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PSYCHOSOCIAL FACTORS AND PROGNOSIS IN CORONARY HEART DISEASE

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ABSTRACT

Aim: This thesis aims to contribute to the better understanding of the role of psychosocial factors in coronary heart disease (CHD) by analysing (1) the relationship of income, anger expression and work stress with prognosis after a cardiac event, (2) potential explanations for these associations and (3) whether a combined intervention consisting of a psychosocial rehabilitation and medical treatment from a cardiologist affects psychosocial risk factors and prognosis in women CHD patients.

Methods: Data from the Healthier Female Heart (HFH) study, a randomized controlled trial enrolling consecutively 247 women cardiac patients aged ≤75 years (papers I, II, IV) and data of 676 non-fatal acute myocardial infarction (AMI) cases from the Stockholm Heart Epidemiology Program (SHEEP) (paper III) were analysed. Patients from the HFH study were assigned either to an intervention group obtaining a 1-year psychosocial rehabilitation based on cognitive-behavioural therapy principles (20 x 2-hour sessions) and medical care by a cardiologist whom they met at least 3 times (n = 119), or to the control group with usual health care (n = 128). Demographic, socioeconomic, psychosocial, lifestyle-related, clinical and biological characteristics were obtained by means of questionnaires or clinical examination. In the HFH study, assessments were carried out at baseline (6-8 weeks after hospitalization and randomization), after 10 weeks, after 1 year (end of intervention) and at 1-2 years after intervention. SHEEP patients completed questionnaires soon after recovery from the AMI and underwent a standardised clinical examination 3 months later. Patients were followed for non-fatal AMI, cardiac/cardiovascular and total mortality for an average time of 6.5 years in the HFH study and of 8.5 years in the SHEEP study. Cox regression and mixed models were used to analyse prospective and longitudinal data, respectively.

Results: During the follow-up of the HFH study a total of 31 patients deceased, 17 of cardiac causes and 41 had the combined outcome of cardiac death and non-fatal AMI. The corresponding figures in the SHEEP study were 96 for total death, 52 for cardiac mortality and 155 for the combination of cardiac death and non-fatal AMI. In paper I, patients with medium and high income had a lower risk for recurrent events relative to those with low income; adjustment for smoking, depression and anger symptoms somewhat attenuated the relationship (paper I). The tendency to suppress angry feelings increased the risk for the combined endpoint of cardiovascular death and recurrent AMI and for all-cause mortality, whereas the outward expression of anger was associated with a higher risk for the combination of cardiovascular death and new AMI. Among the potential biological mediators inflammatory markers somewhat attenuated the relationship (paper II). High job strain was associated with an increased risk of cardiac and total mortality and of the combination of cardiac death and non-fatal AMI relative to low job strain. This relationship could not be explained by lifestyle, blood lipids, glucose, inflammatory and coagulation factors (paper III). After 6.5 years, all-cause and cardiac mortality was lower in the intervention than in the control group, the hazard ratios and the 95% confidence intervals being 0.34 (0.15-0.76) and 0.41 (0.14-1.16), respectively. Differences in drug therapy prescribed by cardiologists and general practitioners partly explained the observed beneficial effect of the intervention. Moreover, favourable changes in some psychosocial variables might have also contributed to the explanation of the lower mortality in the intervention group (paper IV).

Conclusions: Our results suggest that low income, the suppression and the outward expression of anger, and job strain are associated with poor prognosis after a cardiac event. The combined intervention consisting of a psychosocial rehabilitation and medical therapy by a cardiologist reduced the risk of all-cause and cardiac specific mortality during a 6.5-year follow-up compared to usual care from the health care system. These findings have potentially substantial implications for secondary prevention of CHD.

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CONTENTS

LIST OF ABBREVIATIONS

ACE inhibitor	angiotensin-converting enzyme inhibitor
AMI	acute myocardial infarction
BMI	body-mass index
CABG	coronary artery bypass grafting
CBT	cognitive-behavioural therapy
CG	control group
CHD	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
ENRICHD	Enhancing Recovery in Coronary Heart Disease
HDL	high-density lipoprotein
HFH	Healthier Female Heart
HR	hazard ratio
IG	intervention group
IL-6	interleukin-6
LDL	low-density lipoprotein
LP (a)	lipoprotein (a)
M-HART	Montreal Heart Attack Readjustment Trial
PCI	percutaneous coronary intervention
SD	standard deviation
SEK	Swedish crown (currency)
SES	socioeconomic status
SHEEP	Stockholm Heart Epidemiology Program

1 INTRODUCTION

1.1 CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVD) are the major causes of death and disability throughout the world (World Health Organization, 2007). According to estimations of the World Health Organization, 30% of the 58 million deaths that occurred globally in 2005 were due to CVD (World Health Organization, 2007). Global CVD rates will rise further as the prevalence of the disease is expected to increase in the developing countries during the next decades (Reddy, 2003). The most common cardiovascular disorder, coronary heart disease (CHD) is responsible for almost 50% of cardiovascular deaths (World Health Organization, 2004; 2007).

Since the early 1970s, most of the developed countries, including Sweden, have experienced important declines in their age-adjusted CVD rates. These reductions have been largely due to the identification of the major CVD risk factors and thus to the implementation of a series of control strategies including population-based programs aimed to improve the risk factor profiles of communities, targeted interventions to protect individuals with markedly elevated risk factor levels and the widespread use of new diagnostic and therapeutic technologies in patients with a developed disease (Reddy, 2003; Gaziano, 2005).

However, despite these preventive measures and important reductions in age-adjusted CVD morbidity, CVD continues to be by far the leading cause of death and disability in the Western world (Luepker, 2005). Furthermore, the decline in some traditional CVD risk factors and in age-adjusted CVD mortality rates has slowed down nowadays in several of these countries (Reddy, 2003; Luepker, 2005). It was suggested that an important proportion of patients with CVD do not have any of the established coronary risk factors such as hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity and physical inactivity (Braunwald, 1997). These emphasize the need for further research for risk factors, mechanisms through which they influence the development and prognosis of CVD and for potential new treatment modalities. Findings from the INTERHEART study suggest that independently of the traditional risk factors, a substantial proportion of the population attributable risk of acute myocardial infarction (AMI) (33%) is due to psychosocial factors, such stress at work and at home, financial stress, major stressful life events, internal locus of control or depression (Yusuf et al., 2004).

1.2 PSYCHOSOCIAL RISK AND PROGNOSTIC FACTORS FOR CHD

In recent decades an increasing number of studies have suggested that psychosocial factors may increase the risk of CHD. Most of the attention in this research area has been focused on low socioeconomic status (SES) (Kaplan & Keil, 1993; Pickering, 1999), work stress (Schnall et al., 1994; Kivimäki et al., 2006), lack of social support (Mookadam & Arthur, 2004), depression (Rozanski et al., 1999; Rugulies, 2002; Wulsin & Singal, 2003; Kuper et al., 2005), anxiety (Kuper et al., 2005) and on personality traits such as type A behaviour (Johnston, 1993; Rozanski et al., 1999; Kuper et al., 2005) and hostility (Miller et al., 1996). Several new, so far less studied, psychological characteristics, including social dominance, aggression, cynicism, hopelessness, submissiveness, anger, vital exhaustion and type D personality have also been suggested to increase the risk of CHD (Appels & Mulder, 1989; Rozanski et al., 1999; Pedersen & Denolett, 2003; Kuper et al., 2005).

Kuper and associates (2005) conducted recently a comprehensive systematic review regarding the role of psychosocial factors in CHD. The study included only prospective cohort studies and focused on psychosocial factors which were measured in at least two different study populations, i.e. on type A behaviour, hostility, depression, anxiety, psychosocial work characteristics and social support. The authors concluded that, based on prospective epidemiological data, there is indication for an association between depression, low social support and work stress with CHD risk and/or prognosis (Kuper et al., 2005). The evidence for an association between anxiety and CHD was not clear, whereas most of the studies investigating Type A behaviour found no association between this personality trait and CHD.

While there is an impressive number of prognostic studies for several of these psychosocial factors, including SES, type A behaviour, depression, anxiety or social support, for other psychosocial characteristics such as work stress or anger, studies have been conducted mainly in initially healthy samples; thus their role in cardiac prognosis is less known (Kuper et al., 2005).

Furthermore, although CHD is the leading cause of death in both men and women from industrialized countries, much less research has been carried out on this topic in women than in men (Brezinka & Kittel, 1996). Women's psychosocial profile (Frasure-Smith et al., 1993; Brezinka et al., 1998; Hallman et al., 2001) and the pattern of the development and prognosis of CHD (Vaccarino et al., 1995; Marrugat et al., 1998; Vaccarino et al., 1998; Vaccarino et al., 1999; Rosengren et al., 2001) are known to differ from that of men. Consequently, the impact of

several psychosocial factors on prognosis in CHD, might as well be different for the two genders.

This thesis focuses on several of the aforementioned psychosocial factors. A special attention will be given to three psychosocial characteristics, namely to SES, anger expression and work stress. Depressive symptomatology, vital exhaustion, anxiety, social support, daily stress behaviour, type A behaviour and hostility will also be analysed and discussed when investigating explanations for the social gradient in recurrent events or for the effect of a combined intervention on mortality after a cardiac event. Given that women have been underrepresented in cardiovascular research, it is of special interest to analyse and discuss the relationship between psychosocial factors and prognosis in CHD in women.

1.2.1 SES and CHD

SES is the psychosocial factor which has probably most frequently been investigated in relation to CHD. It is most often defined by means of educational attainment, income, occupational class, wealth or as a combination of these factors. In several Western societies, there is now consistent evidence for the existence of a social gradient in CHD incidence (Rosengren et al., 1988; Marmot et al., 1997a; Salomaa et al., 2000; Picciotto et al., 2006; Thurston et al., 2006) and mortality (Marmot et al., 1984; Lynch et al., 1996; Strand & Tverdal, 2004) in initially healthy populations and in poor prognosis in patients with CHD (Salomaa et al., 2000; Alter et al., 2006; Manderbacka et al., 2006; Rasmussen et al., 2006; Georgiades et al., in press).

Though the relationship between SES and CHD is well established, the reasons why individuals who are on lower levels of the social hierarchy have worse health compared to their better situated counterparts are not entirely understood. Two major types of hypotheses have been proposed as explanations for the socioeconomic inequalities in health, including CHD (Marmot et al., 1997b; Goldman, 2001). One of these hypotheses, known as the *"health selection"* or the *"reverse causation" hypothesis* states that health determines social position (Marmot et al., 1997b; Goldman, 2001). This health selection can be direct, when unhealthy individuals reduce their social position as a consequence of their inferior health status or indirect, when it operates on the basis of determinants of both SES and health (Marmot et al., 1997b; Goldman, 2001). The second set of explanations, known as the *"social causation" hypothesis* (Marmot et al., 1997b) posits that SES, through differences between social strata in exposure to environmental challenges, e.g. financial strain, insecure employment, low control over stressful life events, low

self-esteem (Brunner, 1997) and in protective resources (Goldman, 2001; Lynch & Kaplan, 2000) influences the risk of disease and dying.

1.2.2 Anger and CHD

Another psychosocial factor which has received considerable attention in cardiovascular research is type A behaviour, a syndrome characterised by competition, hostility, anger, alertness, time urgency, exaggerated commitment at work and aggressive drive for achievement, advancement and recognition (Rosenman & Friedman, 1961; Johnston, 1993; Rozanski et al., 1999). Friedman and Rosenman described half a century ago this personality type and showed that type A men involved in the Western Collaborative Group Study had a double risk of developing CHD over an 8.5 year period compared to those with type B behaviour (Friedman & Rosenman, 1959; Rosenman et al., 1964). While some studies have replicated these findings from the Western Collaborative Group Study, most of the subsequent investigations did not find an evidence for an association between type A behaviour and CHD (Johnston, 1993). This lead researchers to suggest that not all aspects of the type A behaviour are detrimental for cardiovascular health, but only some of its component traits such as hostility, anger, aggressiveness or exaggerated commitment to work. Among these, hostility was suggested and is believed to be the most detrimental component (Johnston, 1993; Pedersen & Denollet, 2003). However, review articles regarding the association between hostility and CHD have mixed conclusions (Rozanski et al., 1999; Kuper et al., 2005; Myrtek, 2001; Smith et al., 2004).

Another type A behaviour component, related to hostility and which has been suggested to affect CHD is anger. Most of the epidemiological studies in this area have been aethiologic and showed that the propensity to experience anger (Williams et al., 2000; Chang et al., 2002a; Eaker et al., 2004) and the way anger is expressed increases the risk of CHD morbidity and mortality. Findings with respect to whether the outward expression (Siegman, 1993; Kawachi et al., 1996; Bleil et al., 2004), the suppression of anger (Haynes et al., 1980; Julius et al., 1986; Gallacher et al., 1999) or both (Everson et al., 1998) are detrimental for the cardiovascular system have been conflicting.

Only a limited number of studies have investigated the prognostic role of anger or its expression in CHD. Some of these investigations have shown anger to be associated with disease severity (Dembroski et al., 1985; MacDougall et al., 1985; Angerer et al., 2000) and with an increased risk of mortality and recurrent events (Mendes de Leon et al., 1996; Thomas et al., 1997), while others could not confirm this latter relationship (Welin et al., 2000; Frasure-Smith &

Lespérance, 2003). These studies were conducted on predominantly male samples and generally included a very low number of women. Given that women's anger-related behaviour (Haynes et al., 1978; Thomas, 1989; Siegman et al., 2000) and the pattern of the development and prognosis of CHD (Vaccarino et al., 1995; Marrugat et al., 1998; Vaccarino et al., 1998; Vaccarino et al., 1999; Rosengren et al., 2001) are known to differ from that of men, it is plausible that the impact of anger on prognosis in CHD might, as well, be different for the two genders. Thus, this topic needs further investigation.

1.2.3 Work stress and CHD

Studies investigating the effect of the psychosocial work environment on health have most often defined work stress by means of two theoretical models. The job strain model, developed by Robert Karesek in the 1970s (Karasek, 1979), defines work stress as a combination of high demands and low control on the job and proposes that this condition increases the risk of stress-related illness. A third dimension, that of low social support at work, has been added later to the model by Johnson and Hall (Johnson & Hall, 1988; Karasek & Theorell, 1990). Thus the worst psychosocial work environment is the "iso-strain" condition, which is characterised by high demands, low job control and lack of social support from colleagues and supervisors (Johnson & Hall, 1988).

The second model, the Effort-Reward Imbalance model, introduced by Johannes Siegrist in 1996, defines work stress as an imbalance between the efforts spent and the rewards received at work (Siegrist, 1996; Siegrist et al., 2004). Rewards are operationalised in terms of esteem, promotion prospects, job security and financial remuneration. This non-symmetric exchange may be maintained in circumstances (a) when the employee has no alternative choice in the labour market, (b) for strategic reasons (e.g. expecting future gains) and (c) when the employee is characterized by an excessive work-related overcommitment which prevents to accurately assess the cost-gain relationship (Siegrist, 1996; Siegrist et al., 2004). The model proposes that the lack of reciprocity in terms of high "costs" and low "gains" elicits negative emotions in exposed people and causes sustained stress reactions in the autonomic nervous system, which in the long run increases illness susceptibility (Siegrist et al., 2004).

A large number of studies have investigated the role of work stress in the aetiology of CHD. Several, though not all of them, indicate an increased risk of cardiovascular morbidity and mortality among employees working in stressful conditions. A recent meta-analysis of prospective cohort studies suggested that stress at work, defined either according to the job strain model, as an imbalance between efforts and rewards at work or as organizational

injustice, increases the risk of CHD incidence or mortality by approximately 50% (Kivimäki et al., 2006).

To the best of our knowledge only four studies have investigated the prognostic role of work stress in CHD and their findings are inconclusive. A study by Theorell and colleagues (1991) was the first to show that returning to a stressful work environment was associated with increased 5-year cardiac mortality in 79 men hospitalized for their first AMI. Two other studies concluded that levels of job strain did not affect prognosis in patients with CHD (Hlatky et al., 1995; Orth-Gomér et al., 2000). However, a recent large study involving patients who returned to work after an AMI found that in the second half of the follow-up, after 2.2 years, high job strain increased the risk for recurrent events more than two times (Aboa-Eboulé et al., 2007).

1.2.4 Pathways between psychosocial factors and CHD

Two main mechanisms have been suggested to explain the link between psychosocial factors and CHD. The first hypothesis involves a direct pathway; it proposes that through the prolonged activation and the deregulation of the autonomic nervous system and of the hypothalamus-pituitary-adrenocortical axis, chronic stress induces cardiovascular, metabolic, inflammatory and haemostatic changes which increase the risk of cardiovascular events (Brunner, 2001; Kuper et al., 2005, Kivimäki et al., 2006; Siegrist & Rödel, 2006). The second hypothesis states that stress affects cardiovascular health indirectly, through the modification of health behaviours (Brunner, 2001; Kuper et al., 2005, Kivimäki et al., 2006; Siegrist & Rödel, 2006).

1.2.4.1 Neuroendocrine mechanisms

When faced with a physical or psychosocial stressor our organism responds with the immediate activation of the sympathetic nervous system, followed by a somewhat slower response of the hypothalamic-pituitary-adrenocortical axis. During the activation of the sympathetic nervous system, catecholamines are released from nerve endings and the adrenal medulla into the blood. The secretion of catecholamines produces cognitive arousal, sensory vigilance, bronchodilatation, tachycardia, alterations of organ blood flows, raised blood pressure and energy mobilisation (Brunner, 2001). The aim is to mobilise rapidly the organism to transport increased amounts of oxygen to vital organs such as the brain and the muscles. During the activation of the hypothalamic-pituitary-adrenocortical axis, glucocorticoids, primarily cortisol, are secreted from the adrenal cortex into the blood. Glucocorticoids facilitate coping with the stressor by mobilising the energy reserves of the body. This adaptive ability of the organism to

achieve physiological stability through changes in the neuroendocrine and thus in the metabolic, immune and cardiovascular systems is known as “allostasis” (McEwen, 1998a).

However, when the stress becomes chronic, the increased exposure to stress hormones may lead to an allostatic load and its negative pathophysiological consequences (McEwen, 1998a; McEwen, 1998b). Allostatic load may have damaging effects on the cardiovascular, the metabolic and the immune systems and on the brain’s cognitive functioning (McEwen, 1998a; McEwen, 1998b).

The sympathetic overactivity related alterations in the cardiovascular system which have most frequently been investigated concern blood pressure and heart rate variability (Brunner, 2001). Consistent evidence shows that chronic stress – as indicated by low SES, job stress, depression or lack of social support – may result in substantial elevations in blood pressure, sometimes of clinically important magnitude (Colhoun et al., 1998; Markovitz et al., 2001; Rutledge & Hogan, 2002; Belkic et al., 2004; Scalco et al., 2005). Reduced heart rate variability, a good indicator of the dominance of the sympathetic activity over the parasympathetic one, has also been suggested to be associated with psychosocial factors (Thayer et al., 1996; Horsten et al., 1999; Agelink et al., 2002; Hintsanen et al., 2007). Short term and sustained surges in blood pressure and low heart rate variability are well known to increase the risk of CHD (McEwen, 1998a; Huikuri & Mäkikallio, 2001; Villareal et al., 2002; Ridker & Libby, 2005; Thayer & Lane, 2007).

The prolonged activation of the hypothalamic-pituitary-adrenocortical axis may result in disorders related to glucocorticoid “dysfunction” (Brunner, 2001). Cortisol has an important role in maintaining the metabolic homeostasis; it raises glucose levels in the blood by mobilizing energy reserves and thus affects metabolic functioning. Some studies document a relationship between exposure to chronic stress and metabolic disturbances, such as an unfavourable lipid profile (Brindley et al., 1993), insulin resistance (Innes et al., 2007) and the metabolic syndrome (Abraham et al., 2007). Furthermore, glucocorticoids have an immunomodulatory effect (Brunner, 2001; McEwen, 1998a) and immune mechanisms are also thought to be involved in the relation between chronic stress and CHD (Black, 2002; Black & Garbutt, 2002). Another pathway through which stress is hypothesized to influence CHD is by increasing blood coagulability. Recent reviews have found a positive relation between stress and the level of haemostatic factors (von Känel et al., 2001; von Känel & Dimsdale, 2003). Metabolic disturbances, increased inflammation and coagulation accelerate progression of coronary atherosclerosis and increase the risk of CHD (Ridker & Libby, 2005).

1.2.4.2 Triggering mechanisms

Besides their contribution to coronary atherosclerosis, psychosocial factors may also influence CHD by triggering mechanisms. Through its effect on cathecolamines, acute stress may induce coronary vasoconstriction, myocardial ischemia, haemodynamic shear stress, increased blood coagulability and platelet activation in coronary arteries (Servoss et al., 2002; Strike et al., 2004). This may eventually cause plaque rupture, thrombus formation and vessel occlusion. Studies documenting an increase in the incidence of AMI at community level immediately after stressful, traumatic events such as earthquakes (Suzuki et al., 1995; Leor & Kloner, 1996; Leor et al., 1996) or threat from missile attacks (Meisel et al., 1991) provide a support for this hypothesis. Findings from case-crossover studies investigating potential triggers for AMI indicate that considerably less stressful or traumatic events than the above ones may also induce AMI; short term situations of anger, increased workload, work competition or conflict were found to be more frequent in the period preceding the AMI compared to a control period one day before (Mittleman et al., 1995; Möller et al., 1999; Möller et al., 2005).

1.2.4.3 Health behaviour as mediating mechanism

Besides the induced physiological changes which may contribute to the progression of atherosclerosis or that may act as triggers of a coronary event, chronic stress has also been suggested to influence cardiovascular health through the modification of health behaviours such as smoking, diet, physical activity or alcohol consumption (Kuper et al., 2005). The social gradient in health behaviour is well documented (Pickering, 1999) and persons experiencing low social support (Hanson et al., 1990; Treiber et al., 1991; Murray et al., 1995; Nides et al., 1995), work stress (Siegrist & Röedel, 2006), depression (Joynt et al., 2003) or those characterised by a hostile behaviour (Thomas & Donnellan, 1991; Musante et al., 1992; Whiteman et al., 1997; Rutledge et al., 2001) have been found in some studies to have a less favourable lifestyle than those with a better psychosocial profile.

Sleep quality may also be a putative explanation for the link between stress and cardiovascular health. Sleep problems are more prevalent among those experiencing psychosocial stress (Drake et al., 2003; Åkerstedt, 2006) and poor sleep is known to increase the risk of incident CHD (Schwartz et al., 1999) and of adverse cardiac outcomes in developed disease (Leineweber et al., 2003).

Furthermore, it is also plausible that cardiac patients with unfavourable psychosocial characteristics such as high stress, depression or low social support have poorer compliance with their medical treatment than those with less stressful experiences.

However, despite this theoretical background, the biological and behavioural pathways through which several psychosocial factors may affect cardiovascular functioning are less well studied, especially in patient populations.

1.3 PSYCHOSOCIAL REHABILITATION IN CHD

Besides analyzing the impact of psychosocial factors on cardiovascular health, increasing attention is being focused on determining whether psychosocial interventions offered for cardiac patients will reduce the level of these potentially health detrimental factors and consequently the associated risk for mortality and recurrent events. Findings in this field are not equivocal, some meta-analyses suggesting that psychosocial interventions can affect psychosocial targets (Linden et al., 1996; Rees et al., 2004; van Dixhoorn & White, 2005), while others did not find support for this hypothesis (Dusseldorp et al., 1999). Similarly, results concerning the effect of psychosocial rehabilitation programs after an AMI on mortality and recurrent events are also inconclusive (Linden et al., 1996; Dusseldorp et al., 1999; Rees et al., 2004; van Dixhoorn & White, 2005).

Though it has been suggested that women have on average poorer psychosocial health than men (Frasure-Smith et al., 1993; Brezinka et al., 1998; Hallman et al., 2001), few large scale randomized controlled trials have investigated the effect of psychosocial interventions in women with CHD. Findings regarding their impact on psychosocial outcomes are mixed, some studies suggesting interventions to have a beneficial effect (Schneiderman et al., 2004; Claesson et al., 2005; Appels et al., 2006), while others did not find evidence for an effect of psychosocial treatment (Frasure-Smith et al., 1997). Two large scale randomized trials included a sufficiently high number of women to analyze the effect of a psychosocial rehabilitation program on 'hard' cardiac endpoints in women. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study could not demonstrate that reducing depression and social isolation by means of cognitive-behavioural therapy (CBT) improves event-free survival in women with CHD (Berkman et al., 2003; Schneiderman et al., 2004). Stratified analyses showed a beneficial effect of the therapy on prognosis in certain groups of men (Schneiderman et al., 2004). The Montreal Heart Attack Readjustment Trial (M-HART), implementing a home-based psychosocial nursing intervention in both men and women, unexpectedly found a higher mortality rate in women undergoing treatment compared to control women (Frasure-Smith et al., 1997).

Failures of trials like M-HART or ENRICHD to positively affect mortality rates in women might be explained by the fact that the applied interventions were based primarily on experience gained from cardiovascular trials conducted in predominantly male samples (Frasure-Smith et al., 1997; Cossette et al., 2001; Schneiderman et al., 2004). The two genders' psychosocial profile (Brezinka & Kittel, 1996), vulnerability (Hallman et al., 2001) and therefore needs (Burell & Granlund, 2002; Linden, 2000) after a cardiac event differ, thus justifying the need for research on effectiveness of psychosocial interventions adapted to the special needs of women.

2 OBJECTIVES

On a *general level*, the aim of this thesis is to contribute to the better understanding of the relationship between psychosocial factors and prognosis in CHD.

The *specific* aims are:

- To analyse the association between income, a measure of SES, and prognosis in women CHD patients and to determine whether lifestyle-related, biological and psychosocial factors may explain this relationship (paper I).
- To analyse whether anger expression increases the risk of recurrent events in women with CHD and if so, to investigate factors that may explain this association (paper II).
- To investigate whether work stress predicts recurrent events after AMI and if so, to determine behavioural and biological factors that may contribute to the explanation of this association (paper III).
- To evaluate whether a 1-year intervention consisting of a psychosocial rehabilitation based on CBT principles tailored to women's needs in addition to medical treatment from a cardiologist affects prognosis in women CHD patients and to determine which psychosocial and biomedical factors may explain an eventual survival benefit of this intervention (paper IV).

3 METHODS

3.1 STUDY POPULATIONS AND DESIGNS

3.1.1 The Healthier Female Heart (HFH) study

3.1.1.1 Study population

Data from the HFH study were used in papers I, II and IV. The study base of the HFH study consisted of women aged ≤75 years who had survived an AMI and/or undergone a revascularization procedure, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and were hospitalized between August 1996 and January 2000 at Karolinska University Hospital, Huddinge or St Göran's Hospital in Stockholm, Sweden. The diagnosis of AMI was based on the World Health Organization's criteria of typical enzyme patterns and chest pain and/or diagnostic electrocardiographic changes (Alpert et al., 2000). All eligible women were approached and offered to participate in a cardiac rehabilitation program specifically designed for women. They were offered verbal and written information describing the 1-year psychosocial rehabilitation. Women > 75 years of age, those not communicating in Swedish, those who participated in other research studies, who did not belong to the hospital catchment area or who had serious co-morbidity that would preclude taking part in the 1-year intervention program, such as malignancy or psychiatric disease, were excluded. Patients were asked to participate in the study only if they thought they would be able to attend all of the planned 20 sessions during one year.

According to the hospital records, a total of 387 eligible patients were hospitalized during the enrolment period (Figure 1). Of them, 140 patients were not included in the study either because they did not meet the inclusion criteria or because they thought they would not be able to attend all of the planned 20 sessions during one year or did not want to commit themselves to the intervention program. These 140 patients were older (age 65±8, range 43-75 years) compared to the randomized patients (age 62±9, range 35-75 years, $p = 0.001$) and had less often PCI (20% vs. 31%, $p<0.001$), but not AMI (63% vs. 57%, $p = 0.24$) or CABG (25% vs. 32%, $p = 0.16$) as inclusion diagnosis. Therefore, a total of 247 patients were included in the study, 165 patients being from the Karolinska University Hospital, Huddinge and 82 patients from St Görans Hospital, respectively.

3.1.1.2 Description of the psychosocial intervention

The psychosocial rehabilitation program was based on CBT principles with various strategies to be practiced between sessions (Koertge et al., 2008; Blom et al., in press). It consisted of 20 x 2-hour sessions; the first 10 were held weekly and the subsequent 10 monthly. The program was a broadened adaptation (Burell & Granlund, 2002) of the one created for the Recurrent Coronary Prevention Project (Friedman et al., 1982). Our program targeted feelings of vital exhaustion, anxiety, depressive symptoms, daily stress behaviour, type A and anger-related behaviour. All sessions included education and discussions. The initial ones were focused on CHD, lifestyle variables and the physiologic stress response. Thereafter, they focused on how to identify and modify the physical, cognitive, affective and behavioural stress-responses by using cognitive-behavioural strategies. These included replacing negative and irrational thoughts with alternative ones, practicing a relaxed behaviour style as opposed to type-A behaviour, by using progressive relaxation techniques, assertive communication, and strategic problem-solving skills. Furthermore, the session-material illustrated stressors and stress reactions typically common among women including topics such as coping with the challenge of being a full-time employee while being the main caregiver in the family, experiencing stress from interpersonal conflicts, suffering from low self-esteem, vital exhaustion, depressive symptoms and anxiety. Therapists in this psychosocial intervention were qualified cardiovascular nurses who were trained by the program developer to deliver the intervention to the patients. A non-controlled feasibility study of the 1-year program was previously performed in a sample of women with CHD (n = 23) with a mean age of 59 years (Burell & Granlund, 2002). It was found to be attractive, having an attendance rate of 80%.

3.1.1.3 The study design

During their hospital stay for the cardiac event, the 247 patients who accepted to participate in the study were randomized by means of a chance table to either the intervention (119 patients) or to the control group (128 patients) (Figure 1). Control patients obtained regular medical care in the health care system, including pharmacological treatment with e.g. aspirin, beta-blockers, statins and ACE inhibitors. Initially, after hospitalization, if a patient was not doing well, further examination and modification of therapy was taking place through routine care of the doctor responsible for the patient, otherwise the patient was sent to a general practitioner for further follow-up. Patients in the intervention group, in addition to the 1-year psychosocial rehabilitation were treated by a cardiologist. During the 1-year intervention period, they were treated by one cardiologist at Karolinska University Hospital, Huddinge or by one out of four

participating cardiologists at St Görans Hospital, respectively. They met their cardiologist at least 3 times, i.e. just after baseline, after ½ year and 1 year, respectively.

Six to eight weeks after the index event, baseline examinations were performed. The reason for this design was that maximal exercise tests could not be performed earlier in patients having been operated on. Research nurses sent questionnaires to all patients before this examination and the intention was that the questionnaires should have been answered by then. However, some patients in both groups completed their first questionnaires only after the intervention group's first session. Intervention patients met for the first time after the baseline examination in a group format of 4-6 patients/group.

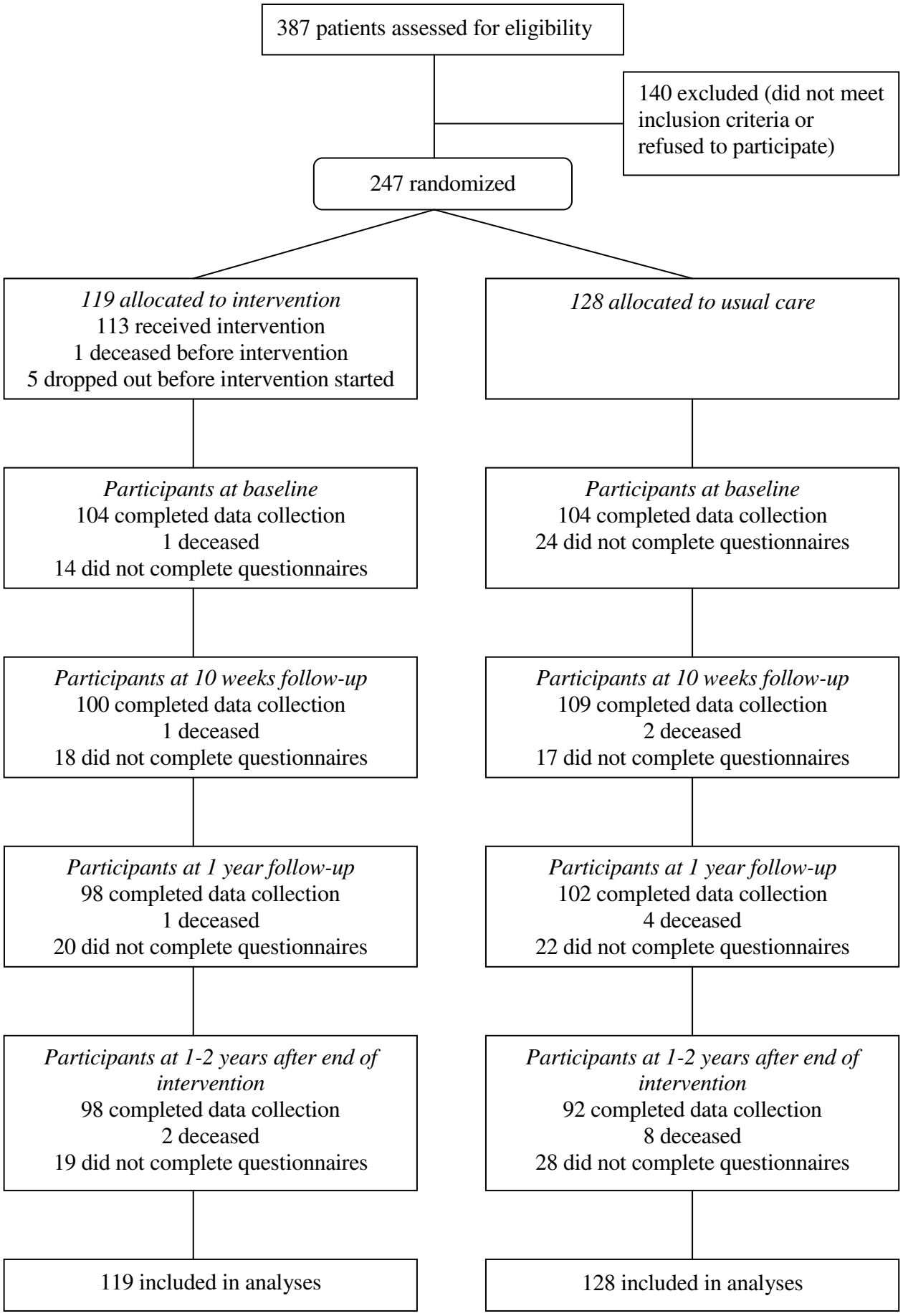
At four time points, i.e. at baseline, 10 weeks later (i.e. after 10 intervention sessions), one year after baseline (end of intervention), and 1-2 years after the intervention ended, both the intervention and the control patients were examined. The mean period between the third and fourth measurement was 513±144 days.

In both groups detailed medical history, exercise test, echocardiography, anthropometric measurements and data on pharmacotherapy were obtained. Attendance rates were monitored in the intervention group.

The evaluation of psychosocial risk factors were all based on questionnaires. Altogether 208 patients completed the questionnaires at baseline, 209 after 10 weeks of intervention therapy, 200 at one year (end of intervention) and 190 patients at the 1-2 year follow-up, respectively. For the intervention and control groups the corresponding figures were: 104 vs. 104, 100 vs. 109, 98 vs. 102, and 98 vs. 92, respectively (Figure 1).

The Ethics Committee of the Karolinska Institute at Karolinska University Hospital approved the study (nr. 196/94) and all participating patients signed an informed consent form.

Figure 1. Patient flow-chart and data collection



3.1.2 The Stockholm Heart Epidemiology Program (SHEEP)

Paper III was based on the data from non-fatal AMI cases enrolled in the SHEEP, a population-based case-control study of incident AMI (Reuterwall et al., 1999). The study base for the SHEEP comprised of all Swedish citizens living in the Stockholm County, 45-70 years of age, free of previous clinically diagnosed AMI. Male cases were identified during a 2-year period (1992-93) and female cases during 3 years (1992-94). Cases were identified through a special organization at the 10 emergency hospitals in the region. Criteria for AMI included (a) certain symptoms according to case history information, (b) specified changes in blood levels of the enzymes CK and LD and (c) specified electrocardiogram changes. The diagnosis for AMI required two of the criteria (a-c) to be met. Later comparison with a population-based incidence register indicated close to complete ascertainment of all first AMIs (Linnersjö et al., 2000). A total of 1603 non-fatal cases of AMI were identified, defined as surviving the AMI for at least 28 days. Of these patients we included in our analyses 676 individuals, i.e. those younger than 65 years (the official retirement age in Sweden) and in paid employment at the time of their AMI.

The Regional Ethics Committee of the Karolinska Institute, Stockholm approved the study (nr. 03/353).

3.2 MEASURES

3.2.1 Exposures

3.2.1.1 Personal income

Six to 8 weeks after their index event, i.e. at the baseline assessment, patients in the HFH study were asked to disclose their yearly personal income from the previous year. Six answer possibilities were provided: 1) <119 999, 2) 120 000-159 999, 3) 160 000-199 999, 4) 200 000-229 999, 5) 230 000-259 999 and 6) ≥260 000 Swedish crowns (SEK)/year, respectively. In paper I these answer alternatives were categorised into tertiles based on their distribution. Those with income below 119 999 SEK formed the low income group, the medium income group consisted of those in the 120 000-159 999 SEK interval, while those with yearly income above 160 000 SEK were assigned to the high income group.

3.2.1.2 Anger expression

The four scales of the Framingham Anger Questionnaire (Haynes et al., 1978) were used in the HFH study to assess ways of anger expression. The questionnaire ascertains the modes of

reacting and coping in situations when "really angry or annoyed". Responses are given on a four-point scale, from "not too likely" (0) to "very likely" (3). The *Anger symptoms* scale (5 items) assesses the intensity of physiological reactions, i.e. tension or worry, headache, nervousness or shakiness, feeling weak and depressed when experiencing anger. The *Anger-in* scale (3 items) ascertains the likelihood of suppressing one's feelings of anger. Examples of statements are: "Try to act though nothing much happened" or "Keep it to yourself". The *Anger-out* scale (2 items) inquires about the tendency to express angry feelings outwardly towards others. Items are "Take it out on others" and "Blame someone else". The *Anger-discuss* scale measures by means of 2 items, i.e. "Get it off your chest" or "Talk to a friend or relative", the likelihood of relieving one's anger by talking with someone.

Scale scores were obtained by summing the item scores in each scale. Thus the total score ranges from 0 to 15 for the Anger symptoms, from 0 to 9 for the Anger-in, from 0 to 6 for the Anger-out and from 0 to 6 for the Anger-discuss scale. In our study the Cronbach α coefficients for the four scales were between 0.58 and 0.78.

3.2.1.3 Work stress

Job strain was measured in the SHEEP study with the Swedish version of the Job Content Questionnaire (Karasek et al., 1985). The questionnaire consists of two scales with answers being given on a 4-step scale ranging from "almost always" to "almost never". The 5 items of the *psychological demands* scale inquire about having to work fast, to work hard, too much effort, encountering conflicting demands and lack of time to do the work. The 6 items of the *job control* scale assess whether the person has the possibility to decide what and how to do on his/her job (decision latitude) and whether the work offers possibilities to learn new things, requires high levels of skills, creativity and has variety (skill discretion). Cronbach α coefficients were 0.72 for the psychological demands scale and 0.70 for the job control scale.

In the primary analyses for paper III, job strain was defined according to the "quadrant" definition. Psychological demands and job control scores were dichotomized at the median and four job strain categories were created: (a) patients with low job demands and high job control constituted the *low strain* group, (b) those having high demands and high control represented the *active* group, (c) those with low demands and low control formed the *passive* group, (d) while patients with both high demands and low control at work were classified as having *high strain* (Karasek, 1979; Karasek & Theorell, 1990). In secondary analysis, we also used the "quotient" definition of job strain (Schnall et al., 1994). For this, job demands scores were

divided with the job control scores; this quotient was analyzed both continuously and categorized in quartiles.

3.2.2 Outcomes

The centralized health care system in Sweden provides virtually complete follow-up information for all patients by matching their unique 10-digit personal identification numbers to health care registers. Information on death and cause of death was obtained from the National Cause of Death Register, while the Swedish Myocardial Infarction Register provided data on new infarctions (Hammar et al., 1991). Patients were followed for all-cause and cardiac/cardiovascular mortality and non-fatal AMI in both studies (HFH and SHEEP). The average length of follow-up was 6.5 years in the HFH study and 8.5 years in the SHEEP study.

3.2.3 Covariates

3.2.3.1 Psychosocial factors

All psychosocial factors presented in this section were assessed in the HFH study.

Depressive symptoms were measured using the Beck Depression Inventory (Beck et al., 1961). The 21-item questionnaire asks participants to rate the intensity of their depressive symptoms on a scale ranging from 0 to 3. In our study the Cronbach α coefficient was 0.83, indicating good internal consistency of the scale. A score of 10 is the recommended and generally accepted cut-off point for a likely depressive disorder (Beck et al., 1974).

Vital exhaustion – a mental state characterised by unusual fatigue, irritability and demoralization – was measured by means of the Maastricht Questionnaire (Appels et al., 1987), a scale with 21 items rated from 0 to 2. The scale has adequate internal consistency, the Cronbach α coefficient in our study being 0.89.

Trait anxiety was assessed with the Trait Anxiety scale of the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983). Patients were requested to indicate on a scale ranging from 1 (not at all) to 4 (very much) the frequency and intensity of the anxiety and tension they experience in their life. In our study the Cronbach α coefficient calculated for the 20 items of the scale was 0.93.

Social support was assessed by means of an abbreviated version of the Interview Schedule for Social Interaction (Henderson et al., 1980; Unden & Orth-Gomér, 1989), a questionnaire consisting of two scales: availability of social integration and availability of attachment. The 6 items of the availability of social integration scale measure the more peripheral contacts of social network and support. The total score ranges from 6 to 36. The 6 items of the availability

of attachment scale measures the availability of deep emotional relationships and support from family and close friends. The total score ranges from 0 to 6. Cronbach α coefficients in the HFH study were adequate, 0.80 and 0.80, respectively.

Daily stress behaviour was measured using the Everyday Life Stress scale (Claesson et al., 2005). This instrument includes 20 items rated on a 4-point scale ("almost never", "sometimes", "often", "almost always") and refers to stress behaviour in everyday life situations such as time urgency, impatience or easily aroused irritation and hostility. In our study the item score ranges from 1 to 4 and the total score from 20 to 80. Higher scores indicate a more pronounced self-rated daily stress behaviour. The Cronbach α coefficient for this scale was 0.89 in the HFH study.

Type A-behaviour was measured by means of the Jenkins Activity Survey (Jenkins et al., 1971). It contains 11 items measuring traits such as striving for achievement, competitiveness, aggressiveness, haste, impatience, restlessness, alertness, uneven bursts of amplitude in speech and hurried motor movements. Each item is rated from 1 to 4, higher scores indicate a more pronounced type A behaviour. The Cronbach α coefficient in our study was 0.79. Hostility scores were calculated from the Jenkins Activity Survey as described previously (Jenkins et al., 1971).

3.2.3.2 Biological factors

In the *HFH study,* blood samples from the patients were drawn at 10±1 hour AM. Blood lipids, glucose, cortisol, creatinine and free thyroxine were assessed. Levels of high-sensitivity C-reactive protein (CRP) were measured by nephelometry using N-dilutent for Nephelometry, Behring OUMT 61 (Dade Behring GmbH, Marburg, Germany). Interleukin-6 (IL-6) concentrations were determined by enzyme-linked immunoassay (R & D Systems, Abingdon, UK) and high sensitivity kits were used to accurately determine low levels of the cytokine (Janszky et al., 2005a). Blood pressure was measured twice by a trained research nurse with the patient in supine position and the mean value was considered. Left ventricular ejection fraction was determined by echocardiography.

In the *SHEEP study,* lipids, glucose, coagulation and inflammatory factors were measured from blood samples drawn by venous puncture after overnight fasting at the health examination (Wiman et al., 2000; Bennet et al., 2003). Hypertension was defined as being on active antihypertensive drug therapy, having a history of regular antihypertensive drug therapy within the last 5 years, or having a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥

90 mmHg, based upon the mean of two measurements in supine position after a 5 minute rest at the health examination. Subjects were classified as diabetics if they had a history of diabetes, or insulin or drug treatment for diabetes, or if their fasting blood glucose level exceeded 6.7 mmol/L at the health examination. Killip classification was determined during the hospital stay and refers to the clinical status regarding heart failure during the AMI episode.

3.2.3.3 Lifestyle-related factors

In the *HFH study* smoking status was categorized as never, current or former smoker. Average daily alcohol intake was registered in grams (Janszky et al., 2005b). Height and weight was measured, and body-mass index (BMI) was calculated (kg/m^2). Physical activity was assessed by asking how active the patients were during their spare time. The answers were grouped into 4 alternatives: (a) reading, watching television or other sedentary leisure activities, (b) walking, bicycling or other forms of light physical activity, (c) exercise regularly to keep fit, heavy gardening, etc at least 4 hours/week, or (d) hard training or participation in competitive sports regularly, several times/week. In the analyses for paper IV, the variable was classified as sedentary lifestyle (alternative a) vs. at least light physical activity (alternatives b-d).

In *paper III,* based on data from the SHEEP study, patients with a measured BMI over 30 kg/m^2 were classified as obese. Patients who reported inactive leisure time, including occasional walks, during the last 5-10 years were categorized as physically inactive. Subjects who had never smoked regularly (i.e. for at least 1 year) were considered as never-smokers. Subjects, who smoked when included into the study, or had stopped smoking within the last 2 years, were classified as smokers. Subjects, who had stopped smoking for more than 2 years before inclusion, were classified as ex-smokers. Consumption of alcoholic beverages was assessed with a semi-quantitative food frequency questionnaire and average daily alcohol intake was calculated in grams (Janszky et al., 2008).

Frequency of insomnia symptoms, i.e. difficulties in falling asleep, repeated awakenings and difficulties in falling asleep again, tiredness when awakening, early morning awakening and tiredness during the day, during the last 12 months were assessed with a 5-step scale. The variable was categorized based on the median split as presenting the symptoms sometimes per year at most versus sometimes per month or more often.

3.2.3.4 Other covariates

In the *HFH study* patients were asked to indicate their household's income for the previous year; answer categories were identical with those provided to the item concerning personal income. The number of persons relying on the family income was also recorded. In paper I educational attainment was classified into two levels: mandatory schooling only and completion of high school, college or university, whereas in paper II we classified education as mandatory school only, completion of high school and college or university degree. Marital status was classified as married or cohabiting versus not living with a partner. Age, data on retirement, drug therapy (beta-blockers, calcium channel blockers, statins, aspirin, ACE inhibitors and diuretics), participation in other rehabilitation programs and whether the patient has been hospitalized due to heart disease in the last few years were also registered.

In *paper III,* based on data from the SHEEP study, we classified educational attainment into two levels: mandatory schooling only and completion of high school, college or university. Occupational class was categorized as blue or white collar worker. Marital status was classified as married or cohabiting versus not living with a partner. Information on age, sex, shift work, frequent overtime work and on whether the study participant was a foreperson (manager or supervisor) was registered. Patients also indicated whether they were doing the household work themselves, together with someone else, or someone else did it. Information on family history of CHD, on chest pain and on stroke prior to the AMI was also collected.

3.3 STATISTICAL ANALYSES

For all papers, un- and multiadjusted Cox proportional hazard models were performed to examine the association between the exposure and (a) the combination of cardiac/cardiovascular death and non-fatal AMI (papers I-IV), (b) cardiac/cardiovascular death (papers I, III and IV) and (c) total mortality (papers I-IV). There was no evidence of non-proportionality of hazards when investigated by log-log curves or by formal two-sided tests of interaction with time or the log of time.

The change-in-point estimate strategy was used to select confounders to be included in the base model (Rothman & Greenland, 1998). In papers I and II, we included in the base model only variables that were found to modify the regression coefficient for the association between exposure and the outcome by at least 10%. The higher statistical power in the SHEEP study allowed us to include in the base model confounders that modified the regression coefficient by

at least 5%. Potential confounding factors investigated in paper I were age, marital status, education, retirement, hospitalization for CHD during the last years, inclusion diagnosis, drug therapy, participation in our subsequent rehabilitation program and participation in other rehabilitation programs. In paper II, we analysed potential confounding from age, education, inclusion diagnosis, participation in our rehabilitation program, drug therapy, history of diabetes mellitus, alcohol consumption, BMI and smoking habits. In paper III we investigated age, sex, education, occupational class, marital status, overtime work, shift work, managerial status, exposure to household work, family history of CHD, Killip class, hypertension, history of chest pain, of stroke and of diabetes mellitus as potential confounders.

When examining potential mediators of the association between exposure and the outcome several lifestyle factors (papers I and III), glucose (papers II and III), cortisol (papers I and II), lipids (papers I-III), inflammatory (papers I-III), coagulation (paper III) and psychosocial factors (paper I and IV), medications (paper IV) and revascularization procedures (paper IV) were added one-by-one to the base model. We regarded a change in the point estimate of at least 10% as indication of potential mediation (Rothman & Greenland, 1998).

Stratified analyses and formal tests for interactions were conducted in papers I-III to assess possible effect modification. Rothman's synergy indexes with 95% confidence intervals (CI) were calculated to evaluate the interaction between exposure and potential effect modifiers (Lundberg et al., 1996; Rothman & Greenland 1998).

In paper IV, all analyses were based on the intention to treat principle, that is all patients were included in the calculations as being randomized. Student's t-tests were used to compare the two groups on continuous variables. Categorical data were compared by chi-square tests. When investigating the changes over time on psychosocial as well as on biomedical variables, mixed models were run using a 2 (intervention vs. control groups) x 4 (time: at baseline, at 10 weeks, at 1 year (end of intervention), and at 1-2 years follow-up) design. With the mixed model approach we did not have to exclude from the analyses subjects with missing values on different measurements. The interaction term between treatment and time was interpreted as a potential effect of intervention. When adjusting for potentially explanatory factors of the intervention-outcome relationship, time-dependent covariates were used in these models.

Analyses were performed using SAS 9.1. and SPSS 15 for Windows.

4 RESULTS

4.1 INCOME AND RECURRENT EVENTS (PAPER I)

Out of the originally randomized 247 patients of the HFH study, 12 (6 from the intervention group and 6 from the control group) did not participate in any of the assessments, resulting in 235 patients who could potentially provide data at the first assessment. Due to missing data on personal income at the baseline measurement, 188 women were included in the analyses for paper I. Women with complete data on personal income did not differ significantly from those with missing data in terms of most of the demographic, lifestyle, psychosocial or clinical characteristics. However, those with missing data were more likely to be from the control group of our intervention program, to have CABG as inclusion diagnosis and to have higher levels of cortisol. During the 6-year follow-up period, there were 18 deaths from any cause (9.6%), 10 cardiovascular deaths (5.3%), while 31 patients had either cardiovascular death or non-fatal AMI (16.5%).

Table 1 presents the hazard ratios (HR) and the 95% CI when the medium- and high-income groups were compared to the low-income group. After adjustment for confounders, i.e. age, marital status, education and the interaction between marital status and age, both the medium and high income groups had lower risk for recurrent events than those with low income. Patients in the middle-income group had significantly lower risk for the combination of cardiovascular death and non-fatal AMI than those in the low-income group, the HR and the 95% CI being 0.38 (0.15-0.97). When the groups with high and low income were compared, the multiadjusted models showed significantly lower risk for total mortality and for the combination of cardiovascular death and non-fatal AMI for the first group. The corresponding HRs (95% CI) were 0.19 (0.05-0.75) and 0.39 (0.17-0.93), respectively. When alternatively we categorized income as quartiles we obtained similar results in essence though with less power.

We have also examined possible effect modifications. We performed stratified analyses according to age (median split), marital status, education, retirement, previous hospitalizations due to CHD, participation in our rehabilitation program, hospital catchment area and inclusion diagnoses. We found roughly similar associations between income and recurrent events in these selected subgroups.

Table 1. Hazard ratios and 95% confidence intervals for the association between personal income and prognosis after AMI

Outcome	Income tertile	N	Number of events	HR (95% CI)	
				Unadjusted model	Base model[1]
Cardiovascular mortality and non-fatal AMI	Low	53	14	1	1
	Medium	53	7	0.47 (0.19-1.16)	0.38 (0.15-0.97)
	High	82	10	0.46 (0.20-1.04)	0.39 (0.17-0.93)
Cardiovascular mortality	Low	53	5	1	1
	Medium	53	4	0.77 (0.20-2.86)	0.57 (0.13-2.39)
	High	82	1	0.12 (0.02-1.09)	0.12 (0.01-1.18)
All-cause mortality	Low	53	11	1	1
	Medium	53	4	0.34 (0.11-1.08)	0.33 (0.10-1.09)
	High	82	3	0.17 (0.04-0.63)	0.19 (0.05-0.75)

AMI = acute myocardial infarction, HR = hazard ratio, CI = confidence interval.

[1] Base model includes confounders, i.e. age, marital status, education and the interaction between marital status and age.

In secondary analyses, we investigated the association between two other measures of SES – educational attainment and household income – and recurrent events. After adjustment for potential confounders, i.e. age, education, marital status and the number of persons relying on the family income, household income was not significantly related to the combined endpoint of cardiovascular mortality and new AMI, the HR (95% CI) being 0.78 (0.32-1.91) for the middle versus the low household income tertile and 0.41 (0.12-1.39) when comparing groups with high and low household income. Education was not significantly associated with the combined endpoint of cardiovascular mortality and new AMI, the HR (95% CI) being 0.92 (0.41-2.06) when those having at least high school were compared to those with less than high school education.

We have investigated whether lifestyle and psychosocial factors, lipids, inflammatory markers, cortisol or creatinine contribute to the explanation of the association between income and recurrent events. We found a slight decrease in the risk associated with the lower income category when adjusting for smoking, depression and anger symptoms. Adjustment for smoking resulted in a decrease of 12.8% in the absolute value of the regression coefficient for the high

versus low income group. With depression, the corresponding change was 13.5% when the middle and low income groups were compared and 9.3% when the high and low income groups were compared. When adding the anger symptoms scale to the base model the absolute value of the regression coefficient for the middle versus low income group was reduced by 16.7%, whereas that corresponding to the high versus low income groups by 10.2%. After controlling for alcohol consumption, anger-in and anger discussion the association between income and the combined endpoint of cardiovascular death and non-fatal AMI became even stronger. The effect of the additional adjustment for the rest of the potential mediators was negligible.

4.2 ANGER EXPRESSION AND RECURRENT EVENTS (PAPER II)

Analyses for paper II were restricted to the 203 women who completed at least one of the scales of the Framingham Anger Questionnaire at the baseline assessment of the HFH study. Women with complete data did not differ significantly from those with missing data in terms of any demographic, lifestyle, or clinical characteristics. During the follow-up period, 20 patients died. Thirty-two patients had suffered either cardiovascular death (n = 11) or a non-fatal AMI (n = 21).

In table 2 we present the HR and the 95% CI for the association between anger expression and recurrent events. After adjustment for confounders, i.e. age, inclusion diagnosis and smoking, women who tended to suppress their anger had an increased risk for cardiovascular death or recurrent AMI and for all-cause mortality. The outward expression of anger was associated with the combined endpoint of cardiovascular death and new AMI, but not with total mortality. The anger symptoms and the anger discuss scales were not associated with recurrent events.

To assess possible effect modifications we performed stratified analyses as well as formal tests for interaction with age (median split), education, participation in our rehabilitation program, inclusion diagnosis, alcohol consumption and smoking habits. We found no evidence for effect modification from these factors on the association between the anger variables and prognosis.

Table 2. Hazard ratios and 95% confidence intervals for recurrent events for 1-unit increase in anger expression scores

Exposure	N	HR (95% CI)					
		Cardiovascular mortality and non-fatal AMI			Total mortality		
		Number of events	Unadjusted model	Base model*	Number of events	Unadjusted model	Base model*
Anger symptoms	198	31	1.06 (0.96-1.17)	1.04 (0.94-1.15)	20	1.04 (0.92-1.18)	1.06 (0.94-1.20)
Anger-in	200	32	1.27 (1.07-1.51)	1.19 (0.99-1.42)	20	1.38 (1.11-1.72)	1.29 (1.03-1.60)
Anger-out	202	32	1.19 (0.87-1.64)	1.42 (1.01-2.00)	20	0.66 (0.35-1.25)	0.84 (0.45-1.57)
Anger-discuss	200	32	1.16 (0.94-1.44)	1.13 (0.91-1.40)	20	1.13 (0.86-1.47)	1.10 (0.83-1.48)

*Base model includes confounders, i.e. age, inclusion diagnosis and smoking.

HR = hazard ratio, CI = confidence interval, AMI = acute myocardial infarction.

In additional analyses we investigated whether the relationship between anger suppression and recurrent events was mediated by lipids, inflammatory markers, cortisol and glucose. When controlling for IL-6 we found a 19% decrease in the regression coefficient for the association between anger-out and the combined endpoint of cardiovascular death and new AMI. Adjustment for CRP reduced the regression coefficient for the relationship between anger-in and total mortality by 20%. The associations between the four anger characteristics and prognosis did not alter considerably after controlling for BMI, history of diabetes mellitus, cortisol, glucose, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol.

4.3 JOB STRAIN AND RECURRENT EVENTS (PAPER III)

During the follow-up period, a total of 96 patients (14.2%) died from those included in our analyses from the SHEEP study, 52 of these deaths being of cardiac cause. One hundred three patients (15.2%) experienced a new AMI.

Table 3 presents the un- and multiadjusted HR and 95% CI for the association between job strain and the three outcomes: the combination of cardiac death and non-fatal AMI, cardiac mortality and total death. In multivariate analyses, when adjusting for age, sex, education, occupational class, managerial status, overtime, shift and household work and the interaction between household work and age, patients with high job strain had an increased risk for recurrent events relative to those with low job strain. Rothman's synergy indexes for the interaction between high demands and low control were 1.24 in the case of the combined endpoint of cardiac death and non-fatal AMI and 1.81 for cardiac death. However, the corresponding CIs were large and included 1.

Analyses with the "quotient" definition of job strain yielded comparable results to those of our primary analyses. The HR (95% CI) for the combined endpoint of cardiac death and non-fatal AMI was 1.64 (0.90-2.99) when the job strain quotient was treated as a continuous variable and 1.33 (0.84-2.10) for the second, 1.05 (0.63-1.73) for the third and 1.59 (0.99-2.56) for the fourth vs. the first job strain quartile.

Table 3. Hazard ratios and 95% confidence intervals for the association between job strain and recurrent events

Work stress group	Events/N	HR (95% CI)	
		Unadjusted model	Base model*
Combination of cardiac death and non-fatal AMI	155/674		
Low strain	32/160	1.00	1.00
Active	45/217	1.05 (0.67-1.65)	1.28 (0.79-2.07)
Passive	35/145	1.22 (0.75-1.96)	1.31 (0.79-2.17)
High strain	43/152	1.51 (0.95-2.38)	1.73 (1.06-2.83)
Cardiac mortality	52/674		
Low strain	9/160	1.00	1.00
Active	13/217	1.08 (0.46-2.53)	1.35 (0.54-3.38)
Passive	12/145	1.49 (0.63-3.55)	1.65 (0.64-4.26)
High strain	18/152	2.20 (0.99-4.90)	2.81 (1.16-6.82)
Total mortality	96/674		
Low strain	23/160	1.00	1.00
Active	24/217	0.77 (0.44-1.36)	0.81 (0.44-1.50)
Passive	20/145	0.96 (0.53-1.74)	1.00 (0.52-1.90)
High strain	29/152	1.38 (0.80-2.39)	1.65 (0.91-2.98)

HR = hazard ratio, CI = confidence interval, AMI = acute myocardial infarction.

*Base model includes age, sex, education, occupational class, managerial status, overtime work, shiftwork, household work and the interaction term between household work and age.

To investigate whether the association between job strain and recurrent events was modified when removing the exposure due to retirement, we conducted analyses when censoring at age 65, i.e. the official age of retirement in Sweden. We found similar results in these analyses for the association between job strain and two outcomes; the HR (95% CI) when the groups with high and low job strain were compared were 1.74 (1.03-2.96) for the combination of cardiac death and non-fatal AMI and 1.72 (0.87-3.39) for total mortality. The association between job strain and cardiac mortality became stronger, the HR (95% CI) being 3.46 (1.18-10.10) when comparing the high strain with the low job strain group.

To assess possible effect modifications we performed stratified analysis as well as formal tests for interaction with sex, age (median split at 55 years), education, occupational class, managerial status, shift work, overtime work, marital status, household work, Killip class, chest pain, hypertension and family history of CHD. The effect of job strain on the combined outcome of cardiac death and non-fatal AMI appeared to be stronger in older than in younger patients, the HR (95% CI) when comparing high vs. low job strain being 2.67 (1.34-5.34) and 1.16 (0.57-2.36), respectively. Similarly, the effect of job strain on adverse outcomes was stronger among those with Killip class ≥2 than in those with Killip class of 1; the HR (95% CI) when comparing high vs. low job strain were 5.05 (1.57-16.20) and 1.16 (0.61-2.21), respectively. However, the interactions between these variables and job strain, as indicated by Rothman's synergy indexes, were not significant. There was no indication for an effect modification on the association between job strain and prognosis from the rest of the factors.

When investigating potential mediators we found that the observed association between job strain and the combined endpoint of cardiac death and non-fatal AMI did not alter considerably after adding to the base model glucose, total, HDL and LDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, lipoprotein (a) (Lp (a)), CRP, IL-6, tumor necrosis factor-alfa, fibrinogen, plasminogen activator inhibitor 1, tissue plasminogen activator/plasminogen activator inhibitor complex, von Willebrand factor, alcohol consumption, physical activity, smoking, BMI, difficulties in falling asleep, repeated awakening and difficulties in falling asleep again, tiredness when awakening or tiredness during the day. Adjustment for early morning awakenings resulted in a stronger association between job strain and the outcome variable. The HR (95% CI) for the high vs. low strain group was 2.02 (1.22-3.33).

4.4 THE EFFECT OF THE COMBINED INTERVENTION ON RECURRENT EVENTS (PAPER IV)

4.4.1 Baseline characteristics of the patients in the two study groups

Table 4 presents the main baseline demographic, psychosocial and biomedical characteristics of the control and the intervention group from the HFH study. The mean age at baseline was 62.7 (8.7) years and 61.4 (9.1) years for the control and the intervention group, respectively. As inclusion diagnosis, 73 (57.0%) control and 67 (56.3%) intervention patients had AMI ($p = 0.91$), 43 (33.6%) and 36 (30.3%) patients had CABG ($p = 0.57$), 41 (32%) and 36 (30.3%) had PCI ($p = 0.76$) in the control and intervention group, respectively. The mean scores for vital exhaustion, daily stress behaviour, trait anxiety and anger symptoms were somewhat higher in

the intervention group when compared to the controls. The corresponding p values for these differences were 0.036, 0.063, 0.033 and 0.016, respectively. The baseline level of triglycerides was lower among the intervention compared to control patients (p = 0.046). The use of diuretics was less frequent in the intervention group at the beginning of the study (p = 0.025), a tendency registered also for ACE inhibitors (p = 0.088). The groups were balanced on the rest of the baseline demographic, psychosocial and biomedical characteristics.

4.4.2 Adherence to intervention

Adherence to intervention was generally high. A total of 45 patients (37.8%) participated in all 20 sessions, 50 (42%) in 15-19, 6 (5%) in 5-14 and 6 (5%) in 1-4 sessions. There were 12 (10.1%) patients randomized to the intervention group who never participated in any session at all.

4.4.3 Changes in psychosocial measures

Table 5 shows values of psychosocial measures at all four occasions, i.e. at baseline, at 10 weeks, at 1 year (end of intervention) and at the 1-2 years follow-up. A significant intervention-time interaction was found for vital exhaustion (p = 0.005) and daily stress behaviour (p = 0.012). A similar trend appeared for anger symptoms (p = 0.06). Both groups showed a decrease for these scores over time, somewhat more pronounced in the intervention group. However, as mentioned above, vital exhaustion, daily stress behaviour and anger symptoms scores were higher for the intervention group at baseline, and apart from these baseline differences the scores did not differ according to group assignment at any other time points, i.e. vital exhaustion, daily stress behaviour and anger symptoms in the intervention group never went significantly below that of the control group.

There was no evidence for a difference in change over time and therefore for a potential effect of the intervention concerning any other psychosocial variables, i.e. trait anxiety, availability of social integration, availability of attachment, anger-in, anger-out, anger-discuss, type A-behaviour and hostility.

Table 4. Baseline characteristics of the patients in the HFH study, 6-8 weeks after randomization

Variable	CG (N = 128) N (%)	IG (N = 119) N (%)	P[1] for group differences
Hospital			0.89
Karolinska University	85 (66)	80 (67)	
St Göran	43 (34)	39 (33)	
Inclusion diagnosis			
AMI	73 (57)	67 (56)	0.91
PCI	41 (32)	36 (30)	0.76
CABG	43 (34)	36 (30)	0.57
Education			0.55
Elementary and high school	89 (86)	91 (88)	
University	15 (14)	12 (12)	
Married or cohabitating	51 (49)	52 (51)	0.78
Diabetes mellitus	25 (22)	18 (16)	0.26
Smoking status			0.99
Never	38 (34)	36 (34)	
Former	60 (54)	58 (55)	
Current	13 (12)	12 (11)	
Sedentary lifestyle	27 (27)	23 (22)	0.47
Medication			
ACE inhibitors	30 (26)	19 (17)	0.09
Statins	63 (55)	64 (57)	0.78
Aspirin	97 (85)	102 (91)	0.17
Calcium channel blockers	21 (18)	23 (21)	0.69
Beta blockers	87 (76)	91 (81)	0.37
Diuretics	50 (44)	33 (30)	0.025
Participation in other rehabilitation programs	28 (22)	20 (17)	0.31

	Mean±SD	Mean±SD	
Age (years)	62.7±8.7	61.4±9.1	0.23
Depressive symptoms	10.7±7.1	11.2±6.2	0.66
Vital exhaustion	19.4±9.6	22.7±10.6	0.036
Trait anxiety	40.1±10.5	43.5±11.1	0.033
Availability of social integration	20.5±4.6	21.0±5.2	0.48
Availability of attachment	5.3±1.3	5.4±1.2	0.37
Daily stress behaviour	37.2±9.1	39.5±8.1	0.063
Anger symptoms	4.6±3.3	5.7±3.2	0.016
Anger-in	2.4±1.9	2.7±1.8	0.35
Anger-out	0.5±1.0	0.7±0.9	0.43
Anger discuss	3.0±1.7	3.1±1.7	0.62
Type A behaviour	25.6±4.8	26.2±5.3	0.41
Hostility	6.0±0.9	6.4±1.7	0.12
Maximal exercise capacity (Watts)	92.5±28.6	90.4±26.5	0.63
Left ventricular ejection fraction (%)	50.8±8.7	50.8±9.1	0.99
Total cholesterol (mmol/l)	5.0±1.1	5.1±1.2	0.84
HDL cholesterol (mmol/l)	1.1±0.4	1.1±0.4	0.13
LDL cholesterol (mmol/l)	3.1±1.0	3.2±1.1	0.56
Triglycerides (mmol/l)	2.0±1.0	1.7±1.1	0.046
Lp (a) (g/l)	429±474	392±373	0.52
CRP (g/l)	5.6±8.7	5.2±9.9	0.78
IL-6 (g/l)	4.9±5.7	4.3±4.4	0.44
Systolic blood pressure (mmHg)	137.0±24.2	138.3±24.2	0.69
BMI (kg/m²)	26.5±5.3	25.8±4.2	0.36

[1]Chi-square test and t-test for independent samples for discrete and continuous variables, respectively.

CG = control group, IG = intervention group, AMI = acute myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, ACE = angiotensin-converting enzyme, SD = standard deviation, HDL = high-density lipoprotein, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), CRP = C-reactive protein, IL-6 = interleukin-6, BMI = body-mass index.

Table 5. Vital exhaustion, depressive symptoms, daily stress behaviour and anger symptoms at all time points

Variable	Baseline		10 weeks		1 year		1-2 year follow-up		p for treatment* time
	CG	IG	CG	IG	CG	IG	CG	IG	
Vital exhaustion	19.4	22.7	19.1	19.4	18.0	18.6	16.9	16.5	0.005
SD	9.6	10.6	10.4	10.5	10.4	11.5	11.3	11.1	
N	83	90	83	83	79	89	72	88	
Depressive symptoms	10.7	11.2	10.6	10.3	9.5	9.8	8.9	8.9	0.24
SD	7.1	6.2	7.2	6.4	6.8	6.0	7.3	6.8	
N	82	87	91	89	77	87	81	89	
Daily stress behaviour	37.2	39.5	35.5	37.2	35.9	36.1	35.3	34.0	0.012
SD	9.1	8.1	9.4	8.0	8.5	7.2	8.7	7.8	
N	100	102	93	91	84	89	82	91	
Anger symptoms	4.6	5.7	4.4	4.6	4.4	5.2	3.9	4.0	0.06
SD	3.34	3.2	3.0	2.7	3.3	3.2	2.8	2.9	
N	96	102	101	100	90	91	88	94	

CG = control group, IG = intervention group, SD = standard deviation

4.4.4 Changes in biomedical variables

As shown in table 6, being in the intervention group was associated with a more favourable change both in total and LDL cholesterol and in Lp (a) levels when compared to patients in the control group. P values for intervention-time interactions were 0.01, 0.02 and 0.03, respectively. Other lipids, like HDL cholesterol, apolipoprotein A and B, triglycerides and other measured blood parameters, including cortisol, creatinine, glucose or CRP showed no statistically significant difference in change over time.

The proportion of patients being prescribed beta blockers, statins, ACE inhibitors, aspirin and calcium channel blockers was higher in the intervention compared to the control group at all times after baseline.

4.4.5 Clinical outcomes

Patients in the intervention group during the 6-year period had lower all-cause mortality than controls (Figure 2a). A total of 8 patients died in the intervention group and 23 in the control group. The HR (95% CI) for total mortality when the intervention group was compared with the control group was 0.34 (0.15-0.76) (table 7). Cardiac mortality showed a similar pattern though with less power (Figure 2b). The number of cardiac deaths was 5 in the intervention and 12 in the control group, respectively. The corresponding HR (95% CI) was 0.41 (0.14-1.16). There was no difference between the groups concerning the combined outcome of cardiac death or non-fatal AMI; there were 20 events in the intervention group, and 21 among controls, HR (95% CI): 0.98 (0.53-1.81).

Table 6. Medication and biomedical variables at all time points

Variable	Baseline		10 weeks		1 year		1-2 year follow-up		p for treatment *time
	CG	IG	CG	IG	CG	IG	CG	IG	
Beta blockers (%) N	76.3 87	81.3 91	75.5 83	79.8 87	75.0 81	84.8 89	78.8 67	79.8 75	0.85
Statins (%) N	55.3 63	57.1 64	60.9 67	75.2 82	64.8 70	77.1 81	68.2 58	77.7 73	0.21
ACE inhibitors (%) N	26.3 30	17.0 19	22.7 25	25.7 28	19.4 21	29.5 31	20.0 17	25.5 24	0.005
Aspirin (%) N	85.1 97	91.1 102	88.2 97	92.7 101	84.3 91	91.4 96	85.9 73	85.1 80	0.26
Calcium antagonists (%) N	18.4 21	20.5 23	20.9 23	28.4 31	21.3 23	31.4 33	18.8 16	26.6 25	0.39
Diuretics (%) N	43.9 50	29.5 33	40.0 44	27.5 30	41.7 45	28.6 30	37.6 32	27.7 26	0.61
Total cholesterol (mmol/l) SD N	5.06 1.06 106	5.09 1.20 104	4.89 1.15 106	4.73 1.10 105	5.33 1.40 105	4.69 1.17 102	5.00 0.98 84	4.82 0.84 92	0.01
HDL cholesterol (mmol/l) SD N	1.05 0.40 106	1.13 0.38 104	1.00 0.39 106	1.07 0.33 104	1.05 0.39 105	1.10 0.43 102	1.31 0.38 84	1.43 0.42 92	0.86
LDL cholesterol (mmol/l) SD N	3.10 0.97 106	3.18 1.06 104	2.99 0.92 106	2.88 0.86 104	3.36 1.36 105	2.86 0.92 102	2.70 0.92 84	2.51 0.67 92	0.019

Triglycerides (mmol/l) SD N	2.01 1.02 106	1.72 1.07 104	2.01 1.19 106	1.72 1.03 104	2.04 1.14 105	1.60 0.92 102	2.17 0.84 84	1.94 0.98 92	0.35
Lp (a) (g/l) SD N	429 474 106	392 373 105	405 463 106	411 428 105	380 399 105	307 288 102	-	-	0.034
CRP (g/l) SD N	5.62 8.70 107	5.22 9.86 105	3.81 5.17 107	3.42 5.18 106	4.10 5.44 105	4.04 6.71 102	2.95 2.99 84	4.49 10.07 92	0.41
IL-6 (g/l) SD N	4.85 5.68 106	4.31 4.44 104	3.30 2.67 107	4.56 8.67 104	3.70 3.13 105	3.99 4.90 101	3.74 3.73 84	4.01 4.34 90	0.07
BMI (kg/m²) SD N	26.5 5.3 114	25.8 4.2 110	26.4 4.9 107	26.0 4.2 107	26.5 4.9 103	26.4 4.1 103	27.2 5.5 85	27.1 4.8 94	0.41
Systolic blood pressure (mmHg) SD N	137 24.2 114	138 24.2 111	138 20.1 108	138 23.0 109	138 23.7 103	135 21.4 102	146 24.2 85	142 21.3 94	0.31
Maximal exercise capacity (Watts) SD N	92.5 28.6 92	90.4 26.5 74	-	-	95.4 26.4 90	97.1 29.9 73	-	-	0.17
Sedentary lifestyle (%) N	26.5 27	22.1 23	-	-	30.3 27	16.8 16	-	-	0.17
Current smoking (%) N	11.7 13	11.3 12	-	-	13.5 15	17.0 18	18.9 21	23.4 25	0.42

CG = control group, IG = intervention group, ACE = angiotensin-converting enzyme, SD = standard deviation, HDL = high-density lipoprotein, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), CRP = C-reactive protein, IL-6 = interleukin-6, BMI = body-mass index.

Figure 2. Kaplan-Meier curves of the intervention and control groups comparing a) all-cause and b) cardiac death.

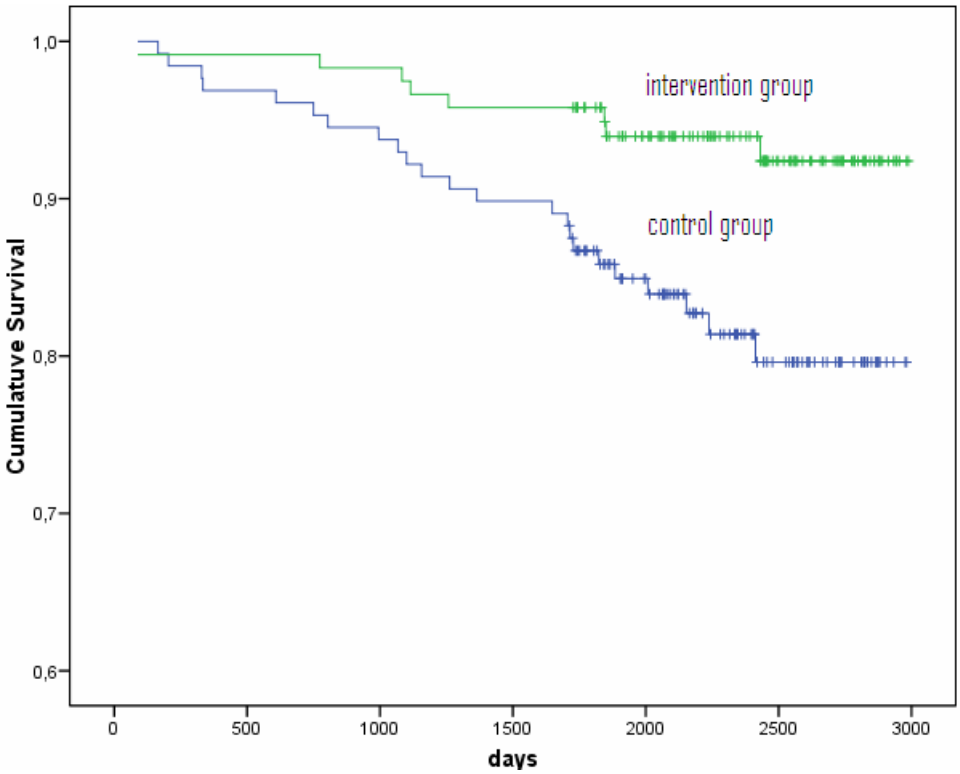


Figure 2 a.

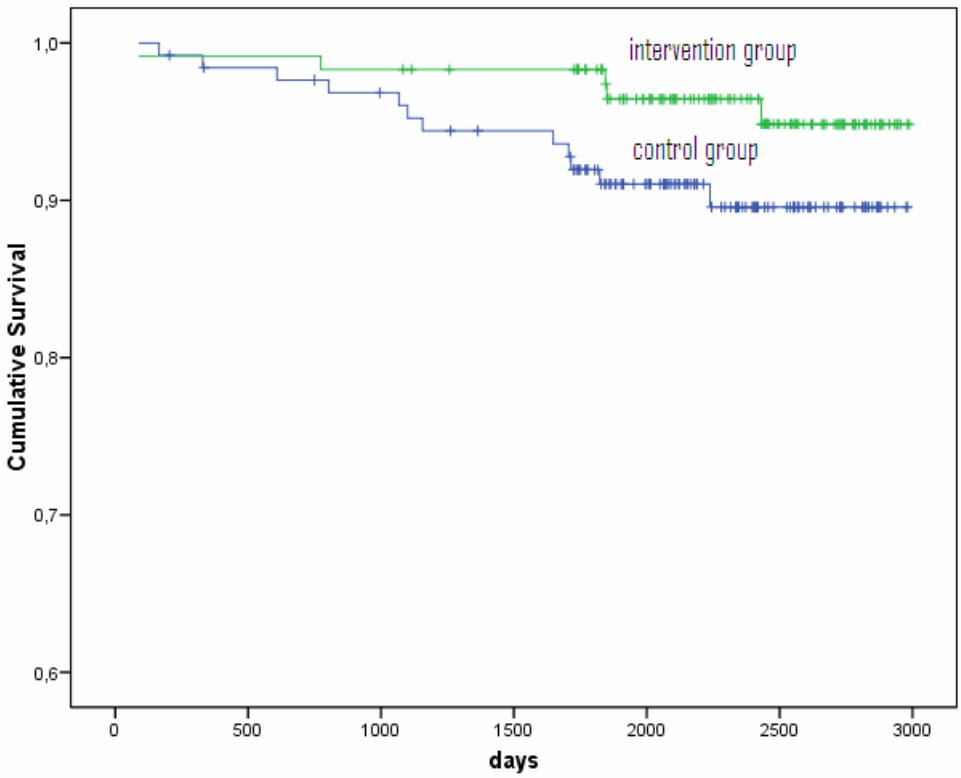


Figure 2 b.

4.4.6 Adjusted and restricted analyses

As shown in table 6, drug therapy differed between the two groups. Thus, one can hypothesize that this difference might explain the observed benefit of being in the intervention group. This could be especially true for statins, beta-blockers, aspirin and ACE inhibitor, which have well-known positive effect on prognosis. These drugs were more frequently prescribed by the cardiologists for patients in the intervention group than for control patients by their doctors. We tested this hypothesis by adjusting for statins, beta blockers, ACE inhibitors and aspirin as time-dependent covariates in the Cox regression analyses. As shown in table 7, adjustment for statins increased the HR for both total and cardiac mortality. The explanatory fraction in terms of change in regression coefficients was 28 and 25% for total and cardiac mortality, respectively, after controlling for statins. Adjustment for other drugs also increased the HR for cardiac mortality.

The difference in mortality might also be reflected by the difference in revascularization procedures after baseline. A total of 21 (17.6%) patients had PCI and 10 (8.4%) had CABG during the 6 year follow-up in the intervention group, the corresponding numbers were 15 (11.7%) and 11 (8.6%) among the controls. However, controlling for revascularisations or censoring patients at the time of their revascularization procedures had very little influence on the results.

We also investigated whether psychosocial characteristics mediate the beneficial effects of being in the intervention group. As shown in table 7, adjustment for vital exhaustion, daily stress behaviour or anger symptoms as time-dependent covariates, i.e. three psychosocial variables which might have been influenced by the intervention, resulted in somewhat increased HR for total and cardiac mortality.

Furthermore, when we restricted our follow-up time from the start of the intervention, we obtained essentially similar results to the primary analyses when we used randomization as a start for follow-up. In another sensitivity analyses, excluding those patients from the intervention group who attended less than 15 sessions did not modify the results considerably.

Table 7. Hazard ratios and 95% confidence intervals for the intervention-outcome relationship, adjusted for potential explanatory factors

Model	HR (95% CI)	
	All-cause mortality	**Cardiac mortality**
Unadjusted model	0.34 (0.15-0.76)	0.41 (0.14-1.16)
Unadjusted model for those with full report on drug data	0.37 (0.15-0.87)	0.42 (0.13-1.37)
Adjusted for statin	0.49 (0.20-1.19)	0.52 (0.16-1.74)
Adjusted for beta blockers	0.36 (0.11-1.16)	0.53 (0.09-3.18)
Adjusted for aspirin	0.35 (0.11-1.13)	0.49 (0.08-2.99)
Adjusted for ACE inhibitors	0.33 (0.10-1.07)	0.47 (0.08-2.84)
Adjusted for diuretics	0.45 (0.18-1.09)	0.57 (0.17-1.89)
Adjusted for revascularization	0.35 (0.16-0.79)	0.42 (0.15-1.18)
Unadjusted model for those with data on vital exhaustion	0.47 (0.19-1.16)	0.54 (0.16-1.85)
Adjusted for vital exhaustion	0.55 (0.22-1.37)	0.71 (0.20-2.50)
Unadjusted model for those with data on daily stress behaviour	0.24 (0.05-1.14)	0.48 (0.15-1.60)
Adjusted for daily stress behaviour	0.46 (0.18-1.13)	0.55 (0.16-1.87)
Unadjusted model for those with data on anger symptoms	0.36 (0.14-0.93)	0.49 (0.15-1.63)
Adjusted for anger symptoms	0.41 (0.16-1.06)	0.58 (0.17-1.96)
Unadjusted model with dropouts being excluded	0.33 (0.14-0.77)	0.39 (0.12-1.25)
Unadjusted model for those who attended more than 15 sessions	0.31 (0.13-0.77)	0.40 (0.13-1.25)
Unadjusted model when the follow-up was restricted to the start of the intervention	0.35 (0.16-0.78)	0.42 (0.15-1.18)

5 DISCUSSION

This thesis aimed to contribute to a better understanding of the role of psychosocial factors in CHD by investigating (1) the relationship of SES, anger expression and work stress with prognosis after a cardiac event, (2) potential explanations for these associations and (3) by analysing whether a combined intervention consisting of a psychosocial rehabilitation and medical treatment from a cardiologist affects psychosocial risk factors and prognosis in women cardiac patients.

The main findings of the thesis are:

- Low income is a risk factor for poor long term prognosis in women patients after a cardiac event and this relationship may be partly explained by smoking, depressive symptomatology and anger symptoms.
- The suppression and the outward expression of angry feelings increase the risk of poor prognosis in women with CHD; inflammatory markers might play a role in the explanation of this relationship.
- Job strain is associated with poor long-term prognosis after a first AMI. This association did not appear to be explained by blood lipids, glucose, inflammatory, haemostatic or lifestyle factors.
- Women patients participating in a 1-year psychosocial intervention program after a CHD event and being treated by a cardiologist during the same period had lower risk of all-cause and cardiac mortality during a 6-year follow-up compared to patients receiving usual care from the health care system. Differences in drug therapy prescribed by cardiologists and general practitioners partly explained the observed beneficial effect of the intervention. Moreover, favourable changes in some psychosocial variables might have also contributed to the explanation of the lower mortality in the intervention group.

5.1 SES, ANGER EXPRESSION, WORK STRESS AND CHD PROGNOSIS

5.1.1 Comparison with previous studies

5.1.1.1 SES and CHD prognosis

In line with previous research investigating socioeconomic differences in CHD (Salomaa et al., 2000; Rao et al., 2004; Alter et al., 2006; Manderbacka et al., 2006; Rasmussen et al., 2006; Georgiades et al., in press), we found that in women cardiac patients low income was associated with a higher risk of total and cardiovascular mortality, as well as with an increased risk for the combination of cardiovascular death and recurrent AMI.

These findings are intriguing given that Sweden is renowned for its social security system and its policies to reduce the gap between the upper and the lower social strata. These policies include tax-free education at all levels, a progressive taxation system, health insurance for everyone, sick leave allowances, unemployment benefits, parental leave and other family allowances (Wamala, 1999). Despite these policies socioeconomic inequalities exist in Sweden as well and have a considerable contribution to disease burden (Ljung, 2006).

5.1.1.2 Anger expression and CHD prognosis

To the best of our knowledge, our study was one of the first ones to investigate the association between the expression of anger and prognosis after a cardiac event in a sufficiently large sample of women cardiac patients. As mentioned in the introduction, it may be hypothesized that the impact of anger on recurrent events might be different in women than in men given that the pattern of the development and of the prognosis of CHD (Vaccarino et al., 1995; Marrugat et al., 1998; Vaccarino et al., 1998; Vaccarino et al., 1999; Rosengren et al., 2001) and the two genders' anger-related behaviour (Haynes et al., 1978; Thomas, 1989; Siegman et al., 2000) are known to differ. Several authors have argued that socialization makes the outward, even aggressive communication of anger, socially more acceptable for men and that women, by comparison, are encouraged to suppress their anger (Haynes et al., 1978; Allcorn, 1994; Harburg et al., 2003; Thomas, 2005).

In line with these assumptions, several studies indicate that anger suppression is associated with poor cardiovascular health in women. The Framingham Heart Study was the first to show that anger-in increases the risk of CHD in initially healthy women (Haynes et al., 1980). Furthermore, compared to its outward expression, anger

suppression in response to anger provoking situations was associated with a higher risk of mortality in women, but not in men participating in the Tecumseh Community Health Study (Harburg et al., 2003). The link between cardiovascular health and anger suppression was confirmed in women by Matthews and associates (1998) as well, who found an increased progression in intima media thickness and higher plaque scores in those reporting high anger-in. The findings of Powell et al. (1993) suggest that indices of suppression of emotions increase the risk of mortality in women CHD patients. Furthermore, the results of Siegman et al. (2000) indicate that subtle, indirect manifestations of antagonism are stronger predictors of CHD risk in women than in men, while overt expressions of anger confer higher risk in men compared to women. However, a recent study involving women with suspected CHD found no association between anger suppression and presence of angiographic CHD (Krantz et al., 2006). In the only study in which female patients were included in a high enough number to allow analysing the effect of anger expression on prognosis following an acute cardiac event among women (Frasure-Smith & Lespérance, 2003) no relationship was found between suppression of anger and long-term prognosis.

The number of studies investigating the effect of the outward expression of anger on CHD in women is more limited. Krantz and his colleagues (2006) showed recently that expressing anger outwardly is associated with the presence of angiographic CHD in women with suspected disease, whereas other studies involving initially healthy (Eaker et al., 1992; Bleil et al., 2004) or CHD patient women (Frasure-Smith & Lespérance, 2003), found no effect of anger-out on cardiovascular health.

Evidence with respect to whether the outward expression of anger (Kawachi et al., 1996; Angerer et al., 2000; McDermott et al., 2001; Bleil et al., 2004), its suppression (Haynes et al., 1980) or both (Gallacher et al., 1999) predict incident CHD in healthy men or prognosis in male CHD patients are not fully consistent either, though most of the studies indicate that anger-out may be more detrimental for men.

These findings regarding the cardiovascular correlates of anger expression in the two genders has led some authors to argue that psychosocial characteristics related to anger and to hostility known to affect in men cardiovascular health may be differentially related to CHD in women (Matthews et al., 1998; Siegman et al., 2000). A tentative explanation for the discrepancy between findings regarding anger-out and CHD from previous investigations and our and Krantz' recent study (Krantz et al., 2006) may be that with the converging of gender roles we are witnessing in modern

societies – probably even more so in Sweden – the way women and men express their anger and therefore the associated risk may also tend to become similar.

5.1.1.3 Work stress and CHD prognosis

As mentioned in the introduction, only four studies investigated the association between work stress and CHD prognosis and they had inconclusive findings. Our results reinforce the results of two of these studies (Theorell et al., 1991; Aboa- Eboulé et al., 2007); both found an increased risk of recurrent events in cardiac patients reporting high job strain. The other two studies in this area did not find evidence for an association between job strain and CHD prognosis over 4 or 5 years (Hlatky et al., 1995; Orth-Gomér et al., 2000). It has been suggested that the null findings in the study of Hlatky et al. (1995) might partly be explained by the selective attrition observed during the follow-up (Belkic et al., 2004); patients with a poor work environment were somewhat more likely to have stopped working at the 1-year follow-up (Mark et al., 1992; Belkic et al., 2004). Thus the association between job strain and recurrent events may have been attenuated by exposure misclassification in patients who ceased to work during the study period (Belkic et al., 2004). In contrast to the other and our investigation, Orth-Gomér et al. (2000) included only women (n = 130) in their study. Beside differences in statistical power, the different gender composition of the samples may possibly contribute to the explanation of the discrepant findings between the study of Orth-Gomér and associates (2000) and our study, both based on data from Swedish cardiac patients. A recent meta-analysis of population-based prospective studies suggests that work stress may have a more deleterious effect in terms of CHD in men than in women (Kivimäki et al., 2006). Whether this applies to prognosis after a cardiac event as well needs to be further investigated.

5.1.2 Potential explanations for the link between the investigated psychosocial factors and CHD prognosis

As mentioned in the introduction, two major hypotheses have been formulated to provide explanations for the way chronic psychosocial stress may lead to incident CHD or to poor prognosis in cardiac patients. The first hypothesis involves a direct pathway; it proposes that through the deregulation of the autonomic nervous system and of the hypothalamus-pituitary-adrenal axis, psychosocial stress may induce cardiovascular, metabolic, inflammatory and haemostatic changes which increase the risk of cardiac events (Brunner, 2001). The second hypothesis states that stress affects cardiovascular

health indirectly, through the modification of health behaviours such as smoking, diet, physical activity and alcohol consumption. Besides analysing the association of SES, anger expression and work stress with CHD prognosis, in papers I-III we also addressed the question whether biological and lifestyle factors contribute to the explanation of these relationships.

5.1.2.1 Explanations for the socioeconomic gradient in CHD prognosis

5.1.2.1.1 The "social causation" hypothesis as potential explanation

Studies conducted in both initially healthy and in CHD patient populations have documented an association between low SES and poor health behaviour (Pocock et al., 1987; Jacobsen & Thelle, 1988; Rosengren et al., 1988; Matthews et al., 1989; Engström et al., 2000; Strand & Tverdal, 2004; Mayer et al., 2004), psychosocial stress (Matthews et al., 1989; Brummett et al., 2001; Kristenson et al., 2001; Eaker et al., 2004; Cheok et al., 2003; Thurston et al., 2006) and biological risk factors for CHD, including hypertension (Colhoun et al., 1998), poor lipid profile (Jacobsen & Thelle, 1988; Rosengren et al., 1988; Engström et al., 2000), inflammatory (Jousilahti et al., 2003; Lubbock et al., 2005; Gemes et al., 2008) and haemostatic factors (Wilson et al., 1993; Wamala et al., 1999). Due to their relation to socioeconomic measures, on the one hand, and to CHD on the other, the above factors may be regarded as potential mediators of the relationship between socioeconomic position and CHD. However, despite this theoretical background, only a limited number of studies have tested whether these characteristics really contribute to the explanation of the socioeconomic differences in cardiovascular morbidity and mortality in initially healthy samples (Rose & Marmot, 1981; Marmot et al., 1984; Pocock et al., 1987; Lynch et al., 1996; Marmot et al., 1997a; Suadicani et al., 1997; Woodward et al., 2003) or in CHD patients.

Previously only two studies, the Beta Blocker Heart Attack Trial (Ickovics et al., 1997) and the Social inclusion through Employment Support for Adults with Mental Illness Study (Alter et al., 2006), have examined systematically potential mediators for the socioeconomic differences in CHD prognosis. These two studies were, however, conducted on either mixed or male samples, therefore paid less or no attention to women patients. Women's socioeconomic position (Arber, 1997), cardiovascular risk factors (Marrugat et al., 1998), the pattern of the development and prognosis of CHD (Vaccarino et al., 1995; Marrugat et al., 1998; Vaccarino et al., 1998; Vaccarino et al., 1999; Rosengren et al., 2001) differ from that of men; consequently, explanatory

factors of the socioeconomic differential in prognosis in CHD might, as well, be different for the two genders.

In the HFH study, we were able to investigate a wide range of lifestyle, psychosocial, metabolic and inflammatory factors as potential explanations for the socioeconomic gradient in recurrent events in women cardiac patients. We found that smoking, depressive symptomatology and anger symptoms modestly contributed to the explanation of the socioeconomic differences in CHD prognosis. However, as both income and the psychosocial factors were assessed at the same time point, caution is needed when interpreting them as mediators of the SES-prognosis relationship. It may be argued that psychosocial factors such as a long history of depression, anxiety, ineffective ways of coping with anger and hostility could eventually lead to lower income. However, several authors reason that by differential exposure to environmental challenges, e.g. financial strain, insecure employment, low control over life, stressful life events, low self-esteem (Brunner et al., 1997) and by differences in protective resources, socioeconomic factors are more likely to influence the development and maintenance of social and psychological characteristics than vice versa (Lynch & Kaplan, 2000; Kristenson et al., 2004). Chandola and colleagues (2003) estimated simultaneously the relative importance of the health selection and the social causation hypothesis in explaining socioeconomic inequalities in mental health. The authors found that there was little evidence for the health selection hypothesis relative to the social causation hypothesis in explaining the observed social gradients in mental health (Chandola et al., 2003).

5.1.2.1.2 Differences in treatment as potential explanations for the social gradient in recurrent events

Differences in access to medical care among socioeconomic strata have also been suggested to contribute to class differences in survival. However, this explanation is not likely in Sweden where the healthcare system is universal. Nevertheless, studies conducted in both countries with and without universal health care indicate that relative to their needs, cardiac patients with low socioeconomic position are less frequently offered revascularization procedures, adequate drug therapy and rehabilitation programs compared to their better situated counterparts (Rathore et al., 2000; Alter et al., 2004; Rao et al., 2004). However, we did not find differences in inclusion diagnosis, medication or participation in cardiac rehabilitation among women with different SES, nor was there evidence that these factors contributed to the explanation

of the relationship between income and recurrent events. These results are in agreement with those of a recent Swedish study which found no socioeconomic differences in cardiac revascularization procedures in women patients with CHD (Haglund et al., 2004).

5.1.2.1.3 Health selection as a potential explanation of our findings

As mentioned in the introduction, beside the "social causation" hypothesis, the "health selection" hypothesis is also a suggested explanation for socioeconomic inequalities in health. Although direct health selection, i.e. the outcome measure determining income at baseline was not possible in our study, we can not exclude that previous health condition influenced both income and prognosis. To address the possibility that those experiencing earlier a cardiac event would be more likely not to be able to work and thereby have a lower income (Goldman, 2001), we included previous hospitalizations due to CHD in our multivariate analyses, but found no evidence for confounding from this factor. Furthermore, during the period when our study was conducted the amount of sick allowance in Sweden represented 90% of the previous salary; therefore a sick leave period due to previous CHD was not likely to cause considerable income reduction, thus health selection is not likely to be an important explanation of the association between income and recurrent events observed in our study.

5.1.2.2 Explanations for the link between anger and CHD prognosis

So far, knowledge regarding explanations for the link between anger or its expression and prognosis in CHD is rather limited. Proposed physiological linking mechanisms involve the excessive and prolonged activation of the stress systems, resulting in increased heart rate (Gabbay et al., 1996), blood pressure (Player et al., 2007) and inflammation (Suarez, 2003) and in metabolic disturbances (Rutledge et al., 2001; Siegman et al., 2002; Raikkonen et al., 2004). These alterations may contribute to the atherosclerotic process and increase the risk of cardiac events (Kop, 1999). Lifestyle factors such as smoking (Rutledge et al., 2001), alcohol consumption (Thomas & Donnellan, 1991) and BMI (Thomas & Donnellan, 1991; Rutledge et al., 2001) have also been suggested to play a role in the anger-CHD relationship.

Acute stress, including anger, increases hemodynamic shear stress and may activate platelets in CHD patients (Strike et al., 2006). Recalling anger has been shown to produce coronary vasoconstriction in previously narrowed coronary arteries in cardiac patients (Boltwood et al., 1993) and consequently decreases blood supply to the heart.

These may induce myocardial ischemia (Ironson et al., 1992; Gabbay et al., 1996) and arrhythmias (Eaker et al., 2004), cause plaque rupture, thrombus formation and vessel occlusion (Kop, 1999). This hypothesis is supported by findings from two case-crossover studies showing that episodes of anger may increase, in the subsequent 1 or 2 hours, the risk of an AMI (Mittleman et al., 1995; Möller et al., 1999).

In our study, we included several cardiovascular risk factors hypothesized to contribute to the explanation of the association between anger expression and CHD, i.e. lipids, inflammatory markers, glucose and cortisol. Our results suggested that pro-inflammatory markers partly mediate the relationship between anger expression and prognosis in women cardiac patients.

5.1.2.3 Pathways between work stress and prognosis in CHD

A proposed mechanism for the association between job stress and cardiac events involves alterations in the cardiovascular, metabolic, haemostatic and immune functioning as a result of the prolonged activation of the stress systems (Kuper et al., 2005; Kivimäki et al., 2006).

There is evidence showing that experiencing high stress at the job may induce ambulatory blood pressure surges of clinically important magnitude (Belkic et al., 2004). These elevations in blood pressure are greatest at work, but are also evident at home and during sleep (Belkic et al., 2004). Short term and sustained increases in blood pressure accelerate atherosclerosis and increase the risk of AMI (McEwen, 1998a). Reduced heart rate variability has also been suggested to be associated both with chronic work stress (Hintsanen et al., 2007) and with poor prognosis in cardiac patients (Janszky et al., 2004). Recent results from the Swedish Onset Study nested in the SHEEP provide support for the hypothesis that acute work-related stressors may trigger AMIs. Möller and associates (2005) found an increased risk of AMI soon after situations of increased workload, competition or conflict at work.

Some, though not all studies documented a relationship between exposure to high work stress and metabolic disturbances related to cortisol dysfunction, such as high levels of fasting glucose (Chandola et al., 2008), poor lipid profile (Siegrist et al., 1997; Peter et al., 1998; Westerlund et al., 2004; Chandola et al., 2008) and the metabolic syndrome (Chandola et al., 2006; Chandola et al., 2008). A few studies have investigated the relation between stress on the job and immune parameters. A Swedish study found increased levels of the IL-6 cytokine in men with low job control and in women with job dissatisfaction (Theorell et al., 2001). A Swiss study also suggested a positive

association between workplace stressors and inflammatory markers such as CRP and tumor necrosis factor-α (Schnorpfeil et al., 2003). Increased blood coagulability is another pathway through which work stress is hypothesized to impact CHD. Several studies have found a relation between stress at work and haemostatic factors (Brunner et al., 1996; Siegrist et al., 1997; Tsutsumi et al., 1999; Kittel et al., 2002; Chang et al., 2002b; Brostedt et al., 2004). Metabolic disturbances, increased inflammation and thrombotic function may further accelerate progression of coronary atherosclerosis and increase the risk of recurrent events (Ridker & Libby, 2005).

Another pathway through which work stress is suggested to influence CHD is related to lifestyle (Kuper et al., 2005; Kivimäki et al., 2006). Analyses from the Whitehall II study provide support for this hypothesis; Chandola and associates (2008) found that the effect of work stress on CHD was partly attributable to its effects on health behaviour. However, a recent review found evidence only for a modest association of work stress with heavy alcohol consumption and obesity, and not consistent evidence for an association with physical activity or smoking (Siegrist & Rödel, 2006). Sleep quality may be another putative explanation for the link between work stress and cardiovascular health. Åkerstedt (2006) concluded in his review that anticipation of high work stress for the next day impairs quality of sleep; poor sleep is known to be associated with adverse cardiac outcomes (Leineweber et al., 2003). Furthermore, it is also plausible that patients who return to a stressful work find it more difficult to adhere to their medical treatment than those with low stress jobs.

Studies investigating the physiological and lifestyle related explanations for the effect of work stress on CHD morbidity and mortality have almost exclusively been conducted in initially healthy samples. In a patient population, Aboa-Éboulé (2007) found evidence for some indication for mediation from dyslipidemia and smoking, but not from hypertension, diabetes mellitus, BMI, alcohol consumption, physical activity, psychosocial distress or low social support for the relation between job stress and recurrent events. In the SHEEP study we were able to analyse a wide range of lifestyle, metabolic, inflammatory and haemostatic factors as potential explanations on the association between job strain and CHD prognosis. Contrary to our hypotheses, we did not find evidence for mediation from any of these factors.

5.2 THE COMBINED INTERVENTION

In paper IV we found that patients allocated to the treatment arm of our intervention had lower risk for long term total and cardiac mortality than controls. The two groups did not differ as regards the 6-year combined outcome of cardiac death and non-fatal AMI. Several factors related to the psychosocial intervention and to the specialty of the physician treating the patients contributed to the explanation of the mortality difference between the two groups.

5.2.1 Effects of the psychosocial intervention

We hypothesized that improving suggested psychosocial risk factors for CHD, i.e. depressive symptoms, vital exhaustion, anxiety, low social support, anger, hostility, type A and daily stress behaviour (Rozanski et al., 1999; Kuper et al., 2005; Claesson et al., 2005) would have a positive impact on long-term prognosis. We found that vital exhaustion, daily stress behaviour and anger symptoms decreased more pronouncedly in the intervention compared to the control arm. However, as intervention patients had higher baseline scores on these characteristics when compared with the control group, and these scores did not differ according to group assignment at later time points we do not know whether the decrease in these factors can be attributed to the intervention or to the regression towards the mean (Koertge et al., 2008; Blom et al., in press). Adjustment for changes in these characteristics attenuated the mortality difference between the groups, suggesting that reduction in these psychosocial factors may have positively affected prognosis in the group taking part in the intervention. There was no evidence for an effect of the therapy on social support (Blom et al., in press), depressive symptoms (Koertge et al., 2008), anxiety, hostility, type A behaviour or ways of anger expression.

As treated analysis from the Women's Heart Trial, which involved a similar psychosocial intervention as that applied in our study, showed a positive effect on vital exhaustion and daily stress behaviour (Claesson et al., 2005). However, this improvement did not affect intermediate biomedical targets related to CHD (Claesson et al., 2006). In women, vital exhaustion was reduced by the psychosocial intervention from the Exhaustion Intervention Trial (Appels et al., 2006). However, there was no evidence that it decreased the risk of a new coronary event within 2 years (Appels et al., 2005).

We observed a borderline significant treatment × time interaction for anger symptoms during the period between baseline and the 1-2 year follow-up. This change seems to have had some impact on 6-year survival (table 7). Other anger-related characteristics, i.e. the tendency to internalize anger, the propensity to express it outwardly and the likelihood of relieving it by talking with someone did not differ between the groups during the study period. One recent study evaluating a CBT-based psychosocial intervention found a significant reduction in trait anger in men who had undergone a CABG (Bishop et al., 2005). Due to the small sample size (n = 58) it did not evaluate the effect of this reduction on subsequent cardiac events.

It is possible that the intervention form the present study did not succeed in alleviating depressive symptoms because most patients were not sufficiently depressed to begin with (Koertge et al., 2008). The ENRICHD study including only depressed post-AMI patients, found that depression can be reduced by means of CBT, although not as much as expected, or to have an impact on subsequent event-free survival (Berkman et al., 2003). One recent study which screened for major depressive disorder and which targeted post-AMI depression by means of interpersonal psychotherapy and/or citalopram found no evidence of added value of this intervention over clinical management, but documented the efficacy of citalopram administered in conjunction with weekly clinical management (Lespérance et al., 2007).

The lack of effect of our psychosocial intervention on type A behaviour and its hostility component are surprising given that daily stress behaviour and symptoms of anger decreased more pronouncedly in the intervention than in the control group and that these constructs are highly correlated (Öhman et al., 1992). Furthermore, our program was a broadened adaptation for women's needs of the intervention employed in the Recurrent Coronary Prevention Project Study, which documented a significant improvement in post-AMI survival as a consequence of reduction in type A behaviour (Friedman et al., 1986). Differences in assessment of this characteristic across the two studies and gender differences in Type A behaviour may have contributed to differences in the findings (Miller et al., 1991; Öhman et al., 1992; Karlberg et al., 1998).

Trait anxiety and social support (Blom et al., in press) did not change significantly during our study period. Previous results of psychosocial interventions aiming to reduce anxiety or to improve social support in women have been mixed, some studies documented beneficial effects of psychosocial rehabilitations (Toobert et al., 1998;

Appels et al., 2005), while others suggested limited or no effect (Frasure-Smith et al., 1997; Schneiderman et al., 2004).

5.2.2 Therapy by the cardiologist

Since the intervention group received medical care from cardiologists after baseline examination and at least during the 1-year intervention, while patients in the control group were usually referred to general practitioners soon after the cardiac event, several factors related to the specialty of the treating physician may have contributed to the mortality differences between the groups (Go et al., 2000).

One likely and important explanation is that patients treated by cardiologists were more often prescribed medications known to improve survival after a CHD event, i.e. statins, beta blockers and ACE inhibitors (Ayanian et al., 1994; Jollis et al., 1996; Ayanian et al., 1997; Ayanian et al., 2002a; Abubakar et al., 2004). Adjustment for these medications reduced the survival benefit of the intervention compared to the control group.

Differences in undergoing invasive coronary procedures is another major factor which has been previously suggested to partly explain the survival advantage of being treated by a cardiologist compared to a general practitioner (Jollis et al., 1996; Ayanian et al., 1997; Frances et al., 1999; Ayanian et al., 2002b). Although there were no differences between the groups in the frequency of new CABG, a higher percentage of women in the intervention arm underwent a new PCI during the 6-year follow-up compared to those in the control group. However, when we censored for CABG and PCI or controlled for revascularization in our statistical models, the higher mortality risk of those in the control group was not reduced considerably.

Furthermore, as the therapists in the psychosocial intervention were nurses with cardiovascular training, it is plausible that their informal discussions with women in the intervention group increased patients' compliance with drug therapy – in addition to the meetings with the cardiologist – and made patients more aware of symptoms of the disease. This could have well contributed to the difference in prognosis between the groups.

It is also plausible that medical treatment, especially beta blockade, affected daily stress behaviour, anger symptoms or vital exhaustion – a construct comprising of several somatic symptoms of CHD (Appels et al., 1987) – thus contributing to the differences

in changes between the control and the intervention group concerning these psychological measures.

5.3 LIMITATIONS

5.3.1 General limitations

First, since only women were included in the HFH study, no conclusions regarding male survivors of CHD can be drawn from papers I, II and IV. However, since women have been underrepresented in cardiovascular research, studies conducted among women cardiac patients have a good potential to add to this area of research.

Second, we included in the HFH study only patients who survived at least 6-8 weeks after hospitalization for a cardiac event. In our analyses from the SHEEP study we had only patients who survived the first 28 days after hospitalization for AMI. These limit the generalisability of our findings only to patients who are in a stable phase after their cardiac event.

Third, except for age and in-hospital diagnoses, we could not compare women who did or did not want to participate in our intervention. It may be speculated that women who refused to participate in our study may have done so because they had a more severe disease and/or worse risk profile, thus finding it more demanding to participate in a 1-year intervention. This again limits the generalisability of our findings. However, enrolling primarily patients who are healthier and otherwise more advantaged is a potential limitation of most randomized controlled trials (McKee et al., 1999; Sorensen et al., 2006).

Fourth, due to the small number of recurrent events occurring during the follow-up of the HFH study participants, the number of confounders we could adjust for in the base model in papers I and II was limited. However, we performed several alternative base models and found no indication for residual confounding.

5.3.2 Specific limitations

5.3.2.1 Paper I

Using income as an indicator of socioeconomic position has the disadvantage of being subject to reverse causation, i.e. health status may affect levels of income. However, as already presented, we found no evidence for confounding from previous hospitalizations due to CHD. Similarly, as personal income and psychological factors were measured at the same point in time, it is not possible to determine the causal

relationship between these factors. However, Lynch and Kaplan (2000) and Kristenson and colleagues (2004) argue that by differences in exposure to environmental challenges and in protective resources, socioeconomic factors are more likely to influence the development and maintenance of social and psychological characteristics than the other way round. This hypothesis is supported by a study conducted by Chandola and colleagues (2003), in which the authors estimated simultaneously the relative effect of health on changes in social position and of social position on changes in health. Little evidence was found for the health selection hypothesis relative to the social causation hypothesis for explaining the observed social gradients in mental and physical health (Chandola et al., 2003).

Despite its drawbacks, income is a useful measure of SES because it relates directly to the material conditions that may influence health (Lynch & Kaplan, 2000); it provides means in purchasing health care, better nutrition, housing, schooling and recreation (Adler & Newman, 2002). It was suggested to be a better indicator of SES in adulthood and old age than education or occupational class because education is more reflective of adolescence and young adulthood SES, while occupational class can be applied only for working individuals (Lynch & Kaplan, 2000).

Similarly, it may be argued that the socioeconomic position of the partner or household income may be a better indicator for women's SES than their personal income. However, we believe that in Sweden, where the majority of women and almost the same proportion as men (80% of women and 86% of men) are gainfully employed (Statistics Sweden, 2006), personal income is a good measure for women's social position. These advantages of the personal income as an indicator of SES may explain eventually why personal and not household income or education were predictive of recurrent events in this sample of women CHD patients.

5.3.2.2 Paper III

First, as work stress was measured only at baseline and referred to work before the AMI, we do not know how long study participants had been exposed to the assessed levels of job strain. It is plausible that some of the patients with a severe disease and also a high level of work stress would change their jobs for less stressful ones or for early retirement. However, this differential misclassification of exposure is likely to result in an underestimation of the strength of the associations observed in our study. Furthermore, given that the age in our sample ranged between 45 and 65 years, several of the study participants must have retired during the follow-up and thus changed their

exposure status. This non-differential exposure misclassification is also likely to result in an underestimation of the observed effects. When we censored patients at age 65, the official age of retirement in Sweden, we found that the associations between job strain and the outcomes were similar or stronger compared to those observed in our primary analyses.

Second, severity of disease or previous morbidity could have influenced perceptions of job strain and thus lead to an overestimation of the associations between working in a stressful environment and prognosis (Kivimäki et al., 2006). However, when adjusting for Killip classification, hypertension, diabetes, history of chest pain and stroke, we found essentially the same results.

5.3.2.3 Paper IV

First, though we controlled for several factors which may be responsible for differences in prognosis in patients treated by cardiologists and general practitioners – i.e. medication, revascularization procedures – we were not able to consider several other factors which may have mediated the intervention-mortality relationship, e.g. experience in dealing with CHD patients (Casale et al., 1998; Nash et al., 1999) or differences in compliance between patients being treated by cardiologists and general practitioners.

Second, we investigated whether a potential decrease in psychosocial risk factors for CHD affects prognosis. However, patients were included consecutively and they were not screened for severity of these characteristics prior to enrolment. Thus, there were patients with low levels of these risk factors, for whom these psychosocial characteristics could not be reduced considerably.

5.4 CONCLUSIONS

The findings of this thesis suggest that low income, the suppression and the outward expression of anger, and job strain are associated with poor prognosis after a cardiac event. Our combined intervention consisting of a psychosocial rehabilitation and medical therapy by a cardiologist reduced the risk of all-cause and cardiac mortality during a 6-year follow-up compared to usual care from a generalist. Differences in drug therapy prescribed by cardiologists and general practitioners partly explained the observed beneficial effect of the intervention. Moreover, favourable changes in some

psychosocial variables might have also contributed to the explanation of the lower mortality in the intervention group.

Future research needs to confirm our findings regarding the prognostic role of anger expression and job strain in CHD and to further investigate the pathways through which psychosocial factors may influence CHD. Studies may evaluate whether screening for severity of psychosocial risk factors should be part of the inclusion procedure in randomized trials evaluating the effectiveness of psychosocial interventions.

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