VITAL EXHAUSTION AND CORONARY ARTERY DISEASE IN WOMEN

Biological Correlates and Behavioral Intervention

JENNY KOERTGE

STOCKHOLM 2003

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PUBLICATIONS

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals.

I Koertge J, Wamala SP, Janszky I, Ahnve S, Al–Khalili F, Blom M, Chesney M, Sundin Ö, Svane B, Schenck–Gustafsson K. Vital exhaustion and recurrence of CHD in women with acute myocardial infarction. Psychology, Health & Medicine 2002;7:117–26.

II Koertge J, Al–Khalili F, Ahnve S, Janszky I, Svane B, Schenck–Gustafsson K. Cortisol and vital exhaustion in relation to significant coronary artery stenosis in middle–aged women with acute coronary syndrome. Psychoneuroendocrinology 2002;27:893–906.

III Koertge J, Ahnve S, Schenck–Gustafsson K, Orth–Gomér K, Wamala SP. Vital exhaustion in relation to lifestyle and lipid profile in healthy women. Int J Behav Med 2003;10:44–55.

IV Koertge J, Sundin Ö, Blom M, Georgiades A, Janszky I, Alinaghizadeh H, Ahnve S. Effects of a stress management program on vital exhaustion, depression, and associated biological changes in women with coronary heart disease: a randomized controlled intervention study. *In manuscript*.

V Koertge J, Weidner G, Ahnve S, Elliott–Eller M, Scherwitz L, Merritt–Worden T, Marlin R, Lipsenthal L, Finkel R, Saunders D, McCormac P, Scheer JM, Collins RE, Ornish D. Improvement in medical risk factors and quality of life in women and men with coronary artery disease in the Multicenter Lifestyle Demonstration Project. Accepted in Am J Cardiol 2003.

ABSTRACT

Background: Vital exhaustion − a state characterized by unusual fatigue, irritability, and demoralization − is a predictor of coronary heart disease (CHD). The physiological mechanisms mediating this effect are not fully understood. Vital exhaustion may be decreased by means of behavioral modification. However, it is yet not established what that may translate into in terms of coronary risk factor modification. Previous studies of vital exhaustion are based on predominantly male samples and it is yet unclear to what extent the results pertain to women. Studies including larger samples of women may be warranted because they, in comparison to men, may have a worse prognosis after a coronary event, are more exhausted, and show a poorer response to cardiac rehabilitation.

Aims: To examine 1) the effect of vital exhaustion on prognosis and 2) the relationship between vital exhaustion, cortisol and coronary artery disease (CAD) in women with CHD, 3) to examine the relationship between vital exhaustion, lifestyle variables, and lipid profile in healthy women, 4) to evaluate the effects of stress management, with regard to vital exhaustion, depression and biological risk factors in women with CHD, and 5) to evaluate the effects of a lifestyle change program, with regard to quality of life (including vitality) and biological risk factors in men and women with CHD.

Materials and Methods: *Study I–III* are based on a population−based case−control study of women ≤65 years who were admitted to a coronary care unit for acute coronary syndrome (ACS), and healthy, age−matched controls. At 3−6 months after hospitalization, vital exhaustion was assessed by means of an early version of the Maastricht Questionnaire (MQ), lifestyle variables were assessed by standardized questionnaires, and biological factors by clinical examination, including coronary angiography. Furthermore, the women with CHD were followed for five years for recurrent coronary events. *Study IV* is based on a randomized controlled intervention study evaluating the effect of a 1-year stress management program, specifically aimed at reducing stress in women with CHD. Patients were 247 women (age 62±9 years) recruited consecutively during the event of either acute myocardial infarction (AMI), percutaneous transluminal angioplasty, or coronary by-pass operation. Patients were randomly assigned to either stress management (twenty 2-hour sessions during 1 year) and medical care by a cardiologist, or to the control group obtaining usual care of the health care system. At 6−8 weeks after randomization, at 10 weeks, at 1 year, and at 1−2 years follow−up vital exhaustion was assessed by means of the MQ, depression by the Beck Depression Inventory, and biological variables were determined by clinical examination. *Study V* is a descriptive study of men and women with CHD who participated in a 1−year comprehensive lifestyle change program. The program aimed at improving diet, exercise, stress management, and social support to prevent coronary morbidity and improve quality of life. Spousal participation was encouraged. At baseline, at 3 months, and at 1 year quality of life (including vitality) was assessed by means of MOS SF−36 Health Survey, and medical variables were determined by clinical examination.

Results: A vital exhaustion score above the median predicted a recurrent coronary event by a factor of two, HR 2.2 (95% CI 1.2−4.1) in women who recently suffered an AMI; vital exhaustion had an additive, but not an independent, effect on probability of CAD in women with ACS (OR=2.9, 95% CI 1.3−6.2); elevated cortisol levels were found in patients with significant CAD ($p<0.01$); vital exhaustion a positive association was found between vital exhaustion and cortisol ($p=0.05$); and divided into quartiles, vital exhaustion was inversely related to high−density lipoprotein and to apolipoprotein A1 in a linear fashion ($p<0.05$). These results remained after adjusting for standard CHD−risk factors. Furthermore, in women with CHD, vital exhaustion was positively related to a sedentary lifestyle. Stress management, as compared to usual care, was associated with a more rapid decrease of vital exhaustion ($p=0.005$); and both men and women participating in a comprehensive lifestyle change program evidenced improvements regarding quality of life (including vitality) and medical characteristics ($p<0.001$), women improved comparably to men despite their worse overall status at baseline.

Conclusions: This thesis demonstrates that vital exhaustion is an independent marker of poor prognosis in women with CHD. Sedentary lifestyle, increased activity of the sympathetic nervous system, and lipid abnormalities may be involved in this relationship. These findings fit with previous investigations performed in predominantly male populations. Furthermore, this thesis shows that women's response to cardiac rehabilitation may be as good as men's, and that stress management in a supportive group setting appears attractive to women with CHD. Implementation of these components into cardiac rehabilitation programs may be one way of increasing female participation−rates, which have been traditionally low.

Keywords: Vital exhaustion, coronary artery disease, women, behavioral intervention

LIST OF ABBREVIATIONS

AHA	American heart association
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AP	Angina pectoris
BDI	Beck depression inventory
BMI	Body mass index
CABG	Coronary artery by−pass grafting
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CRP	C−reactive protein
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HDL−C	High−density−lipoprotein cholesterol
HPA	Hypothalamic−pituitary−adrenocortical
HR	Hazard ratio
HRT	Hormone replacement therapy
IRS	Insuline resistance syndrome
LDL−C	Low−density−lipoprotein cholesterol
LHT	Lifestyle heart trial
OR	Odds ratio
MET	Metabolic equivalents
MI	Myocardial infarction
MQ	Maastricht questionnaire
POMS	Profile of mood states
PTCA	Percutaneous transluminal coronary angioplasty
RR	Relative risk
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
UAP	Unstable angina pectoris
VLDL−C	Very−low−density−lipoprotein cholesterol

INTRODUCTION

Coronary heart disease

Coronary heart disease (CHD) is the leading cause of death in the Western world (Gaziano, 2001). The underlying cause of CHD is atherosclerosis, which may generate plaques that may obstruct the coronary arteries, and consequently decrease the blood-flow. Most damage is caused when the plaques become unstable and rupture (Forrester, 2002). This is usually manifested with chest pain a predominant symptom of angina and acute myocardial infarction (AMI). However, syndromes of CHD also occur when chest pain is not dominant such as heart failure, cardiac arrythmias and sudden death. The prognosis, including mortality, after an acute MI can be defined by using measurement of the status of the left ventricle i.e. left ventricular ejection fraction (Ahnve et al., 1989; Burns et al., 2002), and taking electrocardiographic abnormalities into consideration (Ahnve, 1991; Maisel et al., 1985), including arrythmias (Rehnqvist, 1978; Maisel et al., 1985).

Different strategies of secondary prevention and cardiac rehabilitation can then be implemented. Patients at highest risk for recurrent events or mortality are examined with coronary angiography and the risk may be reduced by coronary by-pass operation (CABG) or percutaneos transluminal angioplasty (PTCA), in addition to drug therapy, and lifestyle modification training, which should be offered to all CHD-patients in order to decrease premature disability, mortality and prolong survival.

The cause of CHD is multifactorial, and in addition to well–known standard risk factors such as cigarette smoking, hypertension, lipid abnormalities, obesity, and a sedentary lifestyle, various forms of psychosocial stress has been linked to the disease (Allan, 1986).

Recently, in 2002, the American Heart Association task force on strategic research direction published a priority science topic list which included lifestyle and psychosocial risk factors (Roberts et al., 2002).

Still, in a recent large multicenter study evaluating risk factors for women with CHD, psychosocial factors were not taken into consideration (Vittinghoff et al., 2003).

Psychosocial factors and CHD in women

In recent years, evidence from epidemiological research as well as studies involving animal models, indicates that psychological states (e.g. depression and vital exhaustion) and traits (e.g. hostility), as well as being subjected to social isolation and workstrain is of importance in the etiology and prognosis of CHD (Hemingway, Marmot, 1999; Kop, 1999; Rozanski et al., 1999). This holds especially true for younger age groups aged 55 and below (Kop, 1997). The magnitude of psychosocial risk factors is similar to traditionally reported cardiovascular risk factors in predicting adverse cardiac events (Kop, 1999). The mediating mechanisms between psychosocial factors and CHD appear to be both direct pathophysiological, as well as indirect through unhealthy lifestyle (Rozanski et al., 1999).

Although women, in comparison to men, are more burdened by psychosocial distress after a coronary event (Czajkowski, 1998), and may have a worse prognosis after acute MI (AMI) and revascularization procedures (Mosca et al., 1997; Vaccarino, et al., 2001; Jacobs, 2003), the vast majority of studies in this field of research have been performed in predominantly male populations. In studies were women have been included, sample sizes and number of clinical events have oftentimes been too small to detect any gender differences. Similarly, prevention, diagnosis and rehabilitation of CHD are based on studies involving predominantly male populations. One explanation for this tradition may be that CHD for many years was considered a disease primarily afflicting middle–aged men. However, today it is widely accepted that CHD is more accurately described as a disease women in general get about 10 years after men, after menopause when the beneficial effects of estrogen have ceased.

Although the number of studies involving women has increased in recent years, there is still a paucity of knowledge regarding the relevance of psychosocial factors for CHD in women (Jacobs, Sherwood, 1996), and most of the psychological constructs tested in women are adapted from studies of men (Eaker, 1989). A comprehensive review of studies involving women characterizes their psychosocial risk profile as comprised by: low socioeconomic status, lack of social support, strain from balancing the simultaneous demands of work and family, depressed affect, and stressful life events – primarily events happening to somebody in the surrounding social network (Jacobs, Sherwood, 1996).

Stockholm Female Coronary Risk Factor Study (FemCorRisk study)

One of the first large studies with the aim to investigate how a broad spectrum of psychosocial factors related to women's coronary health was

the Stockholm Female Coronary Risk Factor Study (FemCorRisk study), a population–based case–control study including a total of 600 middle–aged women aged ≤65 years who resided in the greater Stockholm area and were admitted to a coronary care unit for acute coronary syndrome over a 3–year period. Cases (n=300) were women with AMI or unstable AP, and controls (n=300) were healthy women who were randomly selected from the cencus register and matched by age (Orth–Gomér, 1998). Previous case–control comparisons of this study have shown that low occupational class (Wamala et al., 2000), job-strain, marital discord, problems with children, lack of social support, and depressive symptoms are associated with increased probability of having CHD. However, the hard–driving type–A behavior, typically associated with increased CHD–risk among men, did not discriminate between cases and controls (Orth–Gomér, 1998). In addition, our research group recently compared cases to controls with regard to vital exhaustion – a state characterized by unusual fatigue, irritability, and demoralization – and found that a level above the sample median was associated with a near fourfold (RR=3.8, 95% CI 2.6–5.5) increased risk of having had AMI or UAP within the past 3–6 months (unpublished data).

Further investigations of the FemCorRisk women with CHD, show that those who experience a low level of social support, as compared with those who experience a high level, have more than twice the risk of having significant coronary artery stenosis (Orth–Gomér et al., 1998). Additionally, prospective investigations showed that social isolation, depressed affect (Horsten et al., 2000), and marital stress (Orth–Gomér et al., 2000) independently increased the risk of having a recurrent coronary event within 5 years after adjustment for standard CHD risk factors.

In the healthy women of the FemCorRisk study, analyses have been carried out in attempts to identify mediating mechanisms between psychosocial factors and markers of CHD. Strong associations have been found between low decision latitude at work and an adversive lipid profile, characterized by abnormally low levels of high density lipoprotein cholesterol (HDL–C) (Wamala et al., 1997a). Furthermore, low educational status was related to hemostatic dysfunction (Wamala et al., 1999), and obesity (Wamala et al., 1997b). Psychosocial stress was found to be an important mediator in both these relationships. In addition, social isolation and inability to discuss angry feelings were related to decreased heart rate variability (Horsten et al., 1999), a measure of autonomic function that has been shown to be predictive of poor CHD outcomes. Finally, a low level of social support was found to be associated to the metabolic syndrome – a cluster of cardiovascular

risk factors including central obesity, hypertenstion, dyslipidaemia, and hyperglycaemia (Horsten et al., 1999).

Vital exhaustion

A construct closely related to the established psychosocial risk profile of women is vital exhaustion, a state characterized by unusual fatigue, irritability, and demoralization, typically attributed to prolonged psychological stress (Appels et al., 1993). The idea behind the construct grew out of an interest to understand the nature of the feelings of unusual tiredness that, according to cardiological literature, were commonly reported among patients recently before MI or cardiac death (Appels et al., 1987).

Measurement, validity and reliability

The hypothesis that feelings of exhaustion/depression were predictive of subsequent MI, independently of well−established risk factors, was tested in the Rotterdam Civil Servants Study, a prospective study of male civil servants (N=3877, aged 39−45 and 54−65 years) in Rotterdam, Holland. They underwent extensive medical examination and were given a new questionnaire called the Maastricht Questionnaire (MQ) assessing feelings of exhaustion and depression (Appels et al., 1987). The questionnaire constisted of 58 items: 37 items which had been found to discriminate between cases with coronary artery disease (CAD) and healthy controls in a previous study (Appels, 1980), and 21 new items which had been derived from interviews with CAD−patients. To avoid problems resulting from developing and testing a model in the same study, only the 37 items previously found to be discriminstive of CAD were used to test the hypothesis. The cohort was followed for a mean of 4.2±0.7 years. During this period, a total of 59 cases with MI were ascertained among patients with complete data who were free of CAD and AP at the beginning of the study, and who had not died from non−cardiac causes. To test the hypothesis that feelings of exhaustion/depression were predictive of MI, each case was matched on CHD risk factors to three healthy controls, resulting in a total of 177. Mean baseline−scores of the 37 items measuring vital exhaustion, differed significantly between cases (20.0±14.5) and controls (14.9±12.4; t=2.58, p=0.01). Meanwhile, cases and controls were comparable with regard standard CHD risk factors including age, smoking, blood pressure, and cholesterol levels. Thus, confounding of these factors was unlikely to explain the observed relationship between vital exhaustion and future MI and the model was considered valid.

To reduce the MQ to a set of items of which each predicted future MI or cardiac death, age−adjusted item analyses were carried out, assessing

the relative risk of a future MI for each item. Of the 58–items, 24 were found to be predictive (16 belonged to the previously used scale and 8 were derived from the interviews). Of these, two items were excluded because they were only predictive the first year of follow–up, and one because it did not fit into the concept of vital exhaustion. Hence, the final version of the MQ comprises 21 items, each in itself predictive of a future MI or cardiac death. The scale has a score range from 0 to 42 and an adequate internal consistency (Chronbach's α=0.89) (Appels et al., 1987).

Among the healthy men in the Rotterdam Civil Servants Study (N=3877), the mean MQ–score was 8.8±8.7, median=6 (Appels et al., 1987). This result has been replicated in a group of healthy men (9.0±9.7, N=133; Falger, 1989). Elevated MQ–scores are found in hospitalized participants, particularly female ones. Men hospitalized for non–cardiac reasons (n=192) have reported a mean MQ–score of 11.7±9.8, while the score in those with AMI (n=133) was 18.0±10.8 (Falger & Schouten, 1992). The corresponding scores in women are considerably higher: 17.0±11.2 in those hospitalized for non–cardiac reasons (n=79), and 20.6±11.9 in those hospitalized with MI (n=90; Appels et al., 1993). That cardiac patients have particularly elevated MQ–scores was confirmed in a study of men (n=244) and women (n=63) referred to diagnostic coronary angiography with mean MQ–scores of 18.1±10.5 and 23.4±10.3, respectively (Kop et al., 1996).

Psychosocial and demographic correlates of vital exhaustion

In creating the construct of vital exhaustion Appels followed the reasoning of Selye's General Adaptation model postulating that a prolonged period of perceived uncontrollable stress results in a state of vital exhaustion (Kop, 1997). This hypothesis was supported by an exploratory study, investigating the relationship between vital exhaustion and socio–biographical variables in a mixed sample of women hospitalized for MI (n=79) or general/orthopaedic surgery (n=90). Out of several factors relating to childhood–, worklife–, and family issues, the strongest association was found between vital exhaustion and having a paid job while simultaneously taking care of the household. Other significant positive relationships were found with childhood experiences of family conflicts, unemployment, and financial problems, and adult experiences of single marital status, unwanted childlessness, problems with children's education, as well as marital and financial problems (Appels et al., 1993). The high association found between vital exhaustion and double workload may in part be responsible for the significantly higher levels of vital exhaustion found in women (healthy and with CHD) as compared to men (Kopp et al., 1998, and Kop et al., 1994, respectively).

The idea that prolonged stress may result in vital exhaustion was supported by a large population–based study (N=12640, 55% women) in which vital exhaustion was found to be an effective mediator between different socio–economic factors (including level of education, employment status, father's employment, car ownership, housing conditions, and property ownership) and cardiovascular sick days ($p<0.001$). The effects remained after adjusting for age and sex. The only socioeconomic factor that was directly linked to cardiovascular sick days was father's employment ($p<0.01$). Furthermore, the study found that vital exhaustion increased with age, and was more frequent among women ($p<0.001$; Kopp et al., 1998).

It has been proposed that vital exhaustion is the consequence of the continously hard–driving Type–A behavior pattern (TABP), in particular if combined with negative emotions like frustration and isolation (Burell, 1996). Indeed, Meesters and Appels (1996) found a substantial correlation between vital exhaustion and hostility – a key–component of TABP. However, studies relating vital exhaustion and TABP to physiological parameters suggest that the two constructs are separate risk factors of CHD, acting through different physiological mediators (van Diest, 1990; van Doornen, van Blokland, 1989; Raikkonen et al., 1996a).

Construct validity of vital exhaustion

Vital exhaustion vs burnout

Exhaustion is a central component in the various attempts that have been made formulating a concept of 'burnout'. The most cited is the syndrom–approach of Christina Maslach's, defining burnout as a composite of three variables; emotional exhaustion, depersonalization, and sense of reduced personal accomplishment (Söderfeldt, 1997). At first glance, vital exhaustion appears similar to the component 'emotional exhaustion' as assessed by the Maslach Burnout Inventory (Maslach, Jackson, 1986). However, according to Ad Apples, the founder of the construct vital exhaustion, it distinguishes itself from burnout by describing the result of prolonged life–stress rather than just workstress (personal communication, August, 2000). His idea is supported by the results of the aforementioned exploratory analysis, suggesting that vital exhaustion is related to several stressors in childhood, as well as in the current work– and family–situation (Appels et al., 1993).

Vital exhaustion vs depression

Empirically and conceptually, vital exhaustion appears to overlap with depression. Estimates of their shared variance range from 25–50% (Appels, 1997), and at least two studies have been designed to investigate how the two contructs relate to each other on a conceptual

level. A study of healthy males (20 exhausted, and 10 non–exhausted), investigated the relationship between vital exhaustion, mood states (vigour, fatigue, and depressed mood), and depression, assessed by MQ, Profile of Mood States (POMS, Wald, Mellenbergh, 1990), and the Beck Depression Inventory (BDI; Beck et al., 1961), respectively. Results from the POMS showed that exhausted and non–exhausted men differed with regard to vigour and fatigue, but not with regard to depressed mood. Furthermore, although BDI–symptoms of depression were much more frequent in exhausted, as compared to non–exhausted men (mean score 11.4±9.7 vs 1.0±1.1, p=0.0007), the symptoms reported of the exhausted men were fatigue, work inhibition, sleep disturbance and loss of libido, whereas only one reported depressed mood, and no one reported appetite– and weight–loss, self–accusations, or suicidal ideation – items typically related to depression. The authors suggested that their findings indicated that vital exhaustion was characterized by loss of vigour and fatigue rather than depressed mood (van Diest, Appels, 1991).

In a large population–based study including both men and women, vital exhaustion and depression were found to associate differently to relevant external criteria. Vital exhaustion related significantly more to loss of energy, bodily symptoms, history of hypertension and CHD, whereas depression was more related to dysfunctional attitudes, lack of purpose in life, low self–efficacy, hostility, mental and physical disabilities and disorders, as well as to alcohol– and drug abuse (Kopp et al., 1998).

The difference between the two constructs is further indicated by their different prevalence–rates among cardiac patients. The occurrence–rate of vital exhaustion is considerably higher (35–60%) than that of depression (10–20%). A study of CAD–patients (n=52) investigating the incidence–overlap of vital exhaustion and depression found that 57% of the exhausted participants did not meet the criteria for major depression (as measured by the Diagnostic and Statistical Manual of Mental Disorders, IV edition). However, nearly all participants who were depressed also met the criteria for vital exhaustion (Kop, 1999). Finally, unlike depression that predicts cardiac events over several years, the predictive value of vital exhaustion appears to be short–term (<2 years; Kop, 1997).

Vital exhaustion as a predictor of CHD

Assessed by the MQ, vital exhaustion has been shown to predict MI in a prospective study of men (Appels & Mulder, 1988), and in case–control studies of men (Falger, Schouten 1992) and women (Appels et al., 1993).

In addition, vital exhaustion predicts recurrent coronary events 1.5 years after successful PTCA (OR= 2.7, 95% CI 1.1–6.3, n=127, 17% women; Kop et al., 1994), and 5 years after AMI (HR 2.2, 95% CI 1.2–4.1, n=110 women; Koertge et al., 2002). See Table 1 for detailed description of the studies investigating vital exhaustion in relation to CHD.

Further analyses in patients undergoing PTCA suggest that of the vital exhaustion construct, the fatigue–component may be the most powerful predictor of recurrent coronary events. In comparing the fatigue– and demoralization–components of the MQ, the former showed a relative risk of 2.5 (p=0.03) and the latter 1.9 (p=0.1). When simultaneous adjustment was made for CAD severity and hypercholesterolemia, the fatigue–component was virtually unaffected (RR=2.6, p=0.08), whereas the demoralization–component became non–significant (RR=1.2, p=NS; Kop, 1999). These results indicate that the instruments for assessing vital exhaustion may need further calibration in order to optimize the identification of people at risk for cardiac events.

That fatigue alone carries predictive value was supported by a prospective study of healthy men (n=5053) showing that frequent feelings of exhaustion (except after exercise) are associated with a twofold risk of cardiac death (RR 2.07, 95% CI 1.1–4.0) over a 12–year period, after adjustment for age, body mass index (BMI), smoking status, and history of diabetes and hypertension (Cole et al., 1999).

Vital exhaustion – cause or concequence of CHD?

A key question regarding the relationship between vital exhaustion and CHD concerns the possibility that the feelings of vital exhaustion are merely physical signs of disease in progression rather than signs of psychological distress. This issue has been thoroughly investigated in several studies based on a group of patients undergoing PTCA.

The first of these studies was a prospective study (n=120, 22% women) investigating the relationship between vital exhaustion and severity of CAD, and to what degree vital exhaustion would decrease after PTCA. It was found that extent of atherosclerosis accounted for only 4% of the variance of vital exhaustion scores, and that most patients who were exhausted before the PTCA also remained exhausted afterwards (Kop et al., 1993).

Table 1. Overview of studies with of vital exhaustion in relation to occurrence of CHD.

Study	Study design	Participants	Definition of	Follow-up	Endpoint	Statistical results	Adjustment factors
Appels & Mulder, 1989	Cohort	Healthy men (N=3877, 39-45 yrs, 54-65 yrs)	Exhausted= MQ-score in 3rd tertile, non-exhausted =MQ-score in 1st or 2nd tertile	4.2	angina pectoris at screening unstable angina pectoris at screening previous MI at screening (only in the youngest age group) angina pectoris at follow-up non-fatal MI	RR=4.2, p<0.01 RR=17.2, p<0.001 OR=3.8, p=0.05 RR=1.9, p< 0.03 RR=2.3, p<0.001	Age
Falger & Schouten, 1992	Case-control	Cases=men with AMI (N=133, 53±10), Controls= neighboring men (N=133, 49±9) and Hospitalized men (N=192, 51±10)	Exhausted= core ≥ median (8.0p)		First AMI	RR=6.8 (3.8-12.3) neighbour- controls RR=2.7 (1.6-4.7) hospital-controls	Age and smoking
Appels et al., 1993	Case-control	Cases= women with first MI (N=79, 59±9 yrs), Controls= hospitalized women (N=90, 57±9 yrs)	Exhausted= MQ-score >median (18p), non-exhausted MQ-score ≤ median				Age, smoking, coffe consum., diabetes, hypertension, non-anginal pain, and menopausal status
Kop et al., 1994	Cohort	Patients undergoing PTCA (N=127, 17% women, 55.6±9.1 yrs)	Exhausted= MQ-score in 3rd tertile (>18 p), non-exhausted= MQ-score in 1st or 2nd tertile	1,5	Recurrent cardiac event (N=29), defined as cardiac death, MI, CABG, PTCA, a new coronary lesion, or recurrent angina	OR=2.7 (1.1-6.3) OR=2.3 (CI rakna ut) B=0.85 SE=0.46	Unadjusted value, adjusted for severity of CAD and hypercholesterolemia
Koertge et al., 2002	cohort	Women with AMI (N=110, 55.3±7.6 yrs)	Exhausted= MQ-score >median (36p), non-exhausted MQ-score ≤median	5	Recurrent events (N=45), AMI, cardiac death, PTCA or CABG	HR=2.3 (1.1-4.7)	Severity of chestpain and significant CAD

The second study (n=127, 17% women) prospectively investigated the predictive value of vital exhaustion with respect to recurrent coronary events after adjusting for severity of CAD. If was found that being vitally exhausted was associated with nearly a three–fold increased probability of a recurrent event while adjusting for severity of CAD (Kop et al., 1994).

The third study (n=105, 0 women) investigated the relationship between vital exhaustion and severity of CAD, as well as vital exhaustion as predictor for recurrent events. It was found that vital exhaustion was positively related to number of diseased vessels prior to, but not after, PTCA, and that it predicted recurrent coronary events by a factor of three (Appels et al., 1995).

The fourth study (n=307, 21% women) cross–sectionally examined the relationship between vital exhaustion, severity of CAD, and left ventricular ejection fraction (cardiac pump function). It was found that vital exhaustion was neither associated with extent of CAD nor with left ventricular dysfunction (Kop et al., 1996).

In conclusion, these studies support the hypothesis that the previously established relationship between vital exhaustion and future MI is unlikely to be confounded by underlying cardiac pathology. Thereby, it appears reasonable to interpret vital exhaustion as a psychological variable that may be useful to target in terms of preventive and interventive strategies (Appels et al., 1997).

Potential mechanisms explaining the relationship between vital exhaustion and CHD

While the association between psychosocial factors and CHD has been well demonstrated, it is yet not fully understood how. Two main types of mediating mechanisms are plausible: 1) indirect effects through association with poor lifestyle habits, and 2) direct pathophysiological effects (Rozanski et al., 1999).

Lifestyle habits

Previous investigations of the relationship between vital exhaustion and lifestyle factors (smoking, alcohol consumption, BMI, and exercise habits) in healthy individuals are scarce and/or yield conflicting results (Cole et al., 1999; Conduit et al., 1998; Kop et al., 1998; Kopp et al., 1998; Nicolson, van Diest, 2000; Raikkonen et al., 1996b). Relationships have been found to be positive and non–significant with regard to smoking (Kop et al., 1998; Kopp et al., 1998), positive with regard to obesity (Raikkonen et al., 1996a), negative (Cole et al., 1999; Conduit et al., 1998), and non–significant with regard to alcohol consumption

(Kop et al., 1998; Nicolson, van Diest, 2000), and positive with regard to sedentary lifestyle (Cole et al., 1999). However, it should be noted that these studies have predominately involved men and that it may not be correct to compare men to women as they have been found to cope differently with stress. For instance, a study of lifestyle and work stress found that stressed women (n=317) drank less alcohol, ate healthier, but exercised less than stressed males (n=337; Lindquist et al., 1997).

In addition, exhausted individuals report a sleeping–pattern characterized by disrupted sleep and more frequent napping – a pattern which has been associated to CHD (van Diest, 1990). They have also been found to spend less time in slow–wave sleep, which is regarded as the restoration phase of normal sleep (van Diest, Appels, 1994).

Pathophysiological mechanisms

With regard to direct pathophysiological mechanisms, there is some evidence suggesting that vital exhaustion influences the development of CHD through alterations in lipid metabolism, blood–clotting factors, and inflammatory processes. These processes are involved in plaque instability and thus increase the risk of acute coronary syndrome (Forrester, 2002; Buffon et al., 2002; Ridker, 2002).

LIPID METABOLISM

In healthy men (n=33) exposed to real life stress, vital exhaustion was found to be positively associated with baseline cholesterol levels, stress induced cholesterol change, and noradrenaline– and cholesterol–levels during stress (van Doornen, van Blokland, 1989). In healthy middle–aged men (n=90) vital exhaustion was related to three of the four facets of the insulin resistance syndrome (IRS): obesity, hyperglycemia, and dyslipidemia (Raikkonen et al., 1996a). Previous studies have demonstrated that prolonged stress may result in sustained changes in lipids toward elevated levels of cholesterol and triglycerides, and reduced levels of HDL–C (Brindley et al., 1993; Melamed et al., 1992; Shirom et al., 1997). Conversely, several longitudinal studies report that learning to cope with stress is associated with more favorable cholesterol levels (Dusseldorp et al., 1999). The proposed chain of mechanisms explaining the stress–lipid relationship partly builds on the association between stress and an adversive lifestyle characterized by poor dietary and exercise habits. It has been demonstrated that psychological stress and poor lifestyle habits independently contribute to insuline–restistance causing reduced ability of insuline to suppress free fatty acids. A poor diet and insuline–resistance can furthermore cause hyperinsulinemia, which has indirect effects on the lipid profile through increased activity of the

sympathetic nervous system (SNS) and its lipid mobilizing properties (Howard et al., 1993).

BLOOD–CLOTTING FACTORS

In addition to causing lipid mobilization, the IRS also has adversive effects on blood–clotting factors (Juhan–Vague&Alessi, 1997) which relationship to vital exhaustion has been demonstrated repeatedly (van Diest et al., 2002; Kop et al., 1998; Kop et al., 2002; Raikkonen et al., 1996). In later stages of CAD, elevated levels of blood–clotting factors promote the risk of thrombus formation – and ultimately, acute coronary syndromes – by decreasing the fibrinolytic capacity and increasing the likelihood of fibrin accumulation (Gersh, Braunwald, Bonow, 2001). Elevated plasminogen activator inhibitor–1 has been found in samples of healthy, but vitally exhausted, men (Kop et al., 1998; Kop et al 2002; Raikkonen et al., 1996) and women (Kop et al., 2002), and according to recent findings these elevations are likely to occur early in the day (van Diest et al., 2002). Together, these findings may partly explain the association between vital exhaustion and MI, which is known to occur more frequently in the morning.

INFLAMMATORY PROCESSES

Apart from affecting lipid metabolism and blood–clotting factors, recent evidence suggests the involvement of vital exhaustion in impaired immune function which is associated with the progression of CAD (Appels et al., 2000; Kop et al., 2002). It has been hypothesized that prolonged stress results in decreased hypothalamic––pituitary–adrenocortical (HPA) activity, which increases the susceptibility to inflammation (Appels et al., 2000). A recent study generates some support for this hypothesis, finding lower cortisol levels in exhausted but otherwise healthy men as compared to non–exhausted (Nicolson, van Diest, 2000). However, it remains to be determined whether vital exhaustion increases the susceptibility to inflammation or if having an inflammation generates feeling of vital exhaustion (Appels et al., 2000; Kop et al., 2002).

Behavioral intervention and CHD

Changes in lifestyle and psychosocial status have been shown to reduce morbidity, mortality, and even reverse the course of CAD (Blumenthal et al., 2002a; Gould et al., 1995; Linden, 2000; Ornish et al., 1990; Ornish, 1998; Ornish et al., 1998). A recent review of four meta–analyses concludes that behavioral riskfactor modification reduces recurrence of nonfatal CHD events by 39–46% and fatal CHD events by 20–33% (follow–up time 0.5–7 years) (Linden, 2000). A landmark study,

involving men with CAD, is the Lifestyle Heart Trial (LHT) in which radical lifestyle changes regarding diet, exercise, and stress management resulted in substantial reductions of cardiovascular risk factors and events, reversal of coronary atherosclerosis, and improvement in myocardial perfusion (Gould et al., 1995; Ornish et al., 1990; Ornish et al., 1998). Among the criticism that has been raised towards the LHT is that it is impossible to determine the active agent of change due to the "package" of treatment components (Linden, 2000). However, beneficial effects of stress management alone were recently demonstrated in a randomized controlled study of men with stress–induced myocardial ischemia (N=121, 58±8 years), comparing the clinical outcomes of exercise and stress management training over five years. Relative to usual care stress management was associated with a significant reduction in clinical CAD events and was associated with lower medical costs than exercise and usual care in the first two years, and remained lower relative to usual care at the five–year follow–up (Blumenthal et al., 2002).

Although these data are incouraging, three recent large studies have failed to find positive clinical effects of psychosocial intervention (Blumenthal et al., 2002b; Frasure–Smith et al., 1997; Jones, West, 1996). In fact, one study even reported the intervention to be adversive for the female participants with higher cardiac mortality observed in the intervention group than in the control group (Frasure–Smith et al., 1997). The recent influx of disappointing results is likely to be attributed to further improved medical care, e.g. increased use of revascularization procedures and drug therapy, including statins, which now usually are given during hospitalization after early determination of serum lipids (Ahnve et al., 1989), enrolment of patients without documented signs of psychosocial distress (leaving no room for improvement), and enrolment of women who may have other needs than men (Linden, 2000). Another plausible explanation for the modest effects reported are the use of relatively brief interventions supplied by medical personnel not properly trained in behavioral techniques, as well as follow–up periods restricted to less than a year. Studies of psychosocial interventions have shown that small treatment gains revealed at an early stage of treatment might prove important at subsequent follow–ups, hence prolonged follow–up periods may be warranted when interpreting data from tis type of treatment (Hedback et al., 1987; 1993; Levin et al., 1991).

Behavioral intervention and CHD in women

Making cardiac rehabilitation programs that appeal to women is an important task considering that women, as compared to men, may have a worse prognosis after a coronary event (Mosca et al., 1997; Vaccarino et al., 2001) and therefore are in particular need of successful preventive

treatment. Unfortunately, women's participation rates in cardiac rehabilitation programs are typically low (Wilansky, 2002), some estimate as low as 5% (O'Farrell et al., 2000), and they are more likely to drop out as compared to men (Jacobs, Sherwood, 1996). This may be explained by the fact that women are less likely to be referred to these programs (Wenger, 1998) and that current programs are not meeting women's needs (Toobert et al., 1998; Wilansky, 2002). One major criticism of traditional programs is their almost exclusive focus on exercise, which by itself appears to be of limited value in cardiac rehabilitation (Ades, 2001) and may not appeal very much to female CAD patients (Ades, 2001; Limacher, 1998). Taking into account that women with CHD are particularly prone to depression and vital exhaustion (Czajkowski, 1998; Kop et al., 1994) it is reasonable to assume that they would benefit from a program that pays adequate attention to their psychosocial needs in addition to lifestyle change. Furthermore, it seems important to tailor programs according to the special problems women face, including stresses relating to the family and members of other social networks, and handling the role of being employed while remaining the main caregiver/homemaker.

Behavioral intervention and vital exhaustion

To date, only three studies have investigated the effects of behavioral intervention on vital exhaustion. In a feasibility study, Appels and colleagues (1997) investigated the effects of a 10−week intervention program (followed by four monthly booster sessions) comprised by relaxation exercises, free group discussions, and anger management in patients who remained exhausted after successful PTCA (as indicated by a MQ−score ≥14; N=30, 13% women, mean age 55.6±5.8 years). The intervention was considered successful as compared to usual care received by a control group of patients (N=65, 17% women, mean age 54.7±9.3 years) who were recruited from an earlier study of PTCA−patients (Kop et al 1994). By 15 months following PTCA, patients in the intervention group had reduced their level of vital exhaustion significantly (from 27 to 13) while the controls showed no difference in the corresponding scores (24 vs 24). During the follow−up, the intervention group was less likely (however not significantly) than the control group to experience recurrent coronary events defined as cardiac death, MI, CABG, rePTCA, or restenosis (10% vs 23%). It should however be noted that this study had several limitations which must be considered when interpreting the results: the allocation of patients to intervention− and control groups lacked randomization procedure, the control group had more severe CAD than the intervention group and their follow−up time was on the average three months longer, and the data from the control group was collected several years before the data

from the intervention group − time during which cardiological procedures with all likelihood had improved. These limitations preclude the possibility of determining the cause of the obtained results. However, the study did succeed in its aim, namely to estimate the effect size of the intervention which is needed to compute the number of participants needed for a larger clinical trial. Based on the results (effect size about 50%), it was estimated that a sample of 120 in each group would be needed in order to with 80% power detect a difference between intervention and control group, given that the incidence rate of recurrent coronary events is about 25% (typical in PTCA patients) in the control group and 12.5% in the intervention group.

Quite recently, a larger randomized trial was completed in patients who remained exhausted after successful PTCA (N=710, 23% women) investigating the effects of a 10−week program comprising relaxation, management of excessive anger and tiredness, and education regarding CHD risk factors. Similarly to the results of the pilot−study, vital exhaustion (and depression) was reduced by 55%, however only in patients who had not had a cardiac event before the PTCA. More interestingly, the intervention group had 55% lower risk than the control group for recurrent events (PTCA, CABG, MI, or cardiac death) occurring between 6 and 18 months (personal communication with Ad Appels February 2003, the results were recently presented at the Heart & Mind Conference, Maastricht, The Netherlands, 23 – 25 January 2003 and have been submitted for publication).

In addition, a non−controlled feasibility study of the stress management program being evaluated in this study was performed in a sample of women (n=23), mean age 59 years. It was found to be attractive and had an attendance rate of 80%. After one year of intervention, the women had reduced their vital exhaustion scores from 21.8±6.7 to 15.0±8.0 (32%). Furthermore, self−rated stress was decreased, and quality of life had improved (Burell, Granlund, 2002).

AIMS OF THE STUDY

On a general level, the aims of this thesis were:

1) to investigate the relationship between vital exhaustion and markers of CHD in women
2) to investigate potential mechanisms mediating the relationship between vital exhaustion and CHD in women
3) to evaluate the effects of behavioral intervention in women with CHD with regard to vital exhaustion and biological risk factors

On a specific level, the aims of this thesis were to:

1) examine the effect of vital exhaustion on prognosis in women with CHD
2) examine the relationship between vital exhaustion, cortisol and coronary artery stenosis in women with CHD
3) examine the relationship between vital exhaustion, lifestyle variables, and lipid profile in healthy women
4) evaluate the effects of stress management, specifically tailored to women, with regard to vital exhaustion and depression, as well as associated changes in biological risk factors in women with CHD
5) evaluate the effects of a multi–component lifestyle change program, specifically with regard to quality of life (including vitality) and biological risk factors in men and women with CHD

MATERIAL AND METHODS

Table 2. Participants, study design, and main results of the studies included in the thesis.

Study	Participants (N, mean age±SD)	Predictor variables	Main end points	Main results
I	Women with AMI (n=110, 55±8 yrs)	VE	Recurrence of CHD events over a 5−year period (cardiac death, MI, PTCA or CABG)	Scoring above the median on VE was associated with a HR 2.2 (1.2−4.1)
II	Women with AMI or UAP (n=238, 56±7 yrs)	VE, cortisol, standard risk factors of CAD	Significant CAD	Higher cortisol levels were found in patients with significant CAD ($p<0.01$) each 25% increase of cortisol increased the probability of having significant CAD by OR 1.41 (1.1−1.8) having above median values on both cortisol and VE associated with a HR 2.9 (1.3−6.2)
III	Healthy women (n=300, 56±7 yrs)	VE	lifestyle variables, lipid profile	VE was inversely related to HDL and Apo A1 in a linear fashion ($p<0.05$)
IV	Women with AMI, CABG, or PTCA (n=247, 62±9 yrs)	Treatment: stress management, or treatment as usual	VE, depression, associated changes in standard risk factors of CHD	Stress management was associated with a more rapid decrease of vital exhaustion as compared to controls ($p=0.005$)
V	Men and women (21%) with CHD (n=440, 58±10 yrs)	Multi−component lifestyle change program	Standard risk factors of CHD, quality of life (including a measure of vitality)	Significant improvement in quality of life and medical factors ($p<0.001$). Women improved comparably to men

Study design and participants

Study I–III

The participants were part of a population–based case–control study, the Stockholm Female Coronary Risk Study. Cases included all available Swedish–speaking women aged ≤65 years who resided in the greater Stockholm area and were admitted to a coronary care unit for acute coronary syndrome between February 1991 and February 1994. Of 292 eligible patients, 110 (38%) were diagnosed with AMI and 182 (62%) with unstable angina pectoris (UAP). Cases were age–matched to healthy controls. Baseline examinations were carried out during two consecutive days, three to six months after hospital admission. The matched controls were examined during a corresponding time period. Demographic, psychosocial and lifestyle variables were assessed by standardized questionnaires and biological factors were determined through clinical examination. Furthermore, the women with CHD were followed for five years for recurrent coronary events and selective coronary angiography was obtained in 238 patients. The study was approved by the Karolinska Hospital Ethics Committee (No.91;119).

Study 1 includes the women with AMI (n=110, mean age 55±8 years), study 2 includes the women whose results from coronary angiography could be obtained (n=238, mean age 56±7 years), and study 3 includes the healthy controls (n=300, mean age 56±7 years).

Recruitment of patients with CHD

The patients were recruited at the ten coronary care units of greater Stockholm by nurses who gave weekly reports of all women, aged 65 years and below, who were hospitalized with suspected AMI or UAP. All clinics had developed and agreed upon the same criteria for admission. Women were considered for the study if their hospital records indicated one of the following:

- definite or suspected AMI according to the definition of the World Health Organization (WHO) of typical chestpain, typical enzyme patterns and diagnostic electrocardiogram (ECG) changes (Myocardial infarction community registers, 1976; electrocardiographic changes were classified according to the Minnesota code, Gillum et al., 1984)
- unstable angina pectoris, defined as new onset of severe AP, which had deteriorated during the four weeks prior to admission, with increased pain intensity and duration, or with pain at rest or very low physical exertion (Braunwald, 1989)

- spasmangina, defined as AP at rest with related pathological ST−changes on ECG, and with normal coronary arteries on acute clinical coronary angiography.

During the three−year inclusion period, a total of 335 women with CHD were identified. Patients were first contacted by a letter, inviting them to participate. Those who did not call the clinic as requested were contacted by phone. Of the eligible patients, 43 (13%) could not be included in the study due to death during the time between hospitalization and examination (n=5), illness (n=13), transportation problems (n=2), or miscellaneous reasons (n=23).

RECRUITMENT OF HEALTHY CONTROL SUBJECTS

The healthy controls, matched by age to the women with CHD, were selected from the census register of the greater Stockholm area. For each patient with CHD, a healthy woman of the same catchment area born on the same day, or a day as close as possible, was chosen. To be considered a healthy control, the woman needed to be non−diabetic, free from symptoms of heart disease, and without hospitalization for any illness during the past five years. The controls were approached in the same way as the patients. Of the eligible controls, 17% declined to participate, the main reason being difficulties taking time off from work. When a woman declined to participate, the next availible woman of the same age was approached. A maximum of four women were approached for each case.

ASCERTAINMENT OF RECURRENT CARDIAC EVENTS

Study 1: The women with AMI were followed from the date of their baseline examination, until August 18, 1997, for cardiovascular and all cause mortality, AMI, and PTCA, and CABG. The mean follow up period, from baseline assessments, was 4.7, range 3.2 to 6.2 years. Death was ascertained by linkage to the Swedish National Death Registry maintained for all Swedish residents. Death from cardiovascular causes was considered when the primary cause of death was coded 410−414 (International Classification of Diseases, Ninth Revision). Recurrent AMI was considered to have occurred on the date of admission for hospitalization. Swedish hospital registers of AMI have been previously validated with hospital records and found to be highly reliable (Alfredsson et al., 1997; Hammar et al., 1991). Revascularization procedures were considered to have occurred on the date of treatment, with International Classification of Operations, Ninth Revision codes 3105, 3158, 3127 and 3066 for CABG, and 3080 for PTCA. Data on revascularization procedures were further validated using the cardiac procedures register in the hospitals, respectively.

Study IV

Women aged ≤75 years (n=247, mean age 62±9 years), who had either acute myocardial infarction (AMI), or coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) at Huddinge University Hospital or at St Göran's Hospital, Stockholm, Sweden were randomized into either the intervention group (n=128) or the control group (n=119). Of all patients, 57% had AMI (with or without revascularization procedure), 15% underwent PTCA only, 21% underwent CABG only, and 7% had both PTCA and CABG. Consecutive eligible patients were asked by their attending physician or nurse to participate in the study. Of the 247 patients who were randomized, 22 (8 in the treatment group and 14 in the control group) did not show up at baseline (6–8 weeks after randomization), leaving a final number of n=114 in the intervention group and n=111 in the control group. Control patients obtained regular medical care in the health care system. If a control patient had no angina and was doing well, she was usually referred to a general practitioner for further follow–up. 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. Patients in the intervention group were offered a 1–year stress management program, specially tailored for women. During the intervention period, they were furthermore treated by one cardiologist at Huddinge University Hospital, and by one out of three at St Göran's Hospital, respectively. Patients in the intervention group met their cardiologist at least 3 times during the 1 year intervention period.

During the study period until the end of the follow–up in March 31, 2002, altogether 11 patients had died (2 in the intervention group and 9 in the control group). One patient in the intervention group died between randomization and baseline examination, and one after the intervention period. Among the controls, 2 died between baseline and the 10–week examination, 4 died between 10 weeks and 1 year, and 3 died between 1 year and the end of follow–up.

Both the intervention and the control group patients underwent extensive medical examinations, and completed questionnaires, at baseline (6–8 weeks after the randomization), at the time corresponding to 10 weeks of intensive therapy, and at 1 year after baseline. An additional follow–up was performed 1–2 years after the 1–year examination, when questionnaires were completed and blood samples were obtained. Pharmacotherapy, adherence to medical advice, and attendance rate were monitored in both groups throughout the study period. The study was approved by the Huddinge Hospital Ethics Committee (No.196/94).

Study V

The participants (n=440, mean age 58±10 years, 21% women) were part of a 1–year comprehensive lifestyle change program taking place at 8 clinical centers in the US. Patients had to meet requirements for either "Group 1" or "Group 2", representing different stages of disease. Group 1 consisted of patients who had been approved for a revascularization procedure (n=194, 44% of all men; 43% of all women) and group 2 of patients who had had a prior revascularization procedure and were in stable condition (n=246, 56% of all men; 57% of all women). The program aimed at improving diet, exercise, stress management, and social support to prevent coronary morbidity and improve quality of life. Spousal participation was encouraged. The research protocol was approved by the Committee on the Protection of Rights of Human Subjects at the different sites and written informed consent was obtained from participants before beginning the intervention.

Hospital site selection was based on location in areas with sufficient population density (>500,000 within a 60 minute drive time of the site); a sizable cardiology program as evidenced by the number of invasive procedures done annually and/or the size of their current cardiac rehabilitation efforts; demonstration of interest and support among key physicians; and ability to convince large health insurance payers of the value of including the program in their benefit plan. Potential participants were contacted by a program staff member following referral to the program either by their physicians or by self–referral as a result of local media publicity. A brief description of the program was given and demographics, and health history were obtained. Eligible patients (determined by interview) were sent a description of data collection activities, a release of medical records form, and a medical history questionnaire (including medication), and an informed consent form to be completed prior to an intake interview. Spouses were requested to accompany the patient at the intake interview. During the interview, a baseline physical assessment (anthropometrics) was completed. A second interview was scheduled with the hospital team following the intake interview, which included administration of psychosocial and behavioral questionnaires, instructions for completion of a 3–day diet diary, a blood draw for baseline lipid profile, and a treadmill exercise stress test using the Bruce protocol. Medical and behavioral variables were re–assessed at 3 and 12 months.

Intervention

Study IV

STRESS MANAGEMENT

The stress management program was a broadened adaptation (Burell, Granlund, 2002) of the one initially created for the Recurrent Coronary Prevention Project (Friedman et al., 1982). In addition to type–A behavior, this stress management program targeted feelings of depression and vital exhaustion. The program was carried out by trained research nurses, and consisted of twenty 2–hour sessions in a group–format of 4–6 patients/group. The first ten sessions were held weekly and the subsequent ten monthly. All sessions had elements of both education and discussions. The initial sessions were aimed at teaching facts about CHD, how the disease is affected by an unhealthy lifestyle, and the physiologic stress response. Subsequent sessions aimed at teaching ways to identify the physical, cognitive, affective and behavioral stress–responses and ways to modify these. The theoretical basis for the intervention was cognitive–behavioral, and the following strategies were taught to patients; self–monitoring, cognitive restructuring (replacing negative and irrational thoughts with alternative ones), relaxed behavior practices, progressive relaxation, and assertive communication and strategic problem–solving skills. Furthermore, the session–material was designed to illustrate stressors and stress reactions typically common among women and included 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, and being vulnerable to suffer from low self–esteem, depression and anxiety. A non–controlled feasibility study of the program was previously carried out in a sample of women (n=23, mean age 59 years). It was found to be attractive and had an attendance rate of 80%. Results showed significant improvement in quality of life, and a decrease in self–rated stress and vital exhaustion (Burell, Granlund, 2002).

Study V

The 1–year lifestyle change program included a low–fat, whole foods plant–based diet with no more than 10% of total calories from fat, moderate exercise, stress management, and group support sessions. The program began with a 12–hour intensive orientation seminar at the hospital site that included lectures providing the scientific rationale for the program as well as experiential sessions. Following the orientation, patients attended program sessions three times per week for 12 weeks. Two sessions consisted of the four program components in one–hour blocks. The third weekly session consisted of one hour of aerobic exercise

and one–hour lectures designed to meet the educational objectives and skills training to facilitate long–term adherence to the program guidelines. One weekly session consisting of the four components in one–hour blocks was offered for the following 40 weeks.

THE PROGRAM COMPONENTS

Diet

Two intervention meals per week were provided as part of the evening meetings at the hospital site. In addition, periodic potluck dinners or lunches were held, for which patients and their partners prepared food at home to bring to the group meetings for the meal. A registered dietitian was present during the meals to provide educational support and dietary counseling. The diet excluded caffeine and limited animal products to egg whites and one cup of non–fat milk or yogurt daily; this averaged 10 milligrams of cholesterol intake per day. Alcohol, which was not served and neither discouraged nor encouraged, was restricted to one drink (one cocktail or glass of wine or beer) per day in those without prior alcohol abuse. Sodium intake was restricted only for hypertensive patients or those with congestive heart failure or renal disease. The meals contained approximately 10% daily calories from fat, 15% from protein, and 75% from complex carbohydrates.

Aerobic Exercise

The exercise prescription followed the guidelines of the American College of Sports Medicine (Franklin et al., 1991). Each patient was prescribed an exercise level according to a baseline treadmill stress test; these levels were updated during each of the following times when treadmill tests were performed. Patients were asked to exercise a minimum of three hours per week and to spend a minimum of 30 minutes per session exercising within their prescribed target heart rates and/or perceived exertion levels. The target heart rates were calculated at 45–80% of maximal heart rate achieved during the treadmill test using the Karvonen formula. (Franklin et al., 1991; Karvonen et al., 1957). If ischemia occurred during the baseline stress test, the heart rate at which 1 mm of ST segment depression first occurred was designated the maximum heart rate. Most patients' exercise consisted of walking on their own. On site, patients participated in traditional cardiac rehabilitation exercise sessions and were supervised by trained professionals on treadmills, tracks, exercise bicycles, stair climbers, rowing machines, and hand ergometers.

STRESS MANAGEMENT

The stress management practices integrated stretching, relaxation, yogic breathing techniques, meditation, and guided imagery. Each technique was selected for the purpose of enhancing a patient's sense of relaxation, concentration, and awareness of internal states. Specifically, patients were taught a series of 12 yoga poses designed to stretch and tone the body while developing internal awareness (Ornish, 1990). Patients were asked to practice these stress management techniques for at least one hour per day using an audiocassette for home practice. On site sessions were taught by trained professionals and were medically supervised.

GROUP SUPPORT

The group support sessions provided social support to help patients adhere to and sustain the lifestylechange program. These sessions were directed by a licensed mental health professional who taught communication skills to enhance intimacy and encouraged expression of feelings about relationships in a supportive, safe environment.

Measurement of the study variables

Psychosocial factors

Vital exhaustion

Study I–III: Vital exhaustion was measured by means of an early version of the Maastricht Questionnaire (MQ, Appendix 1). The scale is a 18–item self–administrated scale (rated on a scale 1–3) and includes questions on fatigue, irritability, depressed affect, and personal accomplishment. Compared to the later and more commonly used version of MQ, this scale contained more items of depression and less or no items of fatigue, disturbed sleep, or ability to concentrate.

To examine the psychometric validity of the scale, an inter–correlation analyses was carried out between the early and present version of the MQ in two sub–samples of women residing in Stockholm: one consisting of women with CHD (n=20, mean age 66.9, SD 7.0, range 54–81 years), and one consisting of healthy women (n=20). In both instances, significant associations were found between the scales: $r=0.66$ $p<0.002$ for women with CHD, and $r=0.90$, $p<0.01$ for healthy women. In addition, in both groups of women, the revised scale yielded excellent internal reliability (Cronbach's $\alpha=0.93$).

Study IV: Vital exhaustion was measured by means of the MQ (Appels et al., 1987; Appendix II), a 21–item self–administrated scale (rated on a scale 0–2) measuring the attitudes and symptoms of mental and physical fatigue.

Depression

Study IV: Depression was assessed by means of the Beck Depression Inventory (BDI; Beck et al., 1961; Groth−Marnat, 1990; Appendix III), a 21−item self−administrated scale (rated on a scale 0−3) measuring the attitudes and symptoms of depression. Internal consistency of the BDI is substantial, ranging between Cronbach's α=0.73−0.92 with a mean of 0.86 (Beck et al., 1988). Furthermore, BDI has been found to have high content validity and to discriminate well between depressed and non−depressed people (Richter et al., 1998).

Quality of life

Study V: Quality of life was assessed by means of the widely used MOS SF−36 Health Survey (Ware, Sherbourne, 1992; Appendix IV) a 36−items self−administrated scale yielding eight subscales: (1) physical functioning; (2) role − physical (limitations in usual role activities because of physical health problems), (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role − emotional (limitations in usual role activities because of emotional problems), and (8) mental health.

All dimensions of the scale (except social functioning) have been found to have adequate internal consistency (Cronbach's α>0.85), and reliability (>0.75). Furthermore, the instrument has high construct validity in terms of distinguishing between individuals of different health status (Brazier et al., 1992).

In several studies, strong negative correlations have been observed for all MOS SF−36 Health Survey subscales and the well−established BDI (Callahan et al., 1997; Findler et al., 2000; McKee et al., 2001). Particularly strong associations have been found between BDI and the subscales mental health (r=−0.69), vitality, (r=−0.63), social functioning (r=−0.62), and role−emotional (r=−0.54) (McKee et al., 2001).

In an analysis carried out on patients with CHD taking part in a stress management program at the Karolinska Hospital, Sweden (n=15, 40% women, mean age 61.7±6.5, range 48−70 years), the subscales vitality and mental health were highly associated with vital exhaustion, r=−0.74, p<0.002 and r=−0.82, p<0.001 respectively, and r=−0.87, p<0.001 for the two subscales combined.

Thus, high scores on the SF−36 not only reflect a better overall psychosocial status, but also the relative absence of depression and vital exhaustion.

Lifestyle factors

Physical activity

Study I–II: Physical activity during leisure was assessed based on an abbreviated questionnaire according to WHO criteria (Baecke et al., 1982) using the following four grades; 1) reading, watching TV or other sedentary leisure activities, 2) walking, cycling or other forms of physical activities, 3) exercises to keep fit, heavy gardening etc. for at least four hours per week, 4) hard training or participation in competitive sports several times per week. The results were analysed by dichotomizing the data into a sedentary (grade 1) or a non–sedentary lifestyle (grade 2–4).

Smoking

Study I–III: Smoking behavior was assessed by means of questionnaire and classified in three categories; never a smoker, previously a smoker (≥1 year ago), or current smoker. In study 3, current smokers were further categorized according to number of cigarettes smoked per day: 1–4, 5–10, 11–20, and >20.

Alcohol consumption

Study III: Alcohol consumption was assessed by means of a food frequency questionnaire (Willet et al., 1995) asking open–ended questions about content, quantity, and of consumption. The total amount of alcohol consumed (100% ethanol) was calculated and expressed in grams per day.

Diet

Study V: Participants completed a three–day food diary at baseline and at each time point to assess nutrient intake and dietary adherence (Rimm et al., 1992).

Physiological factors

Clinical history

Study I–III: A physician interviewed the patients about the clinical history of diabetes mellitus, hypertension, medication use, and gynaecological status. Patients were considered to have diabetes mellitus if anti–diabetic therapy was prescribed. Menopause was defined as absence of menstrual bleeding for at least six months prior to examination, or a history of bilateral oophorectomy, or being above 50 years old and taking hormone replacement therapy (HRT) before

menopause. Menopausal status was categorized into: premenopausal, postmenopausal with HRT, and postmenopausal without HRT.

Study V: A nurse case manager reviewed a questionnaire with the patient's completed health history.

Anthropometric measures

Study I–III, V: BMI was calculated as weight/height^2.

Study II: Waist–hip ratio was calculated by dividing the circumference at the narrowest point around the waist by the circumference at the widest point between the umbilicus and the thighs.

Blood pressure

Study I–III: Systolic and diastolic blood pressures (mm Hg), after five minutes supine rest, were assessed by a research nurse. Phases I and V of the Korotkoff sound were used.

Study V: Blood pressure measurements were performed by a trained health professional using a calibrated sphygmomanometer according to American heart association (AHA) practice guidelines (Perloff et al., 1993). Resting blood pressure was obtained in a sitting position and in the right arm unless otherwise indicated.

Angina or chest pain

Study I: Severity of chest pain was assessed by a physician and defined by Canadian class classification (Campeau, 1976).

Study V: Angina was evaluated via a registered nurse–conducted interview using a modified version of the Rose Questionnaire (Rose et al., 1982) whereby the presence or absence of "current" angina was determined by the patients' responses to a number of questions using diagnostic criteria for angina. "Current" angina was defined as the presence of at least one symptom within the 30 days prior to the interview.

Coronary angiography

Study I–II: Adequate selective coronary angiography using the Judkins' technique (Judkins, 1967) was obtained in 80 (study 1) and 238 (study 2) patients, respectively. Limited laboratory resources were the main reason for not performing angiography in all patients. Cine film registrations were made with 25 frames/s. Lesion severity was estimated visually from multiple angiographic views (Judkins, 1967). Left ventricular function was visually classified as normal or

dysfunctional. Coronary artery stenosis was assessed according to how many vessels had a luminal narrowing of at least 50%. In the analyses, coronary stenosis was treated as a dichotomous variable; 1) normal arteries or minor lesions (<50% luminal narrowing), and 2) significant coronary stenosis (luminal narrowing ≥50% in at least one coronary artery). The dichotomization was considered clinically meaningful in the sense that 50% stenosis is usually the cut–off value for intervention.

Lipids, cortisol, glucose

Study I–III: A lipid and routine laboratory profile including glucose, and cortisol, was obtained from venous blood samples taken from the right arm, in a supine state, between 8:00 and 9:00 in the morning with patients fasting from midnight.

Serum separated tubes were centrifuged for ten minutes at 3000 g (revolutions per min.). Four ml of plasma were frozen to −70 C. Tubes were sent in batches to the same processing laboratory (CALAB) once per month. From the samples, total cholesterol, triglycerides, HDL–C, low–density lipoprotein cholesterol (LDL–C), very low–density lipoprotein cholesterol (VLDL–C), Apolipoprotein A1, and apolipoprotein B were derived. Total cholesterol and triglycerides were determined by enzymatic methods with reagents from Boehringer Mannheim (Germany). HDL–C was determined based on the isolation of LDL–C and VLDL–C from serum by precipitation. The cholesterol content of the supernatant, i.e. HDL–C cholesterol, was measured enzymatically, using an automated Multichannel Analyzer (Riepponen et al., 1987). Apolipoprotein A1 and apolipoprotein B were assessed by immunoturbidometry using polyclonal antisera (Orion Diagnostics) (Jungner et al., 1992). The analyses were performed in the same laboratory (CALAB) using an automated multichannel analyser (Glueck et al., 1980).

Cortisol was measured by standardized radioimmunoassays (RIA), using the same batch of reagents under conditions described previously (Hedman et al., 1989). All samples were analysed in duplicate and mean values were computed. Intra–assay and inter–assay coefficients of variation never exceeded 10 and 20, respectively (de la Torre et al., 1997).

Study IV: Determination of total cholesterol, HDL–C, triglycerides and glucose in plasma were performed on Hitachi 917 Automatic Analyser, Roche Diagnostics GmBh, Mannheim, Germany, using the following reagents: CHOD–PAP, GPO–PAP, HDL–C Plus and Gluco–Quant, respectively (Roche Diagnostics (GmBh). LDL–C was calculated according to Friedewald's formula. Serum cortisol was determined by fluoroimmunometry using Wallac AutoDELFIA 1235 Automatic

Immunoassay System and the AutoDELFIA Cortisol kit (Wallac Oy, Turku, Finland). High sensitive CRP in plasma was performed by nephelometry using N−dilutent for Nephelometry, Behring OUMT 61 (Dade Behring GmBh, Marburg, Germany).

Study V: Patients were asked to be in a fasting state for at least 12 hours before venipuncture. Two 9.5 ml vacutainers (SST tubes) of blood were collected at each measurement. Samples were allowed to clot for 30−45 minutes and then centrifuged at 2500xG for 20 minutes or 5000xG for 10 minutes. Following onsite testing, the additional serum was pipetted into five 1ml tubes and frozen per trial protocol (−70 degrees celsius). Sites either stored the frozen aliquots onsite or batches were sent to a central laboratory per serum shipping protocol. Standard lab methods and principals of Baylor School of Medicine Atherosclerosis Laboratory and site laboratories used enzymatic and colorimetric measurement procedures of Boehringer Mannheim (Germany). Monotest Cholesterol Procedure, GPO Triglyceride procedure, HDL magnesium sulfate extraction (Mg2+), and LDL−C was calculated (total cholesterol minus HDL plus 0.16 x Triglycerides. From the samples, total cholesterol, triglycerides, high−HDL−C, and LDL−C, were derived.

Exercise capacity

Study III: Exercise capacity was defined as maximal achieved work capacity (max watt) and was measured by means of symptom limited stress testing performed on an electrically braked bicycle (Megacart 840, Siemens−Elema, Solna, Sweden) with stepwise increasing workload by 10 watt/min from the starting load of 30 watt/min. The procedure has previously been described in detail (Al−Khalili et al., 2000).

Study IV: The effect of 1 year of exercise training in a randomized trial has been investigated before (Myers et al., 1984; Sullivan et al,. 1985; Sebrechts et al., 1986). Exercise training was not part of our randomized study design. However, maximal exercise tests have been performed at baseline and 1 year examination, data not yet analysed.

Study V: Exercise tolerance, expressed in METs (metabolic equivalents) at peak workload was assessed by maximal treadmill using Bruce or Modified Bruce protocols. Indications for stopping the test were provided by ACSM's Guidelines for Exercise Testing and Prescription (Franklin et al., 1991).

Demographic factors

Study I−IV: Age was obtained from the personal number. Educational level was obtained from questionnaires and classified into the following

three grades: 1) mandatory only (corresponding to nine years of school education), 2) high school, or 3) college/university.

Study V: Age, educational attainment, marital and employment status, were assessed during the interview conducted by a nurse case manager.

Statistical methods

The statistical methods in this thesis were performed using JMP 3.2 (Study I–III), SPSS 9.0 (Study I), SPSS 10.0 (Study II, III), SPSS 11.0 (Study IV, V), and SAS (Study IV). Two–tailed tests were used in all analyses.

The statistical methods used in each paper are summarized in Table 3.

Table 3. Statistical methods used in this thesis.

Method	**Study**				
	I	**II**	**III**	**IV**	**V**
χ^2–test	X	X	X	X	X
Analysis of variance (ANOVA)	X	X	X	X	X
Analysis of covariance (ANCOVA)		X	X		
Linear mixed model				X	
Linear regression	X	X	X	X	
Logistic regression		X			
Survival analysis	X				

RESULTS

Study I

The aim of the study was to investigate the effects of vital exhaustion on recurrence of coronary artery disease (defined as cardiac death, AMI, PTCA, or CABG) in women with AMI over a 5−year period.

Participants were women who were included in the Female Coronary Risk study because of AMI n=110 (mean age 55.30±7.63, range 30−65 years). Patients with recurrent events had higher vital exhaustion scores (p=0.006), lower levels of HDL−C (p=0.009), were more likely to have significant coronary artery stenosis (p=0.002), and there was a trend toward them having more severe ventricular dysfunction (p=0.09).

The distribution of baseline medical and lifestyle characteristics in relation to quartiles of vital exhaustion is presented in Table 4 (unpublished data). As seen, patients scoring in the upper quartiles of vital exhaustion were more likely to lead a sedentary lifestyle, to have moderate or severe chest pain, and to have elevated LDL−C levels.

During the five−year follow−up, there were 6 cardiac deaths, 16 recurrent AMI, 17 CABG, and 18 PTCA. If multiple events occurred during the follow−up period only the first event for each subject was considered, resulting in a total of 45 recurrent events. Among the 83 patients involved in the multivariate−adjusted analyses, there were 35 recurrent events.

Measured as a continuous scale, vital exhaustion was associated with an unadjusted hazard ratio (HR) of 1.05 (95% CI 1.02−1.09), meaning that each standard deviation (8.4 points) increase of the vital exhaustion score increased the risk of a new event by 53%. A score above the median increased the risk by 2.24 (1.21−4.14). The results only changes marginally when controlling for potential confounders including severity of chest pain, and significant coronary artery stenosis. Further adjustment for left ventricular dysfunction (an indicator of poor cardiac function which could be argued to cause feelings of vital exhaustion), diabetes and low HDL−C (both of which previously have been found to predict recurrent events in this study population) did not change the results.

Figure 1 depicts the actuarial probability of event−free survival according to degree of vital exhaustion. A score at the median or below=63%, and above the median=45% (Log rank test, 6.92, p=0.009).

Table 4. Distribution of the study variables in relation to quartiles of vital exhaustion.

Variable	Quartile 1 N (%)	Quartile 2 N (%)	Quartile 3 N (%)	Quartile 4 N (%)	P[1]
Menopausal status					
Premenopausal	8 (24)	9 (29)	6 (19)	8 (26)	
Postmenopausal with HRT[2]	3 (9)	4 (36)	3 (27)	1 (9)	
Postmenopausal without HRT[2]	22 (67)	12 (18)	14 (22)	17 (26)	0.71
Cigarette smoking					
Nonsmokers	8 (24)	6 (19)	5 (16)	13 (41)	
Previous smokers	20 (61)	14 (25)	12 (21)	10 (18)	
Current smokers	5 (15)	5 (26)	6 (32)	3 (16)	0.25
Sedentary lifestyle	10 (14)	14 (20)	22 (32)	23 (33)	0.01
History of hypertension	16 (33)	12 (25)	11 (23)	9 (19)	0.69
Diabetes mellitus	2 (17)	2 (17)	4 (33)	4 (33)	0.48
Chest pain (moderate or severe)	6 (18)	19 (38)	16 (70)	14 (56)	0.002
Coronary stenosis ≥50%	14 (25)	16 (28)	15 (26)	12 (21)	0.95
Left ventricular dysfunction	3 (20)	4 (19)	3 (20)	5 (33)	0.68
	Mean (SD)[3]	**Mean (SD)[3]**	**Mean (SD)[3]**	**Mean (SD)[3]**	**P[4]**
Age	55.94 (7.64)	55.36 (6.61)	54.83 (8.33)	54.69 (8.38)	0.96
Systolic blood pressure (mm Hg)	122.58 (19.67)	121.00 (17.41)	119.00 (18.10)	113.81 (17.40)	0.23
BMI (kg/m^2)[5]	26.98 (5.22)	26.05 (3.04)	26.95 (4.41)	27.31 (5.42)	0.96
Triglycerides	1.59 (0.71)	3.10 (5.12)	1.75 (1.21)	1.67 (0.77)	0.97
Cholesterol	6.35 (1.28)	6.46 (1.59)	6.57 (1.15)	6.64 (1.08)	0.60
LDL−C[6]	4.11 (1.17)	3.23 (1.63)	4.23 (1.35)	4.50 (0.99)	0.01
HDL−C[7]	1.42 (0.37)	1.33 (0.43)	1.36 (0.37)	1.33 (0.51)	0.34

[1] probability value for chi−square test,

[2] HRT=hormone replacement therapy,

[3] SD=standard deviation,

[4] probability value for Wilcoxon signed rank test,

[5] BMI=body mass index,

[6] LDL−C= low−density lipoprotein cholesterol,

[7] HDL−C= high−density lipoprotein cholesterol.

In conclusion, our results suggest that vital exhaustion is associated with recurrence in middle−aged post−MI women, independently of standard risk factors of CHD and signs of underlying disease. Our results replicate those previously performed in men, and confirm vital exhaustion as an important risk indicator of recurrent of cardiac events in women as well.

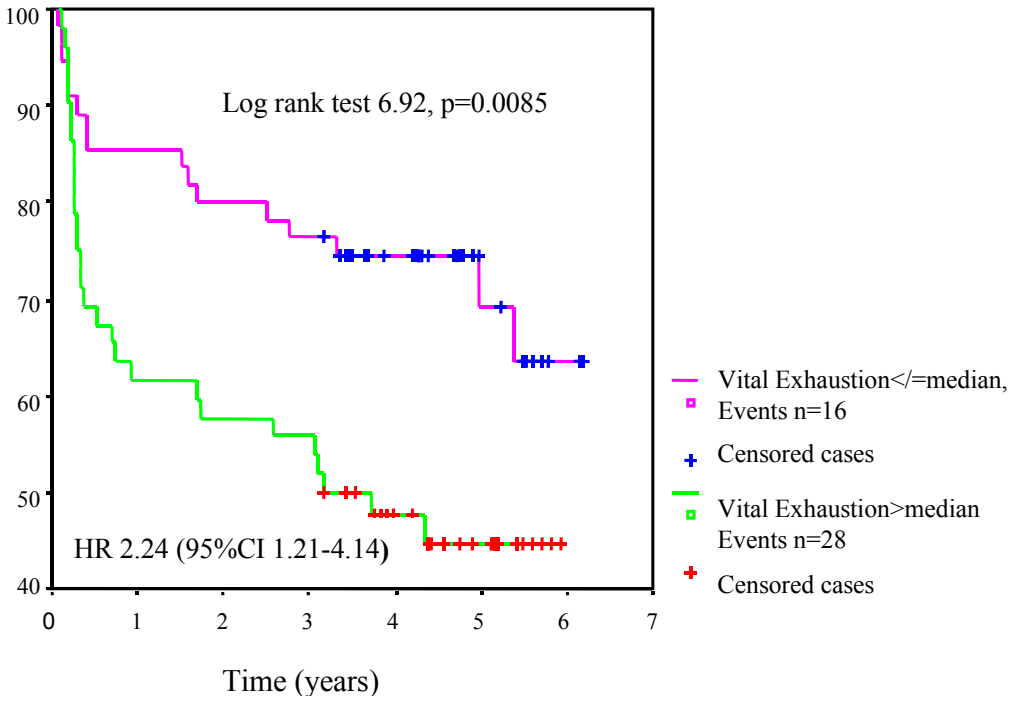

Figure 1. The actuarial probability of event−free survival according to degree of vital exhaustion.

Study II

The aim of the study was to investigate the relationship between chronic stress − assessed by serum cortisol and vital exhaustion − and coronary artery stenosis and the importance of chronic stress in relation to standard risk factors of CAD.

Participants were women of the Female Coronary Risk study, included with AMI (37%) or UAP (63%), who had undergone coronary angiography (n=238, mean age 56±7 years, range 30−65 years). Luminal narrowing of at least 50%, was present in 63% of the patients. Compared to patients with non−significant coronary stenosis, patients with significant coronary stenosis had higher levels of cortisol, triglycerides, LDL−C, and glucose, but lower levels of HDL−C, had a higher waist−hip ratio, and were more likely to have AMI as index event, to be diabetic, obese, and previous smokers. Furthermore, they were more often prescribed beta−blockers but less often calcium channel−blockers. Weak but significant positive associations were found between cortisol and vital exhaustion (r=0.13, p=0.05), smoking (r=0.13, p=0.05), and glucose (r=0.14, p=0.05), respectively. An inverse

association was found between cortisol and physical activity (r=−0.13, p=0.05). Vital exhaustion was inversely related to physical activity (r=−0.17, p=0.01).

Table 5 shows the results of the age− and multivariate−adjusted multiple regression analyses, with the odds ratios for each unit− and 25%−increase of the predictor variables. The main finding was that each 25% increase of cortisol was associated with a 41% increased probability of having significant coronary stenosis (p=0.005) after adjusting for age, and 37% after adjusting for age, glucose, and use of beta−blockers. Further adjustment for diabetes (instead of glucose) and diagnosis at index event only changed the results marginally.

Table 5. Risk for significant coronary artery stenosis (≥50% in at least one vessel) in relation to cortisol, vital exhaustion and standard risk factors of CAD (n=238).

Factor	Age−adjusted OR[a] for each unit−change		Age−adjusted OR for each 25%−change		Multivariate−adjusted OR for each unit−change	
	OR (95% CI)[b]	P[c]	OR (95% CI)	P	OR (95% CI)	P
HDL−C (mmol/L)	0.31 (0.15−0.63)	0.001	1.65 (1.21−2.26)	0.002	0.33 (0.16−0.70)[d]	0.004
Cortisol (nmol/L)	1.01 (1.00−1.02)	0.004	1.41 (1.11−1.80)	0.005	1.01 (1.00−1.02)[e]	0.02
Glucose (mmol/L)	1.16 (1.03−1.31)	0.02	1.36 (1.09−2.38)	0.007	1.13 (1.00−1.27)[f]	0.05
LDL−C (mmol/L)	1.20 (0.97−1.48)	0.10	1.35 (1.07−1.71)	0.01	1.23 (0.99−1.53)[g]	0.06
Total cholesterol (mmol/L)	1.20 (0.95−1.53)	0.12	1.37 (0.97−1.92)	0.07	1.18 (0.93−1.51)[h]	0.18
Triglycerides (mmol/L)	1.16 (0.92−1.46)	0.20	1.14 (1.02−1.27)	0.03	1.10 (0.87−1.39)[i]	0.42
DBP (mmHg)	1.02 (0.99−1.04)	0.21	1.28 (0.85−1.92)	0.23	1.02 (0.99−1−04)[j]	0.21
Vital exhaustion	1.02 (0.99−1.06)	0.27	1.18 (0.91−1.53)	0.22	1.01 (0.98−1.05)[k]	0.47
SBP (mmHg)	1.01 (0.99−1.03)	0.27	1.23 (1.01−1.91)	0.34	1.01 (0.99−1.03)[l]	0.27
BMI (kg/m^2)	1.01 (0.95−1.07)	0.83	1.03 (0.70−1.52)	0.87	1.00 (0.94−1.07)[m]	0.97
Current smoking n=39 (16%)	1.37 (0.67−2.96)	0.41			0.60−2.72)[n]	0.53
Sedentary life−style n=54 (23%)	1.14 (0.61−2.14)	0.68			0.61−2.14)[o]	0.68

[a] OR=odds ratio,
[b] CI=confidence interval,
[c] P=p−value Chi square test,
[d] adjusted for age, glucose, and smoking,
[e] adjusted for age, glucose, and use of beta−blockers,
[f] adjusted for age, cortisol, diagnosis at index event,
[g] adjusted for age and glucose,
[h] adjusted for age, and glucose,
[i] adjusted for age and glucose,
[j] adjusted for age only,
[k] adjusted for age, glucose, and use of beta−blockers,
[l] adjusted for age only,
[m] adjusted for age and SBP,
[n] adjusted for age and cortisol,
[o] adjusted for age only.

Furthermore, analyses were carried out with cortisol as a variable dichotomized by the sample median. Adjusting for age, glucose, and beta−blockers, patients above the sample median had a near two−fold increased probability of CAD, OR=1.97 (95% CI 1.12−3.48). No independent association was found between vital exhaustion and coronary stenosis (p=0.47). However, having levels of both cortisol and vital exhaustion above the sample median was associated with a near three−fold probability of CAD, OR=2.85 (95% CI 1.31−6.18) after adjusting for age, diabetes, and use of calcium channel− and beta−blockers. In comparison with standard risk variables of CAD, cortisol remained an important predictor of significant coronary stenosis. Only HDL−C was associated with a higher probability of coronary stenosis, increasing the risk by 65% for each 25% decrease of HDL−C.

In conclusion, cortisol, but not vital exhaustion, was independently related to significant coronary stenosis in middle−aged women with acute coronary syndrome.

Study III

The aim of the study was to investigate the relationship between vital exhaustion, lifestyle and lipid profile.

Participants were women who were the healthy controls of the Female Coronary Risk study (n=300, mean age 56±7 years). The distribution of baseline characteristics according to vital exhaustion quartiles is presented in Table 6. No significant differences were found between the levels of vital exhaustion. Vital exhaustion was inversely related to HDL−C and apolipoprotein A1 in a linear fashion while adjusting for age, exercise capacity, BMI, and alcohol consumption (Table 7). Similar, but non−significant trends were observed for triglycerides and VLDL−C. A vital exhaustion−score in the top quartile, as compared to one in the lowest, was associated with significantly lower levels of HDL−C (12%) and apolipoprotein A1 (8%), and non−significant higher levels of triglycerides (10%) and VLDL−C (17%) after adjustment for potential confounders including age, smoking, alcohol consumption, exercise capacity, menopausal status, and educational level.

In conclusion, an inverse, graded relationship was observed between vital exhaustion and HDL−C and apolipoprotein A1 in healthy women. The differences in lipid levels between different levels of vital exhaustion were clinically relevant in terms of CHD risk. The impact of lifestyle variables in the vital exhaustion−lipid relationship appeared to be weak. Due to the exploratory nature of this study, the results need to be replicated before further conclusions are made.

Table 6. Distribution of the study variables according to quartiles of vital exhaustion in healthy women (N=300).

	Quartile 1 N (%)	**Quartile 2 N (%)**	**Quartile 3 N (%)**	**Quartile 4 N (%)**	**P[1]**	**N**
Menopausal status						
Premenopausal	23(30)	19(25)	21(30)	21(31)		84
Postmenopausal with HRT[2]	5(6)	13(17)	14(20)	8(12)		40
Postmenopausal without HRT[2]	50(64)	44(58)	35(50)	38(57)	0.26	167
Cigarette smoking						
Never/previous smokers (>1year)	56(72)	60(80)	44(60)	42(63)	0.06	202
Current smokers 1−4/day	3(4)	3(4)	3(4)	5(7)		14
Current smokers 5−10/day	4(5)	4(5)	6(8)	7(10)		21
Current smokers 11−20/day	12(15)	8(11)	18(25)	10(15)		48
Current smokers >20/day	3(4)	0(0)	2(3)	3(4)	0.81	8
Educational level						
Elementary school	41(51)	35(45)	47(64)	37(54)		160
High school or college	39(49)	42(55)	27(36)	32(46)	0.16	140
	Mean (SD[3])	**Mean (SD[3])**	**Mean (SD[3])**	**Mean (SD[3])**		
Age (years)	56.78(7.80)	56.69(6.88)	56.05(7.07)	55.97(6.65)	0.86	299
BMI[4](kg/m^2)	25.15(5.06)	25.56(4.52)	25.35(4.79)	26.42(4.78)	0.41	299
Alcohol consumption (g/day)	8.48(8.26)	9.05(9.46)	6.96(8.18)	6.22(5.78)	0.15	269
Exercise capacity (max watt)	124.03(25.30)	128.95(29.78)	125.29(24.12)	129.62(27.85)	0.52	289

[1]P=probability value for χ^2−test and ANOVA for discrete and continuous variables, respectively, [2]HRT=hormone replacement therapy, [3]SD=standard deviation, [4]BMI=body mass index.

Table 7. Effect of vital exhaustion on lipid profile, least square mean mmol-values (standard error).

Factor	Cholesterol	Triglycerides	HDL	LDL	VLDL-C	Apo A1	Apo B
Age-adjusted values							
VITAL EXHAUSTION							
Quartile 1	6.15(0.11)	0.90(0.04)	1.79(0.05)	3.85(0.11)	0.17(0.00)	1.46(0.02)	1.06(0.03)
Quartile 2	6.03(0.11)	0.92(0.05)	1.73(0.05)	3.77(0.11)	0.18(0.00)	1.43(0.02)	1.05(0.03)
Quartile 3	5.95(0.11)	1.02(0.05)	1.69(0.05)	3.70(0.11)	0.20(0.01)	1.43(0.02)	1.06(0.03)
Quartile 4	6.10(0.12)	0.99(0.05)	1.59(0.05)	3.92(0.12)	0.20(0.01)	1.36(0.03)	1.11(0.03)
Difference between quartile 1 and 4							
mean value(%)	0.05(00)	0.09(10.0)	0.20(11.2)[1]	0.07(1.8)	0.03(17.6)	0.11(6.8)[1]	0.05(4.7)
P-value for trend	0.62	0.24	0.04	0.56	0.18	0.03	0.59
Multivariate-adjusted values							
Vital exhaustion							
Quartile 1	6.16(0.11)[2]	0.91(0.04)[3]	1.83(0.05)[4]	3.84(0.11)[2]	0.18(0.00)	1.48(0.02)[5]	1.06(0.03)[2]
Quartile 2	6.05(0.11)	0.94(0.05)	1.72(0.05)	3.79(0.11)	0.18(0.00)	1.42(0.02)	1.06(0.03)
Quartile 3	5.98(0.12)	1.02(0.05)	1.71(0.05)	3.73(0.11)	0.20(0.01)	1.45(0.03)	1.06(0.03)
Quartile 4	6.18(0.12)	1.00(0.05)	1.61(0.05)	3.98(0.12)	0.21(0.01)	1.37(0.03)	1.12(0.03)
Difference between quartile 1 and 4							
mean value(%)	0.02(00)	0.09(10.0)	0.22(12.0)[1]	0.14(3.6)	0.03(16.7)	0.11(8.0)[1]	0.06(5.7)
P-value for trend	0.59	0.31	0.03	0.47	0.17	0.02	0.48

[1] significant difference using Student's t-test for each pair (alpha level 0.05), covariate variables were selected by multiple regression analysis with stepwise forward selection (criteria to enter set at 0.20):

[2] adjusted for age, exercise capacity and BMI,

[3] adjusted for age, exercise capacity, BMI, and smoking,

[4, 5] adjusted for age, exercise capacity, BMI, and alcohol consumption

Study IV

The aim of the study was to evaluate the effects of a 1−year stress management program on vital exhaustion, depression, and biological variables in women with CHD.

The participants were women (n=247, mean age 62±9 years, range 35−75 years) who had just had an AMI (with or without a revascularization procedure, 57%), a PTCA (15%), CABG (21%), or both PTCA and CABG (7%). They were randomized to either stress management or usual care. At baseline, patients in the intervention group (n=111) and the control group (n=114) were comparable with regard to age, hospital site, educational−, marital−, and working status. Depression levels were also similar (intervention group: mean=11.15, median=10, SD=6.18, range=0−28, control group: mean=10.70, median=10, SD=7.06, range=1−34). However, the patients in the intervention group had higher levels of vital exhaustion (p=0.036; intervention group: mean=22.67, median=23.00, SD=10.57, range=0−42, control group: mean=19.42, median=19.00, SD=9.55, range=0−42). No differences in vital exhaustion values were found when analyzing patients included with AMI only and revasculariations only separately.

Treatment effects

For vital exhaustion, significant effects were found for time (F=9.68, p<0.0001) and the time*treatment interaction (F=4.44, p=0.005) (Figure 2). This indicates that both groups decreased their levels of vital exhaustion over time, and that the decrease was more rapid in the intervention group. At the three time intervals, the difference in decrease between the two groups were: −3.57, p=0.006 between baseline and 10 weeks, 1.12, p=0.40 between 10 weeks and 1 year, and –2.22, p=0.066 between 1 year and 1−2 years following intervention. The results remained similar when running separate analyses of patients who were included with a revascularization procedure only (time: F=3.62, p=0.0161, treatment*time: F=3.80, p=0.013). For patients included with AMI only, the effect of time was similar (F=3.38, p=0.022), however, the results for the treatment*time interaction did not reach significance (F=1.34, p=0.266).

For depression, a main effect was found for time (F=8.54, p<0.001) indicating that both groups decreased their levels of depression over time (Figure 3). In analyses stratifying for inclusion event, this effect was found in patients included for revascularization procedure only (F=4.82, p=0.003), but not in patients included with AMI only (F=1.18, p=0.318).

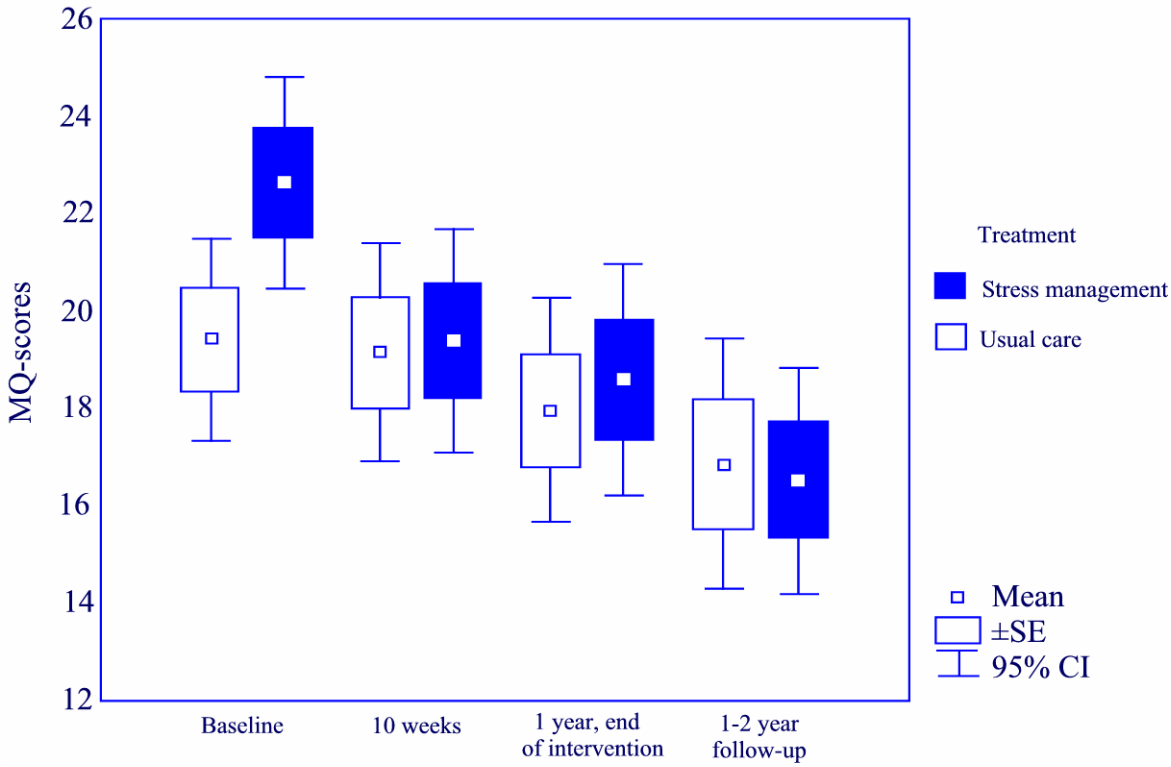

Figure 2. Changes in vital exhaustion according to treatment group.

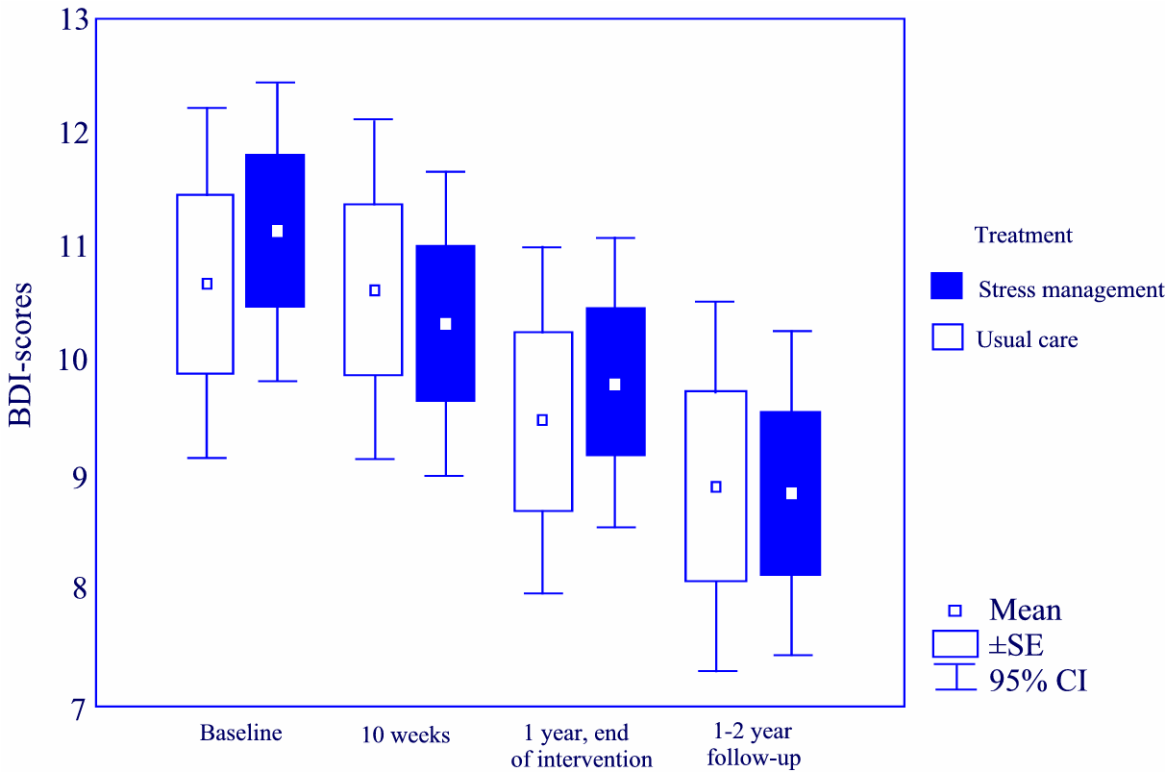

Figure 3. Changes in depression according to treatment group.

Change–variables were created (subtracting a variable–score at 1 year from the score at baseline) to investigate possible effects of changes in vital exhaustion and depression on changes in the aforementioned biological CHD risk factors. The change–variables of vital exhaustion and depression were then entered as independent variables into regression models with biological change–variables as dependent variables, however no significant results were found.

Study V

The aim of the study was to examine baseline characteristics and to evaluate medical and psychosocial effects of a 1–year lifestyle change program for men and women with coronary artery disease.

Participants were men and women (21%) of the Multicenter Lifestyle Demonstration Project (n=440, mean age 58±10 years, range 31–58 years).

Baseline characteristics

At baseline, women were socially more disadvantaged than men, evidenced by having fewer years of education, being less often employed outside the home and more likely to live alone. Women were also less likely to have their partner participate in the program compared to men (25% vs. 49%). Furthermore, they reported more adverse health histories than men; they were more likely to be diabetic; and there were trends for women to be more hyperlipidemic (p=0.067) and to report more angina symptoms in the past 30 days (p=0.078). Women had less often undergone CABG, had less often been smokers, and were more often prescribed calcium channel–blockers and diuretics. Additionally, women consumed fewer alcoholic drinks per week (mean=1.2) than men (mean=3.3; p<0.001).

In regard to medical characteristics, women had a higher BMI, higher resting heart rates, and lower exercise capacity, but did not differ significantly with regard to blood pressure compared to men. Furthermore, women had a more adverse lipid profile with respect to total cholesterol and LDL–C than men, but had higher levels of HDL–C.

In regard to psychosocial and behavioral characteristics women's overall psychosocial profile was more adverse than men's, with the exception of "sense of coherence" and "positive and negative affect," which were similar for the sexes. On the MOS SF–36, women reported more physical, social, and emotional dysfunction, more bodily pain, less vitality, and poorer overall health than men. Women also perceived more stress, were less optimistic, and saw themselves as less efficacious than men in regard to following the diet and the exercise component, but

not the stress management component. Women's current health practices mirrored these sex differences: women exercised less, consumed more calories from dietary fat, but did not differ in time spent on stress management techniques.

Characteristics at Follow–Ups

Changes in medical risk factors and health behaviors can be seen in Table 8. In both sexes, body weight, blood pressure, resting heart rate, total cholesterol, and LDL–C were significantly lowered, and exercise capacity was improved. Improvements in most of these risk factors were evident by 3 months and were maintained at 12 months. Reports of angina among men were reduced from 42% at baseline to 29% 3 months later, to 20% after 1 year. For women, the corresponding percentages were 53%, 35%, and 27%. Both sexes improved at comparable rates. Changes in lipid lowering medications are unlikely to explain the reductions in total cholesterol or LDL–C, as their use was similar at all time points (ca. 50% of patients used these medications).

Both sexes improved their health behaviors over the study period. Although women's intake of dietary fat was higher than men's at baseline, both sexes met the program criteria of limiting their total percentage of calories from fat to less than 10% at both follow–ups. Similarly, at 3 months, both men and women met the program criteria of exercising at least 3 hours/week. However, at all three measurements, women exercised significantly less than men ($p<0.001$). Finally, with regard to stress management, both men and women fell short (by ca. 2.5 hours/week) of the recommended guidelines. However, both sexes did increase time spent in stress management by approximately 4 hours/week.

Attendance of program sessions was higher at 3 months (ranging from 89 to 93%, depending on component) than at 12 months (ranging from 74 to 79%). Overall, women attended fewer exercise and group support sessions than men. No significant sex differences were found for stress management.

With regard to psychosocial variables, only the MOS SF–36 was administered at the follow–ups, allowing for comparisons of changes in quality of life between time points and the sexes (Table 9). Over the study, both men and women had significantly improved all areas of quality of life. Women had made even greater progress than men with regard to physical functioning, role–physical, and role–emotional.

Participants lost to follow–up

The 1–year follow–up was not completed in 27% of the women and 21% of the men. Women completing the follow–up (n=68) were younger (p=0.009) and more likely to be employed (p=0.044). Men completing the follow–up (n=274), were more likely to have a history of PTCA (p=0.026), and a family history of CAD (p=0.004), were more often previous smokers (p=0.033), consumed less alcohol (p=0.042), were more likely to be living with someone (p=0.020) and, among cohabitating men, tended to have their partner participate (p=0.054). They also expressed greater self–efficacy towards adherence to the program components (diet: p=0.071; exercise: p=0.005; stress management: p=0.012).

In conclusion, these results demonstrate that a multi–component lifestyle change program focusing on diet, exercise, stress management, and social support can be successfully implemented at hospitals in diverse regions of the USA. Furthermore, this program may be particularly beneficial for women with CAD, who generally have higher mortality and morbidity than men after AMI or a revascularization procedure.

Table 8. Medical risk factor profile of men and women with complete data at baseline, three months, and at one year.

Variable	Sex	Baseline	3 months	1 year	P–value time	P–value sex	P–value time* sex
Body weight (kg)	Men Women	86.79±17.67 77.07±17.66	82.77±14.32 72.52±16.32	82.39±13.88 71.50±16.16	0.000	0.000	0.366
Systolic blood pressure (mmHg)	Men Women	132.03±18.31 134.67±17.86	126.73±18.06 129.20±17.65	128.66±18.68 132.88±17.38	0.001	0.178	0.812
Diastolic blood pressure (mmHg)	Men Women	79.01±10.27 79.33±9.31	74.09±10.64 75.53±11.63	75.57±10.47 75.76±10.61	0.000	0.602	0.762
Heart rate at rest (bpm)	Men Women	69.05±12.87 76.40±12.84	64.77±12.20 71.62±13.66	67.70±12.60 74.58±11.76	0.000	0.000	0.953
Total serum cholesterol (mmol/L)	Men Women	5.05±1.45 5.63±1.01	4.57±1.49 5.28±1.03	4.62±0.95 5.17±1.11	0.000	0.000	0.509
Low density lipoprotein (mmol/L)	Men Women	3.10±1.19 3.41±0.96	2.60±1.02 2.97±0.97	2.68±0.85 2.86±0.85	0.000	0.028	0.309
High density lipoprotein (mmol/L)	Men Women	0.90±0.27 1.17±0.31	0.79±2.07 1.06±0.37	0.87±0.23 1.16±0.36	0.000	0.000	0.790
Triglycerides (mmol/L)	Men Women	2.63±2.82 2.45±1.28	2.71±2.09 2.85±1.88	2.64±2.15 2.52±1.46	0.200	0.846	0.481
Exercise capacity (METS)	Men Women	10.13±2.96 7.78±2.62	11.77±2.65 8.76±2.77	12.20±2.81 9.44±2.98	0.000	0.000	0.101

Table 9. Quality of life of men and women with complete data at baseline, three months, and at one year.

Variables	Sex	Baseline	3 months	At 1 year	P−value time	P−value sex	P−value time* sex
MOS SF−36[1]							
Physical functioning	Men Women	77.87±19.46 61.67±22.44	86.68±14.08 74.02±20.00	87.75±15.62 78.11±18.29	0.000	0.000	0.022
Role – physical	Men Women	66.60±38.13 48.11±41.21	79.00±33.15 75.00±34.53	81.35±31.72 77.65±34.29	0.000	0.029	0.006
Bodily pain	Men Women	70.66±22.93 63.27±23.83	76.18±21.94 70.89±21.80	79.53±20.29 71.39±20.44	0.000	0.005	0.611
General health	Men Women	59.45±21.01 53.48±20.74	70.24±19.73 65.02±19.00	71.72±21.72 66.33±21.31	0.000	0.026	0.949
Vitality	Men Women	56.13±21.84 45.98±22.16	68.91±16.98 62.20±20.63	68.05±18.64 60.53±21.36	0.000	0.001	0.345
Social functioning	Men Women	79.44±22.80 72.16±24.79	87.06±19.02 85.42±20.17	86.67±20.97 82.95±20.29	0.000	0.066	0.178
Role – emotional	Men Women	75.69±35.02 61.62±39.33	83.40±32.38 81.82±30.48	85.40±29.19 77.27±34.17	0.000	0.025	0.046
Mental health	Men Women	71.14±16.53 65.16±16.56	79.61±13.33 76.18±16.34	79.03±14.93 75.27±17.23	0.000	0.020	0.608

[1] Range 0−100, the higher the scores the better quality of life.

GENERAL DISCUSSION

As reviewed in the introduction vital exhaustion predicts first MI and recurrent coronary events in men and women. The physiological mechanisms mediating this effect are not fully understood. Vital exhaustion may be decreased by means of behavioral modification, however it is yet not established what that may translate into in terms of coronary risk factor modification. Previous of studies of vital exhaustion are based on predominantly male samples and it is yet unclear to what extent the results pertain to women. Studies including larger samples of women may be warranted because they, in comparison to men, may have a worse prognosis after a coronary event, are more exhausted, and show a poor response to cardiac rehabilitation. On the basis of these premises, the purpose of this thesis was to investigate: the relationship between vital exhaustion and markers of CHD in women; potential mechanisms mediating the relationship between vital exhaustion and CHD in women; and the effects of behavioral intervention in women.

Vital exhaustion and markers of CHD

Although the significance of vital exhaustion as a prognostic marker of CHD outcomes has been well demonstrated in men, there has been a paucity of knowledge with regard to women. The results of this study suggest that vital exhaustion is an independent marker of CHD related–outcomes in women as well. After adjusting for standard CHD–risk factors, vital exhaustion was found to predict recurrent coronary events by a factor of two in women who recently suffered an AMI, and to have a significant but not independent effect on probability of CAD in women with acute coronary syndrome. Furthermore, vital exhaustion was positively related to cortisol which, in turn, was positively related to significant CAD.

Despite methodological differences, the main one being usage of a slightly different earlier version of the vital exhaustion–scale, our results replicate those of previous investigations in a predominantly male samples: Kop et al. (1994) found that vital exhaustion predicts recurrent coronary events 1.5 years after successful PTCA (OR=2.7, 95% CI 1.1–6.3). We found a risk magnitude, (HR=2.2, 95% CI 1.2–4.1), during five years after AMI. In the previously mentioned study of patients undergoing PTCA, Kop et al. (1993) found that severity of CAD accounts for only 4% of the variance of vital exhaustion scores (n=120,

22% women). In a later analysis of a larger sample (n=307, 21% women), Kop et al. (1996) found no association between vital exhaustion and extent of CAD.

Together, our results suggest that vital exhaustion is an independent marker of CHD–related outcomes. It remains to be shown whether vital exhaustion is caused by chronic life stress or if it is merely a marker of poor health. One way to investigate this issue would be to observe the effects of stress management on vital exhaustion and biological variables in patients with CHD.

Mediating mechanisms between vital exhaustion and CHD

The mechanisms mediating the effects between vital exhaustion and CHD are not fully understood. In line with previous study results, the associations between vital exhaustion and most lifestyle variables in our studies were weak and inconclusive. However, among the women with CHD, vital exhaustion was related to a sedentary lifestyle. With regard to pathophysiological mechanisms, vital exhaustion was found to associate significantly to high cortisol (in women with CHD), and to low HDL–C and apolipoprotein A1 (in healthy women). In turn, cortisol was positively related severity of CAD, smoking and glucose levels. Together, our findings may indicate that the adversive effect of vital exhaustion is partially mediated by increased activity of the SNS and a sedentary lifestyle. These factors increase the risk of insuline–resistance, a state in which insuline's ability to suppress free fatty acids is reduced, which results in elevated triglycerides and, indirectly, decreased HDL–C. Furthermore, insuline–resistance has adversive effects on the fibrinolytic capacity hence increasing the risk of blood–clot formation.

The presented line of reasoning fits with previous investigations demonstrating that vital exhaustion is associated with obesity, hyperglycemia, and dyslipidemia (Raikkonen et al., 1996), with elevated cholesterol levels, stress induced cholesterol change, noradrenaline– and cholesterol–levels during stress (van Doornen, van Blokland, 1989), and with blood–clotting factors (e.g. Kop et al., 1998). Other measures of prolonged stress have shown associations to sustained changes in lipid profile, including reduced levels of HDL–C (Brindley et al., 1993). Conversely, several longitudinal studies report that learning to cope with stress is associated with a shift to a more favorable lipid profile (Dusseldorp et al., 1999).

Alternatively, prolonged stress and SNS–activity may result in exhaustion of the HPA–axis, resulting in decreased cortisol levels. This state increases the susceptibility to immune–mediated inflammation, which lately has been associated to the onset and progression of CAD (Appels et al., 2000). Some support for this hypothesis was recently

generated in a study demonstrating an association between vital exhaustion and lower cortisol levels (Nicolson, van Diest, 2000). However, in this thesis the reversed relationship was observed.

Behavioral intervention

While men with CHD seem to benefit from behavioral intervention, women's response to these programs has been poor (Blumenthal et al., 2002b; Frasure–Smith et al., 1997; Powell et al., 1993). With rehabilitation groups being predominantly male, and with a heavy focus on exercise, it is possible that programs have not been formatted in a way that is optimal for women. Considering that women consistently have been found to have a poorer socio–demographic and psychosocial status than men (Brezinka, Kittel, 1996; O'Farrell et al., 2000; Ray, 2002) it is possible they have somewhat different needs. A recent study demonstrated that women with CHD are more sensitive than men to psychosocial stress and that the magnitude of emotional and physical stress reactions, burnout, problematic family relationships and daily hassles is comparable to biological risk factors in predicting CHD outcomes (Hallman et al., 2001).

In this thesis, two different approaches to behavioral intervention are evaluated with regard to vital exhaustion/vitality and biological outcomes in women: a stress management program, aimed at reducing stress in women, and a multi–component lifestyle change program including dietary change, exercise, stress management, and social support. Both programs lasted 1 year. It was shown that: women with CHD who participated in stress management showed a more rapid decrease of vital exhaustion as compared to women receiving usual care, and that men and women participating in a multi–component lifestyle change program evidenced improvements regarding quality of life (including vitality), and biological CHD risk factors.

It is worthwhile to note that both intervention programs appeared to be attractive to women, as evidenced by the relatively high attendance rate (85% and 73%, respectively). Possibly, because of the stress management and social support components which were part of both treatments.

Effects on vital exhaustion/vitality

In women receiving stress management, vital exhaustion was reduced by 18% after one year of intervention and by 27% at 1–2 years follow–up (the corresponding scores for women in the control group were 8% and 13%, respectively). However, considering that the patients in the intervention group had higher levels of vital exhaustion at baseline, it

cannot be ruled out that their seemingly faster decrease in vital exhaustion was due to regression towards the mean. Meanwhile, after only three months into the program the female participants of the multi–component lifestyle–change program evidenced a 35% increase in the MOS SF–36 subscale vitality, which correlates substantially to vital exhaustion ($r=0.74$, $p<0.002$; the increase for men was 23%). These findings may be of some clinical value considering that vital exhaustion predicts poor prognosis in women with CHD (Koertge et al., 2002) and the high risk of recurrence directly after a coronary event. However, the efficacy of these interventions to affect the future course of CHD is yet to be determined. Recently, unpublished but promising results were presented from an intervention study designed to decrease vital exhaustion by means of relaxation and anger management (Appels, 2003). It was shown that vital exhaustion was decreased by 55% and that the intervention group had 55% lower risk than the control group for recurrent events (PTCA, CABG, MI, or cardiac death) occurring between 6 and 18 months (personal communication with Ad Appels, February 2003). A substantial decrease of vital exhaustion–scores (32%) after one year of intervention was also demonstrated in a non–controlled feasibility study of the stress–management program evaluated in this thesis (Burell & Granlund, 2002).

Previous results may appear more impressive than the ones achieved in the stress management program being evaluated in this thesis. Possible reasons for the difference in effect include that the present study: had the largest number of women; had patients who were in different condition (57% had had an AMI and 28% had undergone CABG); had patients included who were not vitally exhausted to begin with (27% had an MQ score below 14, which corresponds to less than 7 symptoms of vital exhaustion – an entry–criterion previously applied by Appels et al., 1997); and had the intervention carried out by nurses, as compared to clinical psychologists.

Limitations

Selection

With regard to selection, a number of biases may influence the generalizability of results:

1. The Stockholm Female Coronary Risk study was restricted to women aged 65 and below because one of the main aims of the study was to investigate the cardiovascular impact of psychosocial variables, of which many may pertain primarily to a working life. Hence, the results of Study I–III may not be extended to older women or to men. The stress–management intervention study was restricted to women aged 75 or below.

2. In the lifestyle change program, only patients who were insured by Mutual of Omaha were considered. Furthermore, patients were excluded from the study if they had one or more of the following conditions: (1) left main coronary artery disease (CAD) with greater than 50% occlusion or left main equivalent CAD, (2) a CABG within the past six weeks, (3) an angioplasty within the previous six months, (4) a myocardial infarction within the last one month, (5) chronic congestive heart failure, with New York Heart Association Class symptoms III or greater and unresponsive to medications, (6) malignant uncontrolled ventricular arrhythmias, (7) hypotensive blood pressure response to exercise testing, (8) diagnosed homozygous hypercholesterolemia, (9) psychosis, (10) alcohol or drug abuse, (11) life threatening comorbidity, (12) current tobacco use (within the past three months), and (13) non−ambulatory status. Hence, the study results can be generalized to men and women who can afford medical insurance, who are in a stable condition, and who are motivated enough to abstain from smoking and excessive alcohol use during one year.
3. Patients were excluded who died prior to hospital admission (occurs in 20−30% of female AMI patients in this age−group; American Heart Association, 1994), or in between hospital admission and examiation (n=5 Study I−III; n=1 Study IV), or for other reasons were not admitted to the coronary care unit. This may have diluted the prognostic magnitude of vital exhaustion and cortisol in relation to CHD.
4. The diagnostic specificity might have been decreased by the fact that patients were included with unstable angina pectoris based on the Braunwald criteria alone, without demands for ECG changes (Study I−III). This decision was made on the premise that it reflects the clinical reality at the coronary care unit.
5. As the incidence of CHD was low during the five years of follow−up, revascularization procedures were included in the definition of a recurrent event (Study I). The fact that revascularizations are chosen by the physician implies a large degree of subjectivity, which may have affected the selection of candidates for PTCA and CABG. For instance, a patient with many symptoms of vital exhaustion may be more likely to report symptoms of angina, which might increase her probability of being chosen as a candidate for revascularization. At the same time, from a clinical standpoint, the combined endpoint of AMI, cardiac death and revascularizations seems justified as both ”hard” and ”soft” events represent different stages of CHD progression.

Design

1. The cross−sectional nature of Study II and III precludes any conclusions about cause and effect. It cannot be ruled out that the heart disease causes increased cortisol levels, rather than vice versa, in Study II. Nor is it unlikely that low HDL−C levels reflect poor general health, which results in symptoms of vital exhaustion.
2. The baseline examination of psychosocial variables was administred differently for patients and controls in study IV. Controls had their questionnaires sent to them prior to the visit to the research clinic, while patients filled out their questionnaires *after* they had their first group session. Exposure to the groupleader and groupmembers, as well as to the overview of the treatment focussing on psychosocial stress may very well have influenced their reporting of symptoms. This may explain the fact that the intervention group reported a significantly higher level of vital exhaustion than the control group.
3. In Study IV the patients in the treatment group were in the care of a cardiologist, while the patients in the control group were treated as usual, i.e. they are more likely to have been under the care of a general practitioner. This difference is likely to have resulted in differential treatment with regard to types of medication, dosage, number of visits etc. Knowing that one is in the care of a specialist for a whole year after a coronary event is likely to have a positive influence on ones daily stresslevel and may reduce feelings of vital exhaustion.
4. The design of Study V is of descriptive nature, which precludes conclusions of the treatment's effectiveness.

Measurement

Sources of measurement errors include:

5. The use of an early − rather than the standard − version of the Maastricht Questionnaire measuring vital exhaustion in Study I−III, may have influenced the interpretation of the results. Compared to the standard scale, the earlier one has more items of depression but less of fatigue, disturbed sleep, and ability to concentrate. Hence, the results in the first three studies may be interpreted as being more similar to depression than the results of the fourth study. However, the two scales appear to have the same face validity, and our investigations of the psychometric validity of the scale resulted in a satisfactory association between the earlier and the later version of the scale $r = 0.66$, $p<0.002$ in women with CHD, and $r=0.90$, $p<0.01$ in healthy women.

6. The women's disease status could cause an error of measurement as symptoms of weakened health could lead to and result in an over–reporting of vital exhaustion, or underreporting of vitality (misclassification of exposure status). In Study I, efforts were made to control for this type of bias by controlling for various signs of underlying disease including severity of CAD and severity of chest pain.

7. In Study I and II, nine patients underwent revascularisation procedures during the three to six months between hospitalization and the examination date. As undergoing a difficult procedure may influence the reporting of vital exhaustion, we performed separate analyses controlling for revascularization in between index event and examination date. However, this did not change the results.

8. The crude measurement of cortisol in Study II and IV. Relying solely on one measure of morning cortisol, without controlling for the time of waking up, may have introduced inter–individual differences as cortisol typically peaks 30 to 45 minutes upon awakening and declines thereafter (Schulz et al., 1998). Further differences between individuals could have been induced by the time of year patients had their blood drawn, as light has proven to have an impact on the morning cortisol–peak (Scheer, Buijs, 1999). An additional weakness may be that cortisol was derived from blood samples rather than from saliva, which later has been a preferred method, most importantly because it is non–invasive (Kirchbaum, Hellhammer, 1994). Consequently, some patients may have had a cortisol response influenced by the venipuncture. However, we have no reason to believe that the methodological procedures were differently distributed between patients with or without significant coronary stenosis, or between patients and controls, respectively. Therefore the method used should not influence our results or conclusions.

CONCLUSIONS

This thesis demonstrates that vital exhaustion is an independent marker of poor prognosis in women with CHD. In line with previous investigations in men, no cross-sectional association was found between vital exhaustion and significant coronary artery stenosis. Overall, very few associations were found between vital exhaustion and standard CHD risk factors. However, in women with CHD, vital exhaustion was positively associated to cortisol and a sedentary lifestyle. Furthermore, in healthy women, the results of exploratory analyses revealed a negative association between vital exhaustion and HDL-C and apolipoprotein A1, respectively. These findings fit with previous ones - obtained in men - which support associations between vital exhaustion and the facets of the Insulin Resistance Syndrome. Together, our findings support that vital exhaustion is a state of physical and psychological fatigue, which adversive coronary effects may be mediated by a sedentary lifestyle, increased SNS-activity, and lipid abnormalities.

Results from a multicomponent lifestyle change program show that a program focusing on diet, exercise, stress management, and social support may be successfully implemented across hospitals in diverse regions of the USA, and that women's response to this program was as good as men's. Results from a Swedish randomized controlled intervention study testing the effects of stress management in women with CHD showed that stress management reduced vital exhaustion more rapidly than usual care. Stress management and social support are components that appear attractive to women with CHD. Implementation of these components into cardiac rehabilitation programs may be one way of increasing female participation-rates, which have been traditionally low.

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APPENDIX I

An early version of the Maastricht Questionnaire

During the past few months, how often have you:	Often	Some-times	Never
1. Felt very tired?			
2. Noticed a loss of self–confidence?			
3. Felt that you haven't accomplished as much as you used to?			
4. Felt that you have come to a "dead end"?			
5. Felt more listless than before?			
6. Felt that you can't cope with everyday problems as well as you used to?			
7. Felt that your body is like a battery that is losing its power?			
8. Felt dejected?			
9. Felt you don't have as much control over yourself as you used to?			
10. Felt you ought to accomplish more hadn't you felt so weak all over?			
11. Noticed it took longer than usual getting started?			
12. Felt no one can help you with your most profound problems?			
13. Felt less satisfied with your self.			
14. Felt less capable of doing something useful?			
15. Noticed that little things irritate you more lately than they used to?			
16. Sometimes wished you were dead?			
17. Noticed you don't want to leave the house to go and see someone?			
18. Noticed you have become more quiet and tranquil?			

Scoring: Each "Never" is coded as 1, each "Sometimes" as 2, each "Often" as 3. The total score is obtained by summarizing the score for each of the eighteen questions.

APPENDIX II

The Maastricht Questionnaire

	Yes	?	No
1. Do you often feel tired?			
2. Do you often have trouble falling asleep?			
3. Do you wake up repeatedly during the night?			
4. Do you feel weak all over?			
5. Do you have the feeling that you haven't been accomplishing much lately?			
6. Do you have the feeling that you can't cope with everyday problems as well as you used to?			
7. Do you believe that you have come to a 'dead end'?			
8. Do you lately feel more listless than before?			
9. I enjoy sex as much as ever.			
10. Have you experienced a feeling of hopelessness recently?			
11. Does it take more time to grasp a difficult problem than it did a year ago?			
12. Do little things irritate you more lately than they used to?			
13. Do you feel you want to give up trying?			
14. I feel fine.			
15. Do you sometimes feel that your body is like a battery that is losing its power?			
16. Would you want to be dead at times?			
17. Do you have the feeling these days that you just don't have what it takes any more?			
18. Do you feel dejected?			
19. Do you feel like crying sometimes?			
20. Do you ever wake up with a feeling of exhaustion and fatigue?			
21. Do you have increasing difficulty in concentrating on a single			

Scoring: Each confirmation of a complaint is coded as 2. All question marks are coded as 1. A negative answer is coded as 0. Note that questions 9 and 14 are reversed (no = 2; ? = 1; yes = 0). The total score is obtained by summarizing the score for each of the 21 questions.

APPENDIX III

Beck Depression Inventory

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

8. 0 I don't feel I am worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9. 0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10. 0 I don't cry any more than usual.
    1 I cry more now than I used to.
    2 I cry all the time now.
    3 I used to be able to cry, but now I can't even cry even though I want to.

11. 0 I am no more irritated by things than I ever am.
    1 I am slightly more irritated now than usual.
    2 I am quite annoyed or irritated a good deal of the time.
    3 I feel irritated all the time now.

12. 0 I have not lost interest in other people.
    1 I am less interested in other people than I used to be.
    2 I have lost most of my interest in other people.
    3 I have lost all of my interest in other people.

13. 0 I make decisions about as well as I ever could.
    1 I put off making decisions more than I used to.
    2 I have greater difficulty in making decisions than before.
    3 I can't make decisions at all anymore.

14. 0 I don't feel that I look any worse than I used to.
    1 I am worried that I am looking old or unattractive.
    2 I feel that there are permanent changes in my appearance that make me look unattractive.
    3 I believe that I look ugly.

15. 0 I can work about as well as before.
    1 It takes an extra effort to get started at doing something.
    2 I have to push myself very hard to do anything.
    3 I can't do any work at all.

16. 0 I can sleep as well as usual.
    1 I don't sleep as well as I used to.
    2 I wake up 1–2 hours earlier than usual and find it hard to get back to sleep.
    3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get tired more than usual.
    1 I get tired more easily than I used to.
    2 I get tired from doing almost anything.
    3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.
    1 My appetite is not as good as it used to be.
    2 My appetite is much worse now.
    3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any, lately.
    1 I have lost more than five pounds.
    2 I have lost more than ten pounds.
    3 I have lost more than fifteen pounds.

20 0 I am no more worried about my health than usual.
    1 I am worried about physical problems such as aches or pains, or upset stomach, or constipation.
    2 I am very worried about physical problems and it's hard to think of much else.
    3 I am so worried about my physical problems that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.
    1 I am less interested in sex than I used to be.
    2 I am much less interested in sex now.
    3 I have lost interest in sex completely.

Scoring: The total score is obtained by summarizing the score for each of the twenty–one questions.

Total Score	Levels of Depression
1–10	These ups and downs are considered normal.
11–16	Mild mood disturbance.
17–20	Borderline clinical depression.
21–30	Moderate depression.
31–40	Severe depression.
> 40	Extreme depression.

APPENDIX IV

MOS SF–36 Health Survey

1. **In general, would you say your health is:**

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago, how would your rate your health in general now?**

Much better now than one year ago
Somewhat better now than one year ago
About the same
Somewhat worse now than one year ago
Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Circle One Number on Each Line)

	Yes, Limited a Lot	**Yes, Limited a Little**	**No, Not limited at All**
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Circle One Number on Each Line)

	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Circle One Number)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

21. How much bodily pain have you had during the past 4 weeks? (Circle One Number)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle One Number)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks . . . (Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5