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ORIGINAL RESEARCH PAPER

Female Reproductive Factors and Risk of New-Onset Heart Failure

Findings From UK Biobank

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ABSTRACT

BACKGROUND A comprehensive evaluation of woman-specific risk factors in relation to incident heart failure (HF) is limited.

OBJECTIVES The study sought to investigate the association of multiple female reproductive factors with the risk of HF.

METHODS Between 2007 and 2010, 229,026 women (mean age: 56.5 years) without prevalent HF from the UK Biobank cohort were included and followed until December 2020. The relation between (self-reported) reproductive factors and HF was analyzed using Cox proportional hazards models with adjustment for potential confounding.

RESULTS Menarche at age <12 years, compared to age 12-13 years, carried a 9% larger risk of HF (HR: 1.09 [95% CI: 1.01-1.18]). Younger age at menopause was associated with a higher risk of HF ($HR_{age < 45\ y\ vs\ 50\text{-}51\ y}$: 1.15 [95% CI: 1.03-1.28]; $HR_{age\ 45\text{-}49\ y\ vs\ 50\text{-}51\ y}$: 1.11 [95% CI: 1.01-1.23]). Younger maternal age at first live birth ($HR_{age < 21\ y\ vs\ 24\text{-}26\ y}$: 1.42 [95% CI: 1.28-1.59]; $HR_{age\ 21\text{-}23\ y\ vs\ 24\text{-}26\ y}$: 1.14 [95% CI: 1.03-1.26]) and at last live birth ($HR_{age < 26\ y\ vs\ 29\text{-}31\ y}$: 1.19 [95% CI: 1.07-1.33]) were associated with higher risk of HF. Compared to women with 1 or 2 children, having 3 or 4 children (HR: 1.09 [95% CI: 1.02-1.17]) or >4 children (HR: 1.24 [95% CI: 1.05-1.47]) was associated with higher HF risk. Experiencing miscarriages or abortions was not significantly associated with incident HF, whereas experiencing 1 stillbirth and recurrent stillbirths conferred a 20% and 43% larger risk of HF, respectively, compared to no stillbirth.

CONCLUSIONS The findings emphasize the importance of female reproductive history in the assessment of HF risk. (J Am Coll Cardiol HF 2023;■:■-■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Heart failure (HF) is among the leading causes of hospitalization, inflicting considerable morbidity and mortality. It affects more than 40 million people worldwide, and the overall incidence increases parallel to the aging of the population.[1] Sex affects almost every facet of HF, from epidemiology and risk factors to pathophysiology, clinical manifestation, and progression.[2,3]

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CVD = cardiovascular disease

HF = heart failure

However, large gaps in knowledge exist in sex-specific mechanisms, especially for women, and treatment guidelines are predominantly based on data from male patients.[2] This warrants a better understanding of woman-specific risk factors in the development of HF.

The complex interplay between reproductive health and the development of cardiovascular disease (CVD) in women is increasingly gaining attention. From menarche to menopause and pregnancy, women undergo important changes in sex hormones. Sex hormones affect cardiovascular health, including lipid profiles, response to insulin, blood pressure, vascular reactivity, inflammation, cardiac remodeling, and HF development.[4-9] In addition, pregnancy involves alterations in cardiovascular hemodynamics, inflammatory, and metabolic disorders.[10-12] As such, women's reproductive characteristics are implicated in the pathophysiology of HF. Although a variety of reproductive factors have been examined in association with atherosclerosis and CVD, a comprehensive evaluation of the potential impact of a wide range of reproductive factors on HF development is sparse.[5,13,14] One recent UK Biobank Study by Peters et al[15] reported associations between factors related to menstruation, menopause, pregnancy, and childbirth with the increased risk of CVD but did not include HF events. Exploring the association of woman-specific risk factors with HF risk could improve our understanding of HF pathogenesis and facilitate strategies to modify potential risks at an early stage.

Using the UK Biobank cohort, we investigated the association of a comprehensive set of female reproductive factors, including age at menarche, age at menopause, maternal age at the first and last live birth, number of live births, and pregnancy complications with incident HF.

METHODS

STUDY POPULATION. The UK Biobank is a prospective population-based cohort that recruited more than 500,000 participants aged 37 to 73 years from 22 assessment centers across England, Scotland, and Wales. Details of the study design and data collection have been described previously.[16] Between 2007 and 2010, individuals were invited to attend the baseline assessment, which included questionnaires soliciting information on lifestyle, medical history, and reproductive history. Physical measurements were collected, and a blood sample was taken. All UK Biobank participants provided written informed consent, and the North West Multi-Center Research Ethics Committee granted ethical approval.

Among women within UK Biobank (n = 273,329), we extracted 229,614 participants with available information on reproductive factors (including age at menarche and menopause, number of live births, hysterectomy, and/or bilateral oophorectomy). We further excluded those with a history of HF or without follow-up (n = 588). Finally, 229,026 women were included. Of note, associations of different reproductive risk factors with incident HF were explored in specific subgroups with valid data. The association of age at menopause with incident HF was explored among postmenopausal women with a valid menopausal age (n = 159,645); the associations of maternal age at the first and last live births with incident HF were explored among parous women with information on age at live birth (n = 155,004).

ASSESSMENT OF WOMAN-SPECIFIC RISK FACTORS. Self-reported reproductive factors included in this research were age at menarche, age at menopause, (age at) hysterectomy, (age at) oophorectomy, maternal age at the first and last live birth, number of live births, number of stillbirths, number of miscarriages, number of abortions, and history of use of hormone replacement therapy and use of oral contraceptives. Reproductive lifespan duration was defined as the duration between menopause age and menarche age. The answers "Prefer not to answer" and "Do not know" were set as "missing."

OUTCOME. This study set the baseline as the visit at which a participant attended the UK Biobank baseline assessment (2007-2010). HF was defined using International Classification of Diseases-10th Revision (ICD-10) with code I50. Participants were followed for the occurrence of the HF event, death, or end of the follow-up time (December 31, 2020), whichever came first.

MEASUREMENT OF OTHER COVARIATES. Socioeconomic status was determined using the Townsend Deprivation Index. Blood pressure was taken at baseline using the Omron HEM-7015IT digital blood pressure monitor as the mean of 2 measurements. Serum lipid concentrations were measured using the Beckman Coulter AU580. Height and weight were measured, and body mass index was calculated as weight (kg)/(height [m])^2. Self-reported information on ethnicity, smoking status, alcohol intake, and medication use were collected. Ethnicity was categorized as White population and other races. Smoking status was categorized as never, former, and current smokers. Alcohol intake was categorized into following 4 groups: daily, 1-4 times/week, <1 time/week, and

never. Prevalent cardiometabolic disorders at baseline were defined using the ICD-10 codes, including hypertension (I10-I15), diabetes mellitus (E10-E14), coronary heart disease (CHD) (I21-25), stroke (I60-I63), and atrial fibrillation (I48). A history of CVD was a combination of prevalent CHD, stroke, or atrial fibrillation. The details of data collection have been described elsewhere.[16]

STATISTICAL ANALYSIS. Baseline characteristics of the study population are presented as mean ± SD for continuous variables and number (percentage) for categorical variables.

We used Cox proportional hazards models to estimate HRs and 95% CIs for the association of female reproductive factors with incident HF. All reproductive factors were assessed both on a continuous scale and on a categorical scale. First, the nonlinearity of the associations between the continuous scale of reproductive factors and incident HF was tested with likelihood ratio tests comparing linear terms with natural cubic splines (5 knots). Effect plots were made to display the nonlinear associations. Next, for those risk factors with nonlinear associations with incident HF, we further categorized the variables by cutoffs at 20%, 40%, 60%, and 80% and divided participants into 5 groups to facilitate the interpretation. The middle group was selected as the reference group.

Analyses were adjusted for potential confounders in 2 consecutive models. Model 1 was adjusted for age. Model 2 was further adjusted for ethnicity, Townsend index, body mass index, waist, alcohol consumption, smoking status, systolic blood pressure, blood pressure-lowering medication, total and low-density lipoprotein cholesterol, lipid-lowering medication, history of diabetes, history of CVD, use of hormone replacement therapy, use of oral contraceptives, and history of hysterectomy and/or oophorectomy. We did not include physical activity and high-density lipoprotein cholesterol in the final model, mainly because of their high missing rate (>15%). Of note, these 2 variables were not significantly associated with incident HF in the univariate model ($P > 0.2$). The proportional hazards assumptions were tested using the Schoenfeld residuals and were not violated.

Several sensitivity analyses were conducted. First, we further adjusted for the number of live births (categorical level: 0, 1-2, 3-4, >4) when exploring the association of maternal age at first and last live birth and of pregnancy loss with incident HF, because multiparity may be a confounder. Second, considering that hysterectomy and/or oophorectomy may affect birth-related characteristics and menopause and impose marked differences in sex hormone levels, we performed sensitivity analyses by excluding women who underwent hysterectomy and/or oophorectomy. Third, we repeated analyses among women without prevalent CHD at baseline to help provide additional evidence of pathophysiology. Fourth, we repeated our analyses among the subgroup of women aged >49 years, because the length of follow-up (median: 11.8 years) was not sufficient for occurrence of our outcomes of interest among younger women (eg, those aged 37-49 years at baseline) and because women aged <50 years have a low HF prevalence.[17] Furthermore, we checked multicollinearity between age at first live birth and age at the last live birth.

The maximum missing rate for covariates was up to 6.5% of the participants. Missing values in covariates were imputed using the multiple imputation method using the "mice" package in R. Ten imputed data sets were generated. Two-sided *P* values were considered significant at $P < 0.05$. Statistical analyses were performed with the use of R version 4.0.3.

RESULTS

BASELINE CHARACTERISTICS. **Table 1** shows the baseline characteristics of the study population. The study included a total of 229,026 women with a mean ± SD age of 56.5 ± 8.1 years. Of those, 3.4% had prevalent diabetes, and 2.7% of participants had a history of CVD at baseline; 168,584 (73.6%) women were postmenopausal at baseline; 31,371 (13.7%) women had a history of hysterectomy and/or oophorectomy; and 194,593 (85.0%) women had ever been pregnant.

FOLLOW-UP. HF occurred in 4,202 participants during a median of 11.8 (IQR: 11.1-12.6) years of follow-up, and the incidence rate was 1.58 per 1000 person-years. Crude HF incidence rates among subgroups are reported in Supplemental Table 1.

FACTORS RELATED TO MENARCHE AND MENOPAUSE. In fully adjusted models (**Table 2**, model 2), age at menarche, age at menopause, and reproductive lifespan showed nonlinear associations with incident HF. The effect plots are displayed in **Figure 1**. After categorizing the variables, a younger age at menarche (<12 years), but not older age at menarche (>13 years), conferred a 9% elevated risk of HF (HR: 1.09 [95% CI: 1.01-1.18]) compared to the middle group. A younger age at menopause was associated with a higher risk of HF ($HR_{age < 45\ y\ vs\ 50\text{-}51\ y}$: 1.15 [95% CI: 1.03-1.28]; $HR_{age\ 45\text{-}49\ y\ vs\ 50\text{-}51\ y}$: 1.11 [95% CI: 1.01-1.23]). A shorter reproductive lifespan was also associated with a greater risk of HF ($HR_{age < 33\ y\ vs\ 36\text{-}38\ y}$: 1.16 [95% CI: 1.05-1.29]; $HR_{age\ 33\text{-}35\ y\ vs\ 36\text{-}38\ y}$: 1.23 [95% CI:

TABLE 1 Baseline Characteristics of the Study Population (N = 229,026)

Age, y	56.5 ± 8.1
White ethnicity	207,495 (90.6)
Townsend index	−1.4 ± 3.0
Waist, cm	84.5 ± 12.4
Body mass index, kg/m^2	27.0 ± 5.1
Low-density lipoprotein cholesterol, mmol/L	3.6 ± 0.9
Total cholesterol, mmol/L	5.9 ± 1.1
Lipid-lowering medication	28,328 (12.5)
Systolic blood pressure, mm Hg	135.3 ± 19.3
Blood pressure-lowering medication	39,235 (17.3)
Alcohol intake	
Daily	37,537 (16.4)
1-4 times/wk	107,012 (46.8)
<1 time/wk	63,337 (27.7)
Never	21,005 (9.2)
Smoking status	
Never	135,945 (59.6)
Former	72,459 (31.7)
Current	19,878 (8.7)
History of diabetes mellitus	7,831 (3.4)
History of cardiovascular disease	6,181 (2.7)
History of hysterectomy and/or oophorectomy	31,371 (13.7)
Testosterone, nmol/L	1.1 (0.6)
Sex hormone binding globulin, nmol/L	62.1 (30.6)
Ever use of hormone replacement therapy	86,404 (37.7)
Ever use of oral contraceptive	185,357 (80.9)
Age at menarche, y	13.0 ± 1.6
Postmenopausal	168,584 (73.6)
Age at menopause, y	49.6 ± 5.5
Reproductive lifespan, y	36.9 ± 5.7
Ever pregnant	194,593 (85.0)
Maternal age at the first live birth, y	25.4 ± 4.6
Maternal age at the last live birth, y	30.4 ± 4.9
Number of live births	
0	43,135 (18.8)
1-2	131,193 (57.3)
3-4	51,082 (22.3)
>4	3,616 (1.6)
Number of miscarriages or abortions	
0	123,285 (63.4)
1	27,941 (14.3)
≥2	43,367 (22.3)
Number of stillbirths	
0	188,702 (97.0)
1	5,077 (2.6)
≥2	814 (0.4)

Values are n (%) or mean ± SD.

1.10-1.36]). The years after menopause were associated with a higher risk of HF ($HR_{per\ 10\ years}$: 1.12 [95% CI: 1.06-1.19]).

FACTORS RELATED TO CHILDBIRTH AND PREGNANCY. Maternal age at first and last live births and number of live births showed nonlinear associations with incident HF (Figure 1). A younger maternal age at first live birth ($HR_{age\ <\ 21\ y\ vs\ 24\text{-}26\ y}$: 1.42 [95% CI: 1.28-1.59]; $HR_{age\ 21\text{-}23\ y\ vs\ 24\text{-}26\ y}$: 1.14 [95% CI: 1.03-1.26]) and a younger maternal age at last live birth ($HR_{age\ <\ 26\ y\ vs\ 29\text{-}31\ y}$: 1.19 [95% CI: 1.07-1.33]) were associated with a higher risk of HF. Advanced maternal age at first or last live birth did not show significant association with incident HF. Among women who gave birth (n = 194,593), compared to women with 1 or 2 children, having 3 or 4 children had a 1.09-fold (95% CI: 1.02-1.17) increase in risk of HF, and having more than 4 children had a 1.24-fold (95% CI: 1.05-1.47) increase in risk of HF. The history of miscarriages or abortions did not show significant association with incident HF, whereas women who experienced 1 stillbirth had a 1.20-fold (95% CI: 1.02-1.40) increase in risk of HF, and those who experienced 2 or more than 2 stillbirths had a 1.43-fold (95% CI: 1.00-2.03) increase in risk of HF, compared to those without a history of stillbirth.

SENSITIVITY ANALYSES. There were low correlations between number of live births and maternal age at the first live birth (Spearman correlation coefficient $r = -0.27$), maternal age at the last live birth ($r = 0.23$), number of miscarriages or abortions ($r = -0.07$), and number of stillbirths ($r = 0.04$), which implies low multicollinearity. Therefore, we included number of live births into model adjustment when exploring the association of maternal ages and pregnancy loss with incident HF. The results of sensitivity analyses are similar to the main results (Supplemental Table 2). Age at first live birth and age at last live birth were moderately correlated (Pearson correlation coefficient: 0.677; $P < 0.001$). After we included both last live birth age and first live birth age in the model, age at last live birth was no longer associated with incident HF, which implies multicollinearity.

The associations of early menarche and stillbirth with incident HF became nonsignificant among women without a history of hysterectomy and/or oophorectomy (Supplemental Table 3), and the remaining results were consistent with the main results. After excluding those with a history of CHD at baseline, the association between stillbirth and incident HF was attenuated but remained significant, and all other factors showed larger HRs for incident HF (Supplemental Table 4). Among the subgroup of women aged over 49 years, the association between female reproductive factors and incident HF did not change substantially compared to the main results (Supplemental Table 5).

TABLE 2 Association of Reproductive Factors With Incident Heart Failure

Reproductive Factors	Age-Adjusted Model		Multivariable Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at menarche, y				
<12	1.29 (1.19-1.40)	<0.001	1.09 (1.01-1.18)	0.037
12-13	1.00 (Ref.)	—	1.00 (Ref.)	—
>13	1.07 (1.00-1.14)	0.068	1.06 (0.98-1.13)	0.131
Age at menopause,[a] y				
<45	1.53 (1.38-1.70)	<0.001	1.15 (1.03-1.28)	0.015
45-49	1.20 (1.09-1.33)	<0.001	1.11 (1.01-1.23)	0.037
50-51	1.00 (Ref.)	—	1.00 (Ref.)	—
52-53	0.93 (0.83-1.04)	0.180	0.94 (0.84-1.05)	0.258
>53	1.04 (0.94-1.15)	0.474	0.99 (0.90-1.10)	0.873
Reproductive lifespan,[a] y				
<33	1.47 (1.34-1.62)	<0.001	1.16 (1.05-1.29)	0.003
33-35	1.32 (1.19-1.47)	<0.001	1.23 (1.10-1.36)	0.001
36-38	1.00 (Ref.)	—	1.00 (Ref.)	—
39-41	1.00 (0.91-1.11)	0.950	0.98 (0.89-1.08)	0.683
>41	1.09 (0.98-1.21)	0.104	1.01 (0.91-1.12)	0.863
Years after menopause, per 10 y[a]	1.33 (1.25-1.40)	<0.001	1.12 (1.06-1.19)	<0.001
Maternal age at first live birth,[b] y				
<21	2.08 (1.87-2.31)	<0.001	1.42 (1.28-1.59)	<0.001
21-23	1.37 (1.24-1.52)	<0.001	1.14 (1.03-1.26)	0.015
24-26	1.00 (Ref.)	—	1.00 (Ref.)	—
27-29	0.90 (0.80-1.02)	0.102	0.95 (0.84-1.08)	0.453
>29	0.87 (0.76-1.01)	0.061	0.97 (0.84-1.11)	0.632
Maternal age at last live birth,[b] y				
<26	1.42 (1.28-1.58)	<0.001	1.19 (1.07-1.33)	0.001
26-28	1.16 (1.05-1.29)	0.005	1.09 (0.98-1.21)	0.101
29-31	1.00 (Ref.)	—	1.00 (Ref.)	—
32-35	0.95 (0.84-1.06)	0.348	0.96 (0.86-1.08)	0.515
>35	1.05 (0.92-1.20)	0.459	1.05 (0.92-1.20)	0.437
Number of live births[c]				
0	1.07 (0.88-1.31)	0.484	0.93 (0.76-1.14)	0.483
1-2	1.00 (Ref.)	—	1.00 (Ref.)	—
3-4	1.22 (1.14-1.31)	<0.001	1.09 (1.02-1.17)	0.018
>4	2.01 (1.71-2.37)	<0.001	1.24 (1.05-1.47)	0.011
Number of miscarriages or abortions[c]				
0	1.00 (Ref.)	—	1.00 (Ref.)	—
1	1.03 (0.93-1.13)	0.557	1.01 (0.92-1.11)	0.810
≥2	1.13 (1.04-1.23)	0.005	1.02 (0.94-1.11)	0.628
Number of stillbirths[c]				
0	1.00 (Ref.)	—	1.00 (Ref.)	—
1	1.42 (1.21-1.67)	<0.001	1.20 (1.02-1.40)	0.031
≥2	2.02 (1.42-2.88)	<0.001	1.43 (1.00-2.03)	0.049

Multivariable models were adjusted for age (with 5 natural spline knots), ethnicity, Townsend index, body mass index, waist, smoking status, systolic blood pressure, blood pressure–lowering medication, diabetes mellitus, total and low-density lipoprotein cholesterol levels, lipid-lowering medication, history of cardiovascular disease, use of hormone replacement therapy, use of oral contraceptives, and history of hysterectomy and/or oophorectomy. [a]Among postmenopausal women with valid menopausal age (n = 159,645). [b]Among parous women with live birth age information (n = 155,004). [c]Among parous women with birth information (n = 194,593).

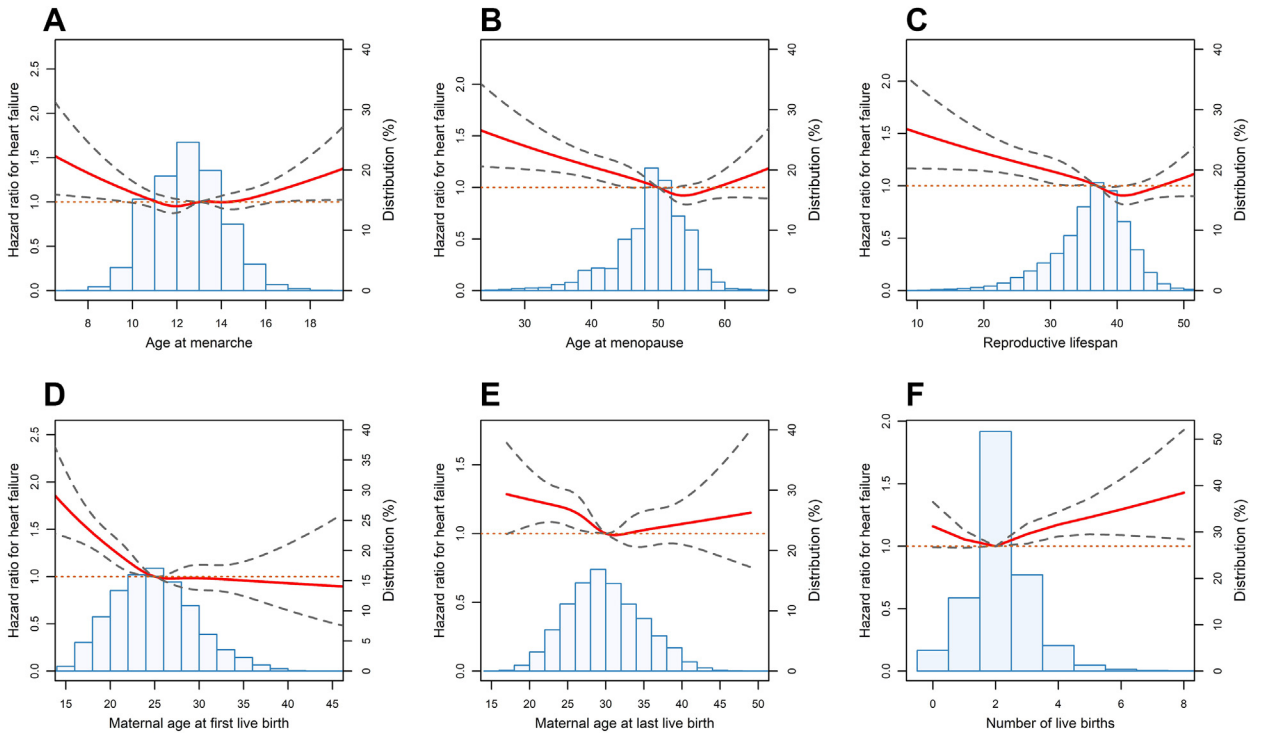
Ref. = reference.

DISCUSSION

In this large prospective study of 229,026 women, we found that younger age at menarche and menopause, shorter reproductive lifespan, younger maternal age at first or last live birth, larger number of live births, and experiencing stillbirth were associated with higher HF risk in later life, independent of traditional cardiovascular risk factors (Central Illustration).

CLINICAL IMPLICATIONS. A woman's reproductive period provides an important window into her lifetime risk of HF. Information on female reproductive

FIGURE 1 Effect Plots for Nonlinear Associations of Reproductive Factors With Incident Heart Failure

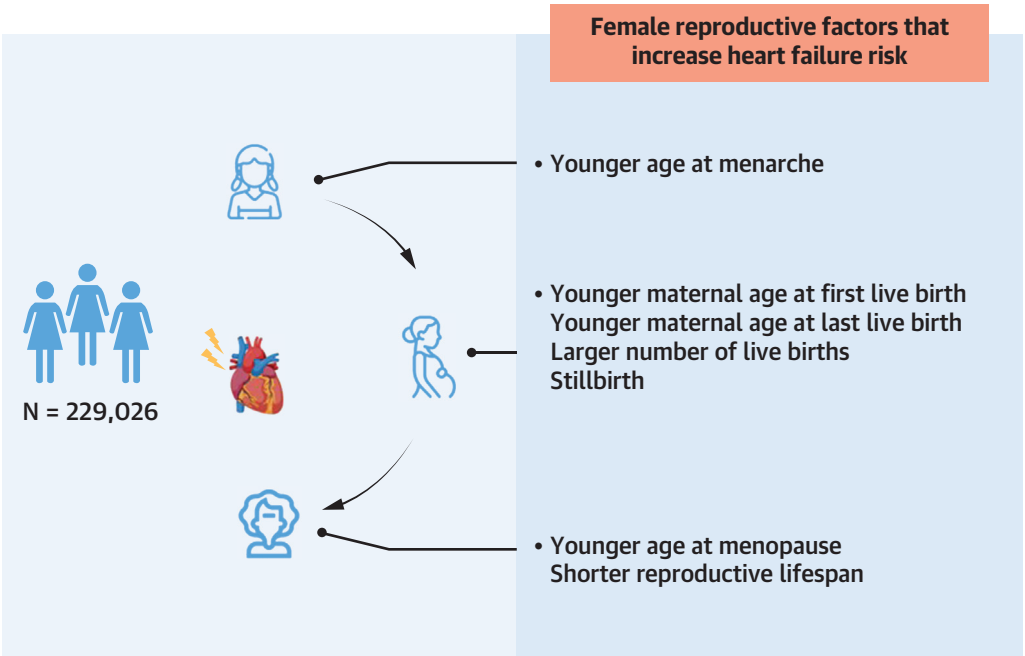


factors are economic and convenient indicators that can be obtained without clinical examinations. Our findings emphasize that age at menarche, maternal age, number of pregnancies, pregnancy loss, and timing of menopause are markers of HF risk. These woman-specific risk factors contribute to sex differences in HF pathogenesis and disease burden. Moreover, risk assessment should be regarded as an iterative process as new information on female reproductive health becomes available. This longitudinal knowledge can facilitate optimization of cardiovascular health for women throughout their life course.

MENARCHE AND MENOPAUSE. Early age at menopause, a surrogate marker for women's lifetime exposure to endogenous estrogens, has been codified as a risk-enhancing factor for atherosclerotic CVD in recent guidelines.[5,18] We confirmed the earlier findings that early menopause and shorter reproductive lifespan predispose women to new-onset HF.[3,13,19-21] Notably, we reported that age at menopause and reproductive lifespan had nonlinear associations with incident HF. In sensitivity analyses, early menopause remained a risk factor of HF among women who experienced natural menopause. Meanwhile, another UK biobank study has reported that premature menopause (menopause age of <40 years), whether natural or surgical, increases risk for various CVD outcomes including HF.[22] The underlying mechanisms could be that early menopause leads to reduced lifetime exposure to endogenous estrogens, and lower exposure to endogenous estrogen may contribute to endothelial dysfunction, inflammation, and immune dysfunction[7] and further impair cardiac function.[7,23] Honigberg et al[24] found that early menopause was related to accelerated left ventricular remodeling and elevated risk of HF. In addition, it has been proposed that cardiovascular risk profiles before menopause determine age at menopause, suggesting a bidirectional relation between premature menopause and cardiovascular risk.[25] Whether early menopause serves as a risk signal or causally affects future cardiovascular risk requires further research.

The observed association of early menarche with higher HF risk was unexpected if based solely on exposure to female sex hormones. Indeed, previous studies have also found early menarche (<12 years) to be a risk factor for CVDs[13,21] and mortality,[26,27] and a U-shaped relationship may exist.[26] Early menarche may even increase risk of premature menopause.[28] Considering that menarche happens in the early stage of a woman's life, later changes, including

CENTRAL ILLUSTRATION **Female Reproductive Factors and Risk of New-Onset Heart Failure: Findings From UK Biobank**



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lifestyle, environment, or various diseases, may alter the observed association. Therefore, future studies including time-varying confounders can shed more light on the observed associations.

MATERNAL AGE AT LIVE BIRTH. We found that younger maternal age at the first or last live birth was a risk factor for incident HF. Previous research has suggested that younger maternal age at pregnancy may be associated with CVD,[15,29] but there is no sufficient evidence for HF events. Two potential hypotheses about the underlying mechanisms could be considered. First, women with younger maternal age at the first live birth are more likely to have a larger number of parities, and multiparity has been defined as a risk factor of HF in the current study. However, further adjustment for the number of live births in our sensitivity analyses did not change the results, indicating that multiparity had a limited impact. Second, women with younger maternal age at first birth are more likely to have lower education level,[30] poorer health status, and larger burden of comorbidities,[31] which increase HF risk. Although we adjusted for the Townsend index, there may still be some residual confounding. Previous research demonstrated that social, cultural, and behavioral factors, rather than biological pathways, may have a larger contribution to the association of younger age at first birth with worse cardiovascular risk profiles,[31] as well as for the risk of later CHD and stroke.[15] Therefore, this calls for more consideration and interventions, including socioeconomic support, for women who experienced premature childbearing because these women have higher cardiovascular risk in later life.

NUMBER OF LIVE BIRTHS. We observed that a larger number of live births was associated with a higher risk of HF among parous women. Pregnancy and childbirth are accompanied by physiologic adaptations, including changes in sex hormones, insulin resistance, abnormal lipid profiles, fat accretion, and inflammation.[12] Although these changes are reversible, the long-term hormonal fluctuations and metabolic disorders associated with multiparity may have latent effects, thus producing long-term alterations in cardiovascular risk factors.[32] Behavioral and lifestyle changes during pregnancy, such as reduction in physical activity levels and increased caloric intake, may contribute to risk of obesity, especially abdominal obesity.[33] These factors may lead to future development of metabolic syndrome[12] and poorer cardiovascular health.

PREGNANCY COMPLICATIONS. Pregnancy complications may affect short- and long-term cardiometabolic trajectories and induce adverse cardiovascular outcomes to women in later life.[10,11,34,35] Although nulliparity (that included having ever experienced miscarriage, abortion, or stillbirth) was not associated with larger HF risk, we found that a history of stillbirth, but not miscarriage or abortion, was a risk factor for incident HF. After excluding those with a history of CHD at baseline, the association between stillbirth and HF was slightly attenuated, indicating that ischemia may be involved in the mechanisms by which stillbirth contributes to later HF development. Using UK Biobank data, Peters et al[15] found that a history of miscarriage was associated with a higher risk of CHD but not of stroke, whereas a history of stillbirth was associated with a higher risk of stroke but not of CHD. Ranthe et al[36] reported that stillbirths and miscarriages were both associated with subsequent risks of myocardial infarction and cerebral infarction and that stillbirth was a stronger risk factor than miscarriage. Pregnancy loss may be etiologically linked to CVD by shared mechanistic pathways, such as endothelial dysfunction[37] and autoimmune disorders,[38] which result in poor placental function and increased CVD risk.[39] It is also worth noting that cardiometabolic disorders partly contribute to pregnancy loss. Further research is warranted to elucidate how different types of pregnancy loss are implicated in the pathophysiology of cardiac dysfunction.

STUDY STRENGTHS AND LIMITATIONS. The major strengths of this study include the large sample size, a long follow-up, and the availability of detailed information on reproductive factors. There are a few limitations. First, the study participants were primarily of White ancestry; whether the findings can be generalized to other ethnic groups requires further investigation. Second, information on reproductive factors was self-reported, which may lead to recall bias. However, the recall bias for reproductive factors is most likely nondifferential with regard to the outcome, because the exposures (ie, age at menarche) were assessed long before the occurrence of the outcome. Third, a healthy volunteer selection bias of UK Biobank has been previously reported,[40] which may underestimate the true associations. Fourth, some factors including gestational diabetes, preeclampsia, and breastfeeding have been linked to HF risk in previous research.[41,42] We did not have information on these, which would otherwise capture a more comprehensive female reproductive risk profile. Fifth, although we adjusted for traditional cardiovascular risk factors, they were single measurements at the baseline of the study, and we cannot rule out the possibility of confounding resulting from the changes of these confounders over time. Furthermore, the lack of adjustment for multiple testing could be a potential limitation. Finally, we cannot define HF subtypes, which also exert substantial sex differences. (HF with preserved ejection fraction is more common in postmenopausal women.[17]) It is plausible that different reproductive factors are responsible for different types of HF. Hence, we added sensitivity analyses by excluding women with prevalent CHD.

CONCLUSIONS

Female reproductive factors were associated with new-onset HF, independent of traditional cardiovascular risk factors. Our findings carry the premise for understanding HF pathogenesis and highlight the opportunities for using reproductive factors to identify women at high risk of HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although various woman-specific risk factors have been examined in association with adverse cardiovascular outcomes, a comprehensive evaluation of the potential impact of a wide range of reproductive factors on HF development is sparse. Using the UK Biobank cohort, we included 229,026 women and found that younger age at menarche and menopause, shorter reproductive lifespan, younger maternal age at first or last live birth, larger number of live births, and a history of stillbirth were associated with higher HF risk in later life.

TRANSLATIONAL OUTLOOK: Our findings carry the promise for a better understanding of the HF pathogenesis in women and emphasize the importance of female reproductive history in HF risk assessment.

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