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Cardiac Rehabilitation in Women

by

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**Karolinska
Institutet**

Stockholm 2012

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Published and printed by Larserics digital print
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ISBN: 978-91-7457-625-2

To

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ABSTRACT

The overall aim of this thesis has been to investigate the prognostic value of exercise capacity and whether a multifactorial rehabilitation program could affect traditional cardiac risk factors as well as self-rated health, quality of life, depression, anxiety, hospital utilization and sickness absenteeism in women younger than 66 years with coronary artery disease (CAD).

Study I

Evaluation of the role of exercise capacity and how physical capacity, leisure time and physical activity influence long term all-cause and cardiovascular mortality. A follow-up nine years after the coronary event showed that sedentary lifestyle, low physical fitness, inadequate blood pressure and heart rate response during exercise test were independent predictors for all-cause mortality as well as cardiovascular mortality.

Study II

To evaluate whether a five-year long randomized controlled trial (RCT) rehabilitation program for women <66 years with CAD had effect on the use of hospital care (official data) and self-reported sick leave. After 5 years the intervention group had reduced their visits at emergency wards significantly more than the control group. There were no differences in sick leave rates between the groups.

Study III

In the same RCT population as in study II, exercise capacity and psychosocial factors were measured yearly during five years. Exercise capacity remained unchanged during the five years and no differences between the intervention and control group was found. Additionally, no differences between the groups were seen in psychosocial factors, however, several of these factors were improved in both groups. In a 10-14 years follow-up questionnaire both groups reported improved quality of life compared with baseline, but not compared with five years. A better trust in future quality of life was seen in the intervention group compared to controls. Depressive symptoms were equally decreased in both groups while symptoms of anxiety were unchanged.

Study IV

Occurrence of baseline depressive symptoms and its relation to angina pectoris (AP) in the women included in study II were investigated. Moderate to severe depression (BDI >19) were strongly correlated to established AP ($p < 0.01$) and higher rates of anxiety, indicating that anxiety is a noteworthy symptom in depressed CAD women. Depressed women were also more likely to have a family history of heart disease and were less likely to care about their future health.

SAMMANFATTNING

Det övergripande syftet med denna avhandling har varit att undersöka det prognostiska värdet av fysisk arbetsförmåga och hur ett långsiktigt rehabiliteringsprogram kan påverka fysisk kapacitet, sjukskrivning, sjukhusvård, livskvalitet, depression, ångest och kardiella riskfaktorer hos kvinnor yngre än 66 år med kranskärslssjukdom (CAD).

Studie I

Utvärdering av betydelsen av fysisk kapacitet (konditionen) och hur graden av motion påverkar överlevnad hos kvinnor med hjärt-kärlsjukdom. Inaktiv livsstil och låg arbetsförmåga gav sämre prognos för överlevnad.

Studie II

Utvärdering av hur ett fem år långt rehabiliteringsprogram för kvinnor yngre än 66 år med kranskärslssjukdom påverkat graden av akut sjukhusvård och sjukfrånvaro jämfört med en kontrollgrupp. Efter 5 år hade interventionsgruppen lägre grad av akut sjukhusvård än kontrollgruppen. Det fanns ingen skillnad i sjukskrivningsgrad mellan grupperna.

Studie III

I denna studie undersöktes huruvida rehabiliteringsprogrammet som genomfördes i studie II hade effekter på fysisk kapacitet, hjärtsymtom och psykosociala faktorer årligen under 5 år. Arbetskapaciteten förblev oförändrad och inga skillnader mellan interventions- och kontrollgrupp hittades. De första fem åren sågs ingen skillnad mellan grupperna avseende psykosociala faktorer.

10-14 år efter studiestart skickades en förkortad version av tidigare enkät ut. Interventionsgruppen skattade sin framtida livskvalitet högre jämfört med kontrollgruppen. Depressiva symtom minskade i samma grad i båda grupperna.

Studie IV

Sambandet mellan depressiva symtom och kärlkramp studerades hos de kvinnor som inick i studie II. Måttlig till svår depression hade ett starkt samband med graden av kärlkramp och ångest. Deprimerade kvinnor var mindre benägna att bry sig om sin framtida hälsa samt hade högre grad av ärftlig belastning för hjärt-kärlsjukdom.

LIST OF ORIGINAL PAPERS

This doctoral thesis is based on the following papers, which will be referred to in the text by Roman numerals. The papers are appended in the end of the thesis.

I

Faris Al-Khalili, I Janszky, **A Andersson**, B Swane and K. Schenck- Gustafsson.

Physical activity and exercise performance predict long-term prognosis in middle-aged women surviving acute coronary syndrome. *Journal of Internal Medicine* (2007) 261:178-187

II

Agneta Andersson, Kristina Lindwall Sundel, Anna-Lena Undén, Karin Schenck- Gustafsson and Ingeborg Eriksson.

A five-year rehabilitation programme for younger women after a coronary event reduces the need for hospital care. *Scandinavian Journal of Public Health* (2010) 38:566-573

III

Agneta Andersson, Ingeborg Eriksson and Karin Schenck-Gustafsson.

Creating a sustainable rehabilitation programme for women with coronary artery disease. In manuscript

IV

Kristina Lindwall Sundel, Rigmor Stain-Malmgren, **Agneta Andersson**, Anna Åberg-Wistedt and Karin Schenck-Gustafsson.

High frequency of Anxiety and Angina Pectoris in Depressed Women with Coronary Heart Disease. *Gender Medicine* (2007) 4:146-156

ABBREVIATIONS

ACS	Acute Coronary Syndrome
ACE	Angiotensin-converting Enzyme Inhibitors
AP	Angina Pectoris
Apo A1	Apolipoprotein A1
Apo B1	Apolipoprotein B1
BMI	Body Mass Index
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
BDI	Becks Depression Inventory
BAI	Becks Anxiety Inventory
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CBT	Cognitive Behavior Therapy
CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
CR	Cardiac Rehabilitation
DM	Diabetes Mellitus
ECG	Electrocardiogram
EU	European Union
ET	Exercise Test
GNP	Gross National Product
HAD	Hospital Anxiety, Depression scale
HDL	High Density Lipoprotein
HR	Heart Rate
HT	Hormone Therapy
ICD	International Classification of Diseases
LDL	Low Density Lipoprotein
PCI	Percutaneous Coronary Intervention
QoL	Quality of Life
RPP	Rate Pressure Product
SBP	Systolic Blood Pressure
SD	Standard Deviation
SRH	Self Rated Health
TG	Triglycerides
UAP	Unstable Angina Pectoris
WHR	Waist to Hip circumference Ratio

INTRODUCTION

Epidemiology

Cardiovascular disease (CVD) including coronary artery disease (CAD), ischemic heart disease (IHD) and stroke, is the most common cause of death for both women and men in the Western world. Psychosocial factors are associated with increased risk for myocardial infarction (MI) (Rosengren, Hawken et al. 2004). The risk factors for MI are shared by women and men but might have different impact (Lundberg 2000). In women CAD is manifested 9-20 years later (Flavell 1994; Moore 1996; Graves and Miller 2003). Women have still some disadvantages compared with men in time to diagnose, treatment, medication, prognosis and cardiac rehabilitation (Mosca, Appel et al. 2004; Stramba-Badiale, Fox et al. 2006; Graham, Atar et al. 2007).

Risk factors in women

Background

Management of women's health seldom includes CVD prevention, in spite of CVD being the most common cause of death in females. A possible reason may be that CVD has traditionally been perceived as a "man's illness". Since many deaths from CVD can be prevented also in women, it is of utmost importance that there is more general awareness about CVD in women and that cardiac rehabilitation is offered also to women. According to the INTERHEART study (Yusuf, Hawken et al. 2004), nine factors are responsible for 90% of all cases of CVD. These factors are dyslipidemia, hypertension, smoking, stress, diabetes, obesity (especially abdominal fat distribution), physical inactivity, poor diet with insufficient fruit and vegetable intake and degree of alcohol consumption. CVD presents 10 years later in women, who are therefore older and more likely to suffer from comorbidities such as diabetes and hypertension. The difference in age at CVD onset is largely explained by higher levels of risk factors at younger ages in men compared with women (Yusuf, Hawken et al. 2004; Anand, Islam et al. 2008).

Premature menopause, gestational diabetes, gestational hypertension, pre-eclampsia, complications at birth, polycystic ovarian syndrome are suggested to be special female risk factors for future CVD (Shaw, Bairey Merz et al. 2008; Drost, Maas et al. 2010; Vujovic, Brincat et al. 2010).

The protective role of female sex hormones on cardiovascular disease has been debated for decades and publications arising from large prospective, randomized controlled trials (RCT) at the beginning of this millennium reduced prescriptions of systemic menopausal hormone therapy (HT) (Hulley, Grady et al. 1998). Today, most cardiologists tend to discontinue HT as soon as a woman has had a cardiac event, irrespective of the indications such as early menopause or control of severe climacteric symptoms. Various types of HT have different actions on the cardiovascular system, lipid metabolism and coagulation factors. A comprehensive risk-benefit evaluation should be performed for each woman on HT (Schenck-Gustafsson, Brincat et al. 2011).

In Europe, the SCORE system (Conroy, Pyorala et al. 2003) is used to evaluate CVD risk. However, this system only goes up to the age of 65 years and will thus miss many women. While guidelines are based on traditional risk factors, cardiac events do not necessarily occur in women with these risk factors. The same risk factors for both sexes have been used in risk calculations for the last 40 years in spite of increasing knowledge about gender differences.

Lipids

In women, as well as in men, the association between total cholesterol and LDL-cholesterol with increased cardiac risk is beyond dispute, as are the benefits of its reduction in high-risk individuals. The follow-up study by the Lipid Research Clinic demonstrated that low HDL-C was the most significant predictor of death from IHD in women, after being adjusted for age (Jacobs, Mebane et al. 1990). Recent publications support the fact that there is no evidence for lipid lowering treatment in healthy women or men without known risk factors. In patients with known risk factors or established CVD, the evidence shows treatment benefits in both genders (Walsh and Pignone 2004; Baigent, Blackwell et al. 2010; Reiner, Catapano et al. 2011).

The Swedish National Guidelines (2008) propose a total cholesterol target of less than 5 mmol/L for primary prevention and less than 4.5 mmol/L for secondary prevention. Low HDL levels have been found in epidemiological studies to have a greater impact in women than in men, but intervention studies independently focused on HDL are difficult to design (Legato 2000). However, there are some ongoing clinical trials with drugs which increase HDL. Most recent guidelines recommend treatment for those with concentrations below 1 mmol/L. An increase of 1% in HDL is associated with 3-5% decrease in CVD risk in women, but only 2% in men. In women, hypertriglyceridemia is an independent risk factor for CVD, while among men this remains an ongoing debate. A change of lifestyle including weight reduction and increased physical activity is recommended (Baigent, Blackwell et al. 2010).

In the two major secondary prevention trials involving significant enough numbers of women, lipid-lowering therapy benefited women to an even greater extent than men (Baigent, Landray et al. 2011; Kostis, Moreyra et al. 2011). In the simvastatin arm of the MRC/BHF Heart Protection Study (2002), there was a significant reduction in all-cause mortality and a 24% reduction in vascular events, women had the same benefits as men. All other statin studies have calculated the risk for women post hoc as a subgroup analysis, and the results should be interpreted cautiously (Aulakh and Anand 2007). Other agents include nicotinic acid, ezetimibe and fibric acid derivatives (gemfibrozil and fenofibrate); however, gender-specific outcomes with these agents have not been reported.

Hypertension

A meta-analysis of prospective data collected from over 1 million adults (40-69 years) has shown that a 20 mmHg systolic or a 10 mmHg diastolic increase in blood pressure (BP) doubles the mortality from CVD (Lewington, Clarke et al. 2002). A three-fold increase in CVD and stroke is found in women with a systolic BP >185mmHg as compared with women with systolic BP <135mmHg. Van der Giezen recommends BP <140/90mmHg in all hypertensive patients and <130/80mmHg in diabetics or other groups with high cardiovascular risk, a target agreed upon by most national societies (van der Giezen, Schopman-Geurts van Kessel et al. 1990). The treatment of hypertension is currently the same for both genders

with, in most cases, pharmacotherapy along with lifestyle changes. The first-line drugs are angiotensin-converting enzyme ACE inhibitors (or, if not tolerated, angiotensin-receptor blockers, ARBs), diuretics and calcium-channel blockers. When the response is inadequate, other medications like beta-receptor blockers can be employed. Women report more cough with ACE inhibitors and peripheral edema with calcium-channel blockers.

Smoking

That smoking predisposes atherosclerosis and major cardiovascular events also in women is indisputable (Doll, Peto et al. 2004; Huxley and Woodward 2011). In the Nurses Health Study, including over 120 000 healthy nurses, four to five cigarettes a day almost doubled the risk and 20 cigarettes a day increased the risk six times (Sarna, Bialous et al. 2008). The reduction of smoking has been a worldwide public health achievement; however, the number of smoking women (initially lower than men) has not declined to the same extent as smoking men. This is particularly true for younger women, leading to significant vascular problems in later life. The INTERHEART study (Yusuf, Hawken et al. 2004) estimated that 29% of heart attack cases in Western Europe are due to smoking; and smokers and former smokers are at almost twice the risk of a heart attack compared with non-smokers (Rosengren, Hawken et al. 2004). Women have more difficulties to stop smoking, one of the reasons could concern weight gain. Cigarette smoking decreases the endogenous levels of estrogen in women, and increases the risk of premature menopause, which in itself is a predisposing factor for CVD.

The adverse effect of smoking is related to the amount and duration of the abuse and smoking induces more powerful cardiovascular effects in women than in men. One possible reason is that the dimensions of the heart and lung are smaller in women, and therefore the same amount of smoking might be more harmful to female than to male organs (Njolstad, Arnesen et al. 1996; Woodward, Lam et al. 2005). In smoking patient's comorbidities like diabetes and hypertension will accelerate the atherosclerotic process.

Diabetes

Cardiovascular events are the leading cause of death especially in type II diabetes, and diabetic women have a 3 to 5-fold increased risk of developing CVD compared with men (Garcia, McNamara et al. 1974).

The INTERHEART study estimated that 15% of the heart attacks in Western Europe are due to diagnosed diabetes (Rosengren, Hawken et al. 2004). The corresponding figure in Central and Eastern Europe is 9%. In the Nurses' Health Study, CHD mortality in women with diabetes was 8.7 times higher than in non-diabetics, and in addition, those who had a known history of CHD had a relative risk of 25.8 for fatal coronary artery disease (Hu, Stampfer et al. 2001). In the Copenhagen City Heart Study including 7198 women over a 20-year period, the relative risk of a new myocardial infarction among diabetics was 1.5-4.5 compared with non-diabetics (Almdal, Scharling et al. 2004). In addition, diabetic women develop CVD earlier and at the same ages as men compared to non-diabetic women. According to a recent study, diabetic women below 65 years of age have poorer outcomes than diabetic men after myocardial infarction, and this relates probably to an increased risk factor burden (Norhammar, Stenestrand et al. 2008). The frequency and severity of atherosclerotic disease in diabetes have led to several recent guidelines to assign the condition as a coronary heart disease equivalent, justifying aggressive intervention.

Obesity

Overweight and obesity together with physical inactivity contribute to 15% of all deaths (Yusuf, Hawken et al. 2004). The relation between body size and body weight is expressed in body-mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. BMI >25 is regarded as overweight and a BMI of >30 as obesity. Obesity is often correlated to impaired insulin sensitivity and impaired endothelial function. Abdominal obesity is a risk factor for impaired glucose intolerance, diabetes and myocardial infarction. The risk for metabolic diseases is increased with a waist circumference of greater than 80 cm in women and 94 cm in men. Much evidence has focused on the distribution of fat with a more android morphology (apple) representing a higher cardiac risk than a more gynaecoid (pear) shape (Yarnell, Patterson et al. 2001). Visceral fatty tissue is playing a central role in lipid and glucose metabolism.

One of the outcomes noted in the Nurses' Health Study was that there is a gradient of coronary risk, with the heaviest category of women having a 3-fold increased risk for CVD compared with lean women (Manson, Willett et al. 1995).

Exercise and physical activity

In a prospective observational study, it was found that a lower level of fitness was associated with a 4.7-fold increased risk of myocardial infarction and stroke, independent of other vascular risk factors (Blair, Kohl et al. 1989). The reported beneficial effects of exercise on CVD risk profile are less marked in women than in men, with smaller increases in HDL and weight loss resulting from similar exercise training (Bush, Fried et al. 1988). Nevertheless, in the Nurses' Health Study, two aspects were particularly important: brisk walking conferred the same benefit as vigorous exercise, and sedentary women who became active late in life had similar benefits as those who were active throughout their life span (Manson, Hu et al. 1999). The recommended level of physical activity is a minimum of 30 min brisk walking daily (Mosca, Banka et al. 2007).

Stress

Psychosocial factors have been shown to account for approximately 30% of the attributable risk of AMI (Rosengren, Hawken et al. 2004). Stress at work as well as at home were more common among the patients with MI than in the controls in this study. Several psychosocial interventions have been shown to have beneficial effects on distress and physiological risk factors (Linden, Stossel et al. 1996; Blumenthal, Sherwood et al. 2005).

Depression and anxiety are both aspects of psychosocial stress and are independent risk factors both in women and men. Women with CAD, compared with men, have more problems with anxiety and depression, both before and after a myocardial infarction (Frasure-Smith, Lesperance et al. 1999; Graves and Miller 2003). Consequently, depression is considered to be a more important risk factor for women compared with men (Naqvi, Naqvi et al. 2005; Doering, McKinley et al. 2011). Therefore, rehabilitation programs aiming at reducing psychosocial stress may be especially effective in female CAD patients. Stress management in cardiac rehabilitation has recently been reviewed (Rees, Bennett et al. 2004; Linden, Phillips et al. 2007), but it is still not properly evaluated for women. Nevertheless, there are several dimensions within the broader definition of psychosocial factors that are now associated with an increased risk of myocardial infarction in women. For example, family

stress including marital stress has been shown to increase the risk of ischemic heart disease (Orth-Gomer, Wamala et al. 2000).

Consequently, patients with myocardial infarction should be screened for depression during hospital stay (Lisspers, Nygren et al. 1997). The validated version of Hospital Anxiety Depression scale (HAD) (Zigmond and Snaith 1983) is useful to detect anxiety and depression in cardiac patients and also a tool to follow up intervention therapies. The treatment of post-MI depression is recommended to include both selective serotonin reuptake inhibitors (SSRIs) and Cognitive behavioral therapy (CBT).

The ENRICHD (Enhancing Recovery in Coronary Heart Disease) study, a RCT study, included CBT for CAD patients with emphasis on depression and social isolation. The main findings in this study were modestly decreased depression and increased social support in the therapy group when compared to the controls (Berkman, Blumenthal et al. 2003).

Low social-economic status is associated with CAD in both women and men and seems to be linked to unhealthy lifestyle patterns such as smoking, higher consumptions of sugar and saturated fat as well as increased stress in some reports (Brezinka 1995; Wamala, Murray et al. 1999).

It is also reported that women have frequent symptoms such as sleep disturbance, fatigue, and shortness of breath as signs of psychosocial stress (McSweeney, Cody et al. 2003). In both sexes, stress can not only induce, but also worsen CVD, by increasing atherosclerosis and pro-coagulation. It can cause negative inflammatory response and endothelial dysfunction as well as micro-macro vascular dysfunction.

Alcohol

While a moderate intake of alcohol may be protective, too much is deleterious for both women and men (Gunzerath, Faden et al. 2004; Fagrell 2006). Moderate intake of alcohol may also have some protective effect in women against the development of atheromatosis, measured with QCA- technique in connection with coronary angiography (Janszky, Mukamal et al. 2004).

However, the protective effect of alcohol has a low grade of evidence because of the obvious risks in undertaking RCT studies. In addition, the control group may include former alcoholics who are now teetotalers. The type of alcohol is not as important as drinking pattern. A low-to-moderate regular daily intake can be protective, while excessive drinking can be harmful to the heart and the liver. Recommendations are difficult but there is no reason to ask people to stop moderate drinking after a myocardial infarction. Conversely, it is not necessary to recommend people to start drinking in order to prevent CVD or further MI if they do not wish to. Light to-moderate alcohol intake is defined as one standard glass daily for women and two for men, as women metabolize alcohol more slowly than men. A standard glass is defined as 12 g alcohol, which is equivalent to 15 cl of wine (www.socialstyrelsen.se).

Diet

The beneficial effects of the Mediterranean diet, which includes high proportions of fruit and vegetables, on total cholesterol, LDL cholesterol, blood pressure and MI are well

known (Knoops, de Groot et al. 2004). In the secondary prevention study, “Lyon Heart”, 600 women and men were randomized to the Mediterranean diet or to a control group, after 27 months significant differences were found in mortality and morbidity, for CVD as well as total mortality in favor of the Mediterranean diet (de Lorgeril, Renaud et al. 1994). The mechanisms behind these beneficial effects are multiple, and diet should always be combined with other lifestyle changes, such as exercise as well as medication when necessary.

Guidelines and inclusion of women in trials

American Heart Association (AHA) has produced special guidelines (Mosca 2007; Mosca, Benjamin et al. 2011) for prevention of CVD in women. In 2006, the European Society of Cardiology wrote a policy document (Stramba-Badiale, Fox et al. 2006) pointing out the importance of sex and gender analysis in CVD. This resulted in a meta-analysis (Stramba-Badiale 2010) of all scientifically accurate articles published about CVD and its treatment between 2006 and 2010. The main message was that there were too few women included in most of the clinical trials in relation to the prevalence of the disease (ischemic heart disease, heart failure, diabetes mellitus, atrial fibrillation, stroke, dyslipidemias, and anticoagulant therapy) and there were gender analysis of the results in only 50% of the articles.

In a systematic review of CR trials, few of the patients enrolled were women (Limacher 1998) and a Cochrane review of CR reported that 11% of the patients enrolled were women (Jolliffe, Rees et al. 2001).

Cardiac rehabilitation in women

The general goals of cardiac rehabilitation (CR) are to restore physical and physiological well-being. Life-style changes include smoking cessation, physical activity at least 30min walking/day, weight-loss if overweight, normal lipid levels and normal blood pressure. An early diagnosis of diabetes mellitus is essential. The best way to diagnose diabetes and pre-diabetes is to perform an oral glucose tolerance test (B-glucose 2h after an oral intake of 1.75 grams glucose per kilograms body weight (normal <7.8 mmol/L)) (Bartnik, Malmberg et al. 2004).

There is good evidence that patients after myocardial infarction should maintain treatment with aspirin, beta-blockers, statins and also ACE-inhibitors. All these medications have a recommendation class 1 and Evidence level A. Levels of evidence A are data derived from multiple randomized clinical trials or meta analyses.

Non-adherence to evidence based treatment after acute coronary syndrome will increase all cause mortality and readmissions. Thus, an important goal of cardiac rehabilitation is also to give the patients good knowledge and motivation in order to be compliant with their medications. Cardiac rehabilitation is a class 1 recommendation in most current clinical practice guidelines. However, according to a recent review (Braverman 2011), cardiac rehabilitation are vastly underused.

CR was originally developed in the 1970's with special regard to the needs of middle-aged men to promote return to work post-myocardial infarction (Limacher 1998). Despite the preponderance of evidence on the numerous benefits of traditional CR, it remains largely under-utilized in women. Studies of the effectiveness of CR have generally revealed no major differences between women and men (Lavie and Milani 1995). However, female-specific data are lacking on the effect of CR on mortality and morbidity (Sanderson and Bittner 2005). The reason for no reduction in cardiovascular death rates in women could be the limited number and size of existing studies. There are also a limited number of studies of women's outcome post-CR that have been positive (Oldridge, LaSalle et al. 1980; Winberg and Fridlund 2002; Grace, Grewal et al. 2008; Sanderson, Shewchuk et al. 2010). Unfortunately, this literature suffers from low sample sizes, and lack of randomization and control groups.

In a study from United States and Canada (Grace, Abbey et al. 2002) only approximately 15-30% of eligible patients participated in CR, with the rate for women being much lower, approximately 11-20% (Jackson, Leclerc et al. 2005). It has also been shown that the percentage of women in CR is 20% lower than what would be expected based on coronary morbidity data (Schuster and Waldron 1991; Radley, Grove et al. 1998).

It is well-established that women are less likely to adhere to CR than men, the degree and pattern of women's CR adherence remains incompletely understood. The reasons why women are missing from CR programs are multifactorial and include health care system as well as provider and patient-level factors (Sanderson, Shewchuk et al. 2010).

As the traditional model of CR care is a hospital-based mixed-gender program, women are in the minority in such programs. Women also report perceiving these programs as male-oriented and failing to meet their care preferences (Moore 1996). Women report being the only woman in a group of men, most of whom younger than themselves. The programs are sometimes being perceived as a "men's club" (Radley, Grove et al. 1998). It has also been suggested that women may find a CR program more appealing if there is a more pronounced psychological emphasis like stress modification, than is currently the case (Dafoe and Huston 1997). Thus, women may be less likely to participate in CR if they do not perceive that the programs meet their needs (Daly, Sindone et al. 2002). Probably women may benefit from alternative and novel CR approaches (Bjarnason-Wehrens, Grande et al. 2007) although this contention should be further studied.

There is some evidence that it is more important for women than for men to share experiences and with other women in the same situation in the rehabilitation situation (Davidson, Daly et al. 2003). Traditional programs tend to not focus enough on psychological and social consequences of a coronary event. In gender-mixed groups women tend to hold in their own feelings (Burell and Granlund 2002). Women are more likely to take care of others, like children and parents, and neglect their own health. These factors might contribute to the observed low attendance among women in cardiac rehabilitation programmes.

Sick leave

Diagnostics and treatment of CAD have improved markedly in Sweden since the 1960's and the knowledge about impacts of risk factors has increased the engagement of both primary and secondary prevention. This has led to a decreased morbidity and mortality (more in men),

as well as fewer patients at working ages having heart failure-related dysfunction and that Swedish people are older when contracting CAD. In 2004, Perk et al reviewed the current knowledge of patients returning to work after CVD (Perk and Alexanderson 2004). The authors concluded: “The duration of sick leave due to CVD in Sweden is longer than in other countries, although there is no scientific evidence to support this practice”.

In spite of these facts, no major effects were seen in the frequency of sick leave up to 2007. The impact of the recommendations from 2007 (Swedish National Board of Health and Welfare), concerning the length of sick leave has recently been evaluated. A total decrease of about 10% for women and 6% for men in all areas was reported 2011 (www.forsakringskassan.se), but in CVD, the changes were not so pronounced.

In the report from the Swedish National Board of Health and Welfare, the effect on sick leave after different forms of CR was investigated. No major effects of different types of CR were found.

In a Swedish RCT study (Hedback, Perk et al. 1992), a post CABG population with 3 months physical training program in combination with a home training program no effects on sick leave duration was reported. Another Swedish study (Lisspers, Hofman-Bang et al. 1999), reported no effects on return to work after a special residential CR program, in patients having had a PCI, in spite of a proven positive effect on risk factors. PCI-patients had shorter sick leave periods immediately after the intervention compared to CABG-patients but in the long-term there was no difference.

Which are the predisposing factors for medically unmotivated sick leave time and why do Swedish patients have longer sick leave periods than other comparable countries? In the sick leave research the severity of the disease including complications had a moderate impact on the duration of sick leave. Psychosocial factors including depression, anxiety and poor self-confidence negatively influenced return to work after myocardial infarction. (Maeland and Havik 1986; Maeland and Havik 1987) The patients own perception for the disease was an obstacle for returning to work (Petrie, Weinman et al. 1996).

Also demographic and social predictors might play a role. The acuteness of the disease and the waiting time of an intervention might also be important. Recently Lynoe et al, reported that positive encounters with health care personnel including feelings of respect facilitated self-estimated ability to return to work (Lynoe, Wessel et al. 2011).

AIMS OF THE THESIS

The overall objective of this research work has been to study women's risk factors for coronary artery disease and to create and evaluate a cardiac rehabilitation program.

Study I

To evaluate the importance of exercise testing parameters and leisure time physical activity in predicting long-term prognosis in women ≤ 65 years, hospitalized for acute coronary syndrome.

Study II

The aim of this paper was to evaluate whether a five-year long rehabilitation program for women ≤ 65 years with coronary artery disease affected the use of hospital care and sickness absenteeism.

Study III

The aims of this study was to follow the women in the rehabilitation program (study II), regarding exercise tests and different aspects of health and quality of life. These factors, except for exercise tests, were followed up 10-14 years after study onset.

Study IV

The purpose of this study was to investigate the relation between depressive symptoms and angina in the women included in study II.

MATERIAL AND METHODS

Study populations

Study I

In a community based study (Stockholm Female Coronary Risk Study), all females aged <66 years that resided in the greater Stockholm area and were hospitalized for an acute coronary event between 1991 and 1994 were asked to participate. Inclusion was based on medical records indicating AMI, based on the WHO criteria of chest pain, enzyme patterns and/or diagnostic ECG changes. The ECG changes were based on the Minnesota code. 335 women were admitted. Unstable angina pectoris (UAP) was defined as new onset of angina pectoris or deterioration of known stable angina pectoris during the last 4 weeks before admission.

Study II, III and IV

The subjects in studies II, III and IV were women below 66 years of age, which fulfilled the inclusion criteria: AMI, ACS, PCI, CABG and who were elected by referring clinicians, or rehabilitation teams, from all hospitals in Stockholm county council. Exclusion criteria were non-swedish speaking, having heart failure, unstable angina pectoris or other disabling diseases including drug abuse. Inclusion started in April 1997 and ended in October 2000.

Study designs and methods

Study I

A clinical screening was carried out 1-6 months after hospitalization. The screening included coronary angiography, exercise test and routine blood sampling including fasting lipids. 292 patients joined the study and were able to attend the screening. Exercise tests were performed in 273 patients. Coronary angiograms were performed in 238 patients.

The following CVD risks were assessed: smoking status (current, previous, or non smoker), clinical history of diabetes mellitus and hypertension. Blood pressure, height, weight and BMI were measured. Hypertension was defined as a history of systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg measured twice after supine rest. Menopausal status was defined as the absence of menstrual bleeding for at least 6 months. Females who had started HT were regarded as postmenopausal. Coronary angiography was performed according to the Judkins technique. Two independent viewers categorized left ventricular function as normal or dysfunctional.

Exercise tests were performed on an electrically braked bicycle (Megacart 840; Siemens Elema, Solna, Sweden) until fatigue or other limiting symptoms were reached. The starting load was on 30 watt. The work load was increased by 10 watt every minute. A continuously single-averaged 12-lead was recorded before and ten minutes after exercise. Cuff brachial artery systolic was recorded at rest and at the end of each work load every minute up to ten minutes after exercise. Anginal chest pain, leg fatigue and a feeling of general exhaustion were graded at the end of each workload using the 10-graded Borg scale (Astrom and

Jonsson 1976; Borg, Holmgren et al. 1981). Exercise-induced ST depression ≥ 1 mm at a time of 60 milliseconds after the J point in at least two consecutive ECG leads, were defined as pathological.

Physical activity (during leisure) was assessed by the patients with a questionnaire based on the WHO criteria (Baecke, Burema et al. 1982). The leisure time activities were graded into four categories that were dichotomized into “physically inactive” (sedentary lifestyle) or “physically active”.

I= Reading, watching television or other sedentary leisure activities

II= Walking, cycling or other forms of physical activity

III= Exercise to keep fit, heavy gardening, etc. for at least 4 h a week

IV= Hard training or participating in competitive sports regularly several times a week

1= Physically inactive included the above I

2= Physically active included the above II-IV

Study II and III

Baseline examinations included medical history, medication, angina pectoris (Canadian class I-IV) (Sangareddi, Chockalingam et al. 2004) (assessment of risk factors for CAD, exercise test and questionnaires (adopted from a similar rehabilitation study (Lisspers, Hofman-Bang et al. 1999)). Fasting routine blood samples including lipids were collected. The baseline examinations were performed before randomization and repeated once a year for the following five years.

The questionnaire covered socio-demographic factors, medical, psychosocial and psychological factors, bodily symptoms, sick leave and disability pension. All scales were previously scientifically validated.

The scale used were Quality of Life (“Ladder of life”) (Cantril 1965), SRH (Eriksson, Uden et al. 2001), BDI (Beck, Ward et al. 1961), BAI (Beck, Epstein et al. 1988), HAD (Zigmond and Snaith 1983; Lisspers, Nygren et al. 1997), The Gothenburg Quality of Life Inventory (Tibblin, Tibblin et al. 1990; Tibblin, Svardsudd et al. 1993), and Job decision latitude (Karasek, Baker et al. 1981).

For study II: The participant’s use of hospital-based health care during the studied period was followed via a register from the Swedish National Board of Health and Welfare. Only hospital visits due to CAD-related diagnosis were documented. Both scheduled and emergency visits at hospitals were included, and yearly numbers of in-patient days were calculated for each year.

For study III: In 2011, 10-14 years after study onset, a simplified questionnaire, based on the one used originally, was sent to the participants. The questionnaire included Quality of life (Cantril 1965), HAD (Zigmond and Snaith 1983; Lisspers, Nygren et al. 1997), SRH (Eriksson, Uden et al. 2001) and physical symptoms. The patients also reported if any new cardiac event had occurred since they left the program and current medication.

Intervention program

The intervention program was group-based and included 6-10 women in each group. The premises were at Saltsjöbaden's Hospital in the Stockholm archipelago.

The program duration was five years. The first rehabilitation course endured for 2 weeks and was followed by five additional days, two months later. Thereafter, the courses were held twice a year for two days, each occasion. All interventions were residential.

The aims of intervention were to identify stress factors such as depression, anxiety and vital exhaustion. Furthermore, the aims were to inform about medication, cardiac symptoms and to differentiate cardiac- from other bodily and psychosomatic symptoms. This included in-depth interviews by a psychologist in order to identify individual problems and needs. Patients perceived as depressed were offered consultation with a psychiatrist associated to the project. The program also contained different types of physical activity in order to promote a healthier life style.

Psychological reactions were discussed and handled both on group- and on individual level during the five years. The psychosocial part of the rehabilitation was based on an interactive, self-instructional program called "Stress as an opportunity" (Moser and Björkegren 1998) that includes manuscript for the group leader and a patient orientated book to prevent stress, (self assessments concerning different causes of stress, homework assignments, cassette tape with relaxation practices and tools to create an individual action plan). The follow-up sessions had specific themes, e.g. burnout symptoms, type A behaviour, assertiveness, coping strategies and self-efficacy. The aim was to identify negative thoughts and replace them with more effective coping strategies. The program has previously been used and evaluated in work-settings (Orth-Gomer, Eriksson et al. 1994; Theorell T, Moser V et al. 1995).

Study IV

BDI is a 21 item questionnaire, often used to classify the severity of depression (Beck, Ward et al. 1961). Each item is scored from 0-3 (0= none to 3= severe) with a total range from 0-63. The questionnaire include the following symptoms: pessimistic mood, sense of failure, lack of satisfaction, feelings of guilt, self-hate, self-accusations, suicidality, crying spells, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigue, loss of appetite, weight loss, somatic preoccupation and loss of libido. BDI-scores ≥ 19 are regarded as mild to severe depression.

Degree of anxiety was measured with the 21-item BAI (Beck, Epstein et al. 1988). The items, scored from 0=none to 3=severe, describes the following common symptoms of anxiety: numbness or tingling, feeling hot, wobbliness in the legs, inability to relax, fear of the worst thing happening, dizziness, heart pounding or racing, unsteadiness, feeling terrified, nervousness, choking feeling, trembling hands, shakiness, fear of losing control, difficulty breathing, fear of dying, indigestion or discomfort in the abdomen, flushed face and sweating.

Sociodemographic factors, anxiety rate, history of heart disease, hereditary cardiovascular disease, prescribed medication, biochemical variables, risk factors for CAD, lifestyle habits,

and attitudes to lifestyle changes, were compared in women with a BDI score ≥ 19 versus those with a BDI score < 19 .

Assessment of lifestyle: To measure lifestyle habits and attitudes toward lifestyle changes, a number of questions were used that examined aspects of self-rated health, belief in the importance of taking care of one's health, now and in the future, current lifestyle and attitude to lifestyle changes. The scales had been previously used in a Swedish rehabilitation program for patients with coronary artery disease (Lisspers, Hofman-Bang et al. 1999).

Blood chemistry: A hospital research nurse obtained fasting morning blood samples through an indwelling catheter. Venous blood was drawn into Vacutainer tubes to obtain serum. Total serum cholesterol and triglycerides were determined with Ektachem dry chemistry (Johnsson & Johnsson, New Brunswick, New Jersey). HDL was determined with enzymatic methods using reagents (Boehringer Mannheim GmbH, Mannheim, Germany). LDL was calculated with the Friedewald formula. S-apolipoprotein A1 (Apo A1), S-apolipoprotein B (Apo B) and S-lipoprotein (a) were determined with immunephelometry using reagents (Beckman Coulter, Inc., Fullerton, California).

Statistical methods

Study I

Comparisons of continuous variables amongst different groups were made by using Mann-Whitney U Test. Chi² test was used to compare categorical data. Cox proportional hazard model was used to compare categorical data and to assess the relative importance of exercise parameters in predicting mortality. Univariate analyses were performed first. Each exercise parameter was entered separately as a continuous variable. Hazard ratios (HR) with confidence intervals were computed for each decrease in standard deviation.

Exercise test variables and sedentary lifestyle were also tested using Cox model, after adjustment for the potential confounders; age, BMI, coronary index event, left ventricular function, history of DM, smoking, serum cholesterol and use of beta-blockers.

Statistical analyses were performed using SPSS 11.5 (SPSS Inc., LEAD Technologies, Haddonfield, NJ, USA) and SAS 8.02 (SAS Institute Inc., Cary, NC, USA).

Study II

Differences between the intervention group and the control group were for continuous variables tested with t-test and for categorical variables with chi². As data of emergency and scheduled hospital visits, as well as in-patient days were strongly skewed (a large portion had zero visits), tests were also made with dichotomized variables: visits-no visits. Result from these test are only presented in text. To test difference in proportion of women on sick leave, with early retirement and with employment chi² were used.

Statistical analyses were performed using SPSS 11.5 (SPSS Inc., LEAD Technologies, Haddonfield, NJ, USA) and SAS 8.02 (SAS Institute Inc., Cary, NC, USA) and Statistica 7 for Windows (StatSoft, Inc., Tulsa, Oklahoma).

Study III

As data were found to have skewed distributions, non parametric methods (Mann-Whitney U-test) were used to test the group differences and changes during the intervention period. Statistical analyses were performed with Statistica 10 for Windows (StatSoft, Inc., Tulsa, Oklahoma).

Study IV

Several variables were found to have skewed distribution; a non parametric Mann-Whitney U-test was used when comparing groups. However, BDI and BAI items were analysed using parametric models such as analysis of variances (ANOVA) and multiple regression. Categorical variables were tested with χ^2 . All statistical analyses were performed with StatSoft Statistica 7 for Windows (StatSoft, Inc., Tulsa, Oklahoma).

Ethical considerations

The protocols and procedures were approved by the local committees for human research at Karolinska Hospital Ethics Committee, No 97-102 (Study I), 1997 00-093 (Study II, III, IV), 2011/465-32 (Study III).

RESULTS

Study I

In 292 female patients <66 years surviving CAD, important independent predictors of long-term, all-cause mortality were studied. Left ventricular dysfunction, sedentary lifestyle, history of diabetes and hypertension were significantly more frequent amongst non-survivor (Table 1). Moreover, non-survivors had higher levels of triglycerides and total cholesterol. Sedentary lifestyle during leisure time was independently predictive of all-cause and cardiovascular mortality.

Table 1. Clinical characteristics of the study population

	All patients n (%)	Survivors n (%) ^c	Non-survivors n (%) ^c	P-value ^a
Diagnosis at index event				
AMI	110 (37)	90 (82)	20 (18)	0.08
UAP	182 (63)	162 (89)	20 (11)	
Menopausal status				
Premenopausal	74 (25)	67 (90.5)	7 (9.5)	0.35
Postmenopausal with HRT	36 (12)	32 (89)	4 (11)	
Postmenopausal without HRT	182 (63)	153 (84)	29 (16)	
Cigarette smoking				
Non smokers	92 (32)	80 (87)	12 (13)	0.91
Previous smokers	140 (48)	121 (48.4)	19 (48.3)	
Current smokers	58 (20)	49 (19.6)	9 (22.5)	
Left ventricular dysfunction	30 (15)	19 (56)	11 (32)	<0.001
Sedentary lifestyle	70 (24)	55 (79)	15 (21)	0.04
Use of β -blockers	197 (66)	171 (87)	26 (13)	0.50
History of hypertension	144 (50)	129 (90)	15 (10)	0.02
History of diabetes mellitus	33 (11)	24 (73)	9 (27)	0.002
Coronary stenosis $\geq 50\%$ ^d	150 (63)	130 (87)	20 (13)	0.66
	Mean (SD)	Mean (SD)	Mean (SD)	P-value ^b
Age (years)	56.7 (7)	55.7 (7.0)	57.7 (7.0)	0.06
BMI	26.9 (5)	27.1 (4.5)	26.6 (4.8)	0.43
Waist-hip ratio	0.84 (0.08)	0.84 (0.08)	0.85 (0.07)	0.48
Systolic blood pressure (mmHg)	123 (21)	121 (16)	125 (24)	0.40
Triglycerides (mmol/l)	1.77 (1.8)	1.67 (1.79)	2.42 (1.95)	0.003
Cholesterol (mmol/l)	6.49 (1.2)	6.43 (1.22)	6.87 (1.32)	0.03
HDL (mmol/l)	1.48 (0.4)	1.48 (0.54)	1.47 (0.40)	0.40
LDL (mmol/l)	4.07 (1.4)	4.09 (1.20)	3.91 (1.78)	0.93

^aChi² test, ^bMann-Whitney U test, ^cpercentage of corresponding parameter, ^dpercentage of lumen diameter in major coronary vessel

Study II

Out of 168 referrals, 19 dropped out and 149 were randomized. Further 19 women dropped out after randomization, but before rehabilitation onset. 69 women were allocated to the intervention group and 61 women to the control group (figure 1). The main reasons for declining participation were family- or work-related factors.

The intervention group had higher mean ratings of depression compared with the control group at baseline (table 2 and 3). No other baseline differences between the groups were observed.

According to national registers: women in the intervention group showed yearly decreases of visits to hospital emergency wards (figure 2a). The same trend was observed in the control group up to the fourth year when number of emergency visits had increased. At year five, the intervention group had significantly less number of visits compared with controls ($p < 0.05$). These differences are reflected in number of in-patient days (figure 2c). Scheduled doctor visits (hospital) decreased in both groups over the years (figure 2b).

Self-reported data on sick leave and disability pension showed no significant differences between groups after one, three and five years.

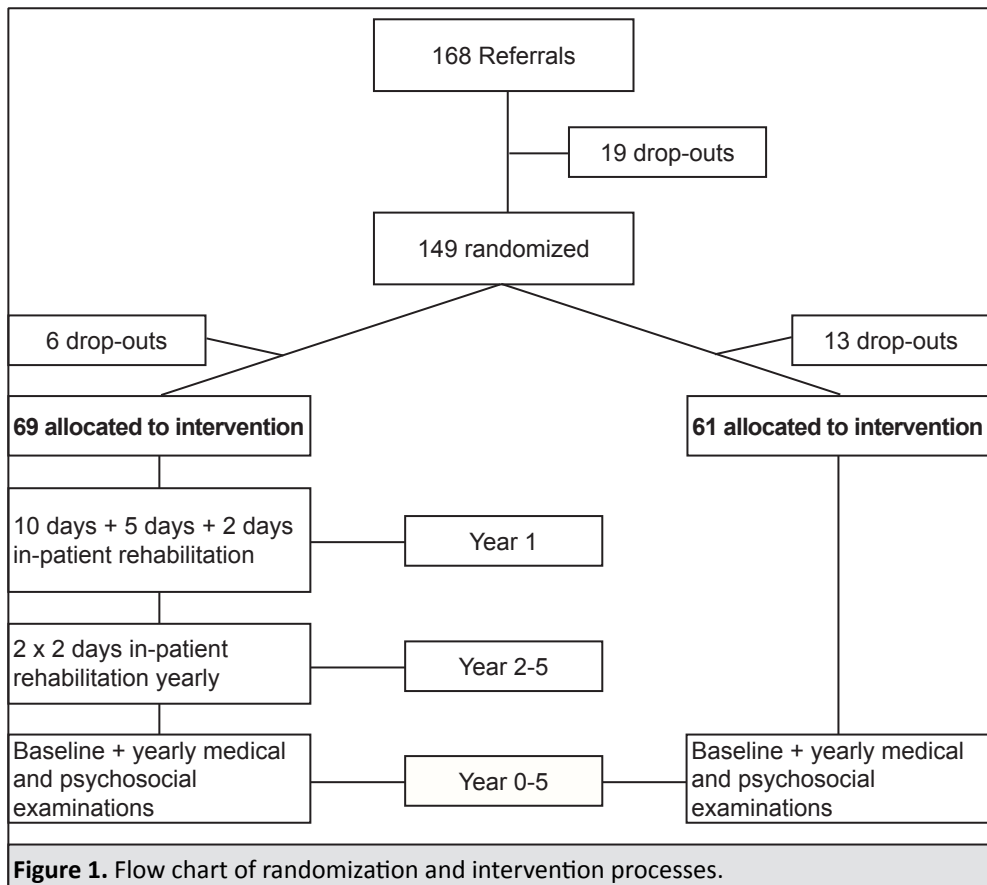


Table 2. Baseline clinical characteristics according to group assignment. Data are presented as no. (%) unless otherwise noted.

	Intervention group (n=69)	Control group (n=61)
Age (yrs), mean (SD)	52.5 (6.2)	54.3 (6.1)
BMI (kg/m ²), mean (SD)	27.6 (5.1)	27.1 (4.5)
Systolic blood pressure (mmHg), mean (SD)	131 (17)	134 (20)
Smoking habits		
-never	21 (30.4)	13 (22.4)
-current	20 (29.0)	14 (24.1)
-previous	28 (40.6)	31 (53.4)
History of AMI	47 (68.1)	39 (62.3)
History of PCI	27 (39.7)	30 (49.2)
History of CABG	12 (17.4)	16 (26.2)
Diabetes mellitus	10 (14.5)	11 (18.0)
Family history of CHD ^a	33 (47.8)	34 (57.6)
Post menopausal ^b	47 (68.1)	44 (72.2)

^aDefined as first degree relative having had MI before the age of 60 yrs.^bDefined as absence of menstrual cycle for ≥12 months before study entry.**Table 3.** Baseline psychosocial and demographic characteristics according to group assignment. Data are presented as no. (%) unless otherwise noted.

	Intervention group (n=69)	Control group (n=58) ^a
Socio economic index (1-5), mean (SD)	3.37 (1.5)	3.24 (1.2)
Education		
-principal/elementary school	18 (26.1)	20 (34.5)
-upper school	19 (27.5)	10 (17.2)
-university/college	32 (46.4)	28 (48.3)
Employment (full- or part time)	54 (78.3)	42 (72.4)
Sickness absence (full- or part time)	45 (65.2)	31 (53.4)
Disability pension (full- or part time)	11 (15.9)	12 (21.1)
Self-rated health (1-5), mean (SD)	3.56 (1.0)	3.55 (0.9)
Quality of life (1-10), mean (SD)	5.12 (2.1)	5.62 (1.9)
Depression (BDI [†] , 0-63), mean (SD)	14.18 (9.3)	10.64 (7.5)

^aThree women in the control group did not fill in the questionnaire.

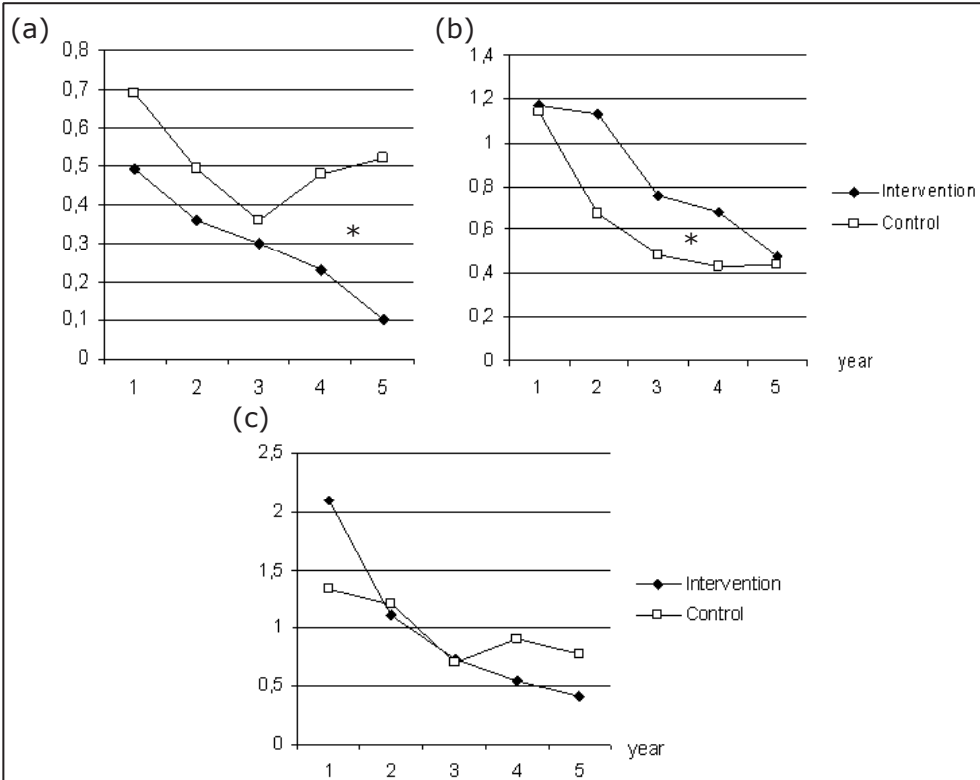


Figure 2. Emergency visits (a), scheduled doctor (b) visits to hospital and number of inpatient days (c) during five years, according to group assignment (means).

* $p < 0.05$

Study III

Out of 168 referrals, 19 dropped out and 149 were randomized. Furthermore, 6 women randomized to intervention and 13 to control group, decided not to participate shortly after randomization. For additional information about participants, see study II and flow chart (figure 1). Mortality and drop out rates are presented in table 4.

Exercise tests were performed after one, three and five years. The exercise capacity remained unchanged during the five years and no differences between the intervention and control group was found (figure 3).

Regarding psychosocial factors, no significant differences between the groups were found after five years (figure 4-6). Ten to fourteen years after study onset, QoL, measured with the “Ladder of Life”, was improved compared with baseline, but not with five years in both groups (figure 4). Trust in future QoL, was slightly decreased in both groups when compared with five years. However, the intervention group rated their future QoL as better than the controls ($p = 0.05$, figure 5). SRH was equally improved in both groups (figure 6).

Table 4. Mortality and drop out rates between baseline and after 10-14 years.

Year after incl.	n	Intervention group		n	Control group	
		Drop outs	Deceased		Drop outs	Deceased
0	69			61		
1	64	4	1 (from CVD)	55	6	
3	64			50	5	
5	60		4 (2 from CVD)	49		1
10-14	56		4 (2 from CVD)	43		8* (2 from CVD)

*Two of the deceased were former drop outs

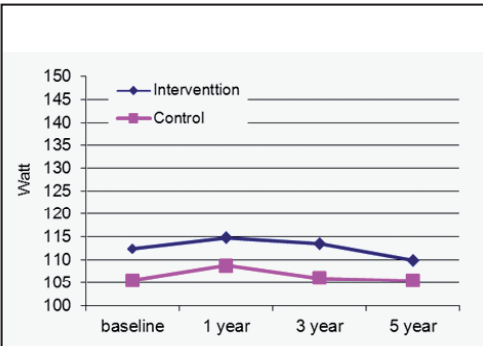


Figure 3. Exercise capacity (max Watt) at baseline, year 1, 3 and 5

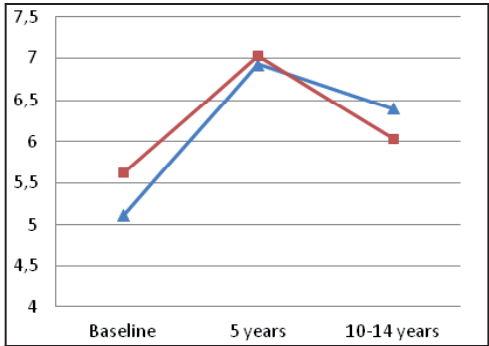


Figure 4. Present Quality of Life at baseline, after 5 and 10-14 years. 1=worst possible life, 10=best possible life.

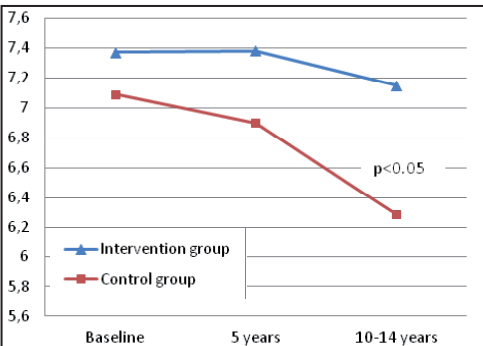


Figure 5. Future Quality of Life at baseline, after 5 and 10-14 years. 1=worst possible life, 10=best possible life.

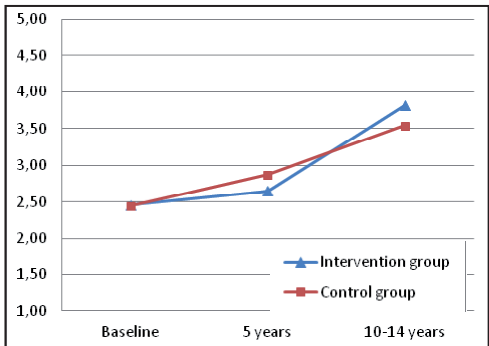


Figure 6. Self rated health at baseline, after 5 and 10-14 years. 1=very bad health, 5=very good health.

Study IV

Data were derived from the baseline examinations in study II and III. Out of the 130 women with CAD, 121 women completed the BDI and BAI questionnaires.

Twenty-three percent had BDI scores corresponding to moderate to severe depression (BDI >19). Scores >19 were strongly correlated to established angina pectoris ($p<0.01$) and higher rates of anxiety according to BAI ($p<0.001$) (table 5). Furthermore, women with low BDI showed very low rates of anxiety compared with more depressed women ($p<0.01$), indicating that anxiety is a noteworthy symptom in depressed women with CAD. Depressed women were also more likely to have a family history of heart disease ($p<0.05$) and were less likely to care about their future health ($p<0.01$).

Table 5. Baseline clinical and biochemical data for 121 women with CAD. All values are shown as mean (SD) unless otherwise noted.

	Total sample (N=121)	BDI <19 (n=93)	BDI 19-63 (n=28) ^c	<i>p</i> [*]
BMI	27.42 (4.81)	27.32 (4.85)	27.76 (4.72)	0.89
WHR, cm	0.84 (0.06)	0.84 (0.06)	0.85 (0.07)	0.54
Blood pressure, mm/Hg				
Systolic	132.23 (18.94)	133.4 (18.33)	128.36 (20.7)	0.25
Diastolic	78.51 (9.78)	78.67 (9.59)	78.00 (10.55)	0.60
Diabetes mellitus, %	20 (16.5)	17.2 (16)	14.3 (4)	0.72
History of hypertension, %	50 (41.3)	38.7 (36)	50.0 (14)	0.29
Hyperlipedemia, %	81 (66.9)	64.5 (60)	75.0 (21)	0.30
Angina Pectoris, %	51 (42.1)	35.5 (33)	64.3 (18)	<0.01
History of AMI, %	78 (64.5)	68.8 (64)	53.6 (15)	0.14
History of CABG, %	27 (22.3)	22.6 (21)	21.4 (6)	0.90
History of PCI, %	55 (45.5)	46.2 (43)	42.9 (12)	0.75
BDI	12.43 (8.63)	8.56 (4.98)	25.29 (4.88)	<0.001
BAI	10.05 (8.31)	8.48 (7.07)	16.00 (9.68)	<0.001
TC, mmol/l	4.77 (0.91)	4.78 (0.82)	4.75 (1.16)	0.49
HDL-C, mmol/l	1.32 (0.36)	1.33 (0.37)	1.27 (0.34)	0.52
LDL-C, mmol/l	2.71 (0.79)	2.71 (0.74)	2.71 (0.95)	0.85
TG, mmol/l	1.67 (0.84)	1.65 (0.82)	1.73 (0.94)	0.77
ApoB/A, g/l	0.82 (0.24)	0.82 (0.25)	0.82 (0.23)	0.73
Lipoprotein (a), g/l	0.33 (0.41)	0.32 (0.39)	0.34 (0.47)	0.72

^{*}Mann-Whitney U test

GENERAL DISCUSSION

This thesis studied two cohorts of women in Stockholm with CAD. The first study, KoK (Kvinnor och Kranskärslssjukdom), was initiated 1991 and the second study in 1997 “The Saltsjöbaden CR study” emanated from the experiences from the KoK study. The aim in the first study was to identify female risk factors for CAD. The experience was that few women were offered and participated in CR programs. Furthermore, the women who participated in the existing CR programs experienced that their individual needs not were considered. The programs were sometimes being described as a “men’s club” (Radley, Grove et al. 1998). The knowledge at that time was very scarce concerning CR in women; a meta-analysis showed that only a few women were included in all CR studies (Limacher 1998).

Therefore, we aimed to create a CR program, adjusted for women. Initially four groups, each group comprising 6-9 patients, were recruited (some of them from the KoK study) as “pilot patients”. Their constructive criticism and ideas resulted in adjustments and a final program. The women in the two studies were below retirement age since there was a need for more knowledge about CAD in younger women and, in the CR study, one aim was to study the impact of rehabilitation on sick-leave. There were high levels of sick leaves in Sweden, especially among women in the 1990’s.

The KoK study comprised consecutive patients after an acute coronary event while recruitment procedure in the CR study followed the standard referral system. Thus, the latter sample might not be representative for female cardiac patients but rather for the group that is referred to and accepts participation in secondary prevention (Grace, Abbey et al. 2002; Witt, Jacobsen et al. 2004). The overall results from this study can therefore not necessarily be extrapolated to CAD-women in general.

The women in the CR study had slightly higher level of education compared to the women in the KoK study. The women in the KoK study were slightly older but did not differ in BMI or systolic blood pressure, compared with the women in the CR study. The levels of total cholesterol and LDL were higher in the KoK-study which can be due to the existing therapy recommendations at the time. The percentage of current smokers was higher in the CR study for unknown reasons. Unfortunately, the attempts to reduce or stop smoking in the CR study evidently failed.

Exercise ECG tests were performed in both studies, mean exercise capacity were the same at baseline examination. Physical exercise has through the years been proven to be an important factor in the CR process. A follow up of mortality in the KoK study show that physical active life style was one of the most important factors for survival 9 years after coronary event (Study I). The CR study was not powered to predict mortality outcome.

The physical capacity, measured each year for 5 years in the CR study, remained unchanged. We expected the physical capacity to decline with increasing age. The women in the CR study (both interventions and controls) received optimal treatment with cardiac medications witch might be beneficial for physical capacity.

In the CR study, no increase in BMI was found during 5 years of observation. This was unexpected since it has been shown by Kuskowska et al, that there is a steady increase with ageing among men in the prevalence of obesity, while women in menopausal age show a sharp weight gain (Kuskowska-Wolk and Rossner 1990).

Psychosocial factors including depression and anxiety have been shown to account for approximately 30% risk of AMI in the INTERHEART study (Rosengren, Hawken et al. 2004). Women with CAD have more problems with depression and anxiety when compared with men, both before and after a myocardial infarction (Rosengren, Hawken et al. 2004).

The prevalence of moderate to severe depression, 25%, in study IV is in agreement with other studies. The women with depressive symptoms showed a higher frequency of anxiety symptoms, whereas the women who were not depressed showed low rates of anxiety. However, the major finding in study IV was the strong connection between depressive symptoms and angina pectoris. This link between depressive and anxiety symptoms and high frequency of angina pectoris indicates that these three symptoms can be misinterpreted by patients, health professionals and others (Katerndahl 1990; Korczak, Goldstein et al. 2007). Stress reducing CR programs including diagnostics for depression and anxiety may thus be useful in female CAD patients.

Stress management in cardiac rehabilitation has recently been reviewed. (Baumeister, Hutter et al. 2011). In 16 trials, psychological interventions showed a small beneficial effect on depression compared to usual care. No beneficial effects on mortality rates, cardiac events, cardiovascular hospitalizations and quality of life were found. Furthermore, no differences in treatment outcomes were found between the various psychological approaches. The review provides evidence of a small beneficial effect of pharmacological interventions with selective serotonin reuptake inhibitors (SSRIs). However, the evidence is scarce due to the low number of high quality trials and the heterogeneity of examined populations and intervention. However, Gulliksson et al (Gulliksson, Burell et al. 2011) found that CBT significantly reduced mortality and CVD reoccurrence in a mixed CAD population. In the largest study within the field, ENRICHED no major positive effects of CBT were found (Yusuf, Hawken et al. 2004). The conflicting results from different CBT studies suggest that more studies are needed in the area. The stress reducing method adopted from Moser et al (Moser and Björkegren 1998), used in our CR program, is a modified group-based cognitive behavior therapy. The program has not previously been evaluated in CAD patients.

During the follow up after 10-14 years, in our CR program a better hope for future quality of life were seen in the intervention group compared to the controls. Better self-rated health, less depressive symptoms and heart symptoms were found in both groups.

This lack of differences between the interventions and controls may reflect the so called Hawthorne effect in the controls (McCarney, Warner et al. 2007). This term refers to the tendency to change behavior due to the special attention from research professionals.

The sample size in the CR study was small, which might explain why we were not able to show either morbidity/mortality effects, or major effects on psychosocial factors.

One of the positive findings of the CR study was the reduced emergency health seeking in the intervention group. There were no effects on sick-leave or retirement, these results were in accordance with other studies (Lisspers, Hofman-Bang et al. 1999). Regarding health economy we were unable to perform such calculations because of the diverse types of conventional post-hospitalization care that the control group went through.

According to our experience and other studies, future CR for women should include detection and treatment of depression/anxiety, since these are of major importance for the prognosis.

Smokers evidently need better support and treatment than in our program. Smoking is a major independent cause of CAD among the causes of death for middle-aged and older women (Schmitz 2003). More research is needed to establish whether smoking cessation programs, targeted specifically for women can improve cessation rates.

Physical activity should be endorsed with emphasis on a daily basis, and be encouraged and followed up at every consultation.

It is impossible from the results of these studies to know whether CR should be residential, in out-patient clinics or home-based.

One positive effect of this CR program for women is that the program is still running in an ordinary clinical setting at Saltsjöbaden Hospital.

The experience from all personnel in our CR study was that the interplay and friendship within the women groups were extremely important factors. Still, after many years, the women continue to meet and support each other.

CONCLUSIONS

- Women < 66 years with CAD were followed for 9 years. Important independent predictors of all-cause mortality were: sedentary life style, low physical fitness impaired pulse rate and SBP response during exercise.
- In a randomized extensive 5 year rehabilitation program with CAD women <66 years, visits at emergency wards were reduced in the intervention group compared to controls. No differences between the groups were found in sick-leave, disability pensions, scheduled doctor's visits and inpatient days during five years. Maximal exercise capacity, blood pressure and pulse reaction were unchanged in both groups. No significant differences were found in psychosocial factors after five years.
- Ten to fourteen years after study onset a better trust in future quality of life was found in the intervention group compared with controls. Self-rated health and symptoms of depression were improved in both groups. Anxiety remained unchanged over the years.
- The women with CAD in the CR study, both interventions and controls with completed BDI questionnaire, were divided into 2 groups according to BDI-scores <19 or ≥ 19 . The women with moderate to severe depression (BDI-score ≥ 19) had more symptoms of angina pectoris and were prescribed long acting nitrates more often even after adjusting for diabetes mellitus and smoking. High BDI-score was correlated to high scores of anxiety. Women with moderate to severe depressive symptoms rated their current health low and were more pessimistic about undertaking a healthy lifestyle in the future than those with BDI<19. Depressive symptoms and angina pectoris were correlated.

ACKNOWLEDGEMENTS

I would like to express my greatest gratitude to all the patients who enabled this study.

Professor Karin Schenck-Gustafsson, MD, PhD, my supervisor for her never ending encouragement and optimism in the research field.

Professor Britt-Marie Landgren, MD, PhD, my co-supervisor for her patience great supportive help and excellent knowledge in science.

Ingeborg Eriksson, Anna-Lena Undén, Vanja Moser and Stig Elofsson who helped me a lot with statistics, interpreting data and for their good knowledge in the psychosocial field.

Ulrika Rosenberg for her great help, good humour and excellent management with the study patients during all this years.

Britt-Marie Höglund for her kind helpfulness and administrative support.

Faris Al-Khalili MD, PhD and Thomas Larsson, PhD for contributing with ideas to my manuscripts.

Professor Emeritus Lars Rydén who once guided me into the field of cardiology.

Professor Cecilia Linde, head of the Department of Cardiology, for her kind support.

Margita Ericsson, Ulla Pripp and Kristina Lindwall Sundel who shared my interest in the same research field.

I have also depended on the enthusiastic, friendly and encouraging people working at Saltsjöbadens Hospital. Leila Gandefelt-Lindblom, Nina Östlund, Ulrika Bildt, Karin Rodhe, Britta Pettersson, Margita Hellqvist, Liisa Reinerstam, Jannike Jevring, Tore Norén, Johan Kock, Elisabet Wijnbladh and Annika Levén.

My former colleagues at the Department of Cardiology at Karolinska Hospital, Claes Hofman Bang, Mårten Rosenqvist, Karolina Nowinski, Anna Norhammar, Per Tornvall and John Pernow.

My dear colleagues and friends at The Department of Cardiology at the Karolinska Hospital especially; Eva Wallgren, Barbro Kjellström, Helena Kagger and Anette Aly who has been involved in the studies.

My coach at Ljungby Hospital MD Karl-Axel Svensson and all my friends and colleagues at Ljungby Hospital.

Carina Nilsson, Ingrid Bodensten and Per-Henrik Nilsson, your help, understanding and back-up made this thesis possible.

My co-authors Ingeborg Eriksson, Rigmor Stain-Malmberg, Kristina Lindwall Sundel, Anna Åberg Wistedt, Anna-Lena Undén, Faris Al Khalili, Imre Janszky and Bertil Swane for your co-operation and scientific advices.

To my sister and our families for all love and fun.

Last but not the least to my mother who brought me up with great love and care.

This work was supported by: The Swedish National Board of Health and Welfare, Saltsjöbadens Sjukhus, Swedish Heart and Lung Foundation, Stockholm County Council, Patient Organization for Heart and Lung Patients in Ljungby, Ljungby Hospital and Erica Lederhausen Foundation at Center for Gender Medicine (Karolinska Institutet).

REFERENCES

- Almdal, T., H. Scharling, et al. (2004). "The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up." *Archives of internal medicine* 164(13): 1422-1426.
- Anand, S. S., S. Islam, et al. (2008). "Risk factors for myocardial infarction in women and men: insights from the INTERHEART study." *European heart journal* 29(7): 932-940.
- Astrom, H. and B. Jonsson (1976). "Design of exercise test, with special reference to heart patients." *British heart journal* 38(3): 289-296.
- Aulakh, A. K. and S. S. Anand (2007). "Sex and gender subgroup analyses of randomized trials." *Women's health issues : official publication of the Jacobs Institute of Women's Health* 17(6): 342-350.
- Baecke, J. A., J. Burema, et al. (1982). "A short questionnaire for the measurement of habitual physical activity in epidemiological studies." *The American journal of clinical nutrition* 36(5): 936-942.
- Baigent, C., L. Blackwell, et al. (2010). "Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials." *Lancet* 376(9753): 1670-1681.
- Baigent, C., M. J. Landray, et al. (2011). "The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial." *Lancet* 377(9784): 2181-2192.
- Bartnik, M., K. Malmberg, et al. (2004). "Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction." *European heart journal* 25(22): 1990-1997.
- Baumeister, H., N. Hutter, et al. (2011). "Psychological and pharmacological interventions for depression in patients with coronary artery disease." *Cochrane database of systematic reviews* 9: CD008012.
- Beck, A. T., N. Epstein, et al. (1988). "An inventory for measuring clinical anxiety: psychometric properties." *Journal of consulting and clinical psychology* 56(6): 893-897.
- Beck, A. T., C. H. Ward, et al. (1961). "An inventory for measuring depression." *Archives of general psychiatry* 4: 561-571.
- Berkman, L. F., J. Blumenthal, et al. (2003). "Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial." *JAMA : the journal of the American Medical Association* 289(23): 3106-3116.
- Bjarnason-Wehrens, B., G. Grande, et al. (2007). "Gender-specific issues in cardiac rehabilitation: do women with ischaemic heart disease need specially tailored programmes?" *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 14(2): 163-171.

- Blair, S. N., H. W. Kohl, 3rd, et al. (1989). "Physical fitness and all-cause mortality. A prospective study of healthy men and women." *JAMA : the journal of the American Medical Association* 262(17): 2395-2401.
- Blumenthal, J. A., A. Sherwood, et al. (2005). "Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial." *JAMA : the journal of the American Medical Association* 293(13): 1626-1634.
- Borg, G., A. Holmgren, et al. (1981). "Quantitative evaluation of chest pain." *Acta medica Scandinavica. Supplementum* 644: 43-45.
- Braverman, D. L. (2011). "Cardiac rehabilitation: a contemporary review." *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 90(7): 599-611.
- Brezinka, V. (1995). "[Gender bias in diagnosis and treatment of women with coronary heart disease. A review]." *Zeitschrift fur Kardiologie* 84(2): 99-104.
- Burell, G. and B. Granlund (2002). "Women's hearts need special treatment." *International journal of behavioral medicine* 9(3): 228-242.
- Bush, T. L., L. P. Fried, et al. (1988). "Cholesterol, lipoproteins, and coronary heart disease in women." *Clinical chemistry* 34(8B): B60-70.
- Cantril, H. (1965). *The pattern of human concerns*. New Brunswick, NJ, Rutgers University Press.
- Conroy, R. M., K. Pyorala, et al. (2003). "Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project." *European heart journal* 24(11): 987-1003.
- Dafoe, W. and P. Huston (1997). "Current trends in cardiac rehabilitation." *CMAJ* 156(4): 527-532.
- Daly, J., A. P. Sindone, et al. (2002). "Barriers to participation in and adherence to cardiac rehabilitation programs: a critical literature review." *Progress in cardiovascular nursing* 17(1): 8-17.
- Davidson, P. M., J. Daly, et al. (2003). "Perceptions and experiences of heart disease: a literature review and identification of a research agenda in older women." *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 2(4): 255-264.
- de Lorgeril, M., S. Renaud, et al. (1994). "Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease." *Lancet* 343(8911): 1454-1459.
- Doering, L. V., S. McKinley, et al. (2011). "Gender-specific characteristics of individuals with depressive symptoms and coronary heart disease." *Heart & lung: the journal of critical care* 40(3): e4-14.
- Doll, R., R. Peto, et al. (2004). "Mortality in relation to smoking: 50 years' observations on male British doctors." *BMJ* 328(7455): 1519.
- Drost, J. T., A. H. Maas, et al. (2010). "Preeclampsia as a female-specific risk factor for chronic hypertension." *Maturitas* 67(4): 321-326.

- Eriksson, I., A. L. Unden, et al. (2001). "Self-rated health. Comparisons between three different measures. Results from a population study." *International journal of epidemiology* 30(2): 326-333.
- Fagrell, B. (2006). "[The benefit of moderate alcohol consumption once again questioned by the Swedish National Institute of Public Health]." *Lakartidningen* 103(44): 3385-3386; discussion 3386.
- Flavell, C. M. (1994). "Women and coronary heart disease." *Progress in cardiovascular nursing* 9(4): 18-27.
- Frasure-Smith, N., F. Lesperance, et al. (1999). "Gender, depression, and one-year prognosis after myocardial infarction." *Psychosomatic medicine* 61(1): 26-37.
- Garcia, M. J., P. M. McNamara, et al. (1974). "Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study." *Diabetes* 23(2): 105-111.
- Grace, S. L., S. E. Abbey, et al. (2002). "Cardiac rehabilitation II: referral and participation." *General hospital psychiatry* 24(3): 127-134.
- Grace, S. L., K. Grewal, et al. (2008). "A prospective, controlled multisite study of psychosocial and behavioral change following women's cardiac rehabilitation participation." *Journal of women's health* 17(2): 241-248.
- Graham, I., D. Atar, et al. (2007). "European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts)." *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 14 Suppl 2: S1-113.
- Graves, K. D. and P. M. Miller (2003). "Behavioral medicine in the prevention and treatment of cardiovascular disease." *Behavior modification* 27(1): 3-25.
- Gulliksson, M., G. Burell, et al. (2011). "Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM)." *Archives of internal medicine* 171(2): 134-140.
- Gunzerath, L., V. Faden, et al. (2004). "National Institute on Alcohol Abuse and Alcoholism report on moderate drinking." *Alcoholism, clinical and experimental research* 28(6): 829-847.
- Hedback, B., J. Perk, et al. (1992). "Predictive factors for return to work after coronary artery bypass grafting: the role of cardiac rehabilitation." *International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation* 15(2): 148-153.
- Hu, F. B., M. J. Stampfer, et al. (2001). "The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up." *Archives of internal medicine* 161(14): 1717-1723.

- Hulley, S., D. Grady, et al. (1998). "Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group." *JAMA : the journal of the American Medical Association* 280(7): 605-613.
- Huxley, R. R. and M. Woodward (2011). "Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies." *Lancet* 378(9799): 1297-1305.
- Jackson, L., J. Leclerc, et al. (2005). "Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors." *Heart* 91(1): 10-14.
- Jacobs, D. R., Jr., I. L. Mebane, et al. (1990). "High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study." *American journal of epidemiology* 131(1): 32-47.
- Janszky, I., K. J. Mukamal, et al. (2004). "Alcohol consumption and coronary atherosclerosis progression--the Stockholm Female Coronary Risk Angiographic Study." *Atherosclerosis* 176(2): 311-319.
- Jolliffe, J. A., K. Rees, et al. (2001). "Exercise-based rehabilitation for coronary heart disease." *Cochrane database of systematic reviews*(1): CD001800.
- Karasek, R., D. Baker, et al. (1981). "Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men." *American journal of public health* 71(7): 694-705.
- Katerndahl, D. A. (1990). "Factors associated with persons with panic attacks seeking medical care." *Family medicine* 22(6): 462-466.
- Knoops, K. T., L. C. de Groot, et al. (2004). "Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project." *JAMA : the journal of the American Medical Association* 292(12): 1433-1439.
- Korczak, D. J., B. I. Goldstein, et al. (2007). "Panic disorder, cardiac diagnosis and emergency department utilization in an epidemiologic community sample." *General hospital psychiatry* 29(4): 335-339.
- Kostis, W. J., A. E. Moreyra, et al. (2011). "Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy." *Journal of clinical lipidology* 5(2): 97-104.
- Kuskowska-Wolk, A. and S. Rossner (1990). "Prevalence of obesity in Sweden: cross-sectional study of a representative adult population." *Journal of internal medicine* 227(4): 241-246.
- Lavie, C. J. and R. V. Milani (1995). "Cardiac rehabilitation and health-care reform." *Chest* 107(5): 1189-1190.
- Legato, M. J. (2000). "Dyslipidemia, gender, and the role of high-density lipoprotein cholesterol: implications for therapy." *The American journal of cardiology* 86(12A): 15L-18L.

- Lewington, S., R. Clarke, et al. (2002). "Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies." *Lancet* 360(9349): 1903-1913.
- Limacher, M. C. (1998). "Exercise and rehabilitation in women. Indications and outcomes." *Cardiology clinics* 16(1): 27-36.
- Linden, W., M. J. Phillips, et al. (2007). "Psychological treatment of cardiac patients: a meta-analysis." *European heart journal* 28(24): 2972-2984.
- Linden, W., C. Stossel, et al. (1996). "Psychosocial interventions for patients with coronary artery disease: a meta-analysis." *Archives of internal medicine* 156(7): 745-752.
- Lisspers, J., C. Hofman-Bang, et al. (1999). "Multifactorial evaluation of a program for lifestyle behavior change in rehabilitation and secondary prevention of coronary artery disease." *Scandinavian cardiovascular journal : SCJ* 33(1): 9-16.
- Lisspers, J., A. Nygren, et al. (1997). "Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample." *Acta psychiatrica Scandinavica* 96(4): 281-286.
- Lundberg, V. (2000). Women versus men with myocardial infarction. Sex differences in risk factors, management and outcome, Umeå Universitet.
- Lynoe, N., M. Wessel, et al. (2011). "Respectful encounters and return to work: empirical study of long-term sick-listed patients' experiences of Swedish healthcare." *BMJ open* 1(2): e000246.
- Maeland, J. G. and O. E. Havik (1986). "Return to work after a myocardial infarction: the influence of background factors, work characteristics and illness severity." *Scandinavian journal of social medicine* 14(4): 183-195.
- Maeland, J. G. and O. E. Havik (1987). "Psychological predictors for return to work after a myocardial infarction." *Journal of psychosomatic research* 31(4): 471-481.
- Manson, J. E., F. B. Hu, et al. (1999). "A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women." *The New England journal of medicine* 341(9): 650-658.
- Manson, J. E., W. C. Willett, et al. (1995). "Body weight and mortality among women." *The New England journal of medicine* 333(11): 677-685.
- McCarney, R., J. Warner, et al. (2007). "The Hawthorne Effect: a randomised, controlled trial." *BMC medical research methodology* 7: 30.
- McSweeney, J. C., M. Cody, et al. (2003). "Women's early warning symptoms of acute myocardial infarction." *Circulation* 108(21): 2619-2623.
- Moore, S. M. (1996). "Women's views of cardiac rehabilitation programs." *Journal of cardiopulmonary rehabilitation* 16(2): 123-129.
- Mosca, L. (2007). "Guidelines for prevention of cardiovascular disease in women: a summary of recommendations." *Preventive cardiology* 10 Suppl 4: 19-25.
- Mosca, L., L. J. Appel, et al. (2004). "Evidence-based guidelines for cardiovascular disease prevention in women." *Circulation* 109(5): 672-693.

- Mosca, L., C. L. Banka, et al. (2007). "Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update." *Circulation* 115(11): 1481-1501.
- Mosca, L., E. J. Benjamin, et al. (2011). "Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association." *Circulation* 123(11): 1243-1262.
- Moser, V. and I. Björkegren (1998). *Stress as an opportunity*. Karlskrona, Futura.
- MRC/BHF Heart Protection Study (2002) of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360(9326): 7-22.
- Naqvi, T. Z., S. S. Naqvi, et al. (2005). "Gender differences in the link between depression and cardiovascular disease." *Psychosomatic medicine* 67 Suppl 1: S15-18.
- Njolstad, I., E. Arnesen, et al. (1996). "Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study." *Circulation* 93(3): 450-456.
- Norhammar, A., U. Stenestrand, et al. (2008). "Women younger than 65 years with diabetes mellitus are a high-risk group after myocardial infarction: a report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA)." *Heart* 94(12): 1565-1570.
- Oldridge, N. B., D. LaSalle, et al. (1980). "Exercise rehabilitation of female patients with coronary heart disease." *American heart journal* 100(5): 755-757.
- Orth-Gomer, K., I. Eriksson, et al. (1994). "Lipid lowering through work stress reduction." *International journal of behavioral medicine* 1(3): 204-214.
- Orth-Gomer, K., S. P. Wamala, et al. (2000). "Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study." *JAMA : the journal of the American Medical Association* 284(23): 3008-3014.
- Perk, J. and K. Alexanderson (2004). "Swedish Council on Technology Assessment in Health Care (SBU). Chapter 8. Sick leave due to coronary artery disease or stroke." *Scandinavian journal of public health. Supplement* 63: 181-206.
- Petrie, K. J., J. Weinman, et al. (1996). "Role of patients' view of their illness in predicting return to work and functioning after myocardial infarction: longitudinal study." *BMJ* 312(7040): 1191-1194.
- Radley, A., A. Grove, et al. (1998). "Problems of women compared with those of men following myocardial infarction." *Coron Health Care* 2: 202-209.
- Rees, K., P. Bennett, et al. (2004). "Psychological interventions for coronary heart disease." *Cochrane database of systematic reviews*(2): CD002902.
- Reiner, Z., A. L. Catapano, et al. (2011). "ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)." *European heart journal* 32(14): 1769-1818.

- Rosengren, A., S. Hawken, et al. (2004). "Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study." *Lancet* 364(9438): 953-962.
- Sanderson, B. K. and V. Bittner (2005). "Women in cardiac rehabilitation: outcomes and identifying risk for dropout." *American heart journal* 150(5): 1052-1058.
- Sanderson, B. K., R. M. Shewchuk, et al. (2010). "Cardiac rehabilitation and women: what keeps them away?" *Journal of cardiopulmonary rehabilitation and prevention* 30(1): 12-21.
- Sangareddi, V., A. Chockalingam, et al. (2004). "Canadian Cardiovascular Society classification of effort angina: an angiographic correlation." *Coronary artery disease* 15(2): 111-114.
- Sarna, L., S. A. Bialous, et al. (2008). "Smoking trends in the Nurses' Health Study (1976-2003)." *Nursing research* 57(6): 374-382.
- Schenck-Gustafsson, K., M. Brincat, et al. (2011). "EMAS position statement: Managing the menopause in the context of coronary heart disease." *Maturitas* 68(1): 94-97.
- Schmitz, J. M. (2003). "Smoking cessation in women with cardiac risk." *The American journal of the medical sciences* 326(4): 192-196.
- Schuster, P. M. and J. Waldron (1991). "Gender differences in cardiac rehabilitation patients." *Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses* 16(5): 248-253.
- Shaw, L. J., C. N. Bairey Merz, et al. (2008). "Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health--National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation." *The Journal of clinical endocrinology and metabolism* 93(4): 1276-1284.
- Stramba-Badiale, M. (2010). "Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project." *Euro Heart J*: 2-9.
- Stramba-Badiale, M., K. M. Fox, et al. (2006). "Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology." *European heart journal* 27(8): 994-1005.
- Theorell T, Moser V, et al. (1995). "Endocrine makers during a job intervention." *Work & Stress* 9(3): 67-76.
- Tibblin, G., K. Svardsudd, et al. (1993). "Quality of life as an outcome variable and a risk factor for total mortality and cardiovascular disease: a study of men born in 1913." *Journal of hypertension. Supplement : official journal of the International Society of Hypertension* 11(4): S81-86.
- Tibblin, G., B. Tibblin, et al. (1990). "The Goteborg quality of life instrument - an assessment of well-being and symptoms among men born 1913 and 1923. Methods and validity." *Scandinavian journal of primary health care. Supplement 1*: 33-38.

- Walsh, J. M. and M. Pignone (2004). "Drug treatment of hyperlipidemia in women." *JAMA : the journal of the American Medical Association* 291(18): 2243-2252.
- Wamala, S. P., M. A. Murray, et al. (1999). "Socioeconomic status and determinants of hemostatic function in healthy women." *Arteriosclerosis, thrombosis, and vascular biology* 19(3): 485-492.
- van der Giezen, A. M., J. G. Schopman-Geurts van Kessel, et al. (1990). "Systolic blood pressure and cardiovascular mortality among 13,740 Dutch women." *Preventive medicine* 19(4): 456-465.
- Welfare, S. N. B. o. H. a. (2010) "National report on social conditions in Sweden".
- Winberg, B. and B. Fridlund (2002). "Self-reported behavioural and medical changes in women after their first myocardial infarction: a 4-year comparison between participation and non-participation in a cardiac rehabilitation programme." *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 1(2): 101-107.
- Witt, B. J., S. J. Jacobsen, et al. (2004). "Cardiac rehabilitation after myocardial infarction in the community." *Journal of the American College of Cardiology* 44(5): 988-996.
- Woodward, M., T. H. Lam, et al. (2005). "Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region." *International journal of epidemiology* 34(5): 1036-1045.
- Vujovic, S., M. Brincat, et al. (2010). "EMAS position statement: Managing women with premature ovarian failure." *Maturitas* 67(1): 91-93.
- Yarnell, J. W., C. C. Patterson, et al. (2001). "Central obesity: predictive value of skinfold measurements for subsequent ischaemic heart disease at 14 years follow-up in the Caerphilly Study." *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 25(10): 1546-1549.
- Yusuf, S., S. Hawken, et al. (2004). "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study." *Lancet* 364(9438): 937-952.
- Zigmond, A. S. and R. P. Snaith (1983). "The hospital anxiety and depression scale." *Acta psychiatrica Scandinavica* 67(6): 361-370.