may be associated with lower mean LV systolic function and increased long-term risk of HFrEF.

The observation that greater parity may have an impact on future cardiovascular disease in women has been suggested by prior studies. Data from the FHS fourth examination and National Epidemiologic Follow-up Study suggested that women with $\geq$ 6 pregnancies had a small but statistically higher risk of CVD as compared to nulliparous women.[3] More recently, data from the Atherosclerosis Risk in Communities Study found that women with $\geq$ 5 births experienced higher rates of incident coronary heart disease and hospitalizations for MI.[4] In the Women's Health Study, the incidence of AF increased linearly with increasing parity in age-adjusted data (P trend = 0.004) and persisted after multivariable adjustment.[5]

The question of why parity itself may increase a woman's risk of CVD, however, has lacked a clear mechanistic explanation. A recent analysis from MESA found that multiparity (particularly $\geq$ 5 births) was associated with a higher burden of cardiovascular risk factors.[18] After multivariable adjustment, however, only BMI emerged as statistically significant, with a lower prevalence of ideal BMI among women with histories of $\geq$ 5 live births.[18] In an analysis of echocardiographic data from MESA, slightly lower mean LV ejection fraction was observed with each pregnancy along with higher mean LV mass and LV end-systolic and end-diastolic dimensions, with changes most notable in women with parity $\geq$ 5.[19] Our findings extend these prior studies; we found both lower mean LV systolic function in individuals with greater numbers of live births and abnormal cardiac mechanics, including global circumferential strain and synchrony measures.

Assessment of LV myocardial strain has emerged as a more sensitive marker of subclinical ventricular dysfunction than assessments of ejection fraction. Across a spectrum of cardiovascular disease states, strain abnormalities are known to emerge, even in the absence of impairments in LV ejection fraction.[20] In patients with histories of anthracycline exposure without LV systolic dysfunction or clinical HF, global circumferential strain may also serve as a more sensitive marker of subclinical LV dysfunction.[21] Our study builds on these observations, with lower global circumferential strain and fractional shortening in women with $\geq$ 3 live births as compared to nulliparous women, though global longitudinal strain did not vary significantly across parity groups.

Notably, other structural changes were not appreciated. Although markers of left atrial size and function have previously emerged as strong predictors of cardiovascular outcomes in FHS, the number of live births was not associated with left atrial size.[22] Similarly, although prior data have suggested an increased risk of carotid plaque at higher levels of live births, CAC did not differ significantly by category of live births in the current analysis.[23]

Among women included in the pooled, multicohort analysis, those with $\geq$ 5 births were at significantly elevated risk for development of HFrEF as compared with nulliparous women, though overall HF risk did not differ. Previous analyses have demonstrated an association between worsening global circumferential strain and development of incident HF.[24] Similarly, our data demonstrating that higher levels of parity were associated with worse fractional shortening and global circumferential strain, as well as greater mechanical dyssynchrony, provide a logical mechanistic explanation for the finding of a higher prevalence of HFrEF that merits further investigation. Interestingly, despite prior data suggesting greater impairments in LV diastolic function with increasing numbers of live births,[25] our data demonstrated a decreased risk of HFpEF among women with $\geq$ 4 live births as compared with nulliparous women, though overall event rates were low, and 37% of events could not be classified by systolic function. This finding was unexpected, especially given the greater age and higher prevalence of risk factors for HfpEF, including BMI, hypertension and DM in those with higher parity. One explanation may be the competing risks of the 2 HF subtypes; therefore Fine-Gray subdistribution hazard models were fitted to account for multiple competing risks. In addition, the Lunn-McNeil method[26] was used to test whether the association of number of live births was different with HFrEF vs HFpEF; the finding showed consistent results for most parity categories.

However, further investigation is required to better understand the potential mechanisms that could account for this finding.

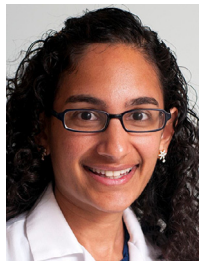
Limitations

Our analysis has several strengths, but there are some limitations that must be noted. First, self-reported reproductive histories did not capture the number of pregnancies women had experienced but that did not result in live births. It is, therefore, possible that women without histories of live births in this analysis had comorbidities (eg, infertility or multiple miscarriages) that increased their risk for adverse cardiovascular outcomes and could not be accounted for. In addition, multifetal pregnancy was not assessed or specified in the available data. Further, although it is well known that hypertensive disorders of pregnancy, preterm delivery, delivery of small-for-gestational-age infants, and gestational diabetes increase women's risk of future CVD, these components of the reproductive histories were not reliably assessed in the available cohorts, highlighting the need to collect comprehensive reproductive histories in contemporary cohorts and trials. The majority of patients were postmenopausal at the time of study enrollment (77% of FHS examination 6, 85% of MESA and 96% of CHS). It is possible that births that occurred after data collection were not accounted for, but it is unlikely that this would significantly alter the results, given the postmenopausal status of most participants. Lack of rigorous collection of these data in the current and in other cardiovascular datasets remains an important limitation to understanding how these important cardiovascular risk factors contribute to future cardiovascular risk. We also acknowledge that the echocardiographic data available did not include LV ejection fraction by the Simpson biplane nor LV volumes, limiting inferences on these measures. Last, stratified analyses by cohort were limited by modest power within each sample, and heterogeneity across cohorts may have influenced results.

Prior studies have suggested that both women and men with higher numbers of offspring are less likely to adhere to optimal cardiovascular lifestyles.[18] The current data were adjusted for BP, BMI, lipids, smoking status, DM, race, and highest level of education completed, but one cannot exclude the possibility of residual confounding that may account for differences observed at higher parity categories. Further, ethnic/racial diversity was limited in several cohorts. Finally, given that all live-birth categories were compared with nulliparous women as the referent group, it remains possible that the associations observed could reflect a protective effect of nulliparity rather than an adverse effect of multiparity.

Conclusion

Compared to nulliparous women, those who experienced greater numbers of live births were at higher risk for later-life LV systolic dysfunction and worse cardiac mechanics, as reflected by worse fractional shortening, global circumferential strain and greater mechanical dyssynchrony. We also observed that although overall risk of HF is not associated with number of live births, women with histories of multiple live births ($\geq$ 5) are at higher risk for HFrEF but may be at lower risk for HFpEF. Taken together, these findings underscore the possibility that greater parity may be associated with adverse effects on LV systolic function and long-term risk of HFrEF. Further research is required to understand better the factors that may contribute to impairments in LV systolic function with higher levels of parity in order to improve the long-term care of multiparous women.



Proposed Tweet

A greater number of live births is associated with (1) worse cardiac structure and function vs nulliparity in participants in the Framingham Heart Study and (2) increased risk of HFrEF @JCardFail.

@sarma_amy

@JenHoCardiology

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.12.014.

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