Death of a child and the risk of heart failure: a population-based cohort study from Denmark and Sweden

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Aims
We aimed to investigate whether the death of a child, one of the most severe stressors, is associated with the risk of heart failure (HF).

Methods and results
We conducted a population-based cohort study involving parents of live-born children recorded in the Danish and Swedish Medical Birth Registers during 1973–2016 and 1973–2014, respectively (n = 6717349). We retrieved information on child death, HF diagnosis and sociodemographic characteristics of the parents from several nationwide registries. We performed Poisson regression models to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for HF in relation to bereavement. A total of 129829 (1.9%) parents lost at least one child during the follow-up. Bereaved parents had a 35% higher risk of HF than the non-bereaved (IRR 1.35, 95% CI 1.29–1.41; p < 0.001). The increased HF risk was observed not only when the child died due to cardiovascular or other natural causes, but also when the loss was due to unnatural causes. The association tended to be U-shaped when we categorized the exposed parents by the number of remaining live children at loss or by the age of the deceased child.

Conclusion
We found that the death of a child was associated with an increased risk of HF. The finding that not only cardiovascular and other natural deaths, but also unnatural deaths were associated with HF suggests that stress-related mechanisms may contribute to the development of HF.
Introduction
Heart failure (HF) represents an important public health concern, primarily due to its high prevalence, poor prognosis, and huge healthcare costs. The prevalence of HF has increased during the last decades in the Western world and will probably continue to rise, along with the aging of the population and improvements in survival of acute coronary syndromes. It is estimated that HF affects more than 60 million individuals worldwide in 2017, while corresponding figures in Denmark and Sweden are around 77,000 and 200,000, respectively. Despite significant advances in its treatment, mortality in HF continues to be very high: 5% at 1 month and 15%, 45%, and 65% at 1, 5, and 10 years after diagnosis, respectively.

Psychological stress may be implicated in the development of HF. The main suggested underlying mechanisms involve the prolonged activation and the dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, as well as adverse changes in mental health, lifestyle and in inflammatory, cardiometabolic and hemostatic activity. These in turn may contribute to the development of and may worsen the prognosis of hypertension, cardiomyopathy, ischemic heart disease (IHD) and atrial fibrillation (AF). Several of the behavioral and physiological consequences of stress, along with hypertension, diabetes, IHD, cardiomyopathy, atrial and ventricular fibrillation are well-known risk factors or causes of HF. Thus, an association between stress and HF is plausible. Nevertheless, to our knowledge only one study investigated this link, but found no association, possibly due to low statistical power to detect a relatively modest effect.

The death of a child is one of the most devastating events that parents may experience, being rated 6 on a six-step scale of severity of sources of stress (i.e. as a ‘catastrophic stressor’). Bereaved parents present intense and long-lasting grief reactions, including distress, rumination, anger, despair and self-doubt and are more likely to suffer from complicated grief and other mental health problems, including depression, anxiety, stress disorders, psychotic illness or substance abuse than unexposed parents and/or than counterparts experiencing other types of losses. Attributing meaning and accepting the child’s loss, important tasks...
for grief resolution, are unusually difficult as the death of a child is not in line with our expectations about the life cycle.\textsuperscript{12} We have earlier shown that parents who lost a child have increased risks of acute myocardial infarction (AMI), IHD and AF.\textsuperscript{13–15} Whether the death of a child may increase the risk of HF has, to our knowledge, not yet been investigated.

In this large bi-national cohort study, we aimed to analyze the association between the death of a child and the risk of incident HF and whether it varies according to the characteristics of the loss, the parents’ sociodemographic characteristics and history of cardiovascular disease (CVD).

Methods
Study design and participants
We performed a population-based cohort study involving parents of live-born children recorded in the Danish and the Swedish Medical Birth Registers (MBR) during 1973–2016 (n = 2 807 548) and 1973–2014 (n = 3 924 237), respectively (Figure 1). Linkage between registers was possible through the unique social security number assigned to each resident in these countries. We identified all the Danish and Swedish mothers from the MBRs, the Danish fathers (98.9\%) from the Danish MBR and the Civil Registration System, and the Swedish fathers (83\%) from the Swedish Multi-Generation Register. Through the Danish Civil Registration System and the Swedish Multi-Generation Register, we linked parents also to their other children, i.e. children born before 1973 (when the MBRs were established) or born outside Denmark or Sweden but who later resided in the two countries. Since the coverage of the Danish Hospital Register and Swedish Patient Register became nationwide from 1978 and 1987, respectively, we defined the follow-up as 1978–2016 for the Danish cohort and 1987–2014 for the Swedish cohort. Parents who had at least one child on 1 January 1978 in Denmark and on 1 January 1987 in Sweden entered the cohort on this date or on the date of immigration if they moved to Denmark or Sweden with their child(ren). Parents whose first child was born later entered the cohort on the birth date of the first child. Parents were eligible for the present study, if they (i) were alive and resided in Denmark or Sweden at study entry, (ii) had at least one live child during the study period, and (iii) did not have a record of a primary inpatient or outpatient diagnosis of HF at baseline. We finally included 6 717 349 study participants in our analysis (Figure 1).

The study was approved by the Danish Data Protection Agency, Copenhagen and the Ethics Review Board in Stockholm.

Exposure
We defined exposure as the death of a child after study entry. We retrieved information on the date and cause of children’s death from the Danish Civil Registration System and the Swedish Cause of Death Register. We considered the first loss as the index exposure in case the parent experienced several losses during the follow-up. We further categorized the exposed group according to (i) the child’s cause of death (death due to CVD, other natural and unnatural deaths) using International Classification of Diseases (ICD) codes (online supplementary Table S1), (ii) the age of the deceased child at loss (0, 1–2, 2–12, 13–17, 18–29, and ≥29 years), (iii) the number of remaining live children at loss (0, 1–2, and ≥3), and (iv) the number of losses during the follow-up (1 and ≥2). We treated the death of a child as a time-varying exposure, i.e. all parents contributed person-time to the unexposed group from study entry, while bereaved parents contributed person-time to the exposed group from the date of child death and afterwards. In the analysis concerning the number of losses during the follow-up, bereaved parents contributed person-time from baseline to the first loss to the unexposed group, from the date of the first to the second loss to the group that lost one child, and to the group that lost two or more children afterwards.

Outcome
We identified incident HF by primary diagnoses in in- and outpatient care in the Danish Hospital Register and in the Swedish Patient Register using the ICD codes presented in online supplementary Table S1. Validation studies of the HF diagnoses in the Danish Hospital Register and in the Swedish Patient Register have reported high positive predictive values, primarily in case of the primary diagnoses (88\%–95\%).\textsuperscript{16–18} The study participants were followed until the date of the first HF diagnosis, death, emigration, or 31 December 2016 in Denmark and 31 December 2014 in Sweden, whichever came first.

Covariates
We retrieved information on study participants’ demographic characteristics, including sex, age, country of origin, education, marital status, and income from nationwide registries, as described in online supplementary Table S2. We defined education, marital status, and income...
Table 1 Characteristics of the study population according to exposure to death of a child

| Variables                                      | Exposure status                                      | p-value* |
|------------------------------------------------|-----------------------------------------------------|----------|
| Age, years, mean (SD)                          | Unexposed (n = 6 587 520)                           |          |
|                                               | Exposed (n = 129 829)                               |          |
| Sex                                            |                                                     |          |
| Man                                            | 3 088 235 (46.9)                                   | <0.001   |
| Women                                          | 3 499 285 (53.1)                                   | <0.001   |
| Country of birth                               |                                                     | <0.001   |
| Denmark or Sweden                              | 5 772 042 (87.6)                                   |          |
| Other countries                                | 815 478 (12.4)                                    |          |
| Year of entry in the study                     |                                                     | <0.001   |
| Before 1980                                    | 698 596 (10.6)                                    |          |
| 1980–1989                                      | 2 304 213 (35.0)                                   |          |
| 1990–1999                                      | 1 369 937 (20.8)                                   |          |
| 2000–2009                                      | 1 382 610 (21.0)                                   |          |
| After 2009                                      | 832 164 (12.6)                                    |          |
| Marital status at baseline                     |                                                     | <0.001   |
| Married or in registered partnership           | 3 003 437 (45.6)                                   |          |
| Single, widowed or divorced                    | 2 579 001 (39.1)                                   |          |
| Missing                                        | 1 005 082 (15.3)                                   |          |
| Highest education at baseline                  |                                                     | <0.001   |
| 0–9 years                                      | 1 417 132 (21.5)                                   |          |
| 10–14 years                                    | 3 585 537 (54.4)                                   |          |
| ≥15 years                                      | 1 266 660 (19.2)                                   |          |
| Missing                                        | 318 191 (4.8)                                     |          |
| Income at baseline                             |                                                     | <0.001   |
| Low tertile                                    | 1 873 526 (28.4)                                   |          |
| Middle tertile                                 | 1 878 250 (28.5)                                   |          |
| High tertile                                   | 1 883 071 (28.6)                                   |          |
| Missing                                        | 952 673 (14.5)                                    |          |
| History of CVD at baseline                    |                                                     | <0.001   |
| No                                             | 6 432 980 (97.7)                                   |          |
| Yes                                            | 154 540 (2.3)                                     |          |
| History of psychiatric disorders at baseline   |                                                     | <0.001   |
| No                                             | 6 324 477 (96.0)                                   |          |
| Yes                                            | 263 043 (4.0)                                     |          |
| Parents’ history of CVD at baseline            |                                                     | <0.001   |
| No                                             | 3 788 344 (57.5)                                   |          |
| Yes                                            | 1 582 237 (24.0)                                   |          |
| Missing                                        | 1 216 939 (18.5)                                   |          |
| Sibling’s history of CVD at baseline           |                                                     | <0.001   |
| No                                             | 5 215 253 (79.2)                                   |          |
| Yes                                            | 155 328 (2.4)                                     |          |
| Missing                                        | 1 216 939 (18.5)                                   |          |
| Hypertension before childbirth at baselinea    |                                                     | <0.001   |
| No                                             | 3 370 763 (96.3)                                   |          |
| Yes                                            | 114 474 (3.3)                                     |          |
| Missing                                        | 14 048 (0.4)                                      |          |
| Diabetes before childbirth at baselinea        |                                                     | <0.001   |
| No                                             | 3 460 474 (98.9)                                   |          |
| Yes                                            | 24 763 (0.7)                                      |          |
| Missing                                        | 14 048 (0.4)                                      |          |
| Smoking in early pregnancy at baselinea        |                                                     | <0.001   |
| No                                             | 1 846 221 (52.8)                                   |          |
| Yes                                            | 397 474 (11.4)                                     |          |
| Missing                                        | 1 255 590 (35.9)                                   |          |
| Obesity in early pregnancy at baselinea        |                                                     | <0.001   |
| No                                             | 1 515 218 (43.3)                                   |          |
| Yes                                            | 125 300 (3.6)                                     |          |
| Missing                                        | 1 858 767 (53.1)                                   |          |

Values are given as n (%), unless otherwise indicated.
CVD, cardiovascular disease; SD, standard deviation.
aData are available only for women.
*p-values correspond to differences between the exposure groups from Student’s t-tests for continuous variables and chi-square tests for categorical variables.
Figure 2 Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for heart failure according to the death of a child. Model 1 adjusted for age at follow-up. Model 2 adjusted for sex, age at follow-up, calendar year at follow-up, country of birth, educational attainment, history of psychiatric disorders and cardiovascular diseases (CVD). We investigated differences in IRR by linear and quadratic trend tests, as appropriate. The analysis regarding the number of losses during follow-up was performed among those who had not lost a child before baseline; bereaved parents contributed person-time from baseline to the first loss to the unexposed group, from the date of the first to the second loss to the group that lost one child, and to the group that lost two or more children afterwards. IR, incidence rate (per 100 000 person-years).

* p-value for IRR and 95% CI from model 1. † p-value for IRR and 95% CI from model 2.

Based on information from the year prior to study entry or, if this information was missing, based on information from the year closest to baseline in the 5 years preceding it. Since the information on income in Denmark and on education in Sweden was available from 1980 and 1990, respectively, we used information on income from 1980 for the Danish participants who entered the cohort before 1980 and on education from 1990 for the Swedish participants who entered the cohort before 1991. We categorized income into tertiles within each 10-year interval of the study entry to consider inflation over years.

We obtained information on study participants’ history of psychiatric disorders from the Danish Hospital Register and the Central Psychiatric Register and the Swedish Patient Register. Information of study participants’ history of CVD was derived from the Danish Hospital Register and the Swedish Patient Register, while information on their family (e.g., parents and siblings) history of CVD was retrieved from the Danish Hospital Register and Civil Registration System as well as from the Swedish Patient Register and Causes of Death Register.

We further identified information on maternal hypertension and diabetes before childbirth at baseline from the Danish Hospital Register and the Swedish MBR. Maternal information on smoking and obesity in early pregnancy at baseline was obtained from the birth registers.

Statistical analysis
We compared exposed and unexposed parents on baseline characteristics using Student’s t-tests in case of continuous variables and chi-square tests in case of categorical variables. We estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the association between death of a child and HF risk by Poisson regression. We ran age- and multivariable adjusted models for child death overall and according to the deceased child’s cause of death, child’s age at death, and...
the number of remaining live children at loss and the number of losses during follow-up. We tested differences in IRR by linear and quadratic trend tests, as appropriate. We adjusted for the following potential confounders in our main multivariable models: age at follow-up (split at every 5 years) and calendar year at follow-up (split at every 10 years), as time-varying variables, as well as sex, country of birth, education, and history of psychiatric disorders and CVD at baseline, as time-fixed variables. In sensitivity analyses, we adjusted for marital status, income, family history of CVD, pregestational and gestational hypertension and diabetes, and maternal smoking and obesity in early pregnancy among participants with data on these variables. We chose confounders to be included in our multivariable models if these: (i) were known to or could be associated with both the death of a child and HF, and (ii) were not on the pathway between exposure and outcome. To test whether an earlier loss could have affected our results, we repeated our main analyses after excluding parents who had lost a child before baseline. Given that in some instances patients with cardiomyopathy may be diagnosed with HF, we re-ran our main model with the combination of HF and cardiomyopathy as the outcome (except for hypertrophic cardiomyopathy which has genetic causes).

To analyze whether the studied association varied by the time since loss, we calculated the IRRs and 95% CIs after splitting the follow-up of the exposed group as 0–3 months, 4–12 months, 2–5 years, 6–10 years, and ≥10 years after loss. We conducted stratified analysis and formal tests of interaction to study effect modification by sex, age (<50 and ≥50 years), education, country (Denmark and Sweden) and history of CVD.

Since bereavement is associated with IHD, AMI,14 AF13 and cardiomyopathy19 which are important causes of HF9 we further adjusted for heart diseases (IHD, AMI, AF, or cardiomyopathy) during follow-up in our main model among those who were free of CVD at baseline. We also investigated whether depression or anxiety after the loss contributed to the association of interest by adjusting for these conditions in our main model among those who were free of psychiatric disorders at baseline. Since mothers and fathers present several differences in their grief process, we performed these analyses also separately among mothers and fathers.

All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 129,829 (1.9%) parents lost at least one child during the follow-up. Baseline characteristics of the exposure groups are compared in Table 1.

During the 22-year median follow-up, 60,724 parents were diagnosed with HF, leading to an incidence rate of 45.2 per 105 person-years (44.3 and 113.4 in the unexposed and exposed groups, respectively). Bereaved parents had a 35% higher risk of HF than the non-bereaved [multivariable IRR (95% CI): 1.35 (1.29–1.41), p < 0.001]. The association was present across all analyzed causes of death (cardiovascular, other natural and unnatural causes). There was a trend toward a U-shaped association according to the deceased child’s age at death and HF risk (p for trend: <0.001; Figure 2). Bereaved parents who lost their only child [multivariable IRR (95% CI): 1.48 (1.25–1.75), p < 0.001] or had three or more live children at the time of loss [multivariable IRR (95% CI): 1.35 (1.27–1.44), p < 0.001] had higher HF risk than those with one or two live children at loss [multivariable IRR (95% CI): 1.32 (1.24–1.42), p < 0.001] (p for trend: 0.017). After losing the first child, losing more children was not associated with an increased risk (Figure 2). We found no clear evidence for a change in the association of interest over time, though the point estimates corresponding to HF in the first 3 months after the loss were somewhat higher than those in later periods (Figure 3).

The association did not substantially change after adjusting for (i) marital status, (ii) income, and (iii) family history of CVD among study participants with data on these variables, or after (iv) excluding the parents who lost a child before baseline. The magnitude of the association in mothers remained similar after additional adjustment for pregestational and gestational hypertension and diabetes as well as maternal smoking and obesity in early pregnancy. Results were not substantially altered when we defined the outcome as the combination of HF and cardiomyopathy (except for hypertrophic cardiomyopathy) (online supplementary Table S3).

We observed stronger associations in mothers than in fathers and in parents aged <50 years than in older parents but there was no evidence of effect modification by country, education, or history of CVD (Figure 4). We found that the strength of the association changed somewhat after adjusting for IHD, AMI and AF after the loss but not after adjusting for cardiomyopathy, depression and anxiety (online supplementary Table S4).

Discussion

In this large population-based cohort study, we found that the death of a child was associated with an increased risk of HF. The association was present not only in case of deaths due to cardiovascular or other natural causes but also in case of unnatural deaths. The association tended to be U-shaped when we categorized the exposed parents by the number of remaining live children at loss or by the age of the deceased child (Graphical Abstract). The association was stronger among mothers than fathers and among parents younger than 50 years than among older parents.
Death of a child and heart failure

**Figure 4** Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for the association between death of a child and the risk of heart failure in different subgroups. IRR = incidence rate (per 100,000 person-years); We adjusted for age at follow-up, calendar year at follow-up, country of birth, history of psychiatric disorders, as well as sex, educational attainment, and cardiovascular diseases (CVD), as appropriate. *The p-value corresponds to the comparison of the estimates between the groups with education 10–14 years versus. 0–9 years. †The p-value corresponds to the comparison of the estimates between the groups with education ≥15 years versus. 0–9 years.

Comparison with earlier studies

To our knowledge, only one previous study investigated the association between psychosocial stress or adverse life events and the risk of incident HF. In their longitudinal study involving data from 8670 Danish individuals, aged 21–93 years at baseline and followed for 15 years, Rod and colleagues found no association between the number of adverse life events (0, 1, 2, or ≥3) in personal (e.g. serious illness, injury or death in the family, children's educational problems, familial discord, financial difficulties) or working life (e.g. job loss, work conflicts, lack of promotion or of achieving educational goals) and the risk of HF. Possible reasons for the discrepancy between our and Rod et al.’s findings may relate to differences in exposure contrast and in statistical power. The events studied by Rod and colleagues are likely to induce lower stress than the death of a child, while the number of HF cases among those exposed to more than one event may have been too low to allow detecting modest effects. The effect size observed in our study are comparable to the effect sizes observed in earlier studies regarding the association between other psychological factors, e.g. depression [hazard ratio (HR) (95% CI): 1.2 (1.1–1.4) to 2.8 (1.2–6.4)], anxiety [HR (95% CI): 1.3 (0.7–2.3) to 2.5 (1.4–4.3)], insomnia [HR (95% CI): 1.3 (1.0–1.6)], or stress-related disorders [HR (95% CI): 1.4 (1.2–1.6)] and HF, though a few other investigations found no associations between psychosocial factors and HF. Our findings thus extend the limited literature on the role of stress, but also other psychosocial factors, in the etiology of HF by studying a severe, objective source of stress in a large bi-national population with a long follow-up; this allowed us to perform several sub-analyses that may contribute to a better understanding of causal mechanisms, and to perform subgroup analyses according to sociodemographic factors.

The findings that the association persisted after adjusting for a large number of confounders and was present not only in case of cardiovascular or other natural deaths, but also in case of unnatural deaths are consistent with findings from our earlier studies concerning the association between death of a child and the risk of IHD, AMI and AF. They may suggest that the associations are not exclusively due to confounding by familial cardiovascular risk factors and that stress-related mechanisms may also be
of importance.\textsuperscript{13,14} Compared to deaths due to natural causes, unnatural deaths are less likely to be affected by cardiovascular risk factors that cluster in families.\textsuperscript{13,15} The stress-related impact may also be supported by our findings according to the number of remaining live children at loss and the age of the deceased child as well as the stratified analyses according to the parent’s gender. The death of the only child may be particularly stressful as it deprives parents from their parental role, while having three or more children after the loss may be associated with high stress because of difficulties in combining own grief work with caring for and supporting several children in their grief.\textsuperscript{13,15} Similarly, the stronger ties with children in old age and the need to care for bereaved grandchildren may explain the trend toward the stronger associations observed in case of loss of children aged \textgreater{}29 years.\textsuperscript{15} The slightly stronger association observed in case of death of an infant than of an older child might be attributed to residual confounding by some pregnancy complications which are likely to increase both the risk of infant mortality\textsuperscript{22} and of maternal CVD.\textsuperscript{23} However, we did not observe substantial changes in this association after adjusting for maternal smoking and obesity in early pregnancy or for hypertension and diabetes before childbirth.\textsuperscript{15} The stronger association observed in mothers than fathers is consistent with previous studies showing that mothers have higher relative risks of IHD,\textsuperscript{15} AMI,\textsuperscript{14,15} AF,\textsuperscript{13} and mortality\textsuperscript{24} than fathers after the loss of a child. Mothers may be more affected by the loss of their child than fathers because of the stronger emotional bonds mothers have with their children in many cultures. Nevertheless, the fact that Takotsubo cardiomyopathy, a reversible acute HF, is more frequent in women than men and in some instances it might have been diagnosed as HF may have also contributed to the observed gender differences.\textsuperscript{19}

Potential underlying mechanisms

There are several mechanisms by which bereavement may increase HF risk. Bereavement may induce adverse changes in daily behaviors, lifestyle, mental health,\textsuperscript{12} health management (non-compliance with prescribed medications),\textsuperscript{26} and stress-related biomarkers, e.g. inflammation, blood lipids, blood pressure and heart rate,\textsuperscript{4,27–29} that may increase the risk of CVD such as AMI or AF.\textsuperscript{13–15} Bereaved CVD patients may neglect their personal health care, e.g. they may be more reluctant to participate in rehabilitation programs and may miss filling prescriptions or taking their prescribed medications. As grief following child death is often complicated and long-lasting, it may continue to affect bereaved parents after the onset of hypertension, IHD or AF leading to an increased risk of HF. Our finding that the association was stronger among those with CVD at baseline than those without and that the effect size changed somewhat after adjusting for incident IHD, AMI and AF during follow-up may be supportive of the hypothesis that these conditions may contribute to the association between the death of a child and HF. The finding of no change in our estimates after adjusting for cardiomyopathy, depression and anxiety may in part be attributed to the low sensitivity of these diagnoses in the patient registers.

Strengths and limitations

The strengths of this study include its population-based prospective design, the large sample size, the long follow-up (up to 39 years), the availability of a large number of confounders, and the independently collected and high-quality information on exposure and outcome. The positive predictive value of the HF diagnosis is high both in the Danish National Hospital Register and in the Swedish Patient Register, particularly in case of the primary diagnosis, i.e. we have few false positives.\textsuperscript{16–18} Several limitations, nevertheless, should be noted. First, though we adjusted for many potential confounders, the possibility of residual confounding by unmeasured familial genetic and environmental risk factors may not be completely excluded. However, the finding of an association between death of a child due to unnatural causes, which are less likely to be affected by confounding by familial cardiovascular risk factors, and an increased risk of HF is indicative of a stress-related effect. Second, because of the specialist care-based nature of the Danish and Swedish patient registers, some of the less severe HF cases might have been missed in our definition of the outcome. It is not clear to what extent this misclassification could be differential between the exposed and unexposed parents. It is plausible that some bereaved parents are more likely to visit health professionals than their non-bereaved counterparts, while others, overwhelmed by their grief, may be less prone than the unexposed to seek care for cardiac symptoms. Similarly, it is possible that some HF cases, primarily in the exposed group, may have actually had stress-related or Takotsubo cardiomyopathy, a reversible form of HF; we believe this eventual misclassification is unlikely to substantially affect our results given the high positive predictive value of the HF diagnosis in the studied patient registers, in particular in case of the primary diagnoses (88% to 95%).\textsuperscript{16–18} Third, compared to younger individuals, in the elderly HF diagnoses are more likely to have been given in inpatient care or as secondary diagnosis (due to comorbidities). Besides the lower underlying risk of HF in young individuals, these missed HF cases may have contributed to the weaker association in older parents (aged \textgreater{}50 years). Fourth, we had data on drug prescriptions only for a relatively small subset of study participants, thus we did not have enough study power to investigate whether the use of antidepressants or cardiovascular medications may modify the association of death of a child with HF risk. However, preliminary evidence suggests that treatment with low-dose metoprolol and aspirin for 6 weeks may reduce the adverse cardiovascular effects of bereavement.\textsuperscript{30} Fifth, our findings may be only generalizable to countries with a similar health care system and socioeconomic context to that of Denmark and Sweden. A further study in different contexts may yield different estimates, particularly in countries with less developed welfare systems.

Conclusions

In this large population-based cohort study, we found that the death of a child was associated with an increased risk of HF. The association was present not only in case the child died due to cardiovascular or other natural causes but also in case of unnatural deaths, suggesting that stress-related mechanisms may contribute
to the development of HF. Bereaved parents might benefit from support from family and health care professionals as well as from participation in cardiovascular prevention programs.

**Supplementary Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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