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BEREAVEMENT IN ADULTHOOD AND RISKS OF INCIDENT AND RECURRENT CARDIOVASCULAR DISEASES

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Bereavement in adulthood and risks of incident and recurrent cardiovascular diseases

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my beloved family!

致我亲爱的家人!

To my friend Chenggui Fan and my cousin Yue Mo.

POPULAR SCIENCE SUMMARY OF THE THESIS

Most individuals will experience the death of a close family member or a close friend at least once in life. Bereaved persons may be affected by the loss in several ways, e.g., they may experience disruptions in daily routines, financial insecurity, anger, loneliness, anxiety, and depression, but also other psychiatric or somatic diseases and death. Cardiovascular diseases (CVD) may be an important concern among those who lost a loved one, given that stress has been found in earlier research to increase the risk of CVD. A large number of studies have shown that compared to their unexposed counterparts, individuals who lost their partners have higher risks of developing CVD or cardiovascular death, particularly in the period shortly after the loss. However, knowledge regarding the risk of CVD after the death of a child – one of the most stressful life events a parent may experience – is limited. Further, no studies have investigated whether bereaved patients with acute myocardial infarction (AMI) have a worse prognosis than their unaffected counterparts. This doctoral thesis aimed to study whether bereaved parents had an increased risk of CVD and whether bereaved AMI patients had a higher risk of poor prognosis than their unexposed counterparts. To answer these questions, we conducted four population-based cohort studies using register data from Denmark and Sweden.

We found that parents who lost a child had a 20% higher risk of ischemic heart disease (IHD), a 21% higher risk of AMI, and a 35% higher risk of heart failure than non-bereaved parents. The increased risks of these heart diseases were found irrespective of the child's cause of death, i.e., due to CVD, other natural causes, or unnatural causes. We observed U-shaped associations when we classified parental bereavement according to the age of the deceased child at loss, i.e., losing an infant or an adult child appeared to be related to higher risks of these heart diseases than the loss of a child aged 2-17 years. The risk of AMI among bereaved parents was particularly high in the week immediately after the loss, but remained increased also on the long term. The strength of the association between the death of a child and the risk of heart failure did not differ according to the time since the loss.

In one of the studied cohorts of AMI patients, i.e., the Stockholm Heart Epidemiology Program, we found that the death of a partner but not of other close family members or close friends one year before the first AMI was associated with an increased risk of non-fatal recurrent AMI or death due to IHD. In a register-based cohort study of AMI patients, we observed that the loss of a close family member was associated with a slightly increased risk of poor prognosis. The association between the death of a close family member and the risk of poor prognosis in AMI did not differ by the family member's cause of death. The risk of poor prognosis in bereaved AMI patients was increased if they lost a close family member one year before the AMI or from the second year after the AMI, but not during the year immediately after the AMI. However, the association between bereavement and poor prognosis in AMI was strongest for the death of a partner, followed by the loss of a child, grandchild, sibling, or parent. Further, the loss of a partner or child was associated with an elevated risk of poor prognosis both in the short and long term after the loss.

In summary, parents who lost a child had a higher risk of IHD and heart failure than parents who did not experience this event. Bereavement in AMI patients, especially for close family members, was associated with an increased risk of poor prognosis. Our findings call for attention and support from family and society for the bereaved and this may be beneficial for their cardiovascular health.

ABSTRACT

Bereavement, the loss of a family member or a loved one, is a severely stressful life event that may occur at least once in most individuals' life. Bereaved persons are likely to be influenced by the loss in multiple aspects of their life, such as daily routines, financial security, or sleep quality. Furthermore, accumulating evidence suggests that bereaved individuals have increased risks of psychological and somatic morbidity, as well as death. The death of a partner in middle- and old age has been found in several studies to be related to increased risks of incident CVD and cardiovascular mortality. However, knowledge about the association between the death of a child, i.e., one of the most stressful life events, and the risk of CVD, is limited. Additionally, the question of whether bereavement could lead to poor prognosis in CVD has received very little attention. Therefore, in this thesis, we aimed to investigate the association between the death of a child and parental risk of CVD (studies I and II) and between the death of a close family member or friend and prognosis in acute myocardial infarction (AMI) (studies III and IV).

In studies I and II, we investigated whether bereaved parents had increased risks of ischemic heart diseases (IHD), AMI, and heart failure (HF). Studies I and II were bi-national population-based cohort studies including 6.7 million parents who had at least one child born during 1973-2016 in Denmark or during 1973-2014 in Sweden. We obtained information on children's death, parental sociodemographic and health-related characteristics, and parental heart diseases from several Danish and Swedish nationwide registries. We observed modest associations between the death of a child and the risks of IHD (incidence rate ratio (IRR) [95% confidence intervals (CIs)]: 1.20 [1.18-1.23]), AMI (IRR [95% CIs]: 1.21 [1.17-1.25]), and HF (IRR [95% CIs]: 1.35 [1.29-1.41]). The associations were found irrespective of the child's causes of death (due to CVD, other natural causes, or unnatural causes). There were U-shaped associations with the risks of IHD, AMI, and HF when we categorized exposure according to the age of the deceased child at loss. Bereaved parents who lost an infant or an adult child had higher risks of the studied heart diseases than those who lost a child aged 2-17 years. The relative risk of AMI was highest in the week immediately after the loss and persisted throughout the follow-up. The relative risk of HF did not differ substantially according to the time since the loss.

In study III, we investigated whether the loss of a family member or a close friend one year before the first AMI was associated with prognosis in AMI. We conducted a population-based cohort study involving 1732 first-AMI patients from the Stockholm Heart Epidemiology Program during 1992-1994 whom we followed for a median of 14 years. We retrieved information on bereavement and several other characteristics of study participants from questionnaires completed by patients or their family members during or shortly after the hospitalization, while information on outcomes (i.e., non-fatal recurrent AMI, death due to IHD, all-cause mortality, HF and stroke) was from national health and mortality registers. We found no association between any loss one year before the first AMI and the combination

of non-fatal recurrent AMI and death due to IHD. However, the patients who lost their partner one year before the first AMI had an increased risk of non-fatal recurrent AMI or death due to IHD (hazard ratio [95% CIs]: 1.55 [1.06-2.27]).

In study IV, we investigated further, using a larger sample, whether AMI patients had a poor prognosis if they experienced bereavement. This study included 266,651 patients with a first AMI recorded in the SWEDEHEART (acronym for Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) from 1991 to 2018. We collected information on bereavement as well as study participants' characteristics and outcomes from several Swedish nationwide registers. We defined exposure as the death of a partner, child, grandchild, sibling, or parent one year before the first AMI or during the 4.4 years median follow-up. We found that bereaved AMI patients had a slightly increased risk of the combination of non-fatal recurrent AMI and death due to IHD. The association was strongest for the loss of a partner, followed by the loss of a child, grandchild, sibling, and parent, but was similar with respect to natural and unnatural deaths. The prognosis of AMI was poor during most of the periods when the loss occurred except for the year immediately after the first AMI. Similar associations were observed for all-cause mortality, HF, and stroke in relation to bereavement.

In conclusion, the death of a child was associated with increased risks of IHD, AMI, and HF. Loss of a partner, child, grandchild, and sibling was associated with an increased risk of poor prognosis in AMI. If our findings are confirmed by future studies, support from family and society as well as attention from health care professionals would be beneficial for bereaved individuals' cardiovascular health.

LIST OF SCIENTIFIC PAPERS

I. **Wei D**, Janszky I, Fang F, Chen H, Ljung R, Sun J, Li J, László KD. Death of an offspring and parental risk of ischemic heart diseases: A population-based cohort study. PLoS Med. 2021;18(9):e1003790.

II. **Wei D**, Li J, Janszky I, Chen H, Fang F, Ljung R, László KD. Death of a child and the risk of heart failure: a population-based cohort study from Denmark and Sweden. Eur J Heart Fail. 2022;24(1):181-189.

III. **Wei D**, Janszky I, Ljung R, Leander K, Chen H, Fang F, Li J, László KD. Bereavement in the year before a first myocardial infarction: Impact on prognosis. Eur J Prev Cardiol. 2021;28(11):1229-1234.

IV. **Wei D**, Janszky I, Ljung R, Fang F, Li J, László KD. Bereavement and prognosis after a first acute myocardial infarction: a Swedish register-based cohort study. [Submitted]

LIST OF ADDITIONAL PUBLICATIONS

I. **Wei D**, Li J, Chen H, Fang F, Janszky I, Ljung R, László KD. Death of a Child and the Risk of Stroke: A Binational Cohort Study from Denmark and Sweden. Neurology. 2022;98(11):e1104-e1113.

II. Lee P, Tse La, László KD, **Wei D**, Yu Y, Li J. Association of maternal gestational weight gain with intellectual developmental disorder in the offspring: a nationwide follow-up study in Sweden. BJOG. 2022;129(4):540-549.

III. Lee P, Tse La, László KD, **Wei D**, Yu Y, Li J. Association of maternal body mass index with intellectual disability risk. Arch Dis Child Fetal Neonatal Ed. 2021;106(6):584-590.

IV. **Wei D**, Olofsson T, Chen H, Janszky I, Fang F, Ljung R, Yu Y, Li J, László KD. Death of a child and the risk of atrial fibrillation: a nationwide cohort study in Sweden. Eur Heart J. 2021;42(15):1489-1495.

V. Wang Y, **Wei D**, Chen H, Chen B, Li J, László KD. Death of a Child and Mortality after Cancer: A Nationwide Cohort Study in Sweden. Cancer Epidemiol Biomarkers Prev. 2021;30(1):150-157.

VI. Warselius P, Cnattingius S, Li J, **Wei D**, Valdimarsdottir UA, Kosidou K, Reutfors J, Olsen J, Vestergaard M, Obel C, László KD. Maternal bereavement shortly before or during pregnancy and risk of postpartum psychotic illness: a population-based study from Denmark and Sweden. Clin Epidemiol. 2019;11:285-298.

CONTENTS

LIST OF ABBREVIATIONS

AMI	Acute myocardial infarction
CI	Confidence intervals
CVD	Cardiovascular diseases
HF	Heart failure
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart diseases
IRR	Incidence rate ratio
MBR	Medical Birth Register
RR	Rate ratio
SHEEP	Stockholm Heart Epidemiology Program
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

1 BACKGROUND

Bereavement is a severely stressful life event that most individuals will experience at least once in life. Approximately 3% of children in the Nordic countries[1] and 7% of children in the US[2,3] lost a parent, while 1% of children in the Nordic countries lost a sibling[4-6] before the age 18 years. Bereavement in adulthood is considerably more frequent, particularly in old age; for example, approximately 8% of middle-aged individuals in Sweden have experienced the death of a sibling during the ages 40-69 years,[7] approximately 40% of women and 13% of men have lost their spouse/partner after the age of 65 years.[8,9] In contrast, the risk of losing a child differs substantially across countries. For example, around 0.5% of mothers in high-income Asian and European countries experienced the loss of an infant.[10] In contrast, the figure is 30 times higher in countries from Africa, Latin America, the Middle-East and Southeast Asia and 50 times higher in sub-Saharan African countries.[10]

According to several widely used rating systems of stress, bereavement is one of the most stressful life events.[11,12] In the axis IV of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, the death of a child and the suicidal death of a spouse are rated 6 on a six-step scale of severity of stress, while the death of other relatives is rated 5.[11] According to Holmes' and Rahe's Scale of adverse life events, the death of a spouse is rated the most stressful life event followed by the death of other relatives.[12] In addition to grief, the death of a loved one is often associated with adverse psychosocial changes such as disruptions in daily routines, financial insecurity, anger, loneliness, anxiety, and depression, as well as other psychiatric or somatic morbidity and mortality.[9]

2 LITERATURE REVIEW

2.1 Health outcomes after bereavement in adulthood

2.1.1 Mental health

Although bereavement is often unavoidable and grief is usually resolved naturally within a relatively short period of time, in some cases the grief resolution may be particularly difficult.[9,13] Complicated grief is characterized by a prolonged and intense negative emotional experience or an inhibited response to the loss.[9] The prevalence of complicated grief in adulthood varies by the age of bereaved individuals at loss, the relationship to the deceased, and the deceased relative's cause of death.[14] For example, a study found that 30% of bereaved individuals aged 65 years or older had complicated grief.[15] Another study found that 19% of young adults experienced complicated grief after losing a close friend or sibling.[16] The proportion of complicated grief among bereaved individuals whose relative died of violent causes (12.5% to 78.0%[17]) is higher than that among those bereaved by the loss due to natural causes (2.4% to 6.7%[13,18]). Furthermore, bereaved mothers have been found to have a higher risk of complicated grief than bereaved fathers after the death of their child.[19]

Other psychological reactions are also important concerns after bereavement. Compared with their unexposed counterparts, bereaved individuals are more likely to experience anger,[20] loss of appetite,[21,22] sleep disruption,[23-26] depression,[27-32] anxiety,[27] and posttraumatic stress disorders.[33-37] Increasing evidence suggests that the conjugally bereaved have an increased risk of depressive disorders in early bereavement.[27-32,38,39] The association between spousal bereavement and depressive symptoms has been found in previous studies to be attributed to grief severity, guilt, loneliness or poor sleep quality.[40-43] Depression is common also among bereaved parents,[44,45] and the increased risk of depression has been found to be present for a long time (2-6 years) after child death.[45] Previous investigations also reported an increased long-term risk of posttraumatic stress disorders after the loss of a child. [33,35,37]

In addition to psychological symptoms, the death of a child has also been suggested to be associated with increased risks of parental psychosis,[46] psychotropic medication use,[47] or hospitalization for mental illnesses.[48,49] The risk of a new psychotropic prescription is higher among conjugally bereaved persons than among non-bereaved married individuals.[50,51] One study reported that bereaved women who lost a partner had an approximately 16-fold higher risk of initiation of anxiolytics/hypnotics and a five-fold higher risk of using antidepressants in the first two months after the loss compared to their non-bereaved counterparts.[50] On the long term, however, the increased risk of prescribed psychotropic medication declined but was still present.[50,51]

2.1.2 Non-cardiovascular somatic disorders

Several somatic diseases have been studied in relation to bereavement, most commonly cancer, diabetes, inflammation, neurological diseases, obesity, pregnancy-related complications and cardiovascular diseases (CVD).[9] Numerous studies have investigated the association between the death of a child and the risk of cancer, however, findings in this field are inconsistent.[52-58] Two studies found an increased risk of any cancer among bereaved parents relative to the non-bereaved.[53,54] In contrast, another study found no differences in the risk of cancer between bereaved and non-bereaved parents.[56] Several studies analyzing specific cancers, suggested that bereaved parents had an increased risk of infection-related cancers,[52,57,58] whereas one study reported no association between child death and maternal breast cancer.[55] Similarly, the results concerning the link between the loss of a child and cancer survival are conflicting.[53,56,59,60] Levav et al. reported an association between the death of an adult son in war or accident and poor cancer survival if the index cancer was diagnosed before the loss, but not in case of a cancer diagnosis after the loss of their child.[53] Schorr et al.[56] and Li et al.[59] did not find differences in parental cancer survival according to the exposure to child death. Further, Kvikstad et al. did not find evidence for an association between the death of a child and cancer survival in female cancer survivors in midlife.[60]

Bereavement may be related to the risk of diabetes, but the association varies by the relationship to the deceased. Children born to mothers who lost a close family member during pregnancy had a higher risk of hospitalization for type-2 diabetes than those whose mothers did not have such experience during pregnancy.[61] Further, two studies showed that bereaved parents had a higher risk of diabetes than non-bereaved parents, regardless of the child's cause of death (suicidal or non-suicidal).[62,63] Spousal suicide, however, was not found to be associated with an elevated diabetes risk in a previous study.[64]

Inflammatory factors have been found to be increased after bereavement,[30,65-67] but findings regarding the association between bereavement and inflammation-related diseases or infection are conflicting. A study found that individuals who lost a spouse/partner consumed more anti-infective medicine than their married counterparts.[68] In contrast, two other studies did not find an association between the death of a child and parental risk of inflammatory bowel diseases or rheumatoid arthritis.[69,70]

2.1.3 Mortality

The risk of all-cause or certain cause-specific mortality, e.g., suicide or death due to CVD, has been shown to be increased after bereavement. Suicide is one of the most fierce consequences of bereavement and the risk of suicide in bereaved individuals is highest in the first months after the loss, particularly in case of losing a spouse/partner or child.[71-77] Furthermore, the risk of suicide in relation to the death of a partner, child, or sibling is higher if the deceased relative died of suicide compared to other causes.[72,73,78,79] The association

between suicidal bereavement and the risk of death by suicide may be attributed to stigma.[80-84]

The findings regarding the increased risk of death are consistent in most types of bereavement in adulthood. Compelling evidence suggests that bereaved individuals who lost a spouse or partner in middle- and old-age have increased risks of all-cause mortality or death due to cardiovascular events and cancer.[85-87] An increasing number of studies also show that bereaved parents have higher mortality risk than their non-bereaved counterparts, regardless of the age of the deceased child.[88-92] Rostila et al., however, observed a decreased mortality risk in the first three years after the death of an adult child (aged>25 years).[90] The loss of a sibling in adulthood is also associated with an increased risk of premature mortality.[7,93,94] Although the death of a parent in adulthood is in line with our expectations about the lifecycle, findings from a previous study showed that adults bereaved by the loss of a parent had a higher risk of death than those whose parents were alive.[95] In contrast, another study suggested a reduced mortality risk among adult children 30 years or older following the death of a parent.[96]

The risk of mortality after bereavement in adulthood varies by the sex of the bereaved. The association between the death of a spouse and mortality has been found to be stronger in men than in women.[9,86,87] Similarly, one study observed an elevated mortality risk among bereaved men but not among bereaved women after the death of a parent.[95] However, compared to fathers, the relative risk of death corresponding to the death of a child (<18 years old) is higher in mothers, particularly if the child died of unnatural causes.[89] The death of an adult child was found in one study to be associated with an increased risk of mortality among mothers but not among fathers.[90] Likewise, a stronger association between the death of a sibling and mortality was also found among women than among men.[7,93,94]

The strength of the association between bereavement and mortality also varies by the age of the bereaved. A meta-analysis reported that the magnitude of the association between the loss of a spouse and the mortality risk decreased along with the increase in the bereaved individuals' age.[87] Another study found a similar trend with respect to the relationship between the death of an adult sibling and the risk of death, i.e., the association became weaker with increasing age.[93] Li et al., however, found that the relative risk for parental death after the death of a child became higher with increasing parental age at child loss.[89]

2.1.4 Cardiovascular diseases

Death due to CVD and incident or recurrent cardiovascular events may also be concerns for bereaved individuals. As mentioned above, the risk of dying is likely to be higher among the bereaved than among their non-bereaved counterparts. CVD are an important cause of these deaths after bereavement.[7,9,94,97,98] A growing number of studies have shown that the death of a spouse/partner or sibling in middle- and old age was associated with an increased risk of

cardiovascular mortality.[7,85,94,97,98] Further, a few studies have also reported that bereavement in adulthood was associated with an elevated risk of non-fatal incident and recurrent CVD. The death of a partner or a loved one has been found to be related to an increased risk of acute myocardial infarction (AMI), stroke as well as atrial fibrillation.[99-101] Li et al. found that bereaved parents had a higher AMI risk than non-bereaved parents since the seventh year after the loss.[102] Another study by the same group did not find evidence for such an association with stroke.[103] Li and colleagues may have had insufficient power to test the short-term effects on the AMI risk after the loss, given the low prevalence of exposure and outcome in young to middle-aged parents in a Western country. Further, the death of an adult child, which could also increase the risk of adverse health outcomes,[56,58,90] had not been considered in the study by Li et al. Other heart diseases, e.g., heart failure (HF) and less severe ischemic heart diseases (IHD) such as angina and atherosclerosis have not been investigated in relation to the death of a child. Therefore, large-scale studies investigating the risk of heart diseases (IHD/AMI and HF) following the loss of a child are needed.

Bereavement may be implicated in the prognosis of CVD, but the evidence in this area is very limited. Given the improvements in early diagnosis and in medical treatments of CVD, a growing number of patients have a history of AMI or are living with HF. Due to the advanced age of patients with CVD, experiencing the death of a loved one or a close friend is common, and it may worsen their prognosis. Few studies, however, have studied whether bereavement is associated with prognosis after CVD and their results are conflicting. Simeonova et al. found a higher all-cause mortality risk after losing a spouse in men with HF compared with their married counterparts.[104] In contrast, Stahl et al. found that partner bereavement was associated with a reduced death risk among women with CVD but observed no difference in survival between bereaved and non-bereaved men with CVD.[105] Carey and colleagues did not find an association between partner bereavement and the risk of AMI or stroke among those with a history of IHD or cerebrovascular diseases.[99] Further studies are, thus, needed to investigate whether bereavement may influence prognosis of CVD.

2.2 Potential underlying mechanisms linking bereavement and CVD

Two main linking mechanisms have been suggested to explain the association between bereavement and CVD (Figure 1).[85,106-108] Bereavement, as a severe stressor, may induce adverse changes in neuroendocrine, metabolic, haemostatic and cardiovascular activities, which in turn may increase the risk of CVD. An alternative pathway, the “indirect pathway”, suggests that the emotional and behavioral changes (such as grief, depression, anxiety, anger, changes in daily routines, unhealthy diet, physical inactivity, etc.) following bereavement, trigger or maintain the above biological changes and increase the risk of CVD.

On the short term, both biological changes as well as emotional and behavioral reactions may play important roles in mediating the association between bereavement and CVD. Bereavement may activate the hypothalamic-pituitary-adrenal axis and the autonomic

nervous system, which may induce acute changes in neuroendocrine, metabolic, haemostatic and cardiovascular activities, in turn contributing to an increased risk of CVD in the period shortly after the loss. As a response to the activation of the hypothalamic-pituitary-adrenal axis, inflammation also contributes to an increased risk of CVD.[109] Cohen et al. found that bereaved adults have a higher level of interleukin-6 after the death of their siblings than the non-bereaved.[65] Buckley et al. reported that study participants who experienced the death of a spouse or child had higher neutrophil count in the first two weeks post-bereavement compared to the non-bereaved, but the elevation of neutrophil count declined at six months in the bereaved group.[66] Others reported that the increased level of inflammatory factors following conjugal bereavement was likely to be observed in a genetically susceptible population (the IL-6-147G homozygotes carriers)[67] or in those with a severe grief.[30] Buckley et al. also reported increased levels of von Willebrand factor and platelet count in early bereavement, with these elevations disappearing at six months after the loss.[66] High blood pressure and heart rate as well as low heart rate variability have also been suggested to be related to bereavement in previous studies.[107,110-112] Additionally, a growing number of studies have found higher risks of depressive symptoms, anxiety, anger, alcohol abuse, and sleep disturbance in the bereaved on the short period after the loss than among the non-bereaved.[20,23-25,27-32,113,114] A previous study also observed that bereaved individuals with CVD were less likely to follow doctor's prescription of cardiovascular medications shortly after the death of a partner compared to their married counterparts.[115] The abovementioned biological or emotional and behavioral changes have been suggested to trigger a cardiovascular event among individuals without any pre-existing cardiovascular conditions and among those who had already had a CVD prior to bereavement.[116-121]

On the long term, the association may be mainly attributed to psychological and behavioral changes after the loss. Accumulating evidence has suggested increased risks of adverse psychological reactions and behaviors in the years after the loss. For example, Rogers et al. reported a higher risk of depressive symptoms among bereaved parents over an average of 18 years after the loss of a child compared to non-bereaved parents.[122] Jonasson et al. found that widowers had higher risks of difficulties in falling asleep and of sleep disruption at night and anxiety four-five years after the loss of their wives compared to non-bereaved married men.[26] Depression, anxiety, and sleeping disorders are well-known risk factors for CVD. Loneliness is a further common consequence of bereavement[40,123] and has also been suggested to increase the risk of CVD.[124] Weight change may also contribute to the associations of interest since weight change has been suggested to be associated with increased risks of AMI and HF.[125] Weight change has been observed after bereavement in previous studies, however, the direction of change was inconsistent.[21,126]

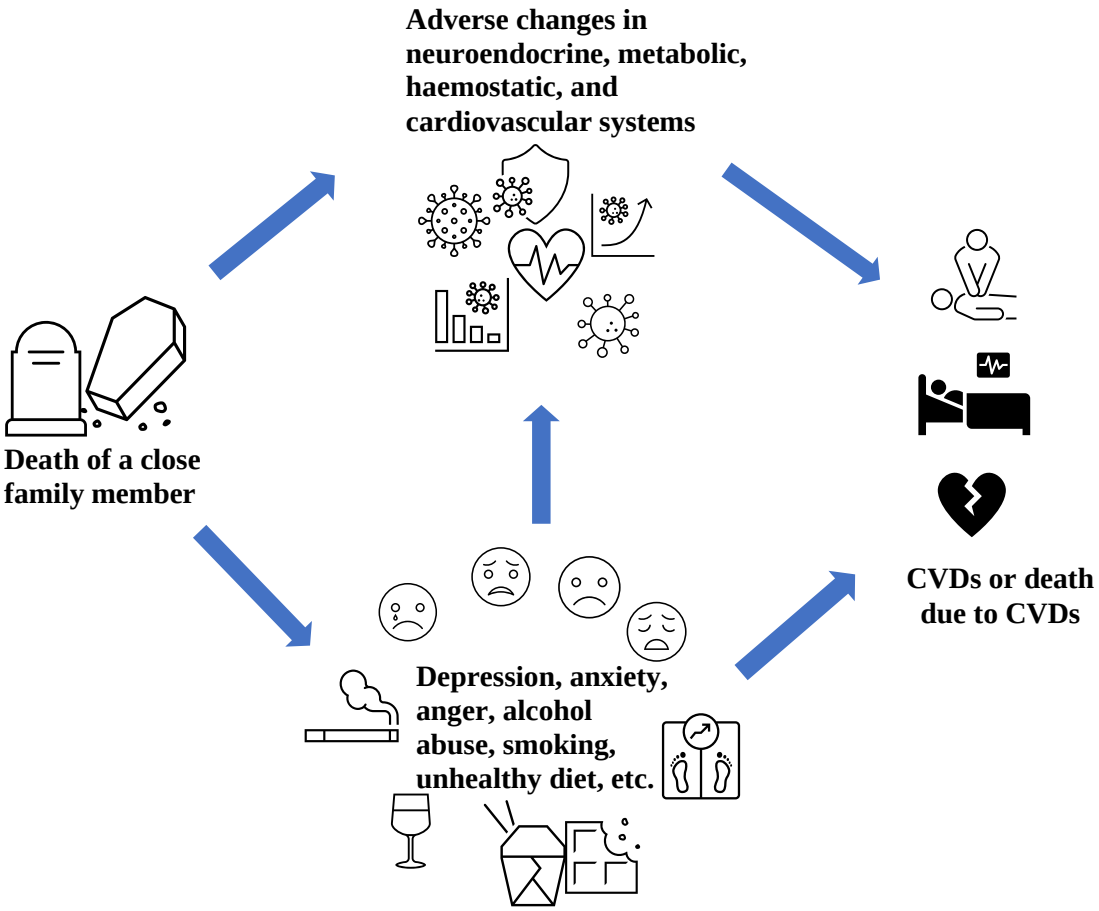

Figure 1. Potential mechanisms linking bereavement to cardiovascular diseases

CVD=cardiovascular disease.

3 RESEARCH AIMS

We aimed to contribute to a better understanding of the association between bereavement and risks of incident and recurrent CVD. The specific research questions studied were (Figure 2):

Study I: whether the death of a child was associated with increased risks of IHD and AMI and whether the associations varied by characteristics of the loss and the time since the loss.

Study II: whether the death of a child was associated with an increased risk of HF and whether the association varied by characteristics of the loss and the time since the loss.

Study III: whether the death of a close family member or close friend one year before the first AMI was associated with an increased risk of poor prognosis in AMI, and whether the association differed by characteristics of the loss and the time since the loss.

Study IV: whether the death of a close family member one year before or after the first AMI was associated with an increased risk of poor prognosis in AMI and whether the association differed by characteristics of the loss and the time since the loss.

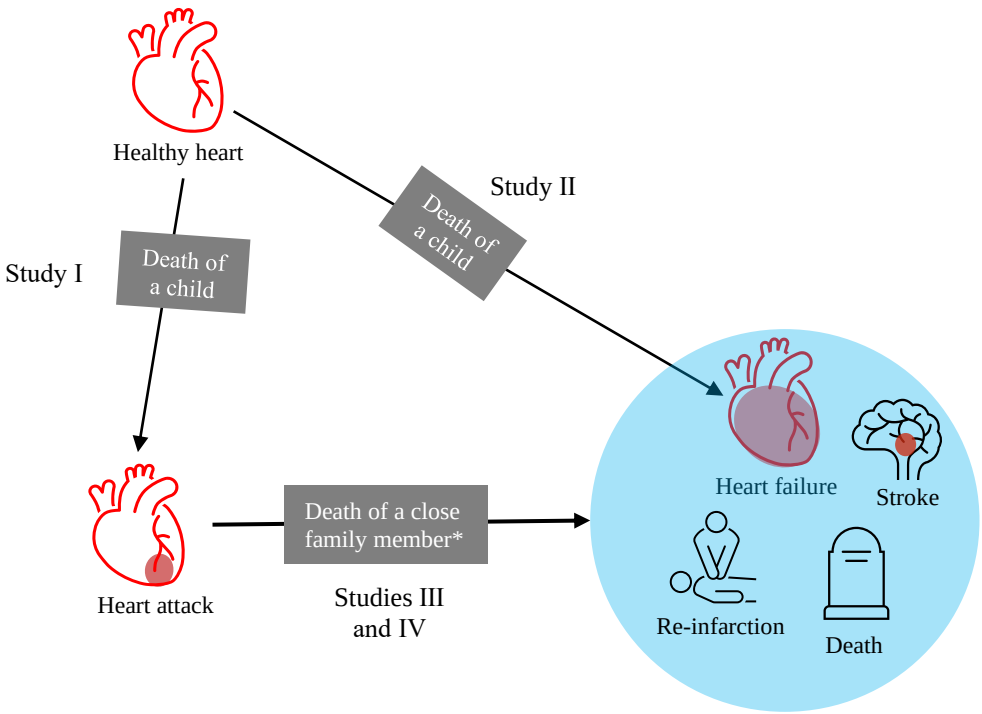

Figure 2. Overview of the thesis and the investigated research questions

*In study III, we studied the death of both a close family member and friend.

4 MATERIALS AND METHODS

4.1 Studies I and II

4.1.1 Study population and design

Studies I and II were bi-national population-based cohort studies. The study participants were parents of live-born children recorded in the Medical Birth Registers (MBR) in Denmark during 1973-2016 (n=2,807,548) and in Sweden during 1973-2014 (n=3,924,237). The unique Danish and Swedish personal number allowed us to link individual-level information between registers. We identified all the Danish and Swedish mothers for children 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. Consequently, a total of 6,731,785 parents were included in the two studies (Figure 3). Through the Danish Civil Registration System and the Swedish Multi-Generation Register, we also linked parents to their other children, i.e., children born before 1973 (when the MBRs were established) or born outside Denmark or Sweden but who later moved to the two studied countries. Given that the Danish Hospital Register and the Swedish Patient Register became nationwide in 1978 and 1987 respectively, we defined the study period as 1978-2016 for the Danish cohort and 1987-2014 for the Swedish cohort.[127-129] Study participants in the two studies entered the cohort in three ways: (1) participants entered the cohort on January 1, 1978 in Denmark and on January 1, 1987 in Sweden if they had at least one live child on these dates; (2) participants entered the cohort on the date of birth of the first child after the abovementioned dates if they did not have any live children on these dates; and (3) participants entered the cohort on the registered date of immigration if they immigrated with child(ren) to Denmark or Sweden after the above dates and had later a child recorded in the birth registers (Figure 4).[127-129] Study participants were eligible if they (1) were alive and resided in either Sweden or Denmark at study entry; (2) had at least one live child during the study period; and (3) did not have a diagnosis of the studied outcomes (IHD in study I and HF in study II) before cohort entry.[127-129]

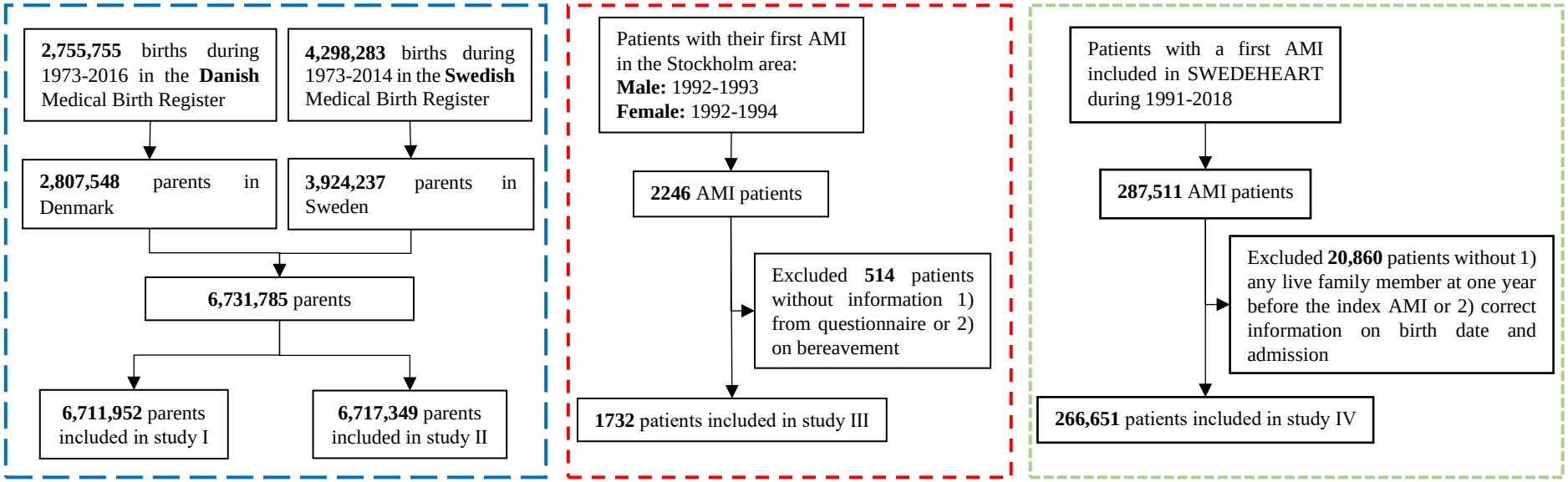

Figure 3. Overview of flowcharts of study participants in studies I-IV

AMI=acute myocardial infarction; SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

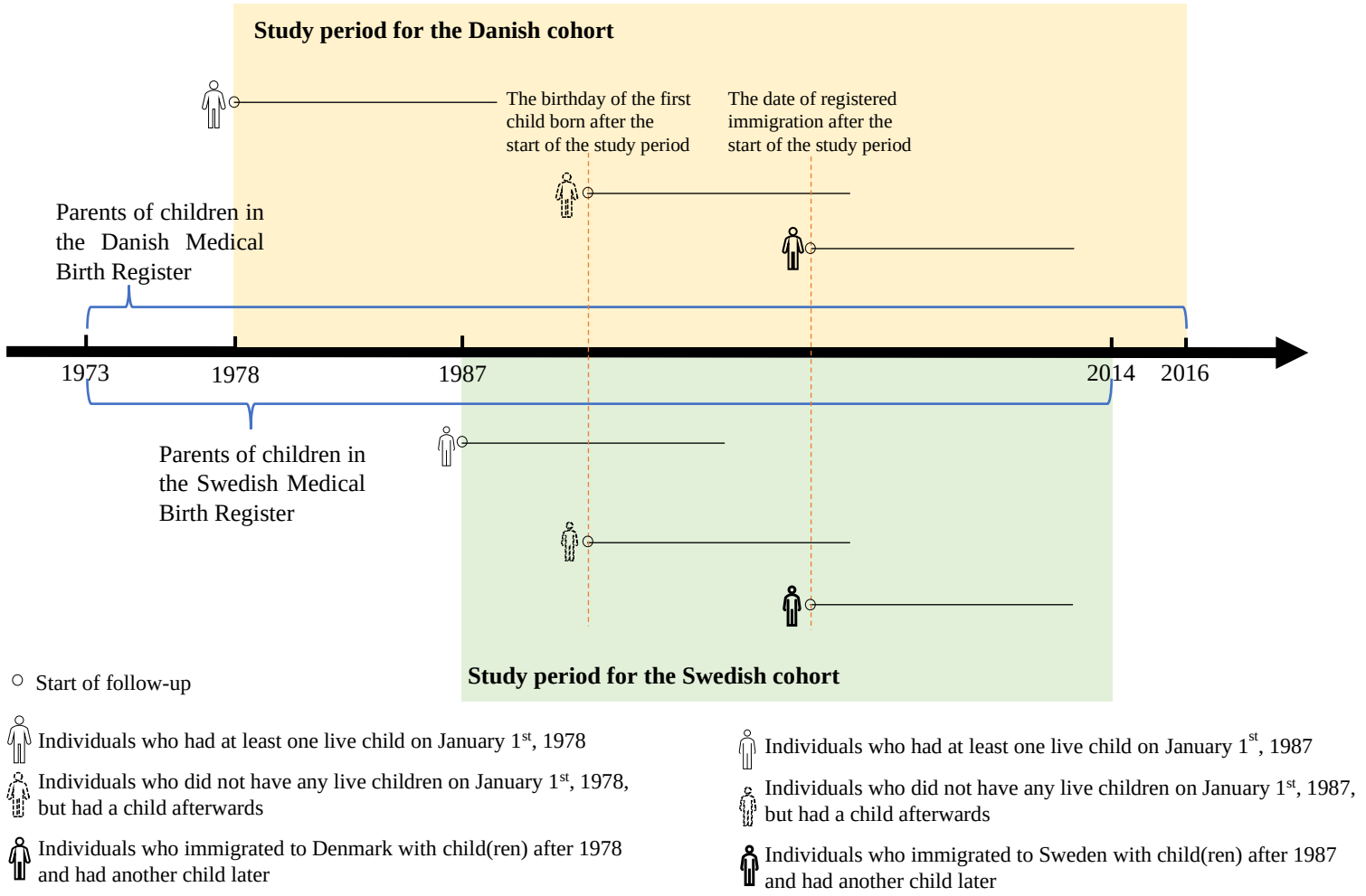

Figure 4. Time for entry in the cohort for study participants in studies I and II

This figure was adapted from eFigure 1 in Wei D., Li J., Chen H., et al., 2022, Neurology.[128] *The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information.*

4.1.2 Study variables

4.1.2.1 Exposure

We defined the exposure in studies I and II as the death of a child after study entry according to information on children's death from the Danish Civil Registration System and the Swedish Cause of Death Register. We treated the exposure as a time-varying variable. Bereaved parents contributed person-time to the unexposed group from study entry until the date of losing a child and to the exposed group afterwards, while non-bereaved parents contributed person-time only to the unexposed group. In case of multiple losses of a child during the follow-up, we defined the first loss as the index exposure. We classified bereaved parents according to the child's main cause of death (due to CVD, other natural causes, or unnatural causes, using the International Classification of Diseases (ICD) codes described in Table 1), the children's age at loss (≤1, 2-12, 13-18, 19-29, or >29 years) and the number of remaining live children at the time of loss (0, 1-2, or ≥3).[127-129]

4.1.2.2 Outcomes

We identified IHD or AMI as outcomes in study I according to the primary diagnosis from the Danish National Hospital Register and the Swedish Patient Register or death according to the underlying cause of death from the Danish Civil Registration System and the Swedish Cause of Death Register using the ICD codes in Table 1. We defined HF according to the primary diagnosis in the in- and outpatient records from the Danish National Hospital Register and the Swedish Patient Register in study II. Follow-up started at study entry and ended at the first occurrence of the outcomes, death, emigration or end of study period (December 31, 2016 in Denmark and December 31, 2014 in Sweden), whichever came first.

4.1.2.3 Covariates

We obtained information of study participants' age, sex, country of birth, and marital status from the Danish Civil Registration System and the Swedish Total Population Register, on education from the Danish Integrated Database for Longitudinal Labor Market Research and the Swedish Education Register, and on income from the Danish Integrated Database for Longitudinal Labor Market Research and from the Swedish Register of Incomes and Taxes. We considered information on marital status, education and income from the year preceding cohort entry. For participants with missing information on that year, we used information of the closest year with available data from five years preceding baseline.

We retrieved study participants' history of psychiatric disorders from the Hospital Register and the Central Psychiatric Register in Denmark, and from the Patient Register in Sweden; the corresponding ICD-codes are present in Table 1. We also obtained data on participants'

history of CVD (other than the studied outcomes) at cohort entry as well as their parents' and siblings' history of CVD (i.e., as a proxy for family history of CVD) from the Hospital Register and the Civil Registration System in Denmark, and the Patient Register and the Cause of Death Register in Sweden.

Table 1. The International Classification of Diseases codes used to identify the diagnoses and the causes of death

Diseases	ICD codes	
	Danish registers	**Swedish registers**
Medical conditions		
CVD	ICD-8: 390-458 ICD-10: I00-I99	ICD-8: 390-458 ICD-9: 390-459 ICD-10: I00-I99
Ischemic heart diseases	ICD-8: 410-414 ICD-10: I20-I25	ICD-8: 410-414 ICD-9: 410-414 ICD-10: I20-I25
Acute myocardial infarction	ICD-8: 410 ICD-10: I21, I22	ICD-8: 410 ICD-9: 410 ICD-10: I21, I22
Heart failure	ICD-8: 427.09, 427.10, 427.11, 427.19 ICD-10: I11.0, I13.0, I13.2, I50	ICD-8: 427.00, 427.10 ICD-9: 428 ICD-10: I11.0, I13.0, I13.2, I50
Stroke*	-	ICD-9: 430, 431, 434, 436 ICD-10: I60, I61, I63, I64
Psychiatric disorders	ICD-8: 290-315 ICD-10: F00-F99	ICD-8: 290-315 ICD-9: 290-319 ICD-10: F00-F99
Causes of death		
Death due to CVD	ICD-8: 390-458 ICD-10: I00-I99	ICD-9: 390-459 ICD-10: I00-I99
Death due to ischemic heart diseases	-	ICD-9: 410-414 ICD-10: I20-I25
Unnatural death	ICD-8: 7959, 79621, 800-999, E800-E999 ICD-10: R95, R96, R98, V01-Y98	ICD-9: 798, 800-999, E800-E999 ICD-10: R95, R96, R98, V01-Y98
Death due to other natural causes	All the other codes	All the other codes

CVD=cardiovascular diseases; ICD=International Classification of Diseases.

*We identified stroke as a secondary outcome in studies III and IV in which the periods of follow-up were 1992-2012 and 1987-2018, respectively. The 9th Swedish revision of International Classification of Diseases was used during 1987-1996 and the 10th revision from 1997 onwards.

4.1.3 Statistical analyses

We used Poisson regression to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for the associations between the death of a child and parental risks of IHD, AMI and HF. We performed analyses with any loss, and with exposure categorized according to child's causes of death, the deceased child's age at loss, and the number of other children at loss. We run multivariable models including age (<20, 20 to 90 by five years, or >90) and calendar year at follow-up (≤1979, 1980-1989, 1990-1999, 2000-2009, or ≥2010) as time-varying variables and sex, country of birth, highest educational attainment, and history of psychiatric disorders and of CVD as time-fixed variables.[127-129]

To visualize the changing pattern of the AMI risk after bereavement, we performed analyses according to the time since the loss (≤7 days, 8-30 days, 1-3 months, 3-12 months, 1-5 years, 5-10 years, or ≥10 years). We visualized the HF risk after child death over time by calculating the IRRs and 95% CIs after splitting the follow-up of the exposed group into the following intervals: 0-3 months, 4-12 months, 2-5 years, 6-10 years, and ≥10 years after loss.

4.2 Studies III and IV

4.2.1 Study populations and designs

We investigated the association between bereavement and prognosis in AMI among AMI patients from the Stockholm Heart Epidemiology Program (SHEEP) in study III and from the SWEDEHEART (acronym for Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) during 1991-2018 in study IV (Figure 3).

The SHEEP study is a population-based case-control study, consisting of individuals aged 45-70 years residing in Stockholm County who had their first AMI or died of AMI without having a record of previous AMI (n=2246).[130] Male and female cases were identified during 1992-1993 and 1992-1994, respectively. Patients were invited to complete an extensive questionnaire regarding sociodemographic, psychosocial, lifestyle and health-related factors, if they were able to answer these questions during their hospitalization. In case of patients who felt too ill to respond or died before reaching the hospital, the questionnaire was completed by a close family member.[130] The responders were chosen according to the closeness of the relationship to the patients, namely: partner, adult children, siblings if <80 years, and parents if <80 years.[131] A total of 1754 patients had the questionnaire data. After excluding 22 patients without information on exposure to bereavement, we finally included 1732 patients in study III.

The SWEDEHEART was launched in 2009 by merging four Swedish quality registers for coronary heart diseases. One of these was the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions that started to collect information on AMI in

several counties of Sweden in 1991 and became a nationwide register in 1995,[132] resulting in 287,511 patients with their first AMI until 2018. The unique personal identification number assigned to each Swedish resident and the linkage to the Swedish Multi-Generation Register and Total Population Register allowed us to identify these patients' family members. We identified fathers for 46.1%, mothers for 48.5%, siblings for 41.0%, children for 82.2%, grandchildren for 72.4%, and spouse/partner for 56.2% of the patients. We excluded 20,860 patients who did not have linkage to any live family member one year before the first AMI or correct information on the date of birth and admission, leading to a total of 266,651 patients included in study IV (Figure 3).

4.2.2 Study variables

4.2.2.1 Exposure

In study III, we defined the exposure as the death of a close family member or close friend one year before the first AMI according to information from the questionnaire. For exposed individuals, we further categorized them according to the psychological impact of the loss (mild or moderate influence of the loss and strong influence of the loss) and the relationship to the deceased (loss of a spouse or partner and loss of the other close family member or a close friend).

In study IV, we defined the exposure as the death of a partner, child, grandchild, sibling, or parent one year before the first AMI or later. Information on the date and cause of family members' death was obtained from the Swedish Cause of Death Register. In case of multiple losses during study period, we considered the first loss as the index exposure. We further categorized bereaved participants by the relationship to the deceased, the cause of death (CVD, other natural causes, and unnatural causes) according to ICD codes (Table 1), and the timing of bereavement in relation to the AMI (the year before the AMI, 0-1, 2-5, and >5 years post-AMI).

4.2.2.2 Outcomes

We followed study participants for the combination of non-fatal recurrent AMI and death due to IHD (as primary outcome) and all-cause mortality, HF, and stroke (as secondary outcome) in both studies. The outcomes were identified in the Patient Register and the Cause of Death Register using the ICD codes shown in Table 1. Non-fatal recurrent AMI was defined as the first hospital visit with the primary diagnosis of AMI 28 days after the first AMI. Follow-up in both studies started at study entry and ended, in study III at the first occurrence of outcomes, death, or December 31st, 2012, whichever came first, and in study IV at the first occurrence of outcomes, emigration, death, or December 31st, 2018, whichever came first.

4.2.2.3 Covariates

In study III, we obtained information on a range of confounders from questionnaires, including age, sex, education, financial difficulties in childhood, physical activity, alcohol consumption, parental smoking status during childhood, personal and partner's smoking status, as well as personal and family (parents and siblings) history of cardiometabolic conditions.

In study IV, we retrieved information on confounders via linkage to several nationwide registers, e.g., sex, age, and country of birth from the Total Population Register, income from the Income and Taxation Register and the Longitudinal Integration Database for Health Insurance and Labor Market Studies, and education from the Longitudinal Integration Database for Health Insurance and Labor Market Studies. We identified study participants' family and partner's history of psychiatric disorders and CVD through the Patient Register and the Cause of Death Register. In addition, we retrieved information on study participants' diabetes at baseline from the SWEDEHEART.

4.2.3 Statistical analyses

In study III, we used Cox proportional hazard regression to estimate hazard ratios (HR) and 95% CIs, while in study IV, we used Poisson regression to estimate rate ratios (RR) and 95% CIs for the association of interest.

In study III, we tested the proportional hazard assumption using log-log curves and tests for interaction with time and the log of time.[131] We included the interaction term with time together with a covariate if the proportional hazards assumption was not met. There was no evidence for non-proportionality in case of the bereavement-related variables.[131] We analyzed the overall association with bereavement the year before the AMI as well as whether the association differed by the relationship to the deceased and the strength of the self-reported psychological influence of the loss. In the main multivariable model, we adjusted for age, sex, education, financial difficulties during childhood, parental smoking during childhood, the index person's smoking, physical activity, stroke and diabetes prior to the exposure to bereavement, the interaction between index persons' physical activity before the exposure period and time, partner's smoking, as well as family (parents and siblings) history of CVD and diabetes or dyslipidemia.[131]

In study IV, we treated the exposure as a time-dependent variable, i.e., study participants contributed person-time to the unexposed group if they did not lose any close family member during the study period, otherwise contributed person-time from study entry until the index loss to the unexposed group and to the exposed group afterwards. We analyzed the association of interest with any loss as well as with the exposure categorized by the relationship to the deceased, the relative's cause of death, and the timing of bereavement in relation to the AMI. In the multivariable model, we adjusted for age and calendar year at

follow-up as time-dependent variables (with a yearly split), sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, having a spouse/partner, number of live children, number of live grandchildren, number of live siblings, number of live parents, personal and family history of psychiatric disorders and CVD one year before the first AMI as time-fixed variables. When studying the association according to the relationship to the deceased, the analyses were restricted to study participants with at least one corresponding close family member one year before the first AMI. For example, we analyzed the association between the death of a partner and prognosis in AMI among those who had a partner one year before the first AMI. Additionally, in the analysis with the death of a partner, we further adjusted for partner's history of psychiatric disorders and CVD one year before the first AMI.

To visualize the association with the primary outcome over time, we re-ran the main model in study IV by splitting the follow-up into 0-1 year, 2-5 years, 6-10 years and >10 years for the exposed group.

All data managements and analyses were performed in SAS 9.4.

4.3 Ethical considerations

There were two important ethical concerns in this thesis, namely informed consent and the protection of sensitive data on study participants. In studies I, II and IV, we used population-based register data from several Danish and/or Swedish registers. According to the Danish or Swedish law, informed consent is not needed for such register-based studies. For studies I and II, the approval was obtained from the Danish Data Protection Agency in Copenhagen (dnr. 2016-051-000001). In Sweden, for studies I, II and IV, the ethical approval was obtained from the Regional Ethics Review Board in Stockholm (dnr. 2016/288-31/1). In study III, we used the data from the SHEEP cohort which enrolled patients with a first AMI during 1992-1994. This study was approved by the Ethics Committee at Karolinska Institutet (91:259) and the Regional Ethics Review Board in Stockholm (2013/1731–31/1). Patients in study III and their relatives received detailed information about the study, were told that the information they provided would be used only for research purposes; the individuals who agreed to participate in the study signed an informed consent form.

To protect the data, we have taken several measures. First, the data was stored on servers with high security level. Only authorized members of the research team could get access. Second, the principal investigator signed a contract with the responsible authorities before receiving access to the data and team members were informed in line with this agreement about the security-related rules. We were not allowed to search for a specific person in the database. Third, all data had been de-identified, i.e., only pseudo-ID numbers were used; this protects anonymity and makes it impossible to link the cohort data to other data sources. Fourth, the data analyses were performed on secure servers and we presented results only on

an aggregated level to prevent the risk of identifying specific individuals. Thus, the personal data of study participants were, to the largest extent possible, protected. We believe that the possible risks to the individuals are smaller than the potential knowledge gains from the project. We hope that the findings of this thesis concerning the cardiovascular risk in bereavement may contribute to a better support for bereaved family members and that these benefits would outweigh the risks for study participants.

5 RESULTS

5.1 The death of a child and the risks of IHD and HF (studies I and II)

5.1.1 Overall associations

During the median follow-up of 21 to 22 years, 1.9% of the 6.7 million study participants lost at least one child, and 297,399 (4.4%) were diagnosed with IHD, 146,739 (2.2%) with AMI, and 60,724 (0.9%) with HF. Bereaved parents had 20%, 21%, and 35% higher risks of IHD, AMI, and HF respectively than non-bereaved parents (Figure 5).

5.1.2 The association according to the child's cause of death

Bereaved parents had higher risks of IHD, AMI, and HF than non-bereaved parents, regardless of the child's cause of death (Figure 5). Further, the risks of IHD, AMI, and HF were highest if the child died of CVD.

5.1.3 The association according to the age of the deceased child at loss

There were U-shaped associations with IHD, AMI, and HF according to the age of the deceased child at loss. The relative risks of IHD, AMI, and HF for the loss of an infant or an adult child were higher than that corresponding to the loss of a child aged 2-17 years (Figure 5).

5.1.4 The association according to the number of remaining live children at loss

We found a U-shaped association with HF according to the number of remaining live children at loss. In contrast, there was no such pattern in case of IHD and AMI; in case of these outcomes the risks were higher among bereaved parents who had three or more children alive at the time when they lost a child than those with fewer children (Figure 5).

5.1.5 The association according to the time since the loss

There was a time-dependent association between the loss of a child and the risk of AMI. The relative risk was highest in the week immediately after the loss and it declined afterwards (Figure 6). We did not observe differences in HF risk in the bereaved group according to the time since the loss.

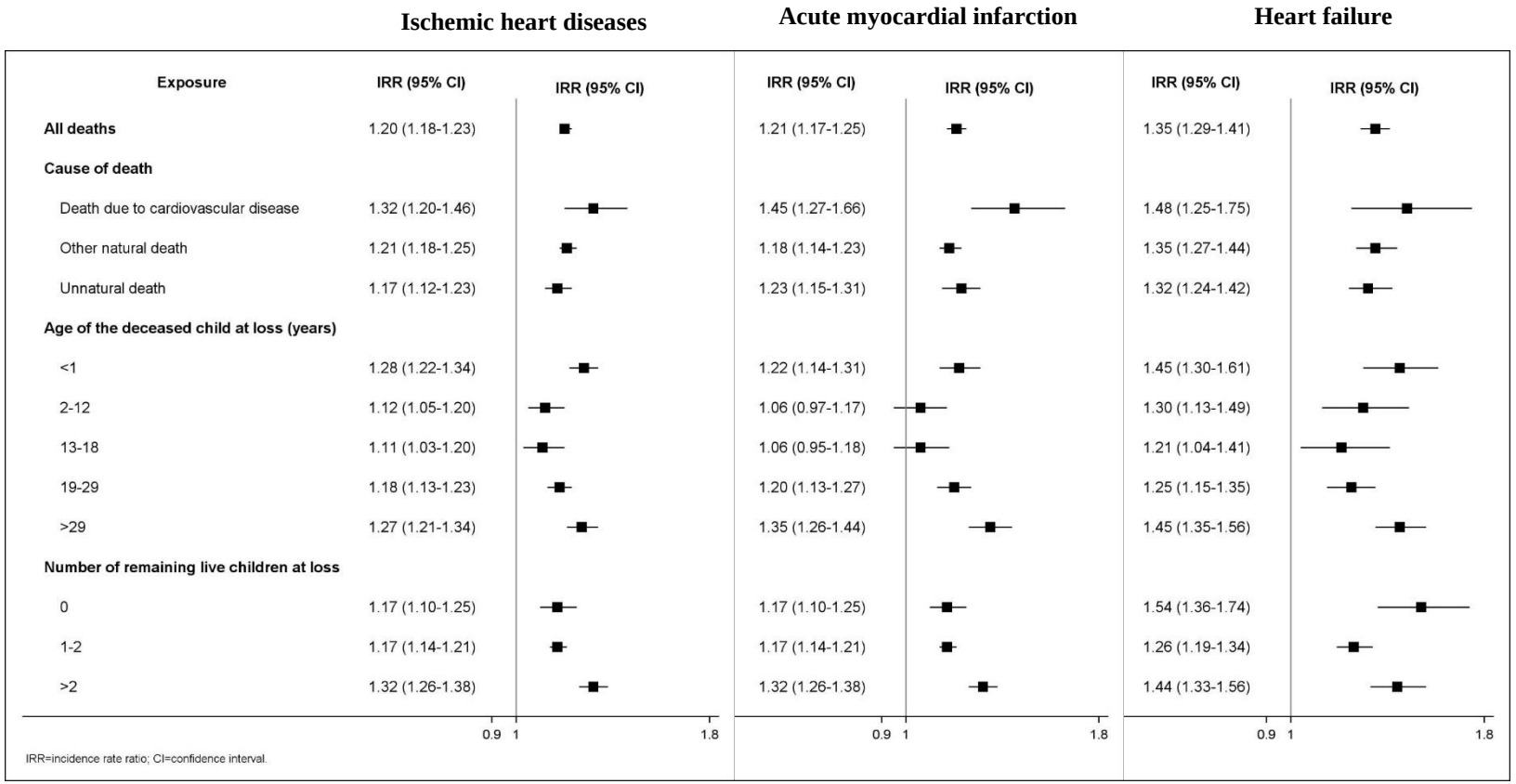

Figure 5. Adjusted incidence rate ratios and 95% confidence intervals for heart diseases according to the death of a child in studies I and II

We adjusted for sex, age at follow-up, calendar year at follow-up, country of birth, highest educational attainment, history of psychiatric disorders and cardiovascular diseases.

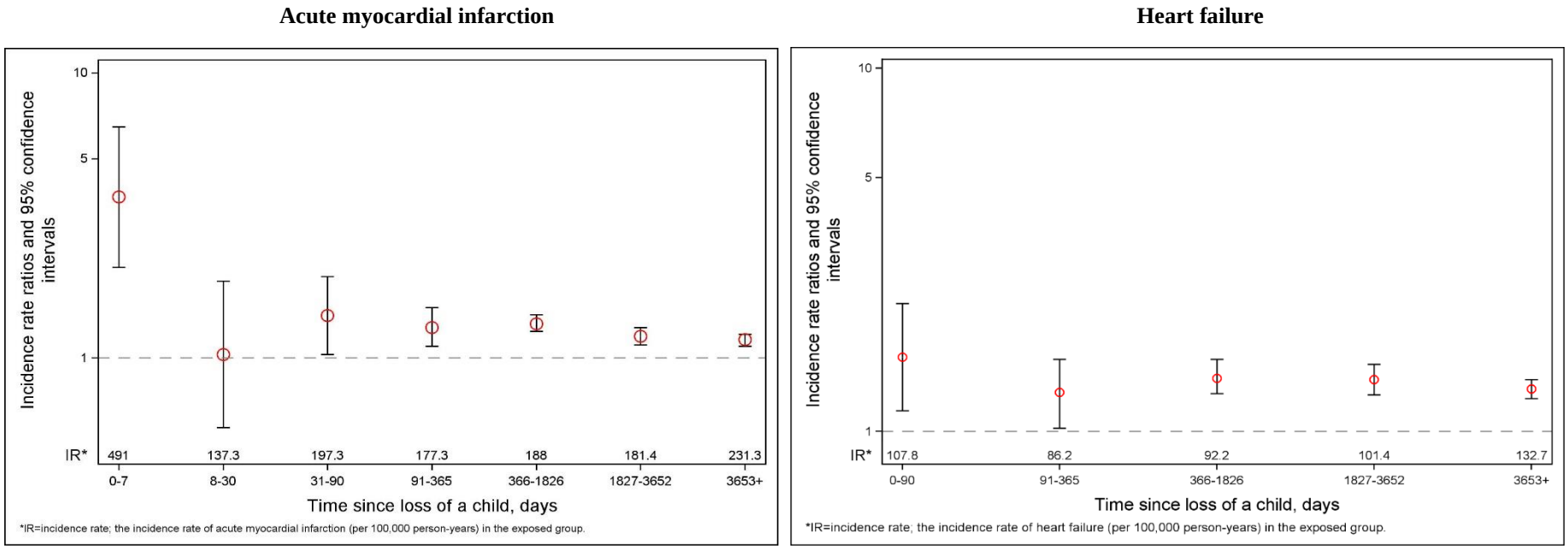

Figure 6. Adjusted incidence rate ratios and 95% confidence intervals for acute myocardial infarction and heart failure according to the time since the death of a child in studies I and II

We adjusted for sex, age at follow-up, calendar year at follow-up, country of birth, highest educational attainment, history of psychiatric disorders and cardiovascular diseases. This figure was adapted from figures from studies I and II.[127,129]

5.2 Bereavement and prognosis in AMI (studies III and IV)

5.2.1 Overall associations

We observed that bereavement was associated with a modestly increased risk of the combination of non-fatal recurrent AMI and death due to IHD in study IV (Table 2). Likewise, in study IV bereaved AMI patients who lost a close family member had 14%, 5% and 9% increased risks of all-cause mortality, HF, and stroke, respectively (Table 2). However, we did not find such associations in the SHEEP cohort (Study III).

Table 2. The association between bereavement and prognosis in acute myocardial infarction in studies III and IV

Outcomes	Study III (n=1732)			Study IV (n=266,651)		
	No. of events	Rate*	Multivariable HR† (95% CI)	No. of events	Rate*	Multivariable RR‡ (95% CI)
Primary outcome⁋						
Unexposed	694	56.4	Ref.	78,773	64.6	Ref.
Exposed	264	57.1	0.97 (0.86-1.15)	13,010	36.2	1.02 (1.00-1.04)
All-cause mortality						
Unexposed	808	55.6	Ref.	99,660	70.7	Ref.
Exposed	306	54.8	0.94 (0.82-1.08)	24,325	56.0	1.14 (1.12-1.16)
Heart failure						
Unexposed	267	20.3	Ref.	40,094	31.1	Ref.
Exposed	97	19.5	0.90 (0.71-1.14)	8320	21.2	1.05 (1.02-1.08)
Stroke						
Unexposed	186	13.8	Ref.	20,548	15.2	Ref.
Exposed	74	14.5	0.98 (0.74-1.14)	5310	13.0	1.09 (1.05-1.13)

HR=hazard ratio; CI=confidence intervals; RR=rate ratio:

* per 1000 person-years.

†We estimated the association by Cox proportional hazard regression and adjusted for age, sex, education, financial difficulties during childhood, parental smoking during childhood, the index person's smoking, physical activity, stroke and diabetes prior to the exposure to bereavement, the interaction between index persons' physical activity before the exposure period and time, partner's smoking, as well as family (parents and siblings) history of CVD and diabetes or dyslipidemia.

‡ We estimated the association by Poisson regression and adjusted for age and calendar year of follow-up, sex, country origin, highest educational attainment, income and diabetes at baseline, number of live family members, having a spouse/partner, number of live children, number of live grandchildren, number of live siblings, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first AMI.

⁋ The combination of non-fatal recurrent acute myocardial infarction and death due to ischemic heart diseases.

5.2.2 The association according to the relationship to the deceased

The association between bereavement and prognosis in AMI was found to vary according to the relationship to the deceased. In study III, the point estimate for the association of the death of a partner with the primary outcome [HR (95% CI): 1.55 (1.06-2.27)] was higher

than that for the association with the death of the other close family members or a close friend [HR (95% CI): 0.95 (0.82-1.11)] (Table 3). Further, in study IV, we found that the death of a partner had the strongest association with poor prognosis, followed by the death of a child, grandchild, sibling, and parent (Figure 7).

Table 3. Adjusted hazard ratios and 95% confidence intervals for the association between bereavement and the combination of non-fatal recurrent acute myocardial infarction and death due to ischemic heart disease according to the relationship to the deceased and the psychological impact of the loss in study III

Exposure	No. of events	Rate*	Multivariable HR (95% CI)†
The relationship to the deceased			
Loss of a family member or a close friend	235	55.9	0.95 (0.82-1.11)
Loss of spouse or partner	29	98.3	1.55 (1.06-2.27)
The psychological impact of the loss			
Mild or moderate influence of the loss	120	50.3	0.89 (0.73-1.08)
Strong influence of the loss	139	65.5	1.08 (0.89-1.31)

HR=hazard ratio; CI=confidence interval.
*per 1000 person-years.
†Adjusted for age, sex, education, financial difficulties during childhood, parental smoking during childhood, the index person's smoking, physical activity, stroke and diabetes prior to the exposure to bereavement, the interaction between index persons' physical activity before the exposure period and time, partner's smoking, as well as family (parents and siblings) history of CVD and diabetes or dyslipidemia.

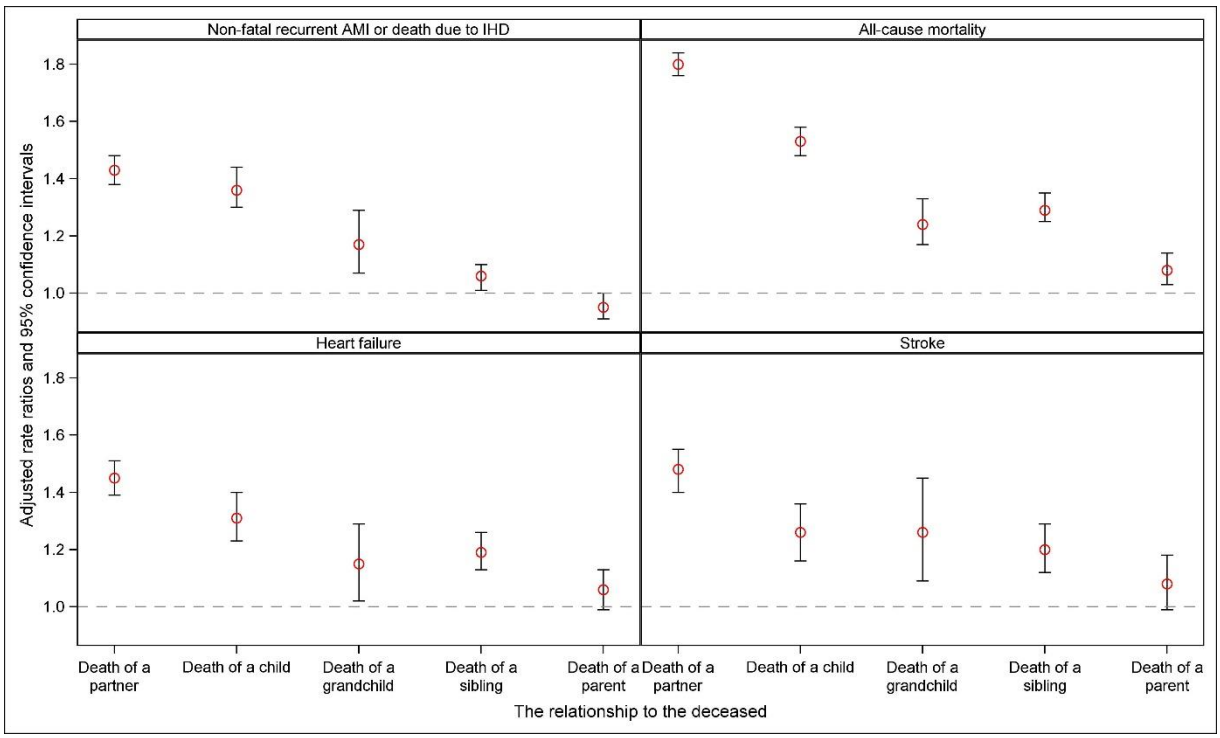

Figure 7. Adjusted rate ratios and 95% confidence intervals for the association between bereavement and the combination of non-fatal recurrent acute myocardial infarction and death due to ischemic heart diseases, all-cause mortality, heart failure, and stroke according to the relationship to the deceased in study IV

The analyses concerning the death of a specific family member were restricted to those who had at least one of the studied family members alive one year before the first acute myocardial infarction. The multivariable model for analyses with the death of a *partner* as exposure was adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, personal and partner's history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. The multivariable model for analyses with the death of a *child* as exposure was adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live children, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. The multivariable model for analyses with the death of a *grandchild* as exposure was adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live grandchildren, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. The multivariable model for analyses with the death of a *sibling* as exposure was adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live siblings, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. The multivariable model for analyses with the death of a *parent* as exposure was adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction.
AMI=acute myocardial infarction; IHD=ischemic heart diseases.

5.2.3 The association according to the psychological impact of the loss

In study III, we found no associations between mild/moderate [HR (95% CI): 0.89 (0.73-1.08)] or strong influence of the loss [HR (95% CI): 1.08 (0.89-1.31)] and the risk of the primary outcome (Table 3).

5.2.4 The association according to the time of the loss in relation to the AMI

The association of any loss one year before the first AMI with the combination of non-fatal recurrent AMI and death due to IHD were not observed in study III (Table 2). However, we found that bereaved AMI patients tended to have an increased risk of poor prognosis if they lost a close family member one year before the index AMI in study IV (Figure 8). Furthermore, when studying the importance of the time when the loss occurred, in study IV we found J-shaped associations with the primary and secondary outcomes; the point estimates were lowest in case of losing a close family member in the year after the first AMI and increased if losing a family member from the second year post-AMI (Figure 8).

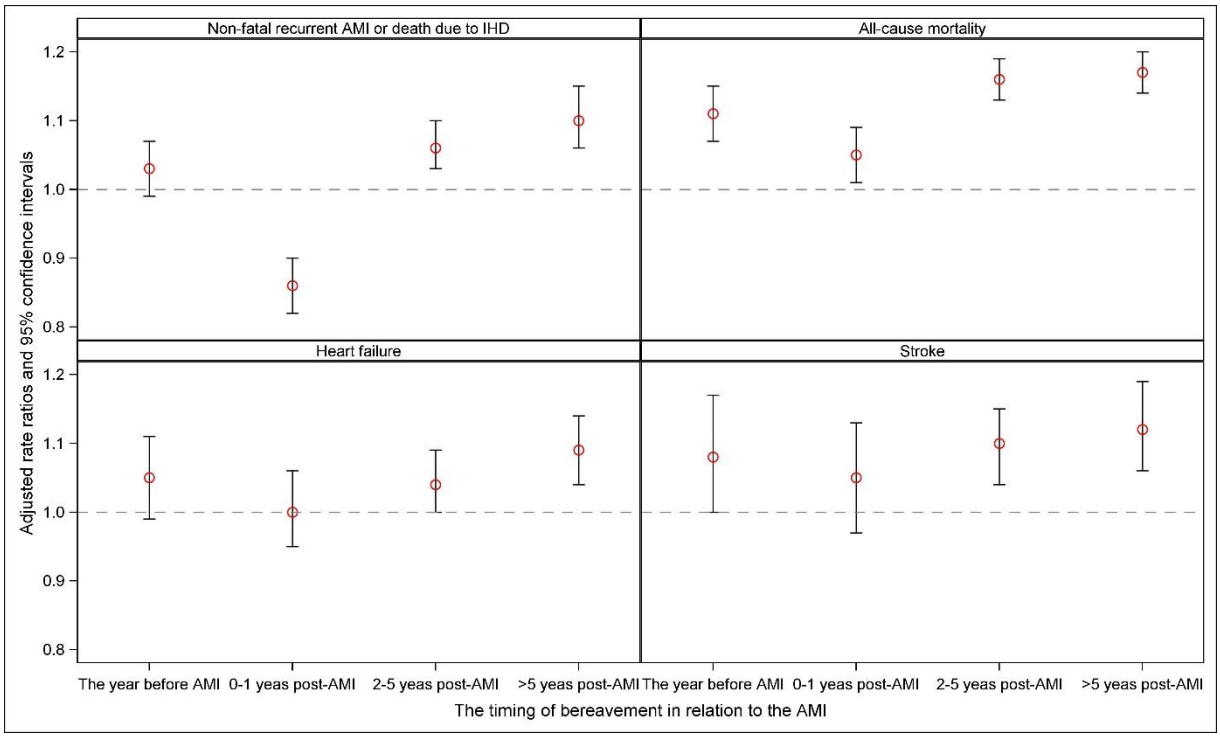

Figure 8. Adjusted rate ratios and 95% confidence intervals for the association between bereavement and prognosis in acute myocardial infarction according to the time from the first acute myocardial infarction to the loss in study IV

We adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, having a spouse/partner, number of live children, number of live grandchildren, number of live siblings, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. AMI=acute myocardial infarction; IHD=ischemic heart diseases.

5.2.5 The association according to the time since the loss

In study IV, we observed an association between any loss and poor prognosis in AMI from the second to the fifth year after the loss (Figure 9). When studying relative-specific type of bereavement, we found that bereaved AMI patients had an increased risk of the primary

outcome on both short and long term after the death of a partner or a child; there was no clear evidence for a time-varying effect (Figure 9).

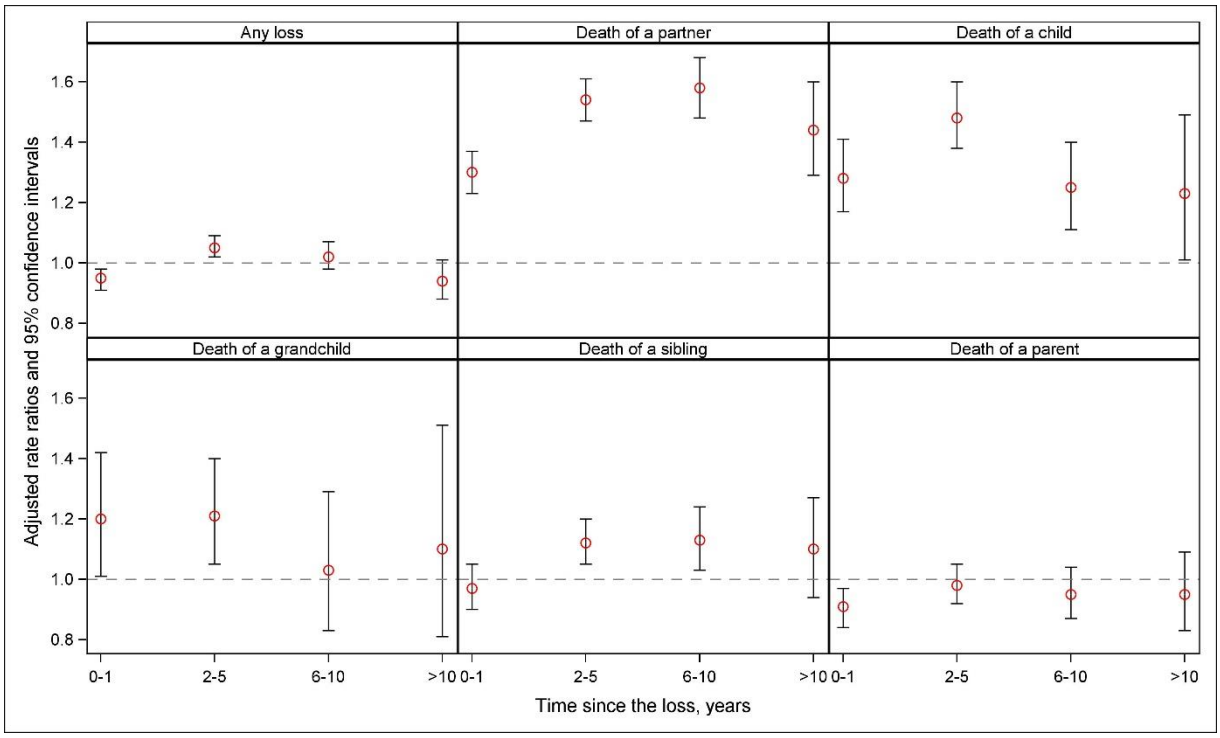

Figure 9. Adjusted rate ratios and 95% confidence intervals for the combination of non-fatal recurrent acute myocardial infarction and death due to ischemic heart diseases according to any loss and with different types of relationships to the deceased according to the time since the loss in study IV

Each relative-specific analysis was performed among those who had at least one of the studied family members alive one year before the first acute myocardial infarction. For *any loss*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, having a spouse/partner, number of live children, number of live grandchildren, number of live siblings, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. For the death of a *partner*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, personal and partner's history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. For the death of a *child*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live children, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. For the death of a *grandchild*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live grandchildren, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. For the death of a *sibling*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live siblings, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction. For the death of a *parent*, we adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction.

5.2.6 The association according to the cause of death

The associations between the death of a close family member and both the primary and the secondary outcomes were similar in case of natural and unnatural deaths in study IV, although the point estimate for the association of unnatural deaths with stroke was slightly higher than that of natural deaths (Table 4).

Table 4. Adjusted rate ratios and 95% confidence intervals for the association between bereavement and prognosis in acute myocardial infarction according to the deceased relative's cause of death in study IV

Outcomes	No. of events	Rate*	Multivariable RR‡ (95% CI)
Combination of non-fatal recurrent AMI and death due to IHD			
Death due to CVD	5281	35.6	1.03 (1.00-1.06)
Other natural deaths	7055	36.3	1.01 (0.99-1.04)
Unnatural causes	674	41.5	1.04 (0.96-1.12)
All-cause mortality			
Death due to CVD	9440	52.5	1.14 (1.11-1.17)
Other natural deaths	13,612	57.8	1.14 (1.12-1.16)
Unnatural causes	1273	65.1	1.12 (1.05-1.18)
Heart failure			
Death due to CVD	3303	20.3	1.05 (1.01-1.10)
Other natural deaths	4580	21.5	1.04 (1.01-1.08)
Unnatural causes	437	24.8	1.07 (0.97-1.18)
Stroke			
Death due to CVD	2100	12.4	1.09 (1.04-1.15)
Other natural deaths	2914	13.2	1.09 (1.04-1.14)
Unnatural causes	296	16.2	1.17 (1.04-1.32)

AMI=acute myocardial infarction; CVD=cardiovascular diseases; CI=confidence intervals; IHD=ischemic heart disease; RR=rate ratio.

* per 1000 person-years.

‡ Adjusted for age and calendar year of follow-up, sex, country of birth, highest educational attainment, income and diabetes at baseline, number of live family members, having a spouse/partner, number of live children, number of live grandchildren, number of live siblings, number of live parents, personal and family history of psychiatric disorders and cardiovascular diseases one year before the first acute myocardial infarction.

6 DISCUSSION

6.1 Summary of the main findings

In this thesis, we found that the death of a child was associated with increased risks of IHD, AMI, and HF. The associations were present not only in case of cardiovascular or other natural deaths but also if the child died of unnatural causes. There were U-shaped associations with IHD, AMI, and HF according to the age of the deceased child at loss. The relative risk of AMI was highest in the week after the loss and persisted throughout the whole follow-up. For prognosis in AMI, in study III, we found that the death of a partner but not of other close family members or a close friend was associated with the combination of non-fatal recurrent AMI and death due to IHD. However, in study IV, bereavement was found to be associated with increased risks of poor prognosis in AMI and that the associations were similar for both natural and unnatural deaths. The association was strongest for the loss of a partner, followed by the loss of a child, grandchild, sibling, and parent. The increased risks of poor prognosis were observed for all periods when the loss occurred except for the year immediately after the AMI.

6.2 Interpretation of the main findings

6.2.1 The death of a child and incident IHD and HF (studies I and II)

Our findings that bereaved parents had increased risks of IHD, AMI, and HF are in line with previous studies showing that bereaved individuals had higher risks of CVDs after the death of a spouse,[99,101] parent,[133-135] sibling,[7,94] child,[102] or significant person in life[100] compared to their non-bereaved counterparts and that bereaved parents had higher risks of mental illness,[37,45,46,49] diabetes,[63] cancer,[54,57,58] and death[89-92] than non-bereaved parents. To our knowledge, only two previous studies analyzed the association between the death of a child and risks of CVD; Li et al. reported an increased risk of AMI among bereaved parents from the seventh year after the loss,[102] but no association with stroke.[103] In line with Li's study on AMI, we also found that unnatural death, which is less likely to be affected by familial and environmental cardiovascular risk factors shared within the family, was associated with increased risks of IHD, AMI, and HF. Together with the finding that the increased risk of AMI was highest in the week immediately after the loss, our results suggest that stress-related mechanisms may contribute to the development of CVDs.

Further, the U-shaped associations with the three outcomes by the age of the deceased child at loss might also be supportive of stress-related mechanisms. Parents may have stronger ties with older children due to the longer time together than with younger children. In line with this hypothesis, we found that the magnitude of the association with the death of an adult child was higher than that with the death of a younger child (not an infant) although the possibility of residual confounding by familial cardiovascular risk factors could not be fully excluded. On the other hand, the higher relative risk for the death of an infant than for the

death of an older minor child may reflect residual confounding, i.e., maternal conditions before or during pregnancy are associated with risks of both infant mortality[136] and CVDs in later life.[137]

The results according to the number of live children at the time of loss may suggest that having one or two live children at the time of loss may attenuate the impact of grief on parent's cardiac health. Having three or more live children at the time of child loss may result in severe stress, as parents need to care for several children and try to support the whole family in grief. On the other hand, the loss of the only child deprives parents of their parental role.

6.2.2 Bereavement and prognosis in AMI (studies III and IV)

Our studies III and IV are the first studies investigating the association between bereavement and prognosis in AMI. Our finding that bereavement was associated with poor prognosis in AMI is in line with previous studies showing that widowers with HF had a higher risk of mortality than their married counterparts[104] and that bereavement is associated with an increased risk of cardiovascular morbidity and mortality.[7,9,85,86,94,99,101,102,111,134,135] Consistent with previous studies that stress plays a role in the progression of CVD,[121,138,139] we found, in study IV, the highest risk of poor prognosis in AMI for the death of a partner, followed by the death of a child, grandchild, sibling, and parent. A similar pattern was observed in study III as well where the point estimate for the death of a partner was higher than that for the death of a relative or close friend. In general, adults of the age of the study participants in studies III and IV have the closest emotional bond with their partner, followed by children, grandchildren, siblings, and parents. Apart from grief, the increased risk of adverse prognosis after AMI in case of the death of a partner might also reflect financial difficulties after the loss.[140,141] Likewise, beside the partner, children also play an important role in caring and supporting individuals in old age. This might explain why we observed a consistently stronger association with the death of a partner or a child than with other close family members. Although we expected a dose-response relationship by the psychological impact of the loss in study III also, there was no clear evidence for such a pattern, potentially due to limited power. In addition, our finding that the association of poor prognosis in AMI was similar in case of natural and unnatural deaths of the relative in study IV may indicate that the association was mainly attributed to bereavement stress rather than residual confounding by familial cardiovascular risk factors that cluster in the family.

Increased attention from health professionals may attenuate the impact of the loss on prognosis post-AMI. Patients are generally under strong surveillance in the year after the AMI to prevent new cardiovascular events. During this year, bereaved AMI patients may be identified as vulnerable individuals, consequently they may have achieved more attention from health professionals than non-bereaved AMI patients. We found that AMI patients who

lost a close family member during the year after the first AMI had a lower risk of the primary outcome than their non-bereaved counterparts.

6.3 Methodological considerations

6.3.1 Confounding

Although we adjusted for a large number of familial health-related and socioeconomic factors and performed several sub-analyses to limit familial confounding, residual confounding could not be fully excluded. The information on genetic factors, familial psychological characteristics, lifestyle (drinking habit, physical activity, diet, etc.) are generally not available in Nordic registers or similar administrative databases. We had information on several lifestyle factors (including drinking habits, physical activity, and smoking) measured prior to exposure only in study III.

6.3.2 Information bias

We expected that misclassification of the exposure in this project was small, even in study III where study participants were asked by questionnaire whether they had lost a family member or a close friend during the year before the first AMI; most individuals can recall accurately such an important adverse life event. In case of the register-based studies, the access to population-based registry data for research purposes made it possible for us to easily retrieve data on exposure, outcomes and relevant covariates and conduct large-scale studies in a more time- and financially efficient way. Registration of death in the Danish and Swedish mortality registers is of high quality; some misclassification with respect to the cause of death is nevertheless possible. The exposure was identified prospectively and independently of the outcome. In contrast, the subjective experience of the loss is not possible to be directly studied using register data. We fortunately had such data in study III and expected to observe a dose-response relationship by psychological impact of the loss. However, we did not find such an association, potentially due to low statistical power. The validity of diagnoses of all the studied outcomes was high. For example, the positive predictive values of AMI and HF in the primary diagnosis are over 90% in the Swedish Patient Register.[142,143] Similarly, the Danish Hospital Register as well has very high positive predictive values for AMI and HF, particularly for the primary diagnoses.[144,145] However, we did not have the information of primary care, leading to the possibility of missing less severe HF. Thus, we may underestimate the association between the death of a child and the risk of HF. In addition, with large-scale studies and extensive information on characteristics of study participants, we were able to detect modest associations even if the exposure or the outcome are rare, to perform various sub-analyses that may contribute to a better understanding of causality or to identify groups or periods at highest risks.

6.3.3 Selection bias

The use of nation-wide register data may limit selection bias. The willingness to participate in a study may vary according to the exposure to bereavement. Bereaved individuals may be less willing to participate in such a study than the non-bereaved, e.g., because they do not feel comfortable to be interviewed about their loss. However, there is no self-selection of participating in administrative registers where the collection of information is mandatory.

Prognostic studies inherently involve a selected group of participants, i.e., those who are already sick. This selection might introduce a special bias, often referred to as index event bias.[146-148] All participants in Studies III and IV had AMI at baseline and the different causes of AMI could make the evaluation of prognostic importance of different factors difficult. For example, obese individuals with an AMI might be overall healthier than other AMI patients, i.e., those who succumbed to AMI due to other reasons than obesity. This might explain the so-called obesity paradox, i.e., that high body mass index might appear to be a positive prognostic factor in AMI.[149] Indeed, we observed that bereaved AMI patients were less likely to be male, have familial financial difficulties in childhood, and have a parent who smoked during childhood than non-bereaved AMI patients in study III. Likewise, in study IV, bereaved AMI patients were younger and more likely to be free of diabetes, psychiatric disorders and CVD at baseline, and have higher income than non-bereaved patients. However, the association between the death of a family member after the first AMI and prognosis in AMI may be less affected by index event bias than the association with the loss before AMI. We observed in study IV an association between bereavement with an increased risk of either the primary or the secondary outcomes if the loss occurred from the second year after the first AMI.

6.3.4 Generalizability

We may generalize our findings only to countries with healthcare systems with free-access, well-developed welfare system and similar sociocultural contexts as that in Denmark and Sweden. Further studies are needed, particularly in regions with less-developed healthcare and welfare system.

7 CONCLUSIONS

In summary, our studies suggested that the death of a child was associated with increased risks of IHD, AMI, and HF. The associations were present across all categories of the child's causes of death (cardiovascular, other natural and unnatural causes). The increased risks of AMI and of HF after the loss of a child persisted throughout the follow-up. The risk of AMI was highest in the week immediately after child death and declined afterwards but there was no clear evidence for a time-varying pattern in case of HF. Moreover, bereavement was associated with poor prognosis in AMI. The association was strongest for the death of a partner, followed by the death of a child, grandchild, sibling, and parent, but did not differ according to the deceased relative's cause of death. The increased risk of poor prognosis in AMI were present for any time when the loss occurred except for the year immediately after the AMI. If our findings are confirmed, increased support from family members and attention from health professionals may be of benefit for bereaved individuals' cardiovascular health.

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