Myocardial Infarction in Parents Who Lost a Child
A Nationwide Prospective Cohort Study in Denmark

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Background—The association between psychological stress and coronary heart disease remains unclear. We conducted a prospective follow-up study based on national registers to investigate if the death of a child, one of the most severe stressors, increases the risk of myocardial infarction (MI) in parents.

Methods and Results—From 1980 to 1996, 19 361 parents who lost a child (<18 years of age) in Denmark were recruited to the exposed cohort, and 295 540 parents matched on family structure were selected for the unexposed cohort. The Cox proportional hazards model was used to evaluate the relative risk (RR) of myocardial infarction (MI). The average RRs for a fatal MI and any first MI among the exposed were 1.36 (95% CI, 0.98 to 1.88) and 1.28 (95% CI, 1.08 to 1.51), respectively. The two cohorts had similar MI risk during the first 6 years of follow-up. From the 7th to the 17th year of follow-up, the exposed cohort had a RR of 1.58 (95% CI, 1.08 to 2.30) for fatal MI and a RR of 1.31 (95% CI, 1.09 to 1.57) for first MI. Parents who lost a child unexpectedly, especially from sudden infant death syndrome, experienced higher RRs.

Conclusions—The death of a child was associated with an increased risk of MI in bereaved parents. **(*Circulation*. 2002;106:1634-1639.)**

Key Words: myocardial infarction ■ stress ■ risk factors

Although several risk factors for cardiovascular disease have been identified,[1,2] they only explain a proportion of the disease burden.[3] Growing evidence indicates that psychological stress is associated with an increased risk of coronary heart disease (CHD).[4–7] However, the quantitative importance of stress remains elusive because of the methodological limitations of previous studies. Self-reported data or various scales were used for stress assessment, which may be vulnerable to recall bias and misclassification.[8–10]

The death of a child has been classified as an extreme stressor.[11] This life event is more difficult to cope with than any other kind of bereavement because it is rare in Western society and in conflict with our life-cycle expectations. Bereaved parents often experience numerous forms of psychological stress, such as depression, despair, anxiety, guilt, anger, hostility, hopelessness, as well as preoccupation with thoughts of the deceased child.[12–15] They may have more somatic complaints and interpersonal difficulties and react with more adverse health behaviors.[12–17] It has been suggested that factors related to the nature of the death, personal characteristics, and interpersonal contexts could modify the effect of the bereavement.[12,13] Unexpected deaths, such as those caused by sudden infant death syndrome (SIDS), are often more stressful than deaths after prolonged illness,[12,13,18,19] and the age of the deceased child may also be related to parents' responses.[12,13] Sex, age, marital status, social support, and education have also been suggested to affect health outcomes of bereavement.[12,13,20–24] Despite reports of various adverse health consequences, the effect of the death of a child on CHD is not known.

This prospective cohort study was to investigate the association between the death of a child and myocardial infarction (MI). We examined the short- and long-term effect of the event according to the follow-up time. We hypothesized that parents who lost a child from SIDS or other unexpected death had a higher risk of MI than parents who lost a child from other causes. We examined whether the age of the deceased child had an effect on MI risk. We also explored the modifying effect of some sociodemographic factors, such as age, sex, education, residence, and marital status, on the risk of MI.

Methods

Study Design and Participants

This study is based on the follow-up of cohorts identified from national registers in Denmark. For each year from 1980 to 1996, we first identified all children who died under the age of 18 years and their family members in the Register of Population Statistics.[25] Their

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parents were selected to the exposed cohort. The exposed family was classified according to the number of parents and number of children in 6 age groups (<1 year, 1 to 2 years, 3 to 6 years, 7 to 9 years, 10 to 14 years, and 15 to 17 years) on January 1 in the year the child died. We then randomly sampled 15 times as many parents from the remaining parents in the entire population to the unexposed cohort. They were matched on family structure on January 1 in the year the child died.

Follow-up started when the participants were recruited to the cohorts and ended when they died, emigrated, or were diagnosed with a MI or at the end of 1996, whichever came first. The outcome of interest was MI as coded by the International Classification of Diseases (ICD), ICD 8 codes 4100 to 4109 from 1980 to 1993 and ICD 10 code I21 from 1994 to 1996. We recorded two MI events, fatal MI and first MI. First MI was either a hospitalization attributable to MI or a MI death, whichever occurred first during follow-up.

Information on the deceased children (age, sex, date of birth, date of death, and cause of death) and information on childbirths after entry for the cohort members was obtained from the fertility database.[25] Other information on cohort members (date of birth, date of death, sex, school education, residence, cause of death, and diagnosis of hospitalization) was obtained from the Prevention Register.[26] All register linkages were made by means of the unique personal identification number.[25,26] The National Board of Health and the Data Protection Agency approved the project.

Statistical Analysis

Relative risk (RR) estimates with 95% CIs were calculated as the measurement of association between the exposure and the MI end points, using the Cox proportional hazards regression model[27] according to the SAS PHREG procedure.[28] Potential confounders included age at entry (18 to 29 years, 30 to 39 years, ≥40 years), sex (male, female), school education (basic, secondary or higher, no information), residence (cities with >100 000 inhabitants, other places), prior hospitalization for hypertension (yes, no), and prior hospitalization for diabetes (yes, no). Two parents at the same address were considered to be cohabitating, which is equivalent to marriage in Denmark. Place of residence was included because it is related to social support. The number of children was also included because it is related to both emotional and social support as well as coping style in bereaved parents. Having a new child during the first 3 years of follow-up (yes, no) was treated as a time-dependent confounder in the analyses, because it may be important for coping with the stress.[14] Change in job category was used as an indication for change in employment; it is not included in the final models because it did not change the effect estimates.

First we looked into the overall and temporal differences of MI risk between the exposed and the unexposed by stratifying on follow-up time, dichotomising follow-up time when the survival curve started to separate at the 6th year of follow-up. We then examined the exposure according to two characteristics of the deceased child, age group (<1 month, 1 month to <1 year, 1 to 2 years, 3 to 9 years, 10 to 17 years) and type of death (SIDS [ICD 8 codes 7950 to 7959 for sudden, nonviolent death without a cause and, when children were 1 month to 12 months of age, ICD 10 codes R95], other unexpected death [ICD 8 codes 7950 to 7959 for sudden, nonviolent death without a cause and not coded as SIDS; ICD 8 codes 8000 to 9999 for accidents, suicide, and other violent death, other sudden death with no cause, and unattended death; ICD 10 codes R96 to R98 and V01 to Y98 for accidents, suicide, and other violent death], and death by other causes). The above analyses were also performed in subgroups according to baseline characteristics such as age, education, and residence.

We performed analyses in which we excluded parents who had a MI hospitalization recorded before study entry. We also did analyses using only first MI hospitalization as an end point and analyses in which we included only parents who lost their children in accidents or only parents who lost their children from cancer into the exposed cohort.

TABLE 1. Characteristics of the Deceased Children That Defined the Exposed Cohort

Characteristic	Boys (n=7128)	Girls (n=4944)	Total (n=12 072)
Age group			
<1 mo	2595 (36.4)	1900 (38.4)	4495 (37.2)
1–11 mo	949 (13.3)	633 (12.8)	1582 (13.1)
1–2 y	1070 (15.0)	863 (17.5)	1933 (16.0)
3–9 y	938 (13.2)	663 (13.4)	1601 (13.3)
10–17 y	1576 (22.1)	885 (17.9)	2461 (20.4)
Cause of death			
Infectious and parasite diseases	200 (2.8)	176 (3.6)	376 (3.1)
Malignant neoplasms	535 (7.5)	382 (7.7)	917 (7.6)
Congenital and perinatal diseases	4003 (55.2)	2844 (56.3)	6847 (56.7)
SIDS*	448 (6.3)	276 (5.6)	724 (6.0)
Accidents	1331 (15.9)	683 (13.8)	2014 (16.7)
Suicide, violent death	203 (2.8)	138 (2.8)	341 (2.8)
Other death	408 (5.7)	445 (9.0)	853 (7.1)

Values are n (%).

*ICD 8 codes 7950 to 7959 for sudden, nonviolent death without a cause; for children who died between 1 month and <1 year of age, ICD 10 code R95.

Results

From 1980 to 1996, 12 512 deceased children in Denmark were identified. There were 440 children whose family links were not registered on the first day of the index year. The remaining 12 072 children were linked to their families, and 19 361 parents were included in the exposed cohort. After matching, 181 083 unexposed families were selected, and 295 540 parents were included in the unexposed cohort.

Selected characteristics of the deceased children are summarized in Table 1. The 314 901 cohort members had an average follow-up time of 9.6 years, equal to 3 019 251 person-years. We found no large differences in baseline characteristics of the two cohorts (Table 2).

During the follow-up period, 564 cohort members died of MI (43 were exposed and 521 were not exposed). A total of 2 264 parents had a first event of MI (168 were exposed and 2096 were not exposed). The average RRs for fatal MI event and first MI were 1.36 (95% CI, 0.98 to 1.88) and 1.28 (95% CI, 1.08 to 1.51), respectively. We did not see any significant difference in MI risk during the first 6 years of follow-up between the two cohorts. During the 7th to the 17th year of follow-up, the RRs for fatal MI and for first event were 1.58 (95% CI, 1.08 to 2.30) and 1.31 (95% CI, 1.09 to 1.57), respectively (Table 3).

Table 4 presents the RRs of MI in bereaved parents according to the deceased children's age and type of death. We found a statistically significant 2- to 3-fold RR of MI in parents who lost a child aged 1 month to 1 year of age. Parents who lost a child from SIDS had a RR of 5.62 (95% CI, 2.50 to 12.63) for MI leading to death and of 2.43 (95% CI, 1.37 to 4.28) for a first MI. However, the numbers of parents who lost a child because of SIDS or a child aged 1 to 12 months were small.

TABLE 2. Baseline Characteristics of the Parents in the Cohorts

Characteristic	Exposed Cohort (n=19 361)	Unexposed Cohort (n=295 540)
Follow-up time, y	9.5 (2–17)	9.6 (2–17)
Age at entry, y	32.7 (22–47)	32.8 (22–47)
Age group (in years) at entry		
<30	7584 (39.2)	110 975 (37.6)
30–39	7966 (41.1)	127 523 (43.2)
≥40	3811 (19.7)	57 042 (19.3)
Sex		
Male	8969 (46.3)	136 756 (46.3)
Female	10 392 (53.7)	158 784 (53.7)
School education		
Basic	13 342 (68.9)	199 731 (67.5)
Secondary or higher	3319 (17.2)	60 307 (20.4)
No information	2700 (14.0)	35 502 (12.0)
Residence		
Cities*	5426 (28.3)	91 595 (31.0)
Other places	13 706 (70.8)	203 735 (69.0)
No information	229 (1.2)	210 (0.1)
No. of children in the family		
1	11 292 (58.3)	173 598 (58.7)
2	5286 (27.3)	80 719 (27.3)
≥3	2783 (14.4)	41 223 (14.0)
No. of parents in the family		
1	867 (9.6)	27 718 (9.4)
2	17 494 (90.4)	267 822 (90.6)

Values are mean (range) or n (%).
*Cities: cities with >100 000 inhabitants.

Table 5 shows RRs according to factors expected to modify the stress effect. We found similar RRs among fathers and mothers. RRs in the two younger age groups were higher than those in the age group of ≥40 years. Parents with only a basic school education and those living in small towns or in rural areas had higher RRs than others. None of these modifying effects reached a level of statistical significance.

In the subanalyses in which we excluded those who had a recorded MI before entry, or in which only the first hospitalization attributable to MI was used as the end point, or in which only parents who lost a child in accidents or from cancer were included, we found similar estimates to the overall risks, as presented in Table 3.

Discussion

We found an increased risk of MI in the parents who lost a child, but only after 6 years of follow-up. Parents whose children died unexpectedly, especially by SIDS, had the highest RR of MI. The study supports the idea that severe psychological stress is associated with an increased risk of MI.[5–7]

We used a single life event, the death of a child, as the stress indicator, which is different from previous studies,[6,7] to minimize the possibility of recall bias and misclassification of exposure. The large sample size and the long follow-up time permitted us to explore both a short-term and long-term effect. By basing the study on existing registers, we obtained complete follow-up.[25,26] We believe the validity of diagnosing MI to be similar in the compared groups, because the data were collected for administrative purposes. Our study populations were relatively young and thus had fewer competing risk factors for MI than older populations, reducing the risk of confounding by various known or unknown factors.

Fatal MI or hospitalized MI is the end stage of a prolonged process in which abnormalities of arterial and myocardial structure and function precede the onset of a clinical event by many years.[22,29] However, the populations in our study were relatively young, and very few of them were expected to have advanced atherosclerotic diseases at baseline. Thus, we did not observe an immediate triggering effect of stress on MI, as in studies elsewhere.[22,30,31] The observed long-term effect on MI risk

TABLE 3. RR of MI in Parents After the Death of a Child According to Time Periods of Follow-Up: Cox Regressions

	Fatal MI Events		First MI Events	
Time Period	n	RR (95% CI)	n	RR (95% CI)
All periods				
Exposed	43	1.36 (0.98–1.88)	168	1.28 (1.08–1.51)
Unexposed	521	1.00 (reference)	2096	1.00 (reference)
1st–6th year of follow-up				
Exposed	10	0.93 (0.48–1.80)	23	1.13 (0.71–1.80)
Unexposed	173	1.00 (reference)	307	1.00 (reference)
7th–17th year of follow-up				
Exposed	33	1.58 (1.08–2.30)	145	1.31 (1.09–1.57)
Unexposed	348	1.00 (reference)	1789	1.00 (reference)

RRs adjusted for age group, sex, school education, residence,, prior hospitalization for hypertension, prior hospitalization for diabetes, number of children in the family, number of parents in the family, and having a new child within the first 3 years of follow-up.

TABLE 4. RR of MI in Parents After the Death of a Child According to Type of Death and Age of the Deceased Child: Cox Regressions

	Fatal MI Events		First MI Events	
Stratification	n	RR (95% CI)	n	RR (95% CI)
Type of death of the deceased child				
SIDS*	6	5.62 (2.50–12.63)	12	2.43 (1.37–4.28)
Other unexpected death†	17	1.17 (0.72–1.90)	72	1.19 (0.94–1.50)
Not unexpected death	20	0.94 (0.60–1.46)	84	1.14 (0.94–1.38)
Unexposed	521	1.00 (reference)	2096	1.00 (reference)
Test for trend		0.0568		0.0049
RR for trend		1.20 (1.00–1.43)		1.14 (1.04–1.25)
Age of the deceased child				
<1 mo	5	0.75 (0.31–1.86)	24	0.94 (0.65–1.36)
1–11 mo	7	3.36 (1.67–6.78)	18	1.88 (0.21–2.93)
1–2 y	3	0.91 (0.29–2.85)	20	1.67 (1.14–2.44)
3–9 y	5	1.07 (0.44–2.59)	21	1.12 (0.76–1.67)
10–17 y	23	1.09 (0.71–1.68)	85	1.13 (0.92–1.40)
Unexposed	521	1.00 (reference)	2096	1.00 (reference)

RRs adjusted for age group, sex, school education, residence, prior hospitalization for hypertension, prior hospitalization for diabetes, number of children in the family, number of parents in the family, and having a new child within the first 3 years of follow-up.

*ICD 8 codes 7950 to 7959 for sudden, nonviolent death without a cause, for children who died between 1 month and <1 year of age, ICD 10 codes R95.

†ICD 8 codes 7950 to 7959 for sudden, nonviolent death without a cause (SIDS excluded); ICD 8 codes 8000 to 9999 for accidents, suicide, and other violent death, other sudden death with no cause, and unattended death; ICD 10 codes R96 to R98 and ICD 10 codes V01 to Y98 for accidents, suicide, and other violent death.

is supported by the recently proposed stress mechanism for CHD.[4–6] The bereavement could exert its effects directly by leading to pathophysiological changes in the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system.[4–6] Such effects include hypercortisolemia, elevation of arterial blood pressure, exacerbation of coronary artery atherosclerosis, endothelial dysfunction, and even necrosis, which all contribute to the pathogenesis of MI.[4–6] It could also operate indirectly by influencing the pattern of health behaviors, like heavier smoking and alcohol ingestion or less physical activity.[4–6,15–17]

Variations in the stress response exist within populations, and what accounts for the difference in vulnerability to CHD remains of interest.[4,12,13,20–24] The highest RRs of MI in parents whose children died of SIDS is consistent with suggestions from previous studies.[12,13,18,19] We did not observe any obvious modifying effect of age of the deceased children, which ranged from birth to 18 years. The highest RRs in the second age group were mainly attributable to SIDS. Our findings of similar RRs of MI in the two sexes are in line with previous studies,[20] suggesting that fathers and mothers often experience similar stress after the death of a child. The role of age in one's reactions to parental bereavement remains unclear.[12,13] We observed lower RRs of MI in the oldest age group. This may be attributable to additional component causes that could attenuate the effect of the bereavement on the relative scale. There have been suggestions that people of lower socioeconomic status or people with limited social support may have more difficulties in coping with stress,[21,22] which may be the reason for the observed higher RRs in single parents, in parents with a limited education, and in parents living in remote areas.

Our study has limitations. We had no information on conventional risk factors, such as cholesterol level, lifestyle factors, physical activities, and family history of MI at baseline, except for data on hospitalized diabetes and hypertension before entry. The study may be confounded by these unknown factors. However, we selected our controls according to family structure on the first day of the index year and adjusted for sociodemographic factors. Furthermore, similar MI risks in the two cohorts were seen during the first 6 years of follow-up, indicating that the two groups had a comparable MI risk at baseline. The bereaved parents could possibly develop more risky lifestyles,[15–17] which may be one of the possible causal pathways for the association.[5,7] The study could be confounded by genetic factors modifying both the risk of cardiovascular diseases and the cause of specific childhood deaths. The fact that we also saw an effect for childhood deaths caused by accidents speaks against this mechanism. Another limitation is that the enrolled parents were young, with a low risk of MI, which reduced statistical power, especially for the subgroup analyses. The results for the subgroups should be interpreted with caution because of the limited number of cases.

TABLE 5. RR of MI in Parents After Death of a Child During the 7th to 17th Year of Follow-Up According to Baseline Characteristics: Cox Regression

	Fatal MI Events		First MI Events	
Characteristic	Exposed/Unexposed, n	RR (95% CI)	Exposed/Unexposed, n	RR (95% CI)
Sex				
Male	23/285	1.47 (0.95–2.56)	103/1471	1.31 (1.07–1.60)
Female	6/63	2.07 (0.95–4.54)	21/318	1.30 (0.85–1.99)
Age group, y				
<30	3/20	3.59 (0.87–14.80)	6/113	1.50 (0.65–3.48)
30–39	6/73	1.83 (0.76–4.46)	40/513	1.75 (1.24–2.46)
≥40	20/255	1.42 (0.92–2.19)	78/1163	1.14 (0.91–1.43)
School education				
Basic	25/252	1.58 (1.08–2.29)	96/1316	1.31 (1.09–1.57)
Secondary or higher	0/26	. . .	5/106	1.02 (0.40–2.64)
Unknown	4/70	0.71 (0.35–2.46)	23/367	1.10 (0.72–1.69)
Residence				
Cities	3/80	0.59 (0.16–2.19)	22/515	0.99 (0.65–1.49)
Other places	26/268	1.82 (1.23–2.69)	102/1274	1.42 (1.17–1.73)
No. of children in the family				
1	11/170	1.22 (0.67–2.23)	44/773	1.23 (0.92–1.65)
2	9/97	1.43 (0.69–2.94)	44/574	1.15 (0.82–1.60)
≥3	9/81	2.31 (1.20–4.46)	36/442	1.55 (1.11–2.16)
No. of parents in the family				
1	3/17	2.78 (0.81–7.85)	9/91	1.79 (0.90–3.62)
2	26/331	1.50 (1.01–2.21)	115/1698	1.28 (1.06–1.55)

RRs adjusted for age group, sex, school education, residence, prior hospitalization for hypertension, prior hospitalization for diabetes, number of children in the family, number of parents in the family, and having a new child within the first 3 years of follow-up.

In conclusion, our data indicate an increased risk of MI in parents after the death of a child.

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