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ORIGINAL RESEARCH

HEART FAILURE

Prenatal Exposure to Severe Stress and the Risk of Heart Failure Up to Middle-Age

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ABSTRACT

BACKGROUND Prenatal stress is a potential risk factor for cardiovascular disease, but its association with heart failure (HF) is unknown.

OBJECTIVES The purpose of this study was to investigate whether prenatal stress, defined as maternal bereavement, was associated with HF risk up to middle-age.

METHODS This cohort study included 6,758,560 live singleton births from the Danish (1973-2016) and the Swedish (1973-2014) Medical Birth Registers. The authors retrieved information on death of the mothers' close family members (partner, older children, parents, and siblings) and offspring's HF (up to 2016 in Denmark and 2020 in Sweden) from nationwide registers. They estimated HRs and 95% CIs for HF in the offspring according to maternal bereavement.

RESULTS During up to 48 years of follow-up, 4,812 offspring (0.07%) had a diagnosis of HF. Maternal loss of any close family member was not associated with HF in the offspring (adjusted HR: 1.04; 95% CI: 0.88-1.23). However, the most severe forms of bereavement, ie, death of a partner or an older child (adjusted HR: 1.47; 95% CI: 1.06-2.04) and unnatural death of a relative (adjusted HR: 2.77; 95% CI: 1.49-5.17), were associated with increased risks of HF. Congenital heart disease and preterm birth contributed substantially to the association of maternal loss of a partner or older child with HF risk in the offspring.

CONCLUSIONS Maternal loss of a partner or older child and loss of a close relative caused by unnatural causes the year before or during pregnancy were associated with increased risk of HF in offspring. (JACC Heart Fail 2024;12:1353–1362) © 2024 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) affects 64.3 million individuals worldwide and 1% to 2% of the general adult population in developed countries.[1] Although HF is considered to be primarily a disease of the elderly,[2] studies from several Western countries reported that HF incidence rates in early adulthood (age <50 years) have increased by about 50% over the past 3

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

CVD = cardiovascular disease

HF = heart failure

SGA = small for gestational age

decades, and this group currently represents 10% of all patients with HF.[3-6] The etiology of early-onset HF may differ from that presenting in older ages,[3] but knowledge regarding risk factors for early HF is very limited. Given the loss of productive years and the high health care costs associated with HF at a young age, better knowledge regarding the etiology of HF in young is warranted.

Based on the "Developmental Origin of Health and Disease" theory,[7] maternal stress shortly before or during pregnancy may lead to an adverse intrauterine environment, which in turn may increase the risk of adverse pregnancy outcomes (fetal growth restriction,[8] preterm birth,[9] and congenital heart disease),[10] worsen the cardiovascular risk profile (eg high blood pressure,[11] diabetes,[12] and excessive adiposity)[13] and increase the risk of cardiovascular diseases (CVD) later in life.[14-18] Nevertheless, only a few studies investigated the association between maternal stress during pregnancy and the risk of overall or specific early-onset CVD and their findings have been inconsistent.[19-24] To our knowledge, no study examined the link between maternal stress during pregnancy and HF risk in the offspring.

Several classification systems of sources of stress rate the death of a close relative as one of the most severe sources of stress;[25,26] this event is likely to emotionally affect most individuals regardless of coping skills and social support. We hypothesize that if prenatal stress during pregnancy plays a role in the development of HF in young age, an association between bereavement, a severe form of stress, shortly before or during pregnancy and the risk of early-onset HF is likely.[24] In this binational cohort study, we investigated whether maternal loss of a close family member the year before or during pregnancy was associated with an increased risk of HF in the offspring.

METHODS

STUDY POPULATION AND DESIGN. We conducted a cohort study by linking several Danish and Swedish national registers through the unique personal identification number assigned to all residents in the 2 countries.[24,27] A description of the registers included in the study is provided in Supplemental Table 1. The study population included all live singleton births from the DMBR (Danish Medical Birth Register)[28] during 1973 to 2016 and from the SMBR (Swedish Medical Birth Register)[29] during 1973 to 2014. After excluding live births whose mother had a missing personal identification number (n = 7,925) or whose mothers could not be linked to any close family member (n = 81,144), our study population consisted of 6,758,560 live births. The study was approved by the Danish Data Protection Agency (number 2013-41-2569) and the Research Ethics Committee at Karolinska Institute in Stockholm (number 2016/288-31/1, 2021-03315).

MEASURES. Exposure. We defined exposure as maternal loss of a close family member, ie, an older child, partner (ie, the index child's father), sibling, or parent, the year before or during the index pregnancy. We did not include pregnancy losses in our definition of exposure. Family members were identified from the Danish Civil Registration System and the Swedish Multi-generation Register. Information on their date and cause of death was retrieved from the Danish and the Swedish Cause of Death Register. In case of several losses during the exposure period, we treated the date of the first loss as the date of exposure. We categorized exposure also according to the following: 1) the mother's relationship to the deceased (older child or partner vs parent or sibling); 2) the deceased family member's cause of death (unnatural death vs natural death, based on the International Classification of Diseases [ICD] codes shown in Supplemental Table 2); and 3) the time of the loss (the year before pregnancy and first, second, and third trimester of pregnancy).[24]

Outcome. Information on the first diagnosis of HF (defined using the ICD codes in Supplemental Table 2) was retrieved from the DNPR (Danish National Patient Registry) and the SPR (Swedish Patient Register), whereas information on death caused by HF was retrieved from the Danish and the Swedish Cause of Death Register. Follow-up started at birth and ended at the first diagnosis of HF, death, emigration, or the latest date with available data (December 31, 2016, in Denmark and December 31, 2020, in Sweden), whichever came first.

Covariates. We retrieved information on the offspring's sex, calendar year at birth, gestational age, and birth weight, and the following maternal characteristics: age at delivery (≤19, 20-24, 25-29, 30-34, or ≥35 years), parity (1, 2, ≥3), smoking status (collected since 1991 in Denmark and since 1982 in Sweden), and body mass index (BMI) in early pregnancy (<18.5, 18.5-24.9, 25.0-29.9, or ≥30 kg/m^2, measured at the first antenatal visit, which usually takes place between 10 to 14 weeks of gestation and available since 2003 in Denmark and since 1982 in Sweden) from the DMBR and the SMBR. We defined

preterm birth as gestational age <37 completed weeks at birth and small for gestational age (SGA) as a birth weight <10th percentile of the sex and gestational age-specific standard curve for normal fetal growth.[30] We extracted offspring's diagnoses of congenital heart disease (CHD), hypertension, and diabetes during the follow-up (prior to HF) in the offspring from the DNPR and the SPR using ICD codes (Supplemental Table 2).

Information on maternal country of origin and marital status was extracted from the Danish Civil Registration System and the Swedish Total Population Register. Maternal highest attained education was obtained from the Danish Integrated Database for Labour Market Research and the Swedish Register of Education, respectively. Data on maternal diabetes, hypertensive disease, and psychiatric disorders before or during pregnancy were retrieved from the DNPR and the SMBR. We obtained information on maternal family history of CVD, ie, CVD diagnoses of the mother's parents and siblings, from the DNPR and the SPR using the ICD codes in Supplemental Table 2. If we identified any CVD diagnoses for a parent or sibling of the mother, we classified her as having a family history of CVD; otherwise, she was categorized as having no family history of CVD.

STATISTICAL ANALYSES. We ran Kaplan-Meier curves to visualize the cumulative incidence of HF by exposure. We estimated HRs and 95% CIs for HF according to maternal bereavement using Cox proportional hazard models. The log-minus-log survival curves suggested a potential violation of the proportional hazard assumption (Supplemental Figure 1). Hence, we employed a flexible parametric survival model[31] to visualize the time-varying association. In addition, we cut off follow-up at 18 years of age to investigate the associations in childhood and young adulthood. We further analyzed whether the association differed by the time of the relative's death (1 year before pregnancy, first, second, and third trimester), the mother's relationship to the deceased (older child or partner vs parent or sibling), and the deceased family member's cause of death (unnatural death vs natural death).[24] The latter 2 analyses aimed to investigate the presence of dose-response relationships between bereavement and HF, considering that losses of children or partners or unexpected deaths are more severe source of stress than other types of losses.[26]

In the main model, we adjusted for the offspring's sex, country, and calendar year at birth, and maternal characteristics such as country of origin, age, education, and marital status at delivery; parity; hypertensive disorders; diabetes; psychiatric disorders; and family history of CVD before delivery. Because data on maternal smoking and BMI in early pregnancy were not collected throughout the whole study period, we repeated our analyses with additional adjustment for these 2 covariates among those who had such data.

Because maternal bereavement is related to preterm birth,[9] SGA birth,[8] CHD,[10] diabetes,[12] or hypertension,[23] which are known risk factors for HF,[14,15,32-34] we investigated their role as potential mediators of the studied associations. Given that we observed an association between maternal loss of a partner or older child and offspring's HF risk, we performed a causal mediation analysis based on a counterfactual framework[35] to examine the potential mediating role of preterm birth, SGA birth, CHD, diabetes, or hypertension. A detailed description of the approach used is provided in the Supplemental Methods. Furthermore, to explore whether the contribution of CHD to the association between maternal bereavement and offspring's HF risk varied across the main CHD types, we performed additional mediation analyses according to the following CHD subtypes[36,37]: 1) conotruncal defects; 2) nonconotruncal defects; 3) coarctation of the aorta; 4) ventricular septal defect; 5) atrial septal defect; and 6) other CHD. Similarly, given the important changes in the treatment and survival of CHD patients during the study period, we also investigated whether the proportion mediated by CHD differed by birth year. We also attempted to perform similar mediation analyses in case of the association between unnatural death and HF, but the low number of exposed to unnatural deaths and of the HF cases in this subgroup limited our possibilities to examine the contribution of these potential mediators.

We conducted stratified analyses and formal tests of interaction to investigate effect modification by sex, country, and calendar year at birth. Because the familial genetic or environmental risk factors that contributed to the death caused by CVD or CHD in the relative may also increase the risk of CVD in the index child,[32,38] we repeated our main analyses after excluding mothers who lost a relative because of CVD or CHD during the exposure period. To reduce the uncertainty related to HF defined based on mortality data, we ran further sensitivity analyses with HF cases identified only from national patient registers. As for the mothers who lacked register links to parents and siblings, we are likely to have an underreporting of the family history of CVD; therefore, we

TABLE 1 Baseline Characteristics of the Study Population

	Exposure to Maternal Bereavement the Year Before or During Pregnancy	
	No (n = 6,591,368)	Yes (n = 167,192)
Characteristics of offspring		
Country		
Denmark	2,604,134 (39.5)	60,442 (36.2)
Sweden	3,987,234 (60.5)	106,750 (63.8)
Calendar year at birth		
1973-1978	959,288 (14.5)	23,980 (14.3)
1979-1984	836,051 (12.7)	24,097 (14.4)
1985-1990	940,130 (14.2)	28,845 (17.3)
1991-1996	1,001,026 (15.2)	28,606 (17.1)
1997-2002	865,761 (13.1)	21,475 (12.9)
2003-2008	933,308 (14.2)	20,062 (12.0)
2009-2016	1,055,804 (16.0)	20,127 (12.0)
Sex		
Male	3,386,993 (51.4)	85,448 (51.1)
Female	3,204,375 (48.6)	81,744 (48.9)
Congenital heart disease		
No	6,493,879 (98.5)	164,480 (98.4)
Yes	97,489 (1.5)	2,712 (1.6)
Preterm birth		
No	5,870,702 (89.1)	152,860 (91.4)
Yes	300,593 (4.5)	8,952 (5.4)
Unknown	420,073 (6.4)	5,380 (3.2)
Small for gestational age[a]		
No	5,537,572 (84.0)	144,738 (86.6)
Yes	611,269 (9.3)	16,461 (9.8)
Unknown	442,527 (6.7)	5,993 (3.6)
Hypertension		
No	6,616,719 (99.2)	165,633 (99.1)
Yes	51,671 (0.8)	1,559 (0.9)
Diabetes		
No	6,626,593 (99.4)	165,931 (99.2)
Yes	41,797 (0.6)	1,261 (0.8)
Maternal characteristics		
Country of origin identical with the study country		
No	867,902 (13.1)	7,267 (4.3)
Yes	5,711,884 (86.7)	159,828 (95.6)
Unknown	11,582 (0.2)	97 (0.1)
Age at child's birth, y		
≤19	200,358 (3.0)	3,297 (2.0)
20-24	1,329,209 (20.2)	25,079 (15.0)
25-29	2,345,796 (35.6)	52,522 (31.4)
30-34	1,848,468 (28.0)	52,438 (31.4)
≥35	867,537 (13.2)	33,856 (20.2)
Highest education at child's birth		
Primary and lower secondary	1,448,436 (22.0)	39,797 (23.8)
Upper secondary	2,987,452 (45.3)	76,489 (45.8)
Bachelor or higher	2,054,889 (31.2)	49,994 (29.9)
Unknown	100,591 (1.5)	912 (0.5)
Marital status at child's birth		
Not married/not in registered partnership	3,043,143 (46.2)	76,032 (45.5)
Married/registered partnership	3,391,506 (51.4)	85,641 (51.2)
Unknown	156,719 (2.4)	5,519 (3.3)
Parity at child's birth		
1	2,873,825 (43.6)	54,613 (32.6)
2	2,427,636 (36.8)	36,478 (38.0)
≥3	1,289,907 (19.6)	49,101 (29.4)
Smoking in early pregnancy[b]		
No	3,676,214 (77.9)	84,807 (71.9)
Yes	766,790 (16.2)	25,518 (21.6)
Unknown	279,805 (5.9)	7,588 (6.5)
Body mass index in early pregnancy, kg/m^2[c]		
<18.5	124,220 (3.1)	2,736 (2.9)
18.5-24.9	1,954,973 (49.3)	43,954 (45.8)
25.0-29.9	746,934 (18.8)	17,959 (18.7)
≥30.0	319,918 (8.1)	8,474 (8.8)
Unknown	823,281 (20.7)	22,845 (23.8)
Diabetes before the index birth		
No	6,492,800 (98.5)	164,259 (98.3)
Yes	98,568 (1.5)	2,933 (1.7)
Hypertensive disease before the index birth		
No	6,362,481 (96.5)	160,937 (96.3)
Yes	228,887 (3.5)	6,255 (3.7)
Psychiatric disorders before the index birth		
No	6,304,508 (95.7)	158,442 (94.8)
Yes	286,860 (4.3)	8,750 (5.2)
Record of family history of cardiovascular disease before the index birth		
No	3,584,263 (54.4)	63,610 (38.0)
Yes	3,007,105 (45.6)	103,582 (62.0)

Values are n (%). [a]Small for gestational age, birth weight below the 10th percentile of the sex-specific standard curve for normal fetal growth. [b]Data on maternal smoking was available since 1991 in Denmark and since 1982 in Sweden. [c]Data on maternal body mass index was available since 2003 in Denmark and since 1982 in Sweden.

repeated our main analyses after excluding births where the mother lacked register links to her parents or siblings. Finally, to consider the similarity among children born by the same mother, we conducted a sensitivity analysis using the "COVSANDWICH" option in SAS. Due to the limited statistical power, all secondary analyses were conducted only for the overall bereavement and for bereavement classified by type of deceased relative.

We conducted the statistical analyses using SAS version 9.4, R version 3.6.3, and Stata version 15.1.

RESULTS

In the cohort of 6,758,560 live births, 167,192 (2.5%) study participants experienced prenatal stress caused by maternal bereavement the year before or during pregnancy. Compared with their unexposed counterparts, the exposed were more likely to be born in the same country as their mothers and to be preterm (Table 1). Mothers in the exposed group were more likely to be older, be married, be smokers, and have a family history of CVD than mothers in the unexposed group (Table 1).

During the 166.8 million person-years at risk (median follow-up time was 24.2 years; Q1-Q3: 13.4-34.5 years), 4,812 offspring (0.07%) had a diagnosis of HF. The HF incidence rates in the exposed and the unexposed groups were 0.32 and 0.29 per 10,000 person-years, respectively (Table 2, Supplemental Figure 2). Overall, maternal loss of any close family member the year before or during pregnancy was not associated with the risk of HF in the offspring (adjusted HR: 1.04; 95% CI: 0.88-1.23); HRs (95% CIs) for the covariates included in our main multivariable model are shown in Supplemental Table 3. However, we observed associations for the severe form of the stress. Maternal loss of a partner or older child was associated with an increased risk of HF in the offspring (adjusted HR: 1.47; 95% CI: 1.06-2.04). Similarly, unnatural (adjusted HR: 2.77; 95% CI: 1.49-5.17) but not natural deaths (adjusted HR: 0.99; 95% CI: 0.83-1.18) were associated with increased HF risks. The association did not substantially differ when exposure was categorized according to the time of bereavement in relation to pregnancy.

The flexible parametric model showed a relatively constant increased risk for HF associated with bereavement from birth to the age of 30 years and a decline afterwards (Figure 1). When we split the follow-up at the age of 18 years, we observed that the association between the loss of a partner or an older child and the risk of HF tended to be stronger for HF in childhood (adjusted HR: 2.24; 95% CI: 1.27-3.97) than in adulthood (adjusted HR: 1.25; 95% CI: 0.84-1.86) (Table 3).

We found that CHD and preterm birth mediated a substantial part of the association between maternal loss of a partner or older child and the risk of HF in offspring; the proportion mediated by SGA birth, hypertension, and diabetes appeared to be modest (Table 4). When exploring mediation by different CHD types, we found that all investigated CHD types, except for coarctation of the aorta, contributed considerably to the observed association (Supplemental Table 4). The contribution of CHD to the association of interest did not differ substantially according to the calendar year at birth (Supplemental Table 4).

TABLE 2 Risk of Heart Failure According to Maternal Bereavement the Year Before or During Pregnancy

	n	Event Rate, per 10,000 Persons-Year	HR (95% CI)	
			Model 1[a]	Model 2[b]
Unexposed	4,674	0.29	1.00 (Ref.)	1.00 (Ref.)
Any loss	138	0.32	1.06 (0.89-1.25)	1.04 (0.88-1.23)
Type of deceased relative[c]				
Older child or partner[d]	37	0.52	1.56 (1.13-2.15)	1.47 (1.06-2.04)
Parent or sibling[e]	101	0.28	0.95 (0.78-1.15)	0.94 (0.77-1.15)
The deceased's cause of death[c]				
Loss caused by unnatural cause	10	0.63	3.24 (1.74-6.02)	2.77 (1.49-5.17)
Loss caused by natural cause	128	0.31	1.01 (0.84-1.20)	0.99 (0.83-1.18)
Time of loss				
1 y before pregnancy	89	0.34	1.09 (0.88-1.35)	1.07 (0.87-1.33)
First trimester	17	0.36	1.18 (0.73-1.90)	1.17 (0.72-1.88)
Second trimester	17	0.26	0.86 (0.53-1.38)	0.85 (0.53-1.36)
Third trimester	15	0.31	1.01 (0.60-1.66)	0.99 (0.60-1.66)

[a]Model 1 was unadjusted. [b]Model 2 was adjusted for sex, country, calendar year at birth, maternal country of origin, parity, age, education and marital status at the time of birth, hypertensive disease, diabetes, psychiatric disorders, and family history of cardiovascular diseases before the index delivery. [c]Differences in the strength of associations between subtypes of maternal bereavement and heart failure in offspring were formally tested using the CONTRAST statement in the SAS software. The *P* values corresponding to the difference in the association when exposure was classified by type of deceased relative, cause of death, and time of loss were 0.007, 0.0004, and 0.600, respectively. [d]Analyses were restricted to children whose mother had register links to her partner (n = 6,108,486) or at least a live older child (n = 6,031,945) at the start of the exposure period. [e]Analyses restricted to children whose mother had at least a live parent (n = 5,614,425) or a live sibling (n = 4,437,712) at the start of the exposure period.

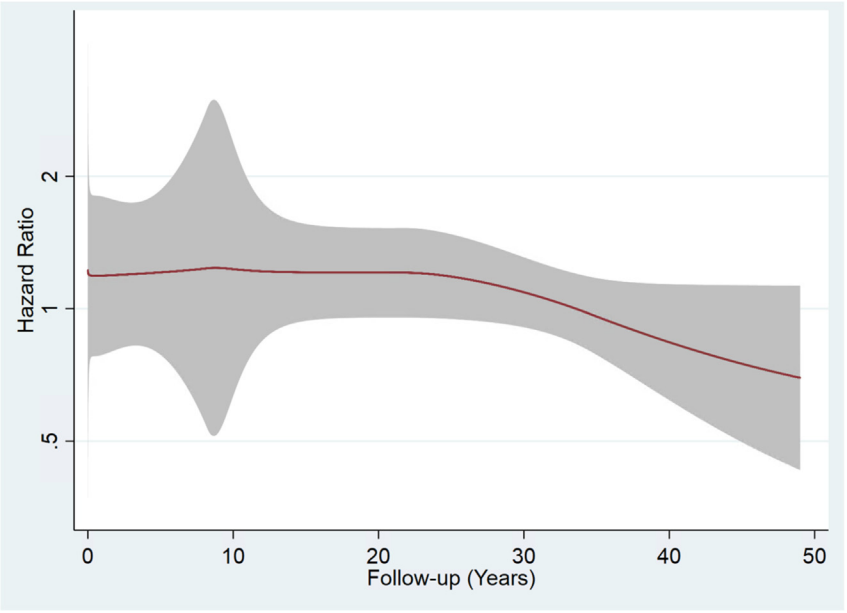
Ref. = Reference.

The associations between maternal bereavement the year before or during pregnancy and HF did not differ considerably according to sex, country or year at birth (Supplemental Tables 5 to 7). Further adjustment for maternal smoking and BMI during early pregnancy did not substantially alter the observed associations (Supplemental Table 8). The results did not substantially change when we repeated our main analyses after the following: 1) excluding mothers who lost a relative because of CVD or CHD the year before or during the index pregnancy; 2) restricting our definition of HF to cases diagnosed in hospitals; 3) after excluding births where the mother lacked register links to her parents or siblings; or 4) applying the SAS "COVSANDWICH" option to consider similarities among individuals born by the same mother (Supplemental Tables 9 to 12).

DISCUSSION

In this large binational cohort study, we found no overall association between prenatal stress, defined as maternal exposure to the death of any close family

FIGURE 1 Time-Varying HRs of HF According to Prenatal Stress



We ran flexible parametric survival model to estimate adjusted HRs and 95% CIs for HF according to maternal bereavement 1 year before or during pregnancy. A spline with 5 df (4 intermediate knots and 2 knots at each boundary, placed at quintiles of the distribution of events) was used for the baseline rate, and a spline with 3 df was used for the time-varying effect. The reference group in case of the exposure variable was that of individuals with no record of maternal loss of a close family member the year before or during pregnancy. We adjusted for sex (reference group: girls); country (reference group: Denmark); calendar year at birth (reference group: 1973-1978); maternal country of origin (reference group: having the same country of origin as the study country); parity (reference group: primiparous); age (reference group: 25-29 years), education (reference group: bachelor or higher), and marital status (reference group: married or in registered partnership) at the time of birth; hypertensive disease (reference group: no record of hypertensive disease); diabetes (reference group: no record of diabetes); psychiatric disorders (reference group: no record of psychiatric disorders); and family history of cardiovascular diseases (reference group: no record of a family history of cardiovascular diseases) before the index delivery. HF = heart failure.

member, the year before or during pregnancy and the risk of HF in the offspring. However, the most severe types of prenatal stress, ie, the death of a partner or older child and the unnatural death of a close family member, were associated with increased risks of HF. We also observed that CHD and preterm birth mediated a substantial part of the association between maternal loss of a partner or older child and the offspring's risk of HF (Central Illustration).

COMPARISON WITH PREVIOUS STUDIES. To our knowledge, this is the first study to investigate the association between maternal stress shortly before or during pregnancy and the risk of HF in the offspring. Two Dutch birth cohort studies reported increased risks of ischemic heart disease in adults prenatally exposed to famine during World War II,[19,20] while another Dutch study did not find an association between a historical period of famine during pregnancy and coronary artery disease in the offspring.[21] Conversely, a Finnish study reported a lower risk of ischemic heart disease in individuals who were prenatally exposed to wartime than in their unexposed counterparts.[22] Only 2 previous studies in this area measured stress at an individual level. A study by our group found no association between maternal exposure to bereavement shortly before or during pregnancy and the risk of IHD and stroke.[24] A Danish study involving 2.6 million individuals observed a modest association between maternal bereavement in the period before birth and the risk of total CVD up to the age of 40 years in the offspring.[23] However, the study did not analyze HF as an outcome, probably because of limited statistical power.

According to several classification systems of severity of sources of stress, death in the nuclear family, ie, of a partner or of child, is likely to be perceived as more stressful and to require a greater life adjustment than deaths in the extended family.[26] Similarly, sudden, unnatural deaths are considered to

be more stressful than natural deaths.[39] The fact that an association between maternal bereavement and HF in offspring was confined to the most severe forms of stress, ie, loss of a partner or older child or unexpected loss, is suggestive of a dose-response effect. The reasons for the slightly stronger association between the loss of a partner or older child and the risk of HF during childhood than in young adulthood is not clear, but we speculate about 2 plausible explanations. First, pediatric HF is primarily caused by CHD,[40] the risk of which was reported to be increased after maternal bereavement.[10] Our finding that CHD accounts for >50% of the observed association further supports this explanation. With advancing age, HF may increasingly be attributed to traditional HF risk factors such as smoking, obesity, and hypertension. Second, children born after the loss of an older sibling may have received closer attention from the health care system, eventually leading to a higher likelihood to detect HF already in childhood.

POSSIBLE UNDERLYING MECHANISMS. Several mechanisms may contribute to the link between maternal stress during pregnancy and HF risk in the offspring. Maternal stress may induce a suboptimal intrauterine environment through the prolonged activation of the hypothalamic-pituitary-adrenal axis[41] and of the autonomic nervous system,[42] leading to adverse changes in mental health, lifestyle, proinflammatory, and cardiometabolic activity. Such intrauterine insults may program the development of the fetal heart, including structural and functional changes that may increase the risk of HF later in life. Because fetal cardiac development primarily occurs during the first trimester of pregnancy,[43] we expected that exposure to stress in the year before pregnancy or during the first trimester of pregnancy would have a stronger association with HF than stress in later trimesters. However, our study did not reveal differences in the studied associations when we categorized exposure by its timing. We speculate that such differences by the time of exposure may present only in cases involving severe forms of stress, such as the loss of a partner or older child, or unnatural deaths. Unfortunately, our study did not have sufficient statistical power to investigate this hypothesis. Furthermore, prenatal stress may lead to HF through adverse birth outcomes such as preterm birth[9] and fetal growth restriction,[8] or established risk factors for HF such as diabetes[12] and hypertension.[23] Our mediation analyses suggested that CHD and preterm birth may explain a substantial part of the studied associations.

An alternative explanation of the association between maternal loss of a close relative shortly before or during pregnancy and the risk of HF in the offspring is confounding by genetic and/or environmental cardiovascular risk factors that cluster in families. Nevertheless, exclusion of deaths caused by CVD or CHD during the exposure period in older children and partners did not substantial change the associations between maternal loss of a partner or older child the year before or during pregnancy and the risk HF. Our finding that losses caused by unnatural but not those caused by natural causes were associated with HF risk in the offspring would also provide support for other explanations than familial confounding; unnatural deaths are less likely to be

TABLE 3 Risk of Heart Failure According to Maternal Bereavement, Stratified by Attained Age

	n	Event Rate, per 10,000 Persons-Year	HR (95% CI) Model 1[a]	HR (95% CI) Model 2[b]
Attained age <18 y (n = 6,758,560)				
Unexposed	1,211	0.12	1.00 (Ref.)	1.00 (Ref.)
Any loss	41	0.16	1.31 (0.96-1.79)	1.26 (0.92-1.72)
Type of deceased relative				
Older child or partner	12	0.29	2.50 (1.42-4.42)	2.24 (1.27-3.97)
Parent or sibling	29	0.13	1.09 (0.76-1.58)	1.06 (0.73-1.54)
Attained age ≥18 y (n = 4,422,510)				
Unexposed	3,463	0.59	1.00 (Ref.)	1.00 (Ref.)
Any loss	97	0.59	0.98 (0.80-1.20)	0.97 (0.79-1.19)
Type of deceased relative				
Older child or partner	25	0.82	1.32 (0.89-1.95)	1.25 (0.84-1.86)
Parent or sibling	72	0.53	0.90 (0.71-1.13)	0.90 (0.71-1.14)

[a]Model 1 was unadjusted. [b]Model 2 was adjusted for sex; country; calendar year at birth; maternal country of origin; parity; age, education, and marital status at the time of birth; hypertensive disease; diabetes; psychiatric disorders; and family history of cardiovascular diseases before the index delivery.

Abbreviation as in Table 2.

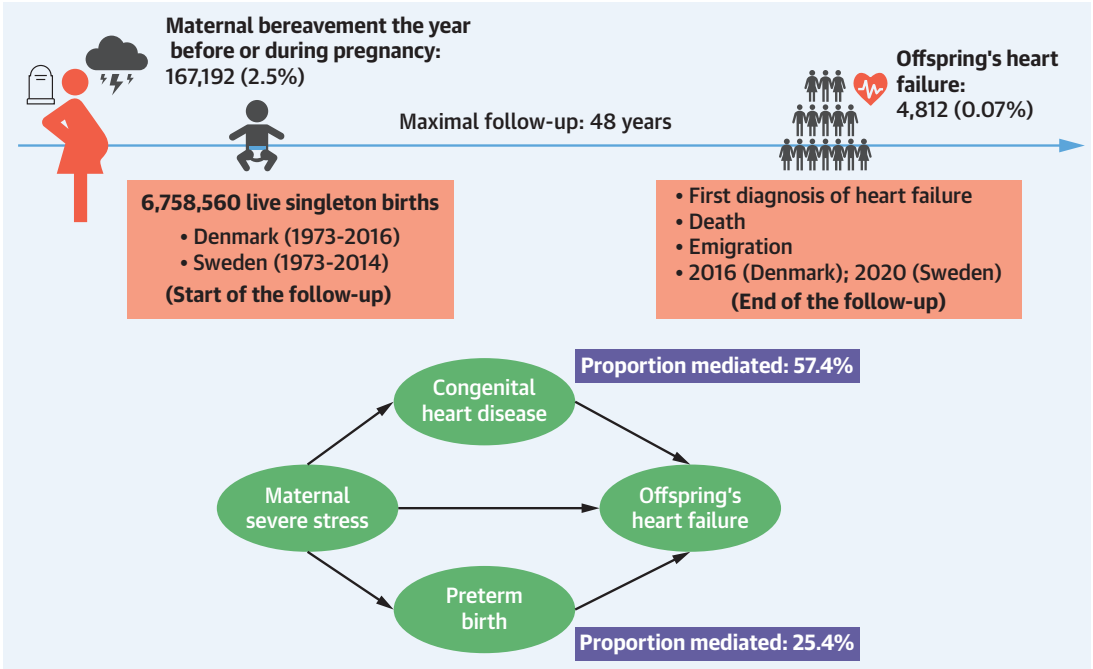
TABLE 4 The Contribution of Potential Mediators to the Association Between Maternal Bereavement and Offsprings' HF

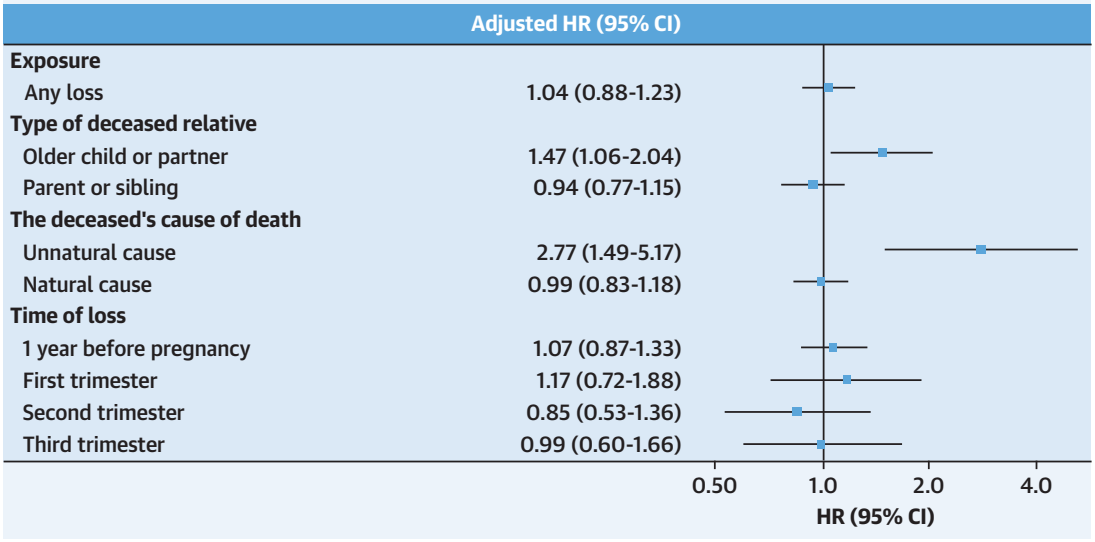
Potential Mediator	HR (95% CI)[a] Total Effect[b]	Direct Effect	Mediated Effect	Proportion Mediated (%)
CHD	1.62 (1.15-2.27)	1.26 (0.91-1.75)	1.28 (1.15-1.43)	57.4
Preterm birth	1.64 (1.16-2.32)	1.48 (1.04-2.11)	1.11 (1.00-1.23)	25.4
SGA birth	1.64 (1.16-2.31)	1.63 (1.15-2.29)	1.01 (0.99-1.02)	2.2
Hypertension	1.54 (1.10-2.17)	1.54 (1.09-2.17)	1.00 (1.00-1.01)	1.3
Diabetes	1.46 (1.06-2.03)	1.46 (1.05-2.02)	1.00 (1.00-1.01)	0.5

[a]We adjusted for sex; country; calendar year at birth; maternal country of origin; parity; age, education, and marital status at the time of birth; hypertensive disease; diabetes; psychiatric disorders; and family history of cardiovascular diseases before the index delivery. [b]The estimates for the total effect of prenatal stress on heart failure may differ among models corresponding to each mediator because of differences in the number of individuals with missing data in case of each mediator.

CHD = congenital heart disease; HF = heart failure; SGA = small for gestational age.

CENTRAL ILLUSTRATION **Maternal Bereavement the Year Before or During Pregnancy and the Risk of Heart Failure in Offspring**





Yang F, et al. JACC Heart Fail. 2024;12(8):1353–1362.

We adjusted for sex, country, calendar year of birth, maternal country of origin, parity, age, education and marital status at the time of birth, hypertensive disease, diabetes, psychiatric disorders, and family history of cardiovascular diseases before the index delivery.

affected by cardiovascular risk factors that cluster in families.

STUDY LIMITATIONS. First, although the positive predictive value of the primary diagnosis of HF in the Danish and Swedish patient registers is high (88% in the DNPR[44] and 95% in the SPR),[45] we may have failed to identify some milder forms of HF from primary care settings. Second, we could not fully rule

out the possibility of residual confounding caused by unmeasured genetic and familial lifestyle and health-related factors. Third, caution is needed when interpreting the results from the mediation analyses because this approach requires strong assumptions about unmeasured confounding.[46] We performed further sensitivity analyses, and the results suggested that the mediated effect would be slightly overestimated in the presence of unmeasured confounders (Supplemental Methods). Fourth, we did not have information on mother's participation in psychotherapy or other interventions for bereaved individuals and could thus not examine their potential role in the studied associations. Similarly, because information on maternal medication use was available only in Sweden after 2005, our ability to study the importance of maternal psychotropic medications in the subcohort with such data was limited because of the low number of HF cases. Fifth, our findings may be generalized only to individuals living in countries that have a universal free health care system and a socioeconomic context similar to that of Denmark and Sweden.

CONCLUSIONS

We found that severe prenatal stress was associated with an increased risk of HF in the offspring in the first 5 decades of life and that CHD and preterm birth substantially contributed to this association. Future studies may investigate whether more frequent but less severe sources of prenatal stress are also involved in the development of early-onset HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Individuals born to mothers who experienced very severe stress during pregnancy are at an increased risk of heart failure up to early middle-age.

TRANSLATIONAL OUTLOOK: If our findings are confirmed by further studies, early screening and prevention may be implemented among individuals prenatally exposed to very severe stress to try to reduce their risk of heart failure later in life.

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22(8):1342–1356.

2. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J*. 2020;5(15):1–6.

3. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J*. 2014;35(1):25–32.

4. Christiansen MN, Køber L, Weeke P, et al. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. *Circulation*. 2017;135(13):1214–1223.

5. Jain V, Minhas AMK, Khan SU, et al. Trends in HF hospitalizations among young adults in the United States from 2004 to 2018. *Heart Fail*. 2022;10(5):350–362.

6. Lecoeur E, Domengé O, Fayol A, Jannot A-S, Hulot J-S. Epidemiology of heart failure in young adults: a French nationwide cohort study. *Eur Heart J*. 2023;44(5):383–392.

7. Arima Y, Fukuoka H. Developmental origins of health and disease theory in cardiology. *J Cardiol*. 2020;76(1):14–17.

8. Khashan AS, McNamee R, Abel KM, et al. Reduced infant birthweight consequent upon maternal exposure to severe life events. *Psychosom Med*. 2008;70(6):688–694.

9. Laszlo K, Li J, Olsen J, Vestergaard M, Obel C, Cnattingius S. Maternal bereavement and the risk of preterm delivery: the importance of gestational age and of the precursor of preterm birth. *Psychol Med*. 2016;46(6):1163–1173.

10. Zhu JL, Olsen J, Sørensen HT, et al. Prenatal maternal bereavement and congenital heart defects in offspring: a registry-based study. *Pediatrics*. 2013;131(4):e1225–e1230.

11. Van Dijk AE, Van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. The association between prenatal psychosocial stress and blood pressure in the child at age 5–7 years. *PLoS ONE*. 2012;7(8):e43548.

12. Li J, Olsen J, Vestergaard M, Obel C, Kristensen JK, Virk J. Prenatal exposure to bereavement and type-2 diabetes: a Danish longitudinal population based study. *PLoS ONE*. 2012;7(8):e43508.

13. Silva C, Vehmeijer FO, El Marroun H, Felix J, Jaddoe V, Santos S. Maternal psychological distress during pregnancy and childhood cardiometabolic risk factors. *Nutr Metab Cardiovasc Dis*. 2019;29(6):572–579.

14. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. *J Pediatr*. 2019;210:69–80.e65.

15. Liang J, Xu C, Liu Q, et al. Association between birth weight and risk of cardiovascular disease: evidence from UK Biobank. *Nutr Metab Cardiovasc Dis*. 2021;31(9):2637–2643.

16. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24(4):683–689.

17. Kenny LC, Everard C, Khashan AS. Maternal stress and in utero programming. *Hormones, Intrauterine Health and Programming*. 2014:41–55.

18. Vehmeijer FO, Guxens M, Duijts L, El Marroun H. Maternal psychological distress during pregnancy and childhood health outcomes: a narrative review. *J Dev Orig Health Dis*. 2019;10(3):274–285.

19. Roseboom TJ, van der Meulen JH, Osmond C, et al. Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. *Heart Fail*. 2000;84(6):595–598.

20. Painter RC, de Rooij SR, Bossuyt PM, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr*. 2006;84(2):322–327.

21. Lumey L, Martini LH, Myerson M, Stein AD, Prineas RJ. No relation between coronary artery disease or electrocardiographic markers of disease in middle age and prenatal exposure to the Dutch famine of 1944–5. *Heart*. 2012;98(22):1653–1659.

22. Schreier NK, Moltchanova EV, Blomstedt PA, Kajantie E, Eriksson JG. Prenatal exposure to wartime stress-long-term effect on coronary heart disease in later life. *Ann Med*. 2011;43(7):555–561.

23. Plana-Ripoll O, Liu X, Momen NC, Parner E, Olsen J, Li J. Prenatal exposure to maternal stress following bereavement and cardiovascular disease: a nationwide population-based and sibling-matched cohort study. *Eur J Prev Cardiol*. 2016;23(10):1018–1028.

24. Yang F, Janszky I, Roos N, Li J, László KD. Prenatal exposure to severe stress and risks of ischemic heart disease and stroke in offspring. *JAMA Netw Open*. 2023 Dec;6(12):e2349463.

25. Holmes TH, Rahe RH. The social readjustment rating scale. *J Psychosom Res*. 1967;11(2):213–218.

26. Cooper AM, Michels R. Diagnostic and statistical manual of mental disorders, revised (DSM-III-R). *Am J Psychiatry*. 1988;145(10):1300–1301.

27. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic health registry-based research: a review of health care systems and key registries. *Clin Epidemiol*. 2021:533–554.

28. Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish medical birth register. *Eur J Epidemiol*. 2018;33:27–36.

29. Cnattingius S, Källén K, Sandström A, et al. The Swedish medical birth register during 5 decades: documentation of the content and quality of the register. *Eur J Epidemiol*. 2023;38(1):109–120.

30. Maršál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatrica*. 1996;85(7):843–848.

31. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J*. 2009;9(2):265–290.

32. Wang T, Chen L, Yang T, et al. Congenital heart disease and risk of cardiovascular disease: a meta-analysis of cohort studies. *J Am Heart Assoc*. 2019;8(10):e012030.

33. Ohkuma T, Komorita Y, Peters SA, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. *Diabetologia*. 2019;62:1550–1560.

34. Kannan A, Janardhanan R. Hypertension as a risk factor for heart failure. *Curr Hypertens Rep*. 2014;16:1–8.

35. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2):143–155.

36. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol*. 2007;79(10):714–727.

37. Liu S, Joseph KS, Luo W, et al. Effect of folic acid food fortification in Canada on congenital heart disease subtypes. *Circulation*. 2016;134(9):647–655.

38. Kelishadi R, Poursafa P. A review on the genetic, environmental, and lifestyle aspects of the early-life origins of cardiovascular disease. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(3):54–72.

39. Parkes CM. Bereavement in adult life. *BMJ*. 1998;316(7134):856–859.

40. Jayaprasad N. Heart failure in children. *Heart Views*. 2016;17(3):92–99.

41. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. *Horm Behav*. 2011;59(3):279–289.

42. Müller JJ, Antonow-Schlorke I, Kroegel N, et al. Cardiovascular effects of prenatal stress—Are there implications for cerebrovascular, cognitive and mental health outcome? *Neurosci Biobehav Rev*. 2020;117:78–97.

43. Dhanantwari P, Lee E, Krishnan A, et al. Human cardiac development in the first trimester: a high-resolution magnetic resonance imaging and episcopic fluorescence image capture atlas. *Circulation*. 2009;120(4):343–351.

44. Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50. 0-I50. 9) in the Danish National Patient Register. *Dan Med J*. 2018;65(4):A5470.

45. Ingelsson E, Ärnlöv J, Sundström J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail*. 2005;7(5):787–791.

46. Lange T, Hansen JV. Direct and indirect effects in a survival context. *Epidemiology*. 2011;22(4):575–581.

KEY WORDS bereavement, early-onset heart failure, fetal programing, stress

APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.