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Studies of Secondary Prevention after Coronary Heart Disease with Special Reference to Determinants of Recurrent Event Rate

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Abstract
Gulliksson, M. 2009. Studies of Secondary Prevention after Coronary Heart Disease with Special Reference to Determinants of Recurrent Event Rate. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 472. 86 pp. Uppsala. 978-91-554-7577-2.

Objectives. The first aim was to examine the effects of secondary prevention with a focus on determinants in the risk of recurrent coronary heart disease (CHD). The second aim was to analyse the effects of a cognitive behavioural therapy (CBT) intervention on the risk of recurrent cardiovascular disease (CVD) and to investigate the psychosocial situation of CHD patients.

Material and methods. Papers I and II were based on the Swedish Acute Myocardial Infarction Statistics Register, 1969 to 2001: 775,901 events in 589,341 subjects. Papers III and IV were based on The Secondary Prevention in Uppsala Primary Care project (SUPRIM), a randomized controlled clinical trial in 362 CHD patients.

Results. The risk of a recurrent acute myocardial infarction (AMI) event was highly dependent on time from the previous event, with the greatest risk immediately after an AMI event. In addition, sex, age, and AMI number influenced the general risk level. Furthermore, there has been a major decline in recurrence risk over 30 years, and there were considerable geographical differences in risk, best explained by residential area population density, with a high recurrent AMI risk in areas with the lowest and the highest population densities, and the lowest risk in areas with moderate population density. Disease status and sex were determinants of psychological well-being the first year after a CHD event. Sex seemed to be the stronger determinant. The CBT intervention focused on stress management during one year in patients with CHD. There was significantly improved outcome in the intervention group on recurrent CVD and recurrent AMI during a 9 year follow up. A dose-response relationship was demonstrated between attendance rate at intervention group meetings and outcome, the higher the attendance rate the better the outcome.

Conclusions. The risk of a recurrent AMI event was dependent on time from the previous event, with major improvement seen in recent decades. Regional differences were best explained by population density. Female CHD patients were at high risk concerning well-being after a coronary event, which deserves special attention. The CBT intervention for CHD patients improved outcomes concerning the risk of recurrent CVD and AMI events.

Keywords: Coronary heart disease, myocardial infarction, epidemiology, population, prevention, recurrence, psychosocial factors, social support, gender, regional variation, co-morbidity

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To my family, Ingalill, Caroline and Olle

List of Papers

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

I Gulliksson M, Wedel H, Köster M, Svärdsudd K. Hazard function and secular trends in the risk of recurrent acute myocardial infarction. 30 years of follow up of more than 775,000 incidents. *Circ Cardiovasc Qual Outcomes* 2009; 2:178-85.*

II Gulliksson M, Wedel H, Köster M, Svärdsudd K. Effects of degree of urbanisation in the risk of recurrent acute myocardial infarction: more than 775,000 incidents followed for 30 years. Manuscript.

III Gulliksson M, Burell G, Lundin L, Toss H, Svärdsudd K. Psychosocial factors during the first year after a coronary heart disease event in cases and referents: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). *BMC Cardiovascular Disorders* 2007;7:36.*

IV Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. A randomised controlled trial of cognitive behavioral therapy versus standard treatment on recurrent cardiovascular events in coronary heart disease. Submitted.

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Contents

Abbreviations

AMI	Acute myocardial infarction
BMI	Body mass index
CABG	Coronary artery bypass grafting
CBT	Cognitive behavioural therapy
CHD	Coronary heart disease
COPD	Congestive pulmonary disease
CVD	Cardiovascular disease
ECG	Electrocardiography
HDL	High density lipoprotein
HR	Hazards ratio
ICD	International classification of diseases
LDL	Low density lipoprotein
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease
n	Number
n.s.	Non-significant
OECD	Organisation for economic co-operation and development
PCI	Percutaneous coronary intervention
SCB	Statistics Sweden (Statistiska centralbyrån)
SCORE	Systematic coronary risk evaluation
SD	Standard deviation
SUPRIM	Secondary prevention in Uppsala primary health care
WHO	The World Health Organisation

Prologe

When I had completed medical school and become an M.D., my ambition was to become a good clinician focused on consultations with patients. I was not even considering research. The years went by and after a few years as a hospital doctor at different hospitals and clinics I qualified as a General Practitioner, a GP. Primary care has long been a deeply rewarding profession with its combination of care for acute, undiagnosed illness and complex, multisystem disease, as well as the provision of extensive preventive care, all in the setting of a long relationship built on mutual trust and knowledge.

One day, sitting in the cafeteria at Uppsala University hospital I talked to one of the thoracic surgeons. I was told that many coronary artery by-pass graft operations were performed, but no one really knew what happened to the newly operated patients, there was hardly any follow-up. Some patients returned for another operation, but what about the rest? Did they see any doctor? Who did the follow up, if any? What were the roles of the GP and the cardiologist? Who was responsible for follow up, the patient, the cardiologist or the GP? Was this routine safe for the patient? Throughout their lives, but particularly at the end, patients want and need physicians who focus on the people who have diseases, not just on the diseases.

All these questions made me interested in finding out more about how we took care of "our" coronary heart disease patients, post-myocardial infarction, after a coronary operation or other interventional cardiology treatments. The main ideas were to study the risk of recurrence in coronary heart disease, and to facilitate for the coronary patients at discharge from hospital in the transition to their GPs at primary health care units and the other way around, referrals from GPs to cardiologists.

Intensified mutual efforts in primary and secondary prevention strategies have led to substantial reductions in myocardial infarction incidence, recurrence and mortality. But there is still room for improvement. I have not yet obtained all the answers, but this is my piece of the puzzle.

Introduction

In Sweden, like in all developed and in many developing countries, cardiovascular disease (CVD) remains the leading cause of premature death and hospitalization among middle-aged and older men and women [1-3], 41% for men and 42% for women [4], despite a decline in incidence [5] and mortality [6] in recent decades in most of these countries. Death from CVD often occurs suddenly, out of hospitals and beyond the reach of medical care. CVD also causes disabilities and contributes to escalating health care costs [7]. CVD is multifactorial and risk factors interact, often multiplicatively [3]. The underlying atherosclerotic disease develops slowly and is often advanced by the time symptoms appear.

Coronary heart disease, acute myocardial infarction, acute coronary event

Cardiovascular disease (CVD), as a term technically refers to any disease that affects the cardiovascular system and includes coronary heart disease (CHD), (ischemic heart disease, acute myocardial infarction (AMI), angina pectoris), and cerebrovascular disease, hypertension, heart failure, peripheral artery disease, rheumatic heart disease, and congenital heart disease.

The underlying cause of AMI is usually a rupture (fissure), erosion or dissection in an atherosclerotic plaque (a formation of fatty material and plaque in the innermost layer of the vessel wall) in the coronary artery and a thrombosis that suddenly suppresses or completely clogs the blood flow in the coronary vessel. Spasm in the vessel can also contribute to the deterioration of blood flow [8, 9]. When the blood flow in the vessel deteriorates or ceases, an imbalance in supply and demand of oxygen appears, in turn causing ischemia in the heart muscle supplied by the affected artery. It leads to a rapid deterioration of pump function so that the supply of oxygen further diminishes, causing shortness of breath during exercise, electrocardiographic (ECG) changes and pressure or pain in the chest (stable angina). If the blood flow ceases for more than 15-30 minutes, damage to the myocardium occurs, resulting in leakage of substances from the affected heart muscle, which can be detected in blood samples (biomarkers of infarction). If there is perma-

nent interruption of blood flows in a heart muscle area unprotected by collateral arteries, an AMI will develop.

AMI can be defined from a number of perspectives related to clinical, ECG, biochemical and pathologic characteristics. The term AMI also has social and psychological implications, both as an indicator of a major health problem and as a measure of disease prevalence in population statistics and outcomes of clinical trials.

In earlier studies of disease prevalence performed by the WHO, AMI was defined by a combination of two out of three characteristics: typical symptoms (*i.e.*, chest discomfort), typical cardiac enzyme rise and decline, and a typical ECG pattern involving the development of Q waves. However, current clinical practice, health care delivery systems, as well as epidemiological studies and clinical trials all require a more precise definition of AMI. Furthermore, the advent of sensitive and specific serological biomarkers and precise imaging techniques necessitate re-evaluation of established definitions of AMI. Current laboratory technology can identify patients with small areas of myocardial necrosis [10]. Thus if any amount of myocardial necrosis caused by ischemia would be labelled as an infarct, then an individual would previously have been diagnosed as having severe, stable or unstable angina pectoris might be diagnosed today as having had a small AMI. Such changes in definition can have a profound effect on the traditional monitoring of disease rates and outcomes [1]. A consensus document for redefined AMI was presented in 2000 by The Joint European Society of Cardiology/American College of Cardiology [12], and followed in 2007 by a universal definition [13], even though the main principles are similar to those proposed by the WHO.

However, the distinction between AMI and unstable angina pectoris is vague and depends on the methods and definitions used to detect heart muscle damage. Today AMI is divided, after the initial ECG image, into ST-segment elevation myocardial infarction (STEMI or left-sided bundelbranch block) and non-ST-segment elevation myocardial infarction (NSTEMI) [14]. NSTEMI and unstable angina are used synonymously in unstable coronary artery disease. Classification in ST-elevation infarction and unstable coronary artery disease is useful in practice for evaluating prognosis and choice of treatment.

Time trends in first ever CHD events

When time trends in CHD are reported, time trends usually mean secular trends. A secular trend is a change of incidence over the years in consecutive population groups of the same age and sex. Secular trends are sometimes called cohort effects, meaning that something has happened resulting in a

lower proportion in consecutive cohorts contracting the disease. The following text refers to time trends in the sense secular trends.

The incidence of a first time AMI is decreasing in most industrialized countries [6, 15, 16]. This decrease is seen in all age groups and among both men and women [6]. It began in the 1970s in the U.S. and Australia, and a few years later in Sweden [17].

Each year approximately 40,000 AMIs occur in Sweden, corresponding to about 110 AMIs per day. The age standardized incidence of AMI has decreased continuously 1987-2000 by between 1 and 2% per year. As a result of the new diagnostic criteria introduced in health care in 2001 (extended definition of AMI) [18], the incidence rate per 100,000 inhabitants increased and was in 2003, about 8% over the level for 2000. In 2004 the age-standardized incidence rate dropped by about 6% for both men and women, down to the same level as before the introduction of the new diagnostic criteria [18] indicating that the impact of the latter has been moderate. The rate in 2006 is 12% less among men and 7% less among women than it was in 2001. The number of incidents of AMI per 100,000 inhabitants in Sweden in 2006, age over 20, was 667 cases for men and 477 for women [18].

Both AMI incidence and mortality are strongly related to sex and age, and below age 60 men form a strikingly high proportion. The incidence for women in any age group is the same as for men five to ten years younger [18].

AMI mortality has also dropped sharply [17]. The World Health Organization (WHO) MONICA project (Multinational monitoring of trends and determinants in cardiovascular disease) reported that the CHD mortality was declining by approximately 2-3% annually [6, 19]. It was estimated that two thirds of this mortality decline was attributable to the decrease in incidence of CHD, while the reduction in case fatality rate, *i.e.* the risk of dying within 28 days after an AMI event, had contributed to the remaining one third [6].

Sweden is among the countries in the world with the lowest AMI mortality, and death rates for CHD have decreased continuously during the period 1987-2006 for men aged 15-74 years, by 59%, (from 352/100,000 to 146/100,000), and for women by 50%, (from 128/100,000 to 61/100,000). The age-standardized mortality for AMI per 100,000 inhabitants in the same period has fallen by an average of 4% annually, totalling more than 40% for both sexes. In 2006 the decrease continued for the men with mortality almost 8% lower than in the previous year. Among women the mortality remained at the same level as in recent years [18].

Case fatality rate is a widely accepted indicator of the effectiveness of hospital acute coronary care [6]. In Sweden, AMI case fatality has fallen sharply in recent decades. In 1990, 42% of men and 46% of women died within 28 days after an AMI. In 2000, the corresponding figures were 35% and 38% respectively. By 2006, these numbers had dropped to 30% for men and 33% for women [18]. However, the majority of those who died early, approximately 20%, die on the incident day. By definition, an AMI event

occurring within 28 days after a previous event is counted as part of the first event.

For individuals treated in hospital the age adjusted case fatality rate fell from more than 32% in 1987 to just over 15% in 2006 for both sexes [18]. The slightly higher numbers for women is attributable to the higher proportion of women than men in elderly age groups. After adjustment for age, men in general have higher case fatality than women [18]. Old age is a more important risk factor for death than sex , according to most studies [20].

The clinical presentation of AMI is changing. Thanks to new, improved diagnostic methods for blood samples, smaller AMIs, with less myocardial damage, which would previously not have been diagnosed, can be detected, with a lower proportion on mortality [10] and case fatality [21].

Recurrent CHD events

An improvement in primary prevention and improved in-hospital medical care have been attributed to the decline in first event AMI incidence and mortality seen in recent decades [6, 19, 22-28]. The incidence and mortality rates of recurrent events have attracted less interest. This thesis is mainly focussed on recurrent events.

A few studies have shown falling AMI recurrence rates over time [29-33]. The positive trend is probably attributable to secondary preventive work [34] and the improvement in the risk factor profile of the general population. Tobacco use has dramatically changed in the adult population over the last 25 years. The proportion of smokers among adults in Sweden has decreased from 32% in 1980 (men 36%, women 28%) to 15% in 2006 (men 12%, women 17%). These are the lowest figures among OECD countries [7], with the relatively slower decrease among women being noteworthy. People in some professions have given up smoking more than others for example, doctors had the same proportion of smokers as in the general population in the 1970s, but now only 6% of Swedish physicians smoke [35]. Among general practitioners, the proportion of smokers is even lower. Smokers tend to die earlier than non smokers [36]. However, there is only one randomized controlled single factor trial of health outcomes of anti-smoking advice, performed in smoking middle aged men. Geoffrey Rose *et al*. reported 13% lower fatal CHD and 7% lower total mortality during 20 years of follow up in those advised to give up smoking compared to those advised to continue [37]. Previous and later observational, case-control, longitudinal, and cohort studies are consistent with the trial results. As summarized in a Cochrane review from 2003, CHD patients who stopped smoking had a more than 32% risk reduction in non-fatal AMI and all-cause mortality [38].

A second meaning of the term time trend is the so-called hazard function. It describes the risk of having a recurrent event in relation to time from a

previous event. Previous attempts to estimate the risk of a recurrent event have usually been based on the cumulative hazards (or survival) function provided by various types of life table methods, including proportional hazards regression. However, in cumulative hazards or survival functions fluctuations across time tend to be evened out, making assessment of the risk in various time intervals difficult. The hazard function may be computed using special software and large data sets. No previous estimate of the hazard function for a recurrent CHD event seems to have been published.

Geographical variation in CHD

There is large geographical variation in AMI incidence and mortality rate both between and within countries [3, 19, 39]. In Sweden, a pronounced geographical variation of CHD mortality rate [40] and first AMI incidence [17, 41] have been shown, with a south-to-north and an east-to-west gradient. Similar geographical gradients have been found in Finland [42, 43], United Kingdom [44], the United States [45], and other countries [39, 46].

The causes of these observed variations are not well understood. A large number of potential geographical determinants have been investigated, such as water hardiness [47], seasonal variation in climatic conditions [48], distance between home and hospital [49, 50], geographical differences in established risk variables (lifestyle, smoking habits, food consumption, socioeconomic status) [44, 51], and genetic susceptibility [52, 53], but the results are inconsistent. No study so far has investigated the impact of demographic variables, such as degree of urbanisation, possibly due to lack of data.

CHD and prevention

Geoffrey Rose: “It is better to be healthy than ill or dead. That is the beginning and the end of the only real argument for preventive medicine. It is sufficient.” [54].

Prevention is defined as measures taken to prevent or delay development of illness. The aim of CHD prevention is to reduce the risk of cardiovascular events and thereby reduce premature disability and morbidity and to prolong survival and maintain or improve quality of life. This applies to both lifestyle factors and medical treatment of traditional risk factors and in some cases invasive treatment of coronary artery stenosis.

For more than forty years there has been active prevention of CHD in Sweden and both primary and secondary prevention have been accomplished in parallel. The strategies for the prevention of CHD may be targeted against the whole population or high-risk population (for instance those with high risk factor levels). It has been shown that a combination of these strategies

yields the best result [55]. Prevention is not to be mixed up with screening, in which individuals from the general population are invited for a screening of risk factors (risk finding) or a disease (case finding). Risk factor as a term was first used in the context of CHD by the Framingham investigators [56]. The traditional preventive measures are avoidance of tobacco, a healthy diet, regular physical activity, avoiding overweight, and maintaining normal blood pressure and blood lipid levels [38, 57-61].

Primary prevention in the general population is partly undertaken by people working in professions other then the medical [7], *e.g.* through the establishment of policies aimed at reducing tobacco consumption, public awareness campaigns, advertising bans and increased taxation. Secondary prevention mainly takes place through the medical services, and is often achieved in primary health care centres by doctors and nurses in consultation with patients on their individual health profile for hereditary, lifestyle, smoking habits, and self reported well-being combined with risk factor measurements such as blood pressure, height, weight, body mass index (BMI), waist-to-hip ratio, and blood tests for cholesterol and glucose. There are many examples from primary health care centres in Sweden of successful primary prevention work [62-67]. A number of practice studies conducted in Swedish primary health care show the value of information to patients and patient compliance in achieving effective blood pressure treatment and smoking cessation as effective secondary preventive tools. By contrast, compliance with high blood lipid treatment has not been fully followed. Almost 40% of patients on lipid lowering treatment are above the treatment goal in cholesterol level [68].

It is well known that patients with diabetes mellitus have an increased risk of CVD [69] and that the risk is related to blood glucose and blood lipid level [70]. In recent times, abnormal glucose tolerance and diabetes, as one of the traditional risk factors, has attracted particular attention [71-73]. Studies by Norhammar *et al*. show that over 30% of patients treated for an AMI have undiagnosed diabetes mellitus, often owing to their limited contact with health services before the acute event [74]. Lifestyle factors relate strongly to CHD as do physiological and biochemical factors. Comprehensive lifestyle changes may be able to bring about regression of even severe coronary atherosclerosis, without use of lipid-lowering drugs [75]. Risk factor modification has been shown to reduce mortality and morbidity in people with well known, as well as unknown CHD [25, 34, 62, 76].

There is strong evidence that psychosocial factors contribute independently to the risk of CHD even after adjustment for the effects of traditional risk factors [77, 78]. Psychosocial factors have been shown to account for approximately 30% of the attributable risk of AMI [3]. Psychosocial factors that may promote CVD belong to two general categories: emotional factors including major depression, hostility, anger, and anxiety, and chronic stressors including low socio-economic status, low social support, marital distress,

and work distress. According to a recent Cochrane report there is little evidence to date that psychological interventions affect total or CVD mortality, but may reduce non-fatal recurrent AMI rate [79]. This hypothesis was further tested in this thesis.

It is more important to evaluate the total risk of a CVD event than to achieve the target for each risk factor. A risk factor scoring instrument may be used to estimate the total and relative cardiovascular 10-year risk of CVD mortality, *e.g.* HeartSCORE, the electronic counterpart of the SCORE (Systematic Coronary Risk Evaluation) risk charts, developed by the European Society of Cardiology [80-85]. This chart was based on a risk function derived from the Framingham project [86]. However, a recent Swedish study by Petersson, *et al*. showed that a primary care consultation-based method equate SCORE and an extensive laboratory-based method in predicting long-term cardiovascular risk [87]. Furthermore, criticism has evolved in that SCORE and Framingham equations may overestimate future cardiovascular risk [88, 89]. Similar results were found when a Swedish risk function was compared with that of the Framingham study [90].

CHD Guidelines

In 1995, the first joint European guidelines for cardiovascular prevention were published by a joint working group for the European Society of Cardiology, European Atherosclerosis Society, European Society of Hypertension, International Society of Behavioral Medicine, European Society of General Practice/Family Medicine and the European Heart Network. Furthermore, the Working Group suggested that the terms of primary and secondary prevention should be replaced by prevention alone since risk is a continuum, but with the difference that in secondary prevention the risk factor control is pursued more aggressively than in primary prevention. The guidelines were revised in 1998 and 2003 and the present version was published in 2007 [57], with additional guidelines focusing on cardiovascular prevention of diabetes and hypertension [91, 92]. They were followed by other international guidelines, *e.g.* those of the American Heart Association [59]. These documents represent a consensus on what risk factors to target in cardiovascular prevention and that risk management requires attention to all modifiable risk factors. Guidelines indicate benchmarks for the traditional risk factors: smoking, blood pressure, diabetes and blood lipid levels, which should not be exceeded.

The European and U.S. treatment advice have led to the development of the corresponding Swedish guidelines [93]. The Swedish Medical Products Agency presented guidelines for prevention of CVD in 2006, focused on background information and treatment recommendations [94, 95].

Aims of the thesis

This thesis had two aims. The first was to gain knowledge about the effects of secondary prevention, with a focus on determinants in the risk of recurrent CHD. The second aim was to assess the effects of cognitive behavioural therapy (CBT) intervention in relation to the risk of recurrent CHD and to investigate the psychosocial and social situation of coronary patients.

Scientific questions

1. Are the secular trends in the risk of a recurrent AMI over the past decades in Sweden similar to those of a primary event, what are the determinants, and what is the hazard function for a recurrent AMI after a previous event?
2. Are the regional differences in first ever AMI risk in Sweden valid also for recurrent AMI after taking regional differences in disease severity and differences in population composition into account? Are regional differences related to geographical position (latitude and longitude) or to population properties (size or density)?
3. Do the well-known differences in social and psychosocial risk factors between CHD patients to be and referents prevail also after the CHD event?
4. Does CBT intervention, given to and modified for CHD patients, influence the risk of recurrent CVD and recurrent AMI?

Study population and Methods

This thesis is based on two types of study populations. The first was derived from national public health care register data, and the second on a randomized controlled clinical trial, the SUPRIM study.

Public health care register data

In Sweden there is a unique possibility of evaluating the risk, hazard function, and secular trends in recurrence rate over time, owing to the availability of reliable, large scale registers with national coverage. All official registers are based on the personal identification number (PIN) given to all Swedish residents at birth or immigration.

Swedish statistics on causes of deaths are among the longest-kept worldwide. They go back to 1749 when a nationwide reporting system was first introduced. Initially this responsibility was with the clergy. From 1 July 1860, physicians were entrusted with the task of making out death certificates. Statistics on causes of death were published annually from 1911-1993 by Statistics Sweden (SCB), and since then by The National Swedish Board of Health and Welfare (Socialstyrelsen). Physicians are responsible for reporting data to the Cause of Death Register. The quality of the statistics varies, mainly with the quality and thoroughness of the examination made to investigate the cause of death and the accuracy with which the physician has reported the findings on the death certificate. Changes in the classification system or the processing methods may also influence time trends. The number of autopsies in the all cause mortality register has decreased from about 50 percent in the early 1970s to about 12% in 2007. The decrease varies between different age groups. In people above 75, the proportion decreased from 38% in 1970 to 6% in 2007. In the age-bracket 0-14, it had dropped from 69% 1970 to 41% in 2007 [4].

The National Cause of Death Register has almost 100% coverage. It is available in electronic form since 1952. The National Hospital Discharge Register was established by gradually merging the regional (landsting) operated hospital discharge registers. The regions are responsible for reporting to the Hospital Discharge Register. Validation on the quality of the register and of the AMI diagnosis have been published by the register holder, and was found to be satisfactory [96-98]. The Swedish Acute Myocardial Infarction

Statistics Register was created linking the Cause of Death Register with the Hospital Discharge Register, beginning in 1969. The AMI register includes data on all patients hospitalized for an AMI (primary or secondary diagnosis), or who died outside the hospital of an AMI (underlying or contributing cause of death), provided that a valid PIN is recorded in the registers and that AMI is registered as a diagnosis.

The Hospital Discharge Register includes the variables: PIN, sex, age, place of birth, date of birth, date of hospital admission and discharge, length of hospital stay, main diagnosis and a number of additional diagnoses, means of admittance and discharge, hospital code, department code, number of care for the case. The Cause of Death Register includes the variables: PIN, date of birth, date of death, underlying cause of death and an additional number of other diagnoses, place of death, autopsy, and if the patient had undergone surgery within the past 30 days. The merged AMI register thus includes a combination of these variables. Diagnoses in the Hospital Discharge Register and the Cause of Death Register were coded according to the International Classification of Diseases, versions 8-10 (ICD 8-10) [99]. ICD codes used for AMI were ICD-8 codes 410 (until 1986) [100], ICD-9 code 410 (1987-1996) [101], and ICD-10 code I21-I22 (from 1997- on) [102].

Information on the annual size and age and sex distribution of the underlying general population, including population density on a local level, was accessed from the official Register of the Total Population, run by Statistics Sweden [103]. Data on geographical coordinates (latitude and longitude) of the subjects' residential address was accessed from the National Land Survey of Sweden (Lantmäteriverket) [104].

From the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA International) [105] detailed data on cardiovascular treatment can be obtained, as a guide to evaluating possible regional differences in treatment and outcome and coronary interventions, *e.g.* Coronary Artery By-pass Grafting (CABG), Percutaneous Coronary Intervention (PCI), blood lipid lowering therapy and the use of other cardiovascular drugs.

Papers I and II

Papers I and II were based on data from the Swedish Acute Myocardial Infarction Statistics (AMI register), covering the period 1 January, 1969 until 31 December, 2001.

At the time of the study the AMI register contained 1,163,930 event records for 890,791 subjects, first ever or recurrent AMIs, Figure 1. Before the sharp analysis began, a quality control was made, which resulted in more than 270,000 data revisions in consultation with the register holder. Initially,

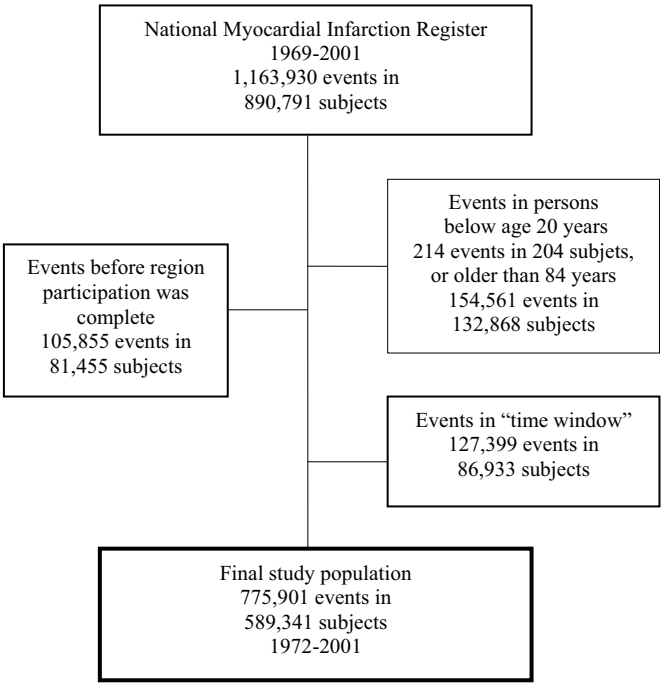


Figure 1. Flow chart of the study population

the register contained only fatal infarctions. The non-fatal events were added successively when the region inpatient data became available in the Hospital Discharge Register. AMI register data were complete for the first council in 1969 and the last at the end of 1986. To determine when the data for a specific council was complete the proportion of fatal AMIs in the region area was followed over time. As the patient data became more complete the proportion of fatal attacks decreased in the AMI register and when the ratio of fatal to all AMIs reached a stable level (usually around 30%) the region was considered to be fully integrated into the AMI register. All AMIs occurring before those years for the specific region were excluded, a total of 105,855 AMIs in 81,455 subjects. Furthermore, 214 events occurring in 204 subjects below 20 years of age and 154,561 events in 132,868 subjects aged 85 or more were excluded, since AMIs in the youngest age group may represent disease with other aetiology, for instance congenital heart disease, and those in the oldest age group because of presumed low diagnosis validity.

In order to study the AMI recurrence on an individual basis the first AMI (index event) had to be identified. The first observation for an individual might not be an index event if the true index event occurred before the register was established. For this reason a time window was defined starting when

the region was fully integrated. The width of the time window was determined after test runs in the database. The effect of this width on the proportion of first observations was analyzed. A time window of 36 months was chosen, since the probability that the first observed event for a subject outside that window would be a true first AMI was 90% or more. All individuals with an event in the time window and all later events for these individuals were excluded, 127,399 events in 88,933 subjects.

After this procedure the final study population consisted of 775,901 events in 589,341 subjects, generating 2,059,726 person years of observation, 656,316 among women and 1,403,410 among men. More than 95% of the study population was of Caucasian origin and about 90% were native Swedes.

In paper II, information on co-morbidity was obtained by re-linking the AMI register with the Hospital Discharge Register. Diagnoses regarding congestive heart failure, diabetes, hypertension, stroke, peripheral artery disease, asthma or congestive pulmonary disease (COPD) and hyperlipaemia until the time of the respective AMI event were identified. ICD codes used for co-morbidity were ICD-8 [100], 9 [101], and 10 [102] codes: congestive heart failure, 427,428, I50; diabetes, 250, E10-E14; hypertension, 400-405, I10-I15; stroke, 431-438, I61-I69; peripheral artery disease, 440-448, I70-I79; asthma or COPD, 490-493, 496, J43-J45; hyperlipaemia, 272, E78.

Paper III

Paper III was based on baseline measurements from the SUPRIM CBT randomized clinical trial and a matched referent group. Patient inclusion criteria were age 75 years or less, discharged from Uppsala University Hospital after an AMI or percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), living in the hospital primary catchment area, referred back to the general practitioner (GP) within one year after the hospital admission, not having previously participated in similar programmes, being Swedish speaking, and agreeing to participate in the study. All patients fulfilling the inclusion criteria were informed about the study at the first outpatient appointment at the hospital two weeks after discharge. During an appointment with the cardiology outpatient department three months after discharge the informed patients were formally invited to participate and verbal informed consent was obtained, a standard requirement at the time. An invitation letter for a baseline examination in the study was mailed to the patients with a baseline questionnaire, and those who accepted the invitation were eventually included. The recruitment period lasted from May 1996 to 2002 and the follow-up data collection was completed in early 2007.

At the time of the analyses for Paper III the recruitment period for the trial was not quite completed. In all, were 778 consecutive patients were consid-

ered for inclusion, of whom 287 did not fulfil the inclusion criteria and 145 patients declined to participate, in most cases because of long distance from home to the hospital or lack of time. The remaining 346 patients (70.5% of eligible cases) agreed to participate, of whom 176 (50.9%) had been admitted for an AMI, 119 (34.4%) for a CABG, and 51 (14.7%) for a PCI. Sixty-three MI patients had a PCI performed during the course of events and two had a CABG. There were no significant age, sex or diagnosis differences between participants and non-participants and no diagnosis differences between men and women. All included patients ("cases") answered a questionnaire at the baseline examination before randomization to the intervention groups.

A random sample of three referents per case from the Swedish general population database in 2002, matched to cases by age, sex, and place of residence. The 1038 matched referents received a postal questionnaire with relevant questions from the baseline questionnaire presented to the cases. Among the cases all 346 (100%) responded and among the referents 610 (59%), altogether 956 individuals. For 92% of the cases at least one of the matched referents responded, yielding 318 case-referent constellations with one case and at least one referent.

Social and demographic data

Information on social background and lifestyle factors was obtained from the questionnaire. For this study marital status was classified as single (including never married, divorced or widowed) or married/cohabiting. Educational level was for Paper III classified as university education or less, and smoking habits as current smoker or non-smoker. Snuff taking was classified accordingly. The participants were asked to indicate whether they had a job, had retired at normal old age retirement age (at the time of the data collection 65), or had received a disability pension. Non-retired subjects were asked whether they had been on sick leave during the past six months, and if so for how many weeks.

Psychosocial data

The Everyday Life Stress Scale instrument [106] was used to assess the level of self-rated stress behaviour. It consists of two major themes, time urgency/impatience and easily aroused irritation/hostility. Responses to the 20 statements were given on four-point scales (0–3), higher scores indicating more stressful reactions. Internal consistency between the 20 items is high. A 5-point difference is of major clinical significance [107].

The Stressful Life Events instrument is derived from a more extensive life event scale [108]. The present version, which comprises ten items, was previously used and validated in a Swedish study of women with cardiac dis-

ease [109]. Subjects are asked to indicate whether they have experienced stressful life events during the past year (2), before the past year (1), or never (0). For this report the events were subdivided into those affecting the respondent or others, high scores indicating more stressful life events.

Vital exhaustion was measured with the Maastricht Questionnaire [110], a standardized self-administered instrument designed to measure exhaustion. Responses to the 19 items were given on three-point scales (0–2), high scores indicating a high degree of vital exhaustion This condition is a marker of longstanding stress and is characterised by excessive fatigue, loss of energy, increased irritability, and demoralisation. In a validation of the instrument a difference of 5 points is considered to be of major inter- or intra-individual significance [110, 111].

The Depressive Mood Scale contains 20 items, selected from the Hamilton Depression Scale [112] and the Beck Depression Inventory (BDI) [113]. Both instruments are widely used, validated measures of depression severity during the past week [112, 113]. The items were partially modified to achieve a standardised unidirectional response format. Possible responses were "not at all" (0), "not quite" (1), "quite well" (2), or "fully" (3), high scores indicating more depressive mood.

The Social Support Scale was originally developed by Henderson *et al*. [114], and later compiled into a short 30 item version by Undén and Orth-Gomer who also validated the short version [115]. In the present study, two of the four subscales were used, "availability of attachment" (AVAT), focusing on affectionately close relationships (social network quality), and "availability of social integration" (AVSI), estimating the size of the social network. AVAT has seven items, with response alternatives "yes" (1) or "no" (0), or "yes" (1), "not sufficient" (0) or "not at all" (0), yielding total score ranges of 0–7 points, high scores indicating more social integration and support. AVSI has six items, response alternatives ranging from "no one" to "more than 15 people" with a total score range of 0–30 points, high scores indicating a large social network.

The original Interpersonal Support Evaluation List (ISEL) was developed and validated by Cohen *et al*. [116]. It has four subscales with a total of 40 statements about the perceived availability of potential social resources. In this study a condensed 13-item version was used, with three subscales. "Appraisal" includes items on perceived availability of someone to talk with about problems. "Belonging" focuses on the availability of people to share activities with, and "Tangible" covers availability of material aid. Total score range (number of responses indicating support) was 0–13 points.

The Mastery Subscale of Factor Items Measuring Coping Resources [117] was used to measure coping. Subjects are asked to indicate their agreement on a four-point scale ranging from "not at all" (0) to "completely" (3) for each of the seven items, high scores indicating more coping resources.

The Life Orientation Test (LOT) was initially developed and validated by Pearlin and Schooler to assess individual differences in generalized optimism versus pessimism [118]. It contains ten items with response alternatives ranging from "I disagree strongly" (0) to "I agree strongly" (3), high scores indicating optimism.

Quality of life

The Gothenburg Quality of Life Instrument, previously validated [119] and used in many studies, was used to measure quality-of-life aspects. For this report, the Complaint Score, the Perceived Health score and the Activity Score subscales were used.

The Complaint Score subscale contains a list of 30 general symptoms, not intended to measure specific symptoms but rather the tendency to report symptoms. The subjects are asked to indicate what symptoms they have experienced during the past three months (yes=1, no=0). The responses were summed up to a total Complaint score, possible range 0-30.

In the Perceived Health subscale the subjects are asked to rate their work situation, home and family situation, fitness, mood, energy, patience, self-esteem, sleep, and well-being on seven-point ordinal scales ranging from "poor" (=1) to "excellent, could not be better" (=7).

The Activity Score subscale contains questions on 32 specified leisure time activities and two open alternatives covering six areas. The subjects are asked to indicate which of these activities they have performed during the last year with response alternatives "never" (0), "occasionally" (1) or "often or regularly" (2). The scores are summed across the area and to an overall activity score, high scores indicating active lifestyle.

The Ladder of Life, developed by Cantril [120] and Andrews *et al*. [121], is often used as an indicator of well-being. The subjects are asked to rank their perceived present well-being, what it was one year ago, and what they think it will be one year from now, on ladder-like scales ranging from the worst (=0) to the best possible situation (=9), high scores indicating better perceived or expected well-being. The instrument was used in the NIH Post-CABG Study [122, 123] and in previous Swedish studies of subjects with CVD [124]. A validation shows that a 1-point difference is regarded as significant on the individual level [122-124].

Paper IV

Paper IV was based on the completed SUPRIM CBT randomized clinical trial. All patients in the study were included after informed consent, a total of 362 patients. The recruitment period lasted from May 1996 until August 2002 and the follow-up data collection was completed in 2008.

At the end of the recruitment period 812 consecutive patients had been considered for inclusion, 302 of whom did not fulfil the inclusion criteria, and 148 subjects declined to participate, in most cases because of distance from home to hospital or lack of time. The remaining 362 subjects (71.0% of eligible cases), 85 (23%) women, and 277 (77%) men, of whom 185 (51.1%) had been admitted for an AMI, 122 (33.7%) for a CABG, and 55 (15.2%) for a PCI were included. Seventy-one AMI subjects had a PCI performed during the course of events and three had a CABG. There were no significant age, sex or diagnosis differences between participants and non-participants and no diagnosis differences between women and men.

Randomization procedure

The group allocation was based on the SAS "ranuni" function, providing random numbers with equal probability [125]. The procedure resulted in pre-prepared sealed envelopes, kept in a safe, with a serial number on the outside and a sheet of paper inside with the group allocation on the front and a blinding print on the back to make it impossible to read the group allocation sheet from the outside. After inclusion of a subject the study monitor (the only person with access to the randomization envelopes) opened the next envelope in turn and noted the group allocation in the computerized monitoring log book. Of those included, 192 were allocated to behavioural intervention and 170 to the reference group. Subjects were informed about the group allocation after the baseline measurement.

Examinations

The subjects received a letter of invitation for a first (baseline) examination with a first postal questionnaire included. The procedure was repeated at the 6th, 12th, 18th and 24th month after baseline a total of five times. The examinations included height, weight, and blood pressure measurement, and blood sampling for blood lipids. Weight was measured on a lever balance with indoor clothing to the nearest tenth of a kilogram. Height was measured without shoes on a wall fixed measure to the nearest centimetre (cm). Sagittal abdomen diameter was measured in the supine position to the nearest cm. Waist circumference was measured without clothes, using a tape measure, and recorded to nearest cm. Systolic and diastolic blood pressure measurements were performed in duplicate in the supine position, on the right arm, after at least 5 minutes of rest, systolic pressure at Korotkoff phase 1 and diastolic pressure at Korotkoff phase 5. Blood was drawn in the morning, after an overnight fast, from an antecubital vein with minimal occlusion, into evacuated glass tubes. After centrifugation the samples for blood lipid analyses were analyzed immediately and the remaining plasma was frozen to -70^{o} Centigrade. Total cholesterol and triglycerides in serum were assayed using

enzymatic techniques with a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA, USA). High density lipoproteins (HDL) were isolated by centrifugation and precipitation with a sodium phosphotungstate and magnesium chloride solution [126]. Low density lipoprotein (LDL) cholesterol was calculated according to Friedewald's formula [127].

Questionnaire data

Information on social background, lifestyle factors and current medication was obtained from the questionnaires at each measurement occasion. For Paper IV marital status was classified as single (including never married, divorced or widowed) or married/cohabiting. Educational level was measured on a 4-point scale ranging from compulsory education only to university education. Smoking habits, regardless of type of tobacco, were classified as never smoked, ex-smoker, smoking 1-14 grams per day, 15-24 grams or 25 grams per day or more. Snuff taking was classified accordingly. The participants were asked to indicate whether they had a job, had retired at normal retirement age (65 years of age at the time), or had been granted a disability pension.

Information on medical history until the baseline measurement regarding congestive heart failure, diabetes, hypertension, stroke, peripheral artery disease, asthma or congestive pulmonary disease (COPD) and hyperlipaemia (yes or no) was obtained from the baseline questionnaire and used as comorbidity variables, a proxy for disease severity.

Hospital admission and survival data

Hospital admission data from 1971 until 31 December 2006 were obtained from the National Hospital Discharge Register, covering all hospital admissions. The variables date of admission and discharge and all diagnoses were used. Mortality data were obtained from the National Cause of Death Registry for all deaths in the study population until 31 December 2006. The variables used here were date of death, underlying and all contributing causes of death, and data on post-mortem examinations, including autopsies. The overall autopsy rate was 23%, and the autopsy rate among those who had a first fatal CVD outcome in the trial was 50%. Hospital discharge diagnoses and causes of death were coded according to ICD, versions 8-10 [99-102]. CVD was defined as ICD-8 codes (until 1986) and ICD-9 codes (1987-1996) 401-459, and ICD-10 codes (from 1997 on) I10-I99. AMI was defined as ICD-8 and ICD-9 codes 410, and ICD-10 code I21-I22. Based on these data the number of AMIs per subject prior to baseline, and all deaths irrespective of cause, the first CVD event, fatal or non-fatal, and the first AMI post baseline were identified.

Intervention

Patients entered the intervention program within a year after the index CHD event. The treatment groups consisted of 5 to 9 participants. The program offered 20 two-hour sessions over the course of 1 year. Sessions were held weekly for the first 10 weeks, and approximately bi-weekly for the rest of the year. Each group was assigned one group leader, especially educated for this purpose, and the same group leader remained with that group for the whole treatment period. The groups were single-gendered, so that male and female patients were treated separately, but the group leaders could be same or opposite sex as the participants. The overall goal of the treatment was to develop emotional and behavioural coping strategies for dealing with stress. The focus was particularly on stress reactivity and stress behaviours characterized by negative affect like hostility, anxiety, and depressive mood reactions.

There were five key components of the program with specific goals: education, self-monitoring, skills training, cognitive re-structuring, and spiritual development. For education, the goal was to develop knowledge about basic anatomy and physiology of the cardiovascular system, manifestations of and treatment procedures for CHD, emotional consequences of a CHD event, health behaviours and lifestyle, symptoms and signs of stress reactions, and the relationship between stress and CHD. The session agendas contained discussion of case illustrations, and use of slide presentations, written, audio- and videotaped material.

The goal for self-monitoring was to become more alert to bodily signals such as muscular tension, heart rate, and pain, to notice behavioural and cognitive cues, to observe, reflect, and to draw conclusions about contingencies of behaviour. This was achieved by observing and monitoring own reactions and behaviours by use of ”diaries”; systematic observation of specific behaviours; use of group processes to enhance observational skills and understanding.

The goal for skills training was to reduce negative affects and to learn to act constructively, rather than merely react, to everyday problems of life. In order to develop behavioural skills as alternatives to anger, frustration, and depressive reactions, a “drill book” was used for daily behavioural exercises. Problem solving and communication skills were practiced in and outside the group. The group format was important in setting the stage for modeling and group processes as an arena for development of coping skills.

The goal for cognitive restructuring was to be able to recognize negative, hostile, and stress-triggering cognitions and attitudes, and to develop self-talk to reduce stress reactivity. A special focus was on hostility, worries, and self-defeating attitudes. Ways to achieve this was to use group discussions to review attitudes and beliefs, self-monitoring of thoughts, attitudes, and interpretations that were evoked by skills training and everyday life experiences,

restructuring of attribution styles, and development of specific cognitive techniques.

The goal for spiritual development was to reflect on spiritual and life values in order to see the change process in the broader context of a future meaningful life. Particularly towards the end of the program, group discussions focused on quality of life issues, goals and values, and the importance of significant others. The social and emotional support of the group was instrumental for the development of self-esteem, optimism, trust and emotional intimacy [128].

The structure of the program was similar to most cognitive-behavioural treatment programs. Each session had an agenda and a specific theme. The session started with a few minutes of progressive muscular relaxation. Next, homework assignments were reviewed and reflected upon. The current theme was discussed and elaborated, and new themes and issues were introduced, building on previous discussions. The session ended with agreements on continued or new homework assignments, which were mostly shared by all group members, but sometimes individually tailored.

A variety of educational material was used, such as case illustrations, readings, working material, slides and films, and handouts. Diaries were used throughout the treatment period, as well as a booklet with daily behavioural exercises. Within the structure of the program, the specific contents and themes were tailored to particular and typical daily life experiences of men and women, respectively. The examples from and applications to daily life experiences were solicited through self-monitoring diaries.

For the women, skills training needed to focus on self-confidence and self-assertion, while in contrast, many men with CHD in these groups needed to develop skills to cope with aggressive and hostile behaviour. Another example of how focus could differ for men and women in the groups was the role of the social network. Many women were over-involved in social ties to the point where their own needs were subdued, while social network for most men provided unconditional support. Also, when dealing with the issue of anger and hostility, the triggers as well as the expression of such affects generally differed between the men and the women, reflecting the gender roles. Therefore, single-gender groups provided shared experiences and good mutual understanding between the participants, thus enhancing therapeutic efficiency. Attendance rate at sessions was monitored. The median attendance rate was 85%, and fewer than 5% of the subjects attended less than 50% of the sessions.

All the studies in this thesis were approved, first by the Research Ethics Board at the Medical School of Uppsala University and later by The National Research Ethics Board, on several occasions throughout the studies.

Statistical considerations

Data were analyzed with the SAS software, versions 6.12 and 9.1 [125]. Summary statistics, such as means, medians, and measures of dispersion were computed with standard parametric methods. Simple (crude) differences between groups in continuous variables were computed with Student's t-test and differences in proportions with the chi-square test. Only 2-tailed tests were used.

Paper I

The hazard function was computed using two methods. First a preliminary analysis was performed with the SAS "lifetest" procedure, yielding the main outline of the hazard function but not permitting adjustment for hazard-affecting variables other than time. In the final hazard function analysis a Poisson model was used in a SAS compatible program developed for the database [129] The logarithm of the hazard rate was modelled as a continuous function of the time-dependent variables by connected linear and quadratic pieces in specified follow-up time intervals. The time-dependent variables (updated once a year) used as covariates were current age, calendar time 1972 to 2001, and time from the previous AMI. The analyses were stratified for sex and for AMI number. A number of potential interaction terms were tested but none was significant.

In these analyses the relation between the hazard function of the various age, sex, and AMI number groups was found to be approximately proportional. Estimates of change of 1-year hazard rate over calendar time was therefore computed with the Cox proportional hazards regression, modelled with connected linear, quadratic, and cubic pieces in specified calendar year intervals. The model fit, assessed by comparison of crude risk analyzed separately by calendar year, and annual risk across the total follow-up period according to the model, was excellent. In the figures no confidence intervals were indicated because they were so small (fractions of a percent). Censoring events were death from other causes than AMI during follow up or no new event by the end of follow up. The outcome variable was recurrent AMI (first, second, third, fourth or more as indicated). Individual follow-up time was right truncated at the end of the 22nd year because of small numbers. The average age specific risk of first-ever AMI in men and women during the study period was obtained by dividing the total number of subjects aged 60, 61, 62 *etc.*, with an index event across the total follow-up period with the number of individuals in the corresponding age–sex segment of the general population.

To test for homogeneity of included regional registers, these were divided into 3 groups, those that were integrated early, those that were integrated late, and a middle group. The annual risk levels for a first recurrent AMI was

computed separately for each group for the years all groups were in the register. There were no detectable differences in risk level, indicating that there was no observable selection bias. Moreover, to be on the safe side, all analyses were adjusted for calendar year. The effects of potential confounders and other effect modifiers on recurrent AMI rate in the Cox analyses were adjusted for by stratification (sex) or by inclusion as covariates in the model (*e.g.* age at incident, recurrent AMI number, and calendar year of incident as a proxy for changes over time in other outcome affecting variables, such as case fatality rate, AMI treatment given, potential bias caused by differences in regional introduction in the AMI register, *etc.*). Probability values less than 5% were regarded as statistically significant.

Paper II

Cox's proportional hazards regression analysis was used to estimate the effects of age, recurrent AMI number, calendar year of incident, co-morbidity variables, and residential area geographical location and population size and density, on the risk of recurrent AMI. Calendar year of incident was used to account for the changing incidence rate and case fatality rate over time. Recurrent AMI number and the co-morbidity variables were used as proxies for disease severity. Censoring events were death during follow up or no new event by the end of follow up. The outcome variable was recurrent AMI. All analyses were stratified for sex. The population size and population density variables were skewed towards high values. Analyses were therefore performed both on log transformed and original data. However, the results were similar and only the original data were used in the final analyses. Wald's chi-square values were used as measures of importance of the independent variables.

The coordinates of the regression line in Figure 8 were computed with Cox's proportional hazards regression technique using a squared population density term and adjusted for all other covariates. The model fit, assessed by inspection, was excellent. No confidence intervals were indicated in the figure since they were so small (fractions of a percent). P-values less than 5% were regarded as statistically significant.

Paper III

The frequency of missing data in returned questionnaires was less than 2%. A power calculation was performed based on data on vital exhaustion from a controlled trial in female CHD patients and referents using the same instrument as that used in our study [106]. Given a modest mean difference between cases and referents of 3.3 points with standard deviation 10.0, an 80% power would be obtained with a study population of 300 persons. The actual study population of 956 persons gave more than 95% power. Similar statisti-

cal power was obtained using the actual differences in activity score found in this study.

Differences in psychosocial and quality of life data between the groups were tested in conditional multiple linear regression or conditional ordinal logistic regression analyses adjusted for the influence of age, education, marital status and smoking habits, and adjusted means were generated using these procedures. The purpose of performing the analyses conditionally was to compare cases only with their own referents and to account for the variable number of referents per case. To account for the many tests performed, p-values <0.005 were considered to indicate statistical significance.

Paper IV

All analysis was based on the intention-to-treat approach. The overwhelming majority of dropouts from the study were attributable to death. In case of missed appointments among survivors, data from the most recent previous appointment were used until new values were available.

The outcome variables included all cause mortality, recurrent first CVD and recurrent first AMI after baseline. Cox's proportional hazards regression analysis with backward elimination of non-significant adjustment covariates was used to estimate the cumulative mortality rate, the first recurrent CVD rate and the first recurrent AMI rate after baseline in the two groups after adjustment for the influence of age, sex, marital status, education, and medical history or co-morbidity variables, (number of previous AMIs, congestive heart failure, diabetes, hypertension, stroke, peripheral artery disease, asthma or COPD and hyperlipaemia), hereinafter called adjustment covariates and were used as proxies for disease severity. Follow-up time was calculated as the number of days from baseline to the time of outcome or end of follow up. Censoring events in the analyses of recurrent CVD and recurrent AMI events were death from other causes during follow up or no new event by the end of follow up. Individual mortality follow-up time was right truncated at 8.4 years, and CVD and AMI follow up at 9.1 years because of small numbers (less than 100 exposed subjects). P-values less than 5% were regarded as statistically significant.

Results

Paper I

Characteristics of the study population

During the 30-year study period 210,437 women and 378,904 men had an index event, generating 559,665 and 1,232,145 person-years of observation, respectively, Table 1. Of these, approximately 20% died out of hospital, 78% to 79% were admitted alive to hospital, and 1% occurred while in hospital. Mean age at the first incident was 72.8 years among women (median, 75; interquartile range, 68 to 80) and 68.1 years for men (median, 70; interquartile range, 61 to 76). The median number of days in hospital for patients with AMI occurring out of hospital and surviving until discharge was 9 days among women (mean, 14.3; range, 30.7 days in 1972 to 8.9 days in 2001) and 8 days among men (mean, 11.4; range, 20.8 days in 1972 to 7.8 days in 2001). The case fatality rate was 24% for women (range, 33.4% in 1972 to 13.8% in 2001) and 19% for men (range, 32.7% in 1972 to 11.3% in 2001).

A total of 61,927 recurrent AMIs occurred among women and 124,633 among men, generating 9,069 and 24,277 person years of observation, respectively. The mean number of recurrent AMIs per subject was 1.48 among women and 1.42 among men (median 1, interquartile range 1 to 2 in both sexes). Among women 43,449 subjects had a first recurrent AMI, 11,940 had a second, 3,979 had a third, and 2,559 had a fourth or more recurrent AMI. The corresponding numbers among men were 89,407; 24,292; 7,200, and 3,734. The proportions of patients dead out of hospital, admitted alive to hospital, and AMIs occurring while in hospital were approximately the same as for index events. Mean time interval to a new AMI event was 30.3 months for women (median, 13.7; interquartile range, 3.4 to 41.6) and 39.5 months for men (median, 19.9; interquartile range, 4.8 to 57.9). Mean number of days in hospital for those admitted to hospital and surviving until discharge was 13.9 for women (median, 9; interquartile range, 6 to 15) and 11.3 for men (median, 8; interquartile range, 5 to 12). The case fatality rate was approximately the same as for the first event.

Hazard function for recurrent event

In Figure 2 the risk, or hazard function, for a first recurrent AMI among men

Table 1. *Characteristics of the study population from the AMI* register*

	Women		Men		
	n	mean (SD) or %	n	mean (SD) or %	p-value
First AMI (index event)					
Total number of events	210,437		378,904		
Person years of observation	559,665		1,232,145		
AMI occurrence					<0.0001
AMI out of hospital and died before admission	41,499	19.7	82,242	21.7	
AMI out of hospital and survived until admission	166,334	79.1	294,089	77.6	
AMI occurred in hospital	2,604	1.2	2,573	0.7	
Age at first AMI, years		72.8 (9.1)		68.1 (10.6)	<0.0001
Number of hospital days for AMIs occurring out of hospital and surviving		14.3 (32.9)		11.4 (23.7)	<0.0001
Case fatality rate within 28 days		23.8		19.3	<0.0001
Recurrent AMI					
Total number of events	61,927		124,633		
Person years of observation	93,069		246,277		
Mean number per subject		1.48 (0.95)		1.42 (0.84)	<0.0001
AMI occurrence					<0.0001
AMI out of hospital and died before admission	13,370	21.6	29,708	23.8	
AMI out of hospital and survived until admission	48,189	77.8	94,384	75.8	
AMI occurred in hospital	368	0.6	541	0.4	
Mean time to recurrent AMI, months		30.3 (40.1)		39.5 (47.5)	<0.0001
Number of hospital days for AMIs occurring out of hospital and surviving		13.9 (30.5)		11.3 (18.9)	<0.0001
Case fatality rate within 28 days		23.2		21.3	<0.0001

* AMI = Acute myocardial infarction

and women of various age groups at the index event is shown. The risk, expressed as proportion (%) of patients with an index event experiencing a first recurrent AMI, fell sharply during the first 2 years after the index event, reached a minimum after 5 years as assessed from the Poisson analysis output, and then increased slowly over the remaining years of follow-up. The curve shape was fairly similar in both sexes and all age groups, but the general level differed. The risk increased on average by 3.8% (95% CI, 3.7% to 3.9%) per year of age for women and by 3.6% (95% CI, 3.5% to 3.7%) for

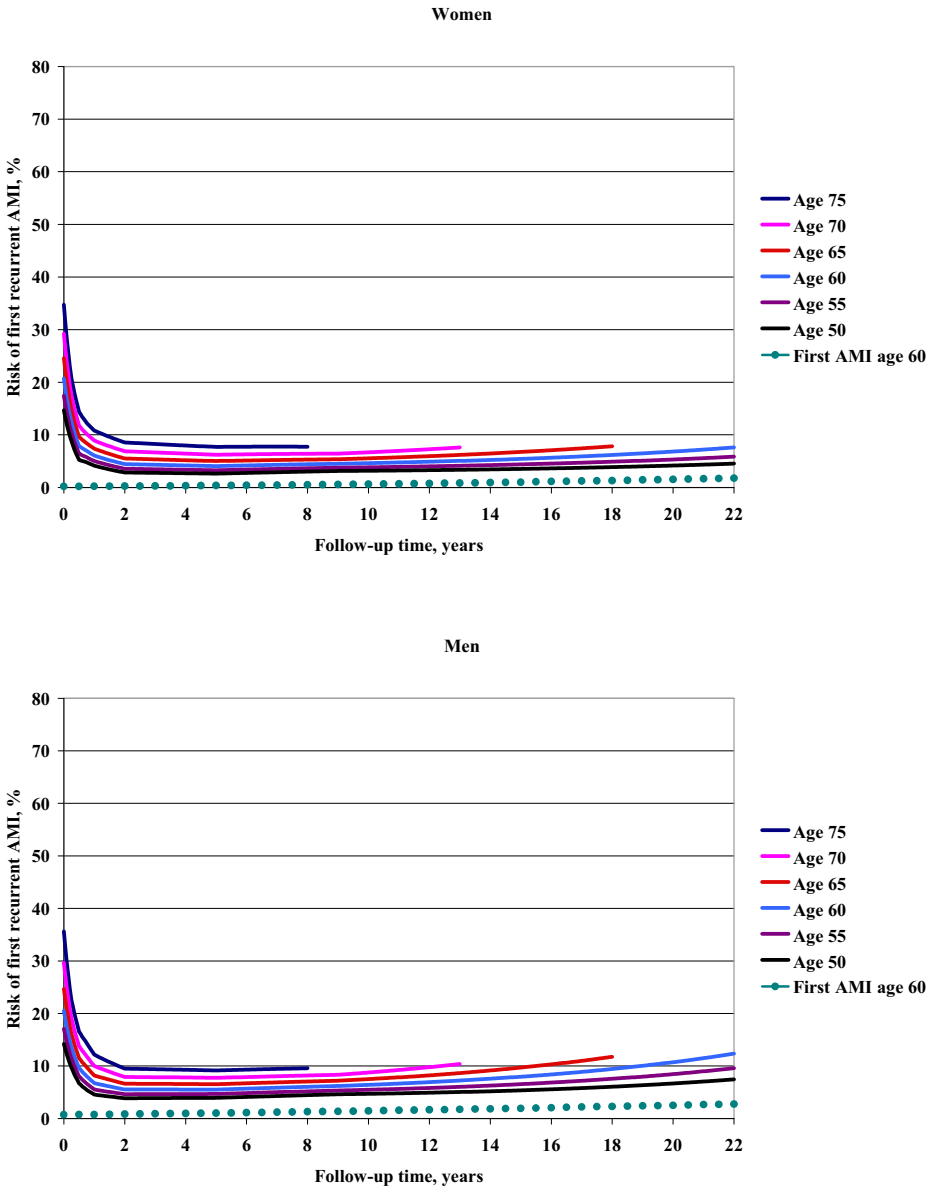


Figure 2. Risk (%) of a first recurrent acute myocardial infarction (AMI) among women and men in groups according to follow-up time and age at first AMI. For comparison, the risk of a first AMI is shown. For the latter, age 60 corresponds to follow-up year 0, 61 to follow-up year 1 *etc*. Female patients at risk: age 50 n=10,072; age 60 n=24,104; age 70 n=67,019; age 80 n=109,242. Male patients at risk: age 50 n=45,590; age 60 n=78,886; age 70 n=131,480; age 80 n=122,948. The rank order of the curves is the same as the rank order of the key to the symbols

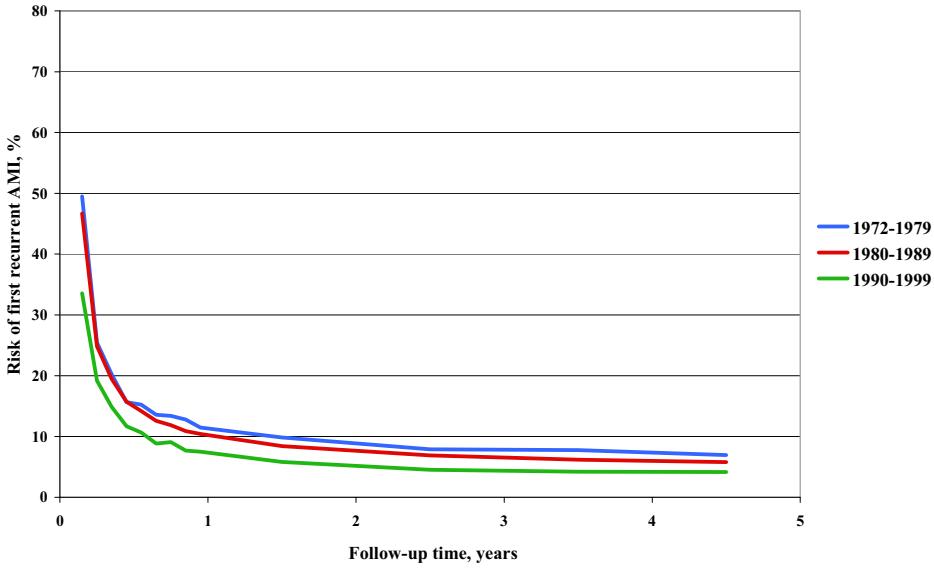


Figure 3. Risk (%) of a first recurrent acute myocardial infarction (AMI) in groups according to time of first AMI (1972 to 1979, 1980 to 1989, and 1990 to 1999)

men. The risk increase accelerated slightly by age for both men and women (data not shown).

In contrast to the recurrent AMI risk for subjects aged 60, Figure 2 also shows the risk for an index AMI in men and women aged 60 years. For both risk functions, age 60 corresponds to follow-up year 0, age 61 to year 1, *etc*. The index AMI risk function ranged from 0.7% and 0.2% for men and women, respectively, at age 60 to 2.7% and 1.8% at age 82. At the point where the recurrent AMI risk curve had its minimum, the risk ratio for a second as compared with an index event was 5.5 among men and 10.7 for women. From then on the index and recurrent AMI curves were approximately proportional.

Figure 3 shows the hazard function during 1972 to 1979, 1980 to 1989, and 1990 to 1999. The shape of the hazard function was similar in all 3 periods, but the general level decreased over time. In Figure 4 the effect of recurrent AMI number on the hazard function is shown. The curve shape was similar for the first and second recurrent AMI. From the third recurrent AMI and onwards the minimum tended to come later. The risk increased on average by 39% (95% CI, 38% to 40%) per recurrent AMI for women and 36% (95% CI, 35% to 37%) for men.

Secular effects in relation to the risk of recurrent events

In Figure 5 the average risk of a first recurrent AMI during the first year fol-

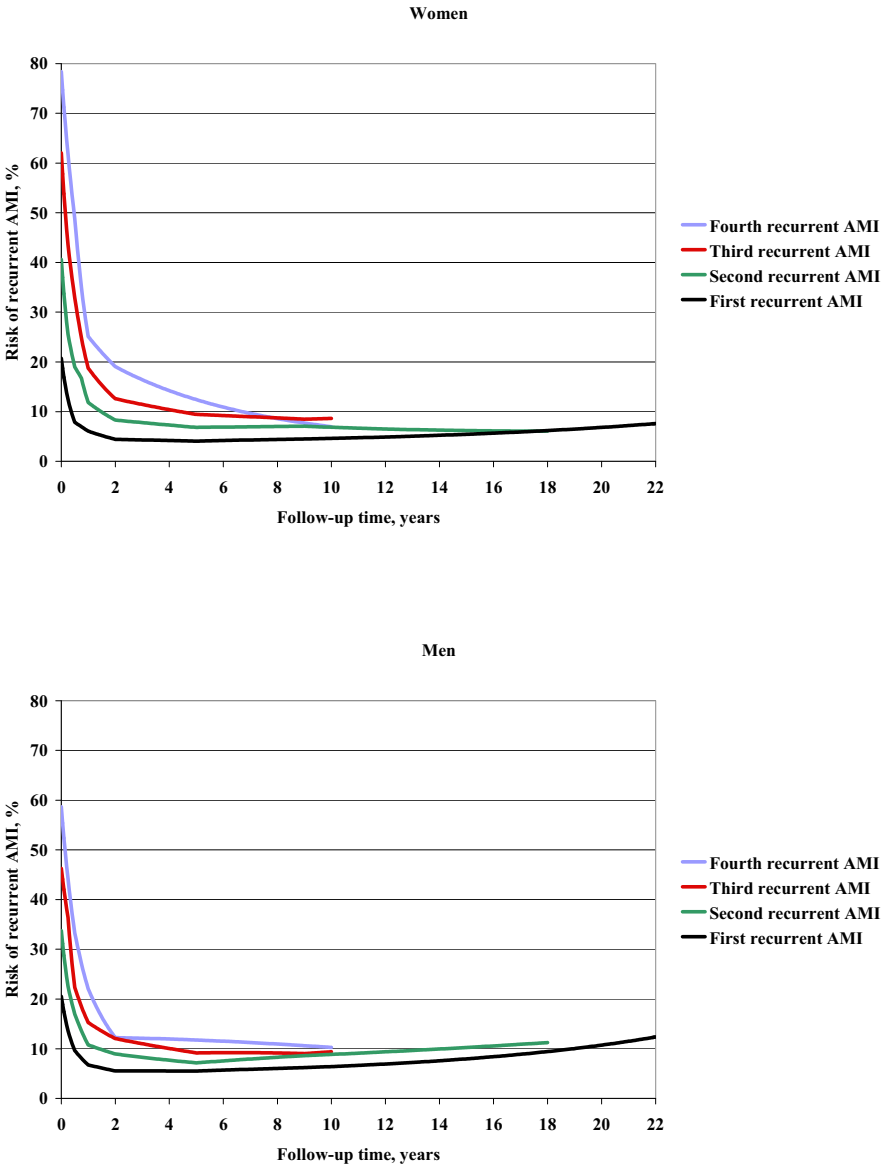


Figure 4. Risk (%) of a first, second, third, and fourth or more recurrent acute myocardial infarction (AMI) among women and men 70 years old at the previous event. Female patients at risk: first reinfarction n=210,437; second n=43,449; third n=11,940; fourth or more n=6,538. Male patients at risk: first reinfarction n=378,904; second n=89,407; third n=24,292; fourth or more n=10,934. The rank order of the curves is the same as the rank order of the key to the symbols

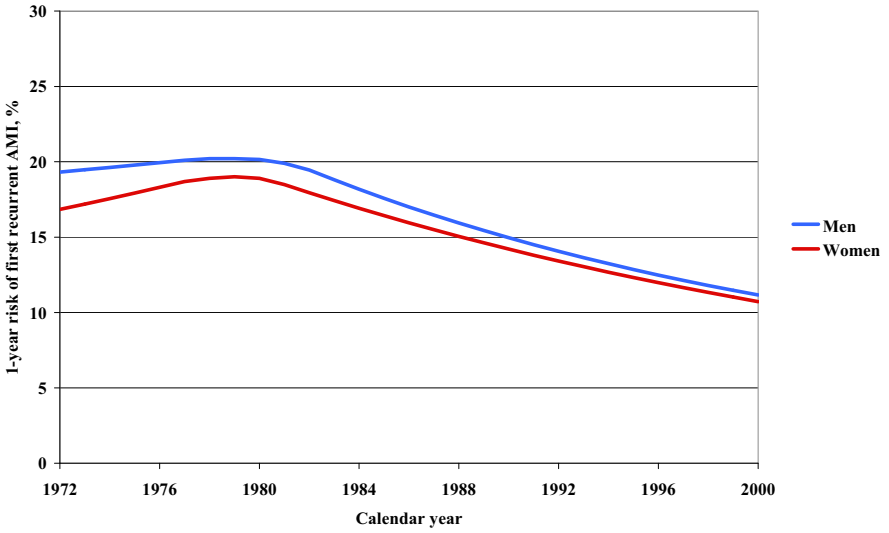


Figure 5. Risk (%) of a first recurrent acute myocardial infarction (AMI) during the first year after the previous event among women and men 70 years of age in relation to calendar year

lowing a previous event is shown for women and men, 70 years of age, over the study period. During the period 1972 to 1979 there was a non-significant tendency toward a risk increase. The risk then levelled off and fell by approximately 40% in men and 36% in women, a highly significant decline (P<0.0001). The functional form of the risk change was similar in both sexes. The average risk decrease was 2.5% (95% CI, 2.5% to 2.7%) per calendar year for women and 3.1% (95% CI, 3.0% to 3.2%) for men. Corresponding data for various age groups is shown in Figure 6. The functional form was the same for all age groups but the switch from slowly increasing to decreasing slope tended to come somewhat later by age and the general risk level increased. As shown in Figure 7 the functional form of the change over calendar years was the same irrespective of recurrent AMI number, but the general risk level increased with AMI number.

Paper II

Characteristics of the study population

During the 30-year study period 210,437 women and 378,904 men had a first AMI (index event), and 61,927 women and 124,633 men had one or more recurrent events, Table 2. Mean age at the incident was 73.2 (SD 8.8) years among women and 68.7 (SD 10.4) years for men. The most common

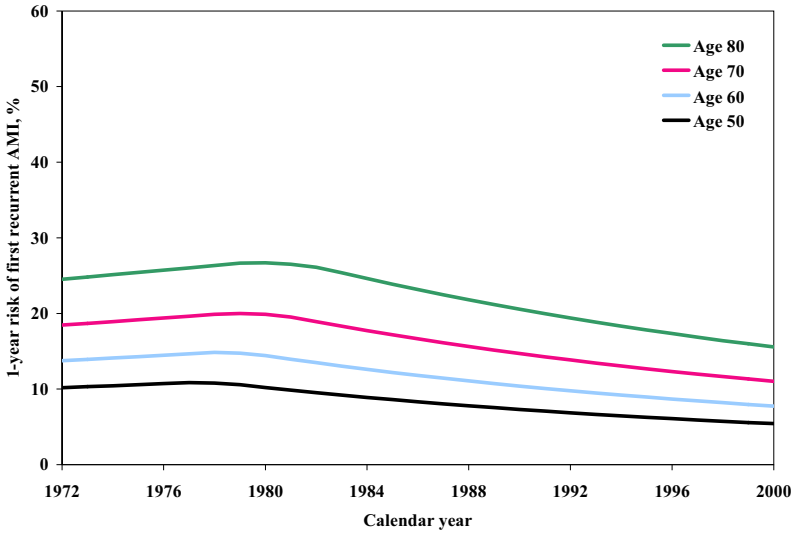


Figure 6. Risk (%) of a first recurrent acute myocardial infarction (AMI) during the first year after the previous event in different age groups in relation to calendar year

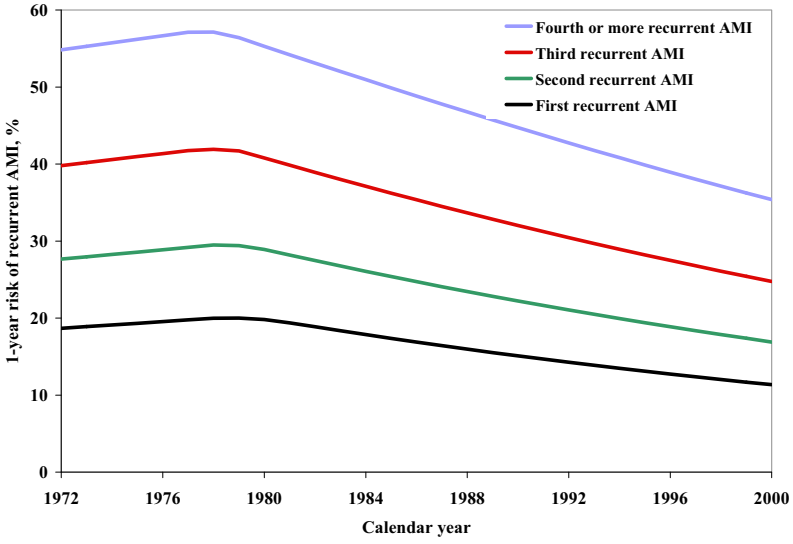


Figure 7. Risk (%) of a recurrent acute myocardial infarction (AMI) during the first year after the previous event for a first, second , third and fourth or more recurrent AMI in relation to calendar year

co-morbidity diagnoses were congestive heart failure, diabetes, hypertension, stroke, peripheral artery disease, asthma or COPD and hyperlipaemia in that order. Co-morbidity diagnoses were in general significantly more fre-

Table 2. *Characteristics of study population from the AMI* register*

	Women		Men		
	n	mean, % median or range	n	mean, % median or range	p-value
Co-morbidity, %					
Congestive heart failure	86,700	31.8	133,690	26.6	<0.0001
Diabetes	54,497	20.0	68,487	13.6	<0.0001
Hypertension	50,972	18.7	65,509	13.0	<0.0001
Stroke	44,233	16.2	70,284	14.0	<0.0001
Peripheral artery disease	28,247	10.4	43,243	8.6	<0.0001
Astma or COPD[1)]	13,726	5.0	24,883	4.9	n.s.
Hyperlipidaemia	5,614	2.1	11,971	2.4	<0.0001
Residental area					
Latitude range, °North		55-68		55-68	
Longitude range, °East		11-24		11-24	
Population size					
Mean		134,271		120,705	
Median		47,755		42,224	
Inter-quartile range		22,247–120,354		20,300–109,907	
Population density[2)]					
Mean		539		477	
Median		67		60	
Inter-quartile range		26-319		24-208	

*Acute myocardial infarction [1)] Congestive pulmonary disease [2)] Population per square kilometre

quent among women than among men (p<0.0001), except for asthma or COPD (no significant difference), and hyperlipaemia that was more common among men (p<0.0001).

The geographical location of the residential area ranged from latitude 55 to 68 degrees north and longitude from 11 to 24 degrees east, equal for men and women. Women tended to live in municipalities with larger population size than men (mean 134,271 versus 120,705, and median 47,755 versus 42,224), and municipalities with higher population density (mean 539 persons per square kilometre versus 477, median 67 versus 60).

Risk of new events in relation to co-morbidity and demography

The risk of a recurrent AMI event increased by age and recurrent AMI number among men as well as among women. In bivariate logistic regression analyses presence of any co-morbidity diagnosis was associated with a significantly increased risk of a recurrent event, except hyperlipaemia, which was associated with a decreased risk among both men and women (p<0.0001 for all determinants), Table 3. The results were the same in multivariate analysis, except that asthma or COPD had no significant effect in women. As

Table 3. *Effects of age, recurrent acute myocardial infarction (AMI) number, and co-morbidity variables on AMI recurrence risk*

	Bivariate analysis				Multivariate analysis					
	Women		Men		Women			Men		
	HR[2)]	95%CI	HR	95%CI	HR	95%CI	Chi-square	HR	95%CI	Chi-square
Age by 10-year age groups	1.46	1.45-1.48	1.42	1.41-1.43	1.36	1.35-1.38	3406	1.33	1.32-1.34	7882
Recurrent AMI number	1.63	1.61-1.64	1.49	1.48-1.50	1.43	1.42-1.45	4549	1.32	1.31-1.33	4600
History of										
Diabetes	1.95	1.92-1.99	1.71	1.69-1.74	1.65	1.61-1.68	2653	1.44	1.42-1.46	2054
Peripheral artery disease	1.83	1.79-1.88	1.85	1.81-1.89	1.41	1.38-1.45	664	1.40	1.37-1.43	983
Congestive heart failure	1.71	1.68-1.74	1.73	1.71-1.75	1.22	1.20-1.24	454	1.25	1.23-1.26	961
Stroke	1.54	1.51-1.57	1.71	1.68-1.74	1.16	1.13-1.19	159	1.24	1.22-1.26	563
Hyperlipidaemia	0.69	0.65-0.73	0.65	0.62-0.68	0.67	0.63-0.72	154	0.67	0.64-0.70	312
Hypertension	1.39	1.36-1.41	1.34	1.32-1.36	1.08	1.06-1.10	58	1.09	1.07-1.11	94
Astma or COPD [1)]	1.19	1.15-1.24	1.53	1.49-1.57	1.02	0.99-1.06	2	1.17	1.14-1.20	134

[1)] Congestive pulmonary disease [2)] HR = hazards ratio

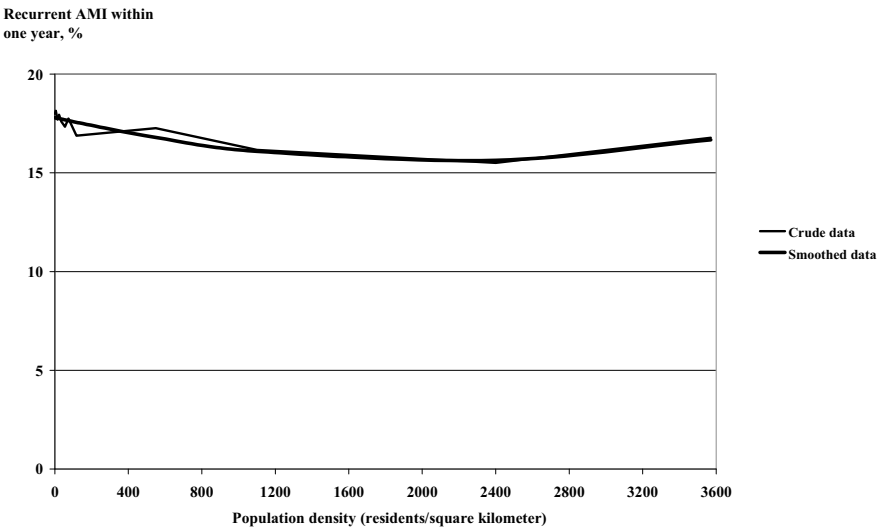


Figure 8. Risk of recurrent acute myocardial infarction (AMI) within a year from previous event in groups according to residential area population density, adjusted for age, sex, recurrent AMI number, calendar year of incidence, co-morbidity variables (congestive heart failure, diabetes, hypertension, stroke, peripheral artery disease, asthma or congestive pulmonary disease, and hyperlipemia)

indicated by the chi-square level the most important co-morbidity variables were diabetes, peripheral artery disease, congestive heart failure, stroke, hyperlipaemia, hypertension and asthma or COPD in that order.

A multivariate analysis of the influence of latitude, longitude, population size and population density on AMI recurrence risk, adjusted for the influence of age, sex, recurrent AMI number, calendar year of incident, and the co-morbidity variables, showed a statistically significant effect of population density, the higher the density the lower the risk ($p<0.0001$), whereas latitude ($p=0.10$), longitude ($p=0.07$), and population size ($p=0.46$) had no statistically significant effect, indicating that population density was the most important of the demographic variables, all things considered. Its chi-square value equalled 160, comparable to the mid-range of the co-morbidity variables.

In order to check whether the relationship between population density and risk of recurrent AMI was linear or non-linear, a square population density term and a cubic population density term were tested. The result indicated that the relationship followed a second-degree polynomial function. As shown in Figure 8, the relationship between population density and risk of recurrent AMI, decreased with increasing population density, reached a minimum at a density of 2400 residents per square kilometre, and then increased again with increasing population density.

Paper III

Characteristics of the study population

Seventy-six per cent of the subjects were men and mean age was 66 years, Table 4. More than half were residents of urban areas, and one third were single. On average 23% had a university education, 15% were daily smokers. Only men were snuff takers. On average 55% were old age pensioners and 12% had disability retirement benefits. Based on the 312 subjects who could be on sick leave 26% of the referents were on sick leave versus 68.8% of the female cases and 61.3% of the male cases.

Psychosocial measures

After adjustment for the influences of age, education, marital status and smoking habits, there were no differences between the groups regarding everyday life stress and stressful life events, Table 5. Events affecting others were more often reported by women than men, as were vital exhaustion ($p<0.0001$) and depressive mood scores ($p<0.001$), while there were no significant differences between cases and referents for these variables. Cases reported higher social support scores than their referents. Men reported higher coping scores than women but with no significant differences between cases and referents. Women reported less optimism than men, and also the lowest optimism scores of all groups.

Quality of life measures

Quality of life data measured as well-being and activity score adjusted for the influence of age, education, marital status and smoking habits are shown in Table 6. Women reported a higher total well-being score then men. However, there were no significant differences between cases and referents or between men and women regarding work situation, home and family situation, mood, energy and patience. Women reported significantly lower self-esteem, sleep, fitness and perceived health than men. Cases reported lower scores for fitness and perceived health than referents.

Women reported lower total activity, home outdoor activity, and physical activity scores than men. Cases reported lower total activity, home indoor activity, pleasure activity, and social activity scores than referents. Complaint Score data are shown in Figure 9. Women reported more complaint score symptoms (10.2 95%CI 9.2–11.2 for female referents and 10.4, 95%CI 9.3–11.4 for female cases) than men (8.2, 95%CI 7.7–8.8 for male referents and 8.1, 95%CI 7.4–8.8 for male cases). The difference between men and women was significant ($p<0.0001$) but not between cases and referents. The

Table 4. *Characteristics of the SUPRIM * study population*

	Women				Men					
	Cases		Referents		Cases		Referents		Sex differences	Case-referent differences
	n	mean or %	n	mean or %	n	mean or %	n	mean or %	p-value	p-value
Age, years, mean	82	67.5	149	66.9	264	64.9	461	65.1	0.0003	0.97
Urban dwellers, %	56	68.3	106	71.1	155	58.7	272	59.0	0.0022	0.77
Single, %	29	35.4	64	43.2	33	12.6	94	20.7	<0.0001	0.0041
University education, %	17	20.7	41	27.7	53	20.3	115	25.1	0.56	0.0634
Daily smokers, %	12	14.8	18	12.2	34	13.0	74	16.3	<0.0001	<0.0001
Snuff takers, %	0	0	1	0.7	26	10.0	57	12.5	<0.0001	0.65
Old age pension, %	48	58.5	99	66.9	120	45.5	255	55.7	0.0016	0.0034
Disability pension, %	16	19.5	15	10.1	31	11.7	51	11.1	0.38	0.21
Sick-listed										
Among all, %	15	19.2	15	10.1	80	31.5	47	10.3	0.12	<0.0001
Among eligible, %	11	68.8	9	26.5	68	61.3	39	25.8	0.68	<0.0001

* Secondary prevention in Uppsala Primary Health Care Project

p-values refer to differences between women and men and between cases and referents in conditional analyses

p-values <0.005 were regarded as statistically significant

Table 5. *Psychosocial measures (mean scores) among female and male cases and referents, adjusted for the influence of age, education, marital status and smoking habits in conditional analyses*

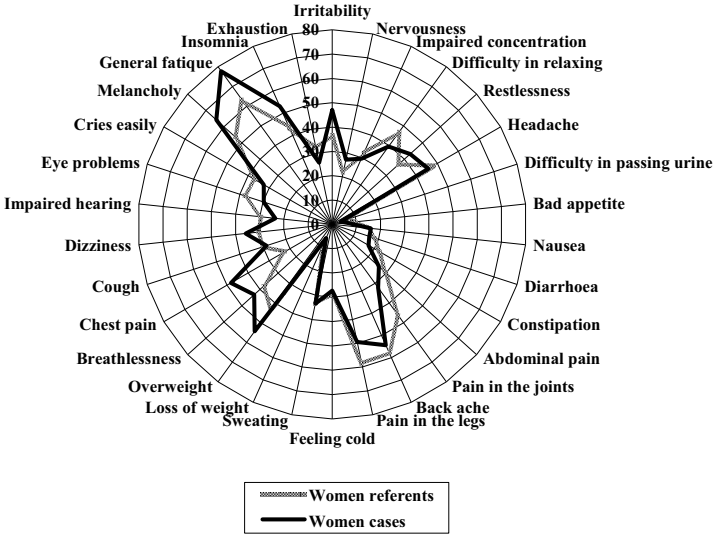
		Women		Men		Sex differences	Case-referent differences
	Score range	Cases	Referents	Cases	Referents	p-value	p-value
Number of subjects		82	149	264	461		
Everyday life stress	0-60	17.5	18.3	18.9	18.6	0.75	0.92
Stressfull life events	0-20	4.0	3.8	3.7	3.7	0.06	0.92
Affecting own person	0-6	1.0	0.8	1.4	1.1	0.15	0.057
Affecting others	0-14	3.0	3.0	2.3	2.6	<0.0001	0.055
Vital exhaustion	0-38	16.8	15.6	12.2	12.7	<0.0001	0.48
Depressive mood	0-60	21.4	20.0	16.8	17.9	<0.0001	0.31
Social support scale	0-39	23.0	21.3	23.4	22.0	0.32	0.0001
Availability of attachment	0-9	8.3	7.8	7.9	7.6	<0.05	0.0008
Availability of socail integreation	0-30	14.6	13.5	15.5	14.3	0.07	0.0007
Interperson support	0-39	29.1	27.7	28.7	28.0	0.81	0.0085
Appraisal	0-15	10.5	10.2	10.4	10.4	0.74	0.28
Belonging	0-15	11.6	10.9	11.3	10.8	0.45	0.0071
Tangible	0-9	7.0	6.7	7.0	6.8	0.92	0.09
Coping	0-21	14.5	14.2	15.7	15.3	<0.0001	0.054
Optimism	0-30	18.8	19.1	20.0	19.8	0.0046	0.44

p-values <0.005 were regarded as statistically significant

Table 6. *Well-being and leisure time activity (mean scores) among female and male cases and referents, adjusted for the influence of age, education, marital status and smoking habits in conditional analyses*

		Women		Men		Sex differences	Case-referent differences
	Score range	Cases	Referents	Cases	Referents	p-value	p-value
Number of subjects		82	149	264	461		
Well-being score	9-63	46.3	49.9	46.1	48.9	0.0001	0.11
Work situation	1-7	4.7	4.8	4.7	5.0	0.28	0.0162
Home and family situation	1-7	5.6	5.4	5.7	5.8	0.21	0.0091
Mood	1-7	5.5	5.8	5.8	5.8	0.18	0.10
Energy	1-7	5.0	5.4	5.5	5.6	0.0264	0.09
Patience	1-7	5.6	5.8	5.6	5.8	0.41	0.0184
Self-esteem	1-7	4.7	5.0	5.6	5.5	<0.0001	0.70
Sleep	1-7	4.5	5.1	5.6	5.6	<0.0001	0.19
Fitness	1-7	4.0	4.5	4.5	4.8	0.0049	0.0008
Perceived health	1-7	4.5	5.1	5.0	5.3	0.0021	0.0001
Activity score	0-64	21.8	24.4	26.1	29.4	<0.0001	<0.0001
Home indoor activities	0-10	4.6	5.1	4.8	5.5	0.19	0.0002
Home outdoor activities	0-8	1.9	2.3	4.5	4.8	<0.0001	0.0423
Physical activities	0-14	4.0	4.4	5.0	5.7	<0.0001	0.0061
Pleasure	0-16	4.1	4.7	4.5	5.3	0.0106	<0.0001
Social activities	0-8	4.7	5.2	4.8	5.3	0.82	0.0003
Clubs and associations	0-8	2.0	2.4	2.0	2.4	0.48	0.0125

p-values <0.005 were regarded as statistically significant



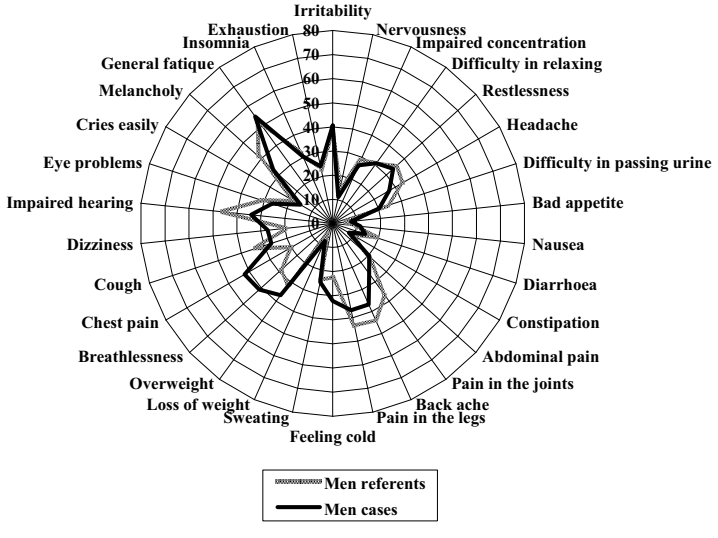


Figure 9. General symptom profiles for cases and referents separated for women and men

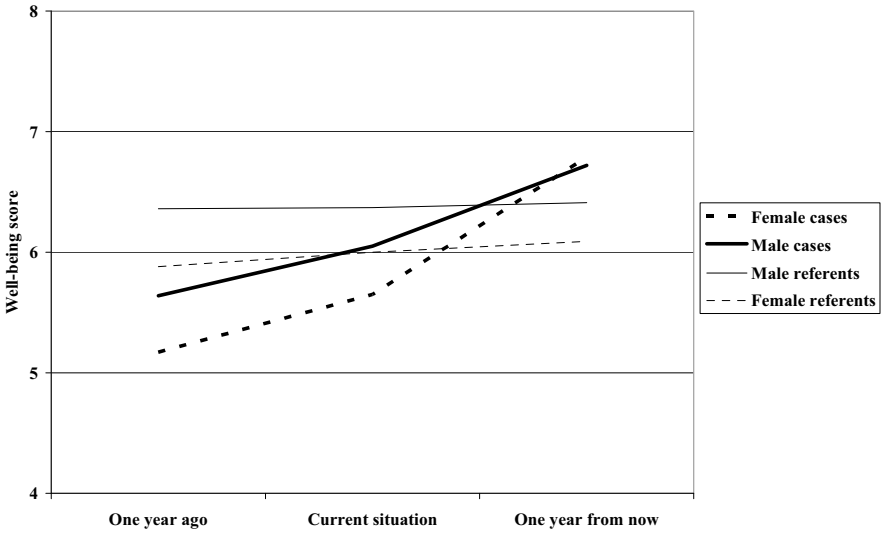


Figure 10. Past, present time and future expectations. The Ladder of Life, expressing self-rated general life situation a year ago, presently and a year from now. The symbols refer to the time point given along the horizontal axis

cases had more of cardiovascular and musculoskeletal symptoms than referents, but otherwise the symptom profiles were similar.

The rating of the general life situation a year ago, today, and what it is anticipated a year from now, is shown in Figure 10. Referents reported a small but non-significant change over the two years, whereas cases started on a low level and had a substantial increase of their life situation scores ending up with a higher score than referents. Especially female cases had a remarkable increase. The difference in slope between cases and referents was significant ($p < 0.005$), but not the difference between women and men.

All results regarding psychosocial and quality of life measures were independent of diagnostic group and time from discharge from hospital to questionnaire response.

Paper IV

Characteristics of the study population

There were no significant differences between the intervention and the reference group regarding age, marital status, education, disability or old age pensioners, tobacco use, alcohol consumption, or leisure time physical activity, Table 7.

Table 7. *Baseline characteristics of the SUPRIM* study population*

	Behavioural intervention group[1)]		Referents	
	n	mean (SD) or %	n	mean (SD) or %
Number of subjects	192		170	
Age at baseline, years		62.0 (7.94)		61.0 (8.28)
Women, %	43	22.4	42	24.7
Married, %	150	78.1	132	77.6
Highest educational level				
Compulsory education, %	67	35.5	62	38.5
Vocational training, %	62	32.8	57	35.4
High school, %	22	11.6	10	6.2
College or university education, %	38	20.1	32	19.9
Disability pensioner, %	33	17.2	15	8.8
Old age pensioner, %	96	50.0	76	44.7
Tobacco use				
Ex-smokers, %	112	59.3	92	57.7
Current smokers, %	24	12.7	24	15.0
Ex-snuff takers, %	15	8.0	20	12.5
Current snuff takers, %	15	8.0	13	3.7
Alcohol intake last week				
Beer, grams		37.6 (51.6)		37.3 (52.9)
Wine, grams		36.4 (62.6)		39.5 (68.5)
Strong liquor, grams		17.8 (37.3)		17.5 (32.4)
Leisure time physical activity				
Sedentary, %	20	10.6	22	13.8
Moderately active, %	137	72.5	118	73.8
Vigorously active, %	32	16.9	20	12.5
Mean follow-up time, months		95.8 (19.2)		91.5 (23.1)
Person months of observation		18,402		15,547

* Secondary prevention in Uppsala Primary Health Care Project (the complete study population)
[1)] Cognitive behavioural therapy intervention

Neither were there any significant differences regarding AMI, angina pectoris, hyperlipaemia, hypertension, congestive heart failure and diabetes, asthma, congestive pulmonary disease, stroke and peripheral artery disease prevalence, systolic and diastolic blood pressure, body mass index, waist circumference, sagittal diameter, blood lipid levels, vital exhaustion or coping at baseline, Table 8.

Mean follow-up time in the intervention group was 96 months, versus 92 months in the reference group. The number of person months of observation was 18,402 and 15,547, respectively. There were no significant differences in antidepressant and cardiovascular drug treatment at baseline, except that the behavioural therapy group had significantly more statin treatment then the reference group (73.4% versus 62.4%, $p<0.05$) (data not shown).

Table 8. *Medical history and some risk factor measurements at baseline*

	Behavioural intervention group[1)]		Referents	
	n	mean (SD) or %	n	mean (SD) or %
Medical history				
Previous AMIs[2)]	60	31.3	60	35.3
Number of previous AMIs		0.4 (0.7)		0.5 (0.9)
Angina pectoris	114	60.6	87	54.7
Hyperlipaemia	105	56.8	89	55.6
Hypertension	96	51.3	69	43.1
Congestive heart failure	45	24.6	42	26.8
Diabetes	24	12.7	25	15.6
Asthma	7	3.7	9	5.6
Congestive pulmonary disease	4	2.1	4	2.5
Stroke	4	2.1	5	3.1
Peripheral artery disease	7	3.7	8	4.7
Baseline measurements				
Systolic blood pressure, mmHg		139.3 (21.4)		135.5 (18.9)
Diastolic blood pressure, mmHg		78.9 (10.0)		77.3 (9.0)
Weight, kilograms		82.5 (14.4)		80.6 (13.6)
Height, centimeters		173.4 (8.8)		172.5 (8.5)
Body mass index		27.4 (3.8)		27.0 (3.4)
Waist circumference, centimeters		93.8 (10.3)		92.8 (9.6)
Sagittal diameter, centimeters		24.3 (2.9)		24.1 (2.7)
Serum cholesterol, mmol/L		5.1 (1.0)		5.0 (0.9)
LDL[3)], mmol/l		3.1 (0.9)		3.0 (0.9)
HDL[4)], mmol/l		1.2 (0.3)		1.2 (0.3)
Serum triglycerides, mmol/L		1.8 (1.1)		1.7 (0.8)
LDL/HDL ratio		2.6 (0.9)		2.6 (1.0)
Psychosocial data				
Vital exhaustion		13.2 (8.4)		13.4 (8.0)
Coping		15.3 (2.9)		15.5 (3.3)

[1)] Cognitive behavioural therapy intervention
[2)] Acute myocardial infarcion [3)] Low density lipoprotein [4)] High density lipoprotein

Effects of intervention on outcome

During 24 months of follow up the intervention group had a significantly better credence in the future (6.7 versus 6.4, p=0.0077) and somewhat lower systolic blood pressure (136.0 mmHg versus 137.9 mmHg, p=0.0248), but otherwise there were no group differences regarding psychosocial self-rated scores or in traditional risk factors (data not shown).

During 8.4 years of follow up 23 subjects in the intervention group and 25 subjects in reference group died, Table 9. In a Cox proportional hazards regression analysis the intervention group had an inconclusive 28% less cumulative all cause mortality than the referents (HR 0.72, 95%CI 0.40-1.30, p=0.28).

Table 9. *Morbidity and mortality outcome during follow up in Cox proportional hazards regression analyses with backward elimination of non-significant covariates*[1)]

	Number of outcome events					
	Behavioural intervention group[2)]	Referents	HR	95%CI	Wald's chi-square	p-value
All cause mortality	23	25				
Behavioural intervention			0.72	0.40-1.30	1.2	0.28
Smoking			1.93	1.37-2.73	13.9	<0.001
Age			1.09	1.04-1.14	12.8	<0.001
First reccurrent cardiovascular disease event	70	80				
Behavioural intervention			0.59	0.42-0.83	9.2	0.002
Age			1.03	1.01-1.06	7.6	0.006
Hypertension			1.28	1.07-1.54	7.0	0.008
Angina pectoris			1.33	1.07-1.64	6.8	0.009
Number of previous AMIs			0.75	0.58-0.97	4.7	0.031
First reccurrent AMI event	41	53				
Behavioural intervention			0.55	0.36-0.85	7.4	0.007
Age			1.03	1.00-1.06	4.5	0.035
Number of previous AMIs			0.70	0.49-1.00	3.9	0.049

1) Age, sex, marital status, education, smoking habits, and medical history or co-morbidity variables (number of previous acute myocardial infarctions (AMIs), angina pectoris, hyperlipaemia, hypertension, congestive heart failure, diabetes, asthma/congestive pulmonary disease, stroke, and peripheral artery disease)

2) Cognitive behavioural therapy intervention

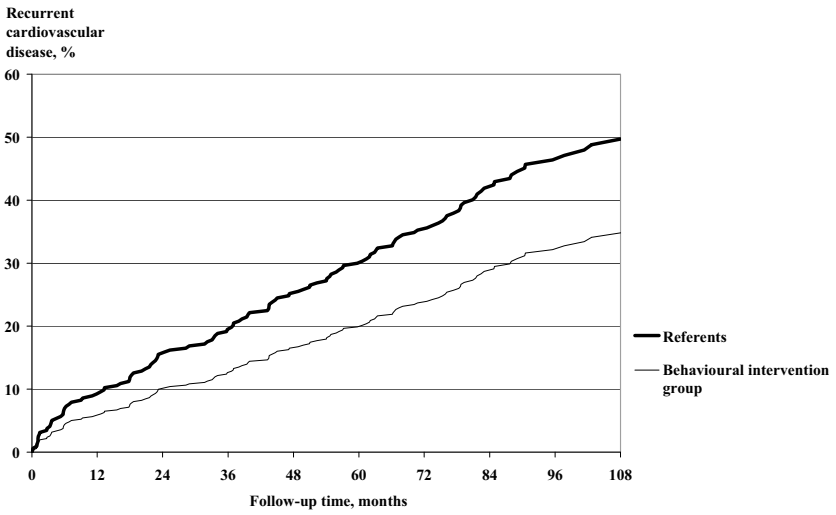


Figure 11. Cumulative first recurrent fatal and non-fatal cardiovascular event, during 9 years (108 months) from baseline, adjusted for the influence of age, sex, marital status, education, smoking habits, co-morbidity (number of previous acute myocardial infarctions, angina pectoris, hyperlipidemia, hypertension, congestive heart failure, diabetes, asthma/congestive pulmonary disease, stroke), and peripheral artery disease, among those subjected to behavioural intervention group and referents

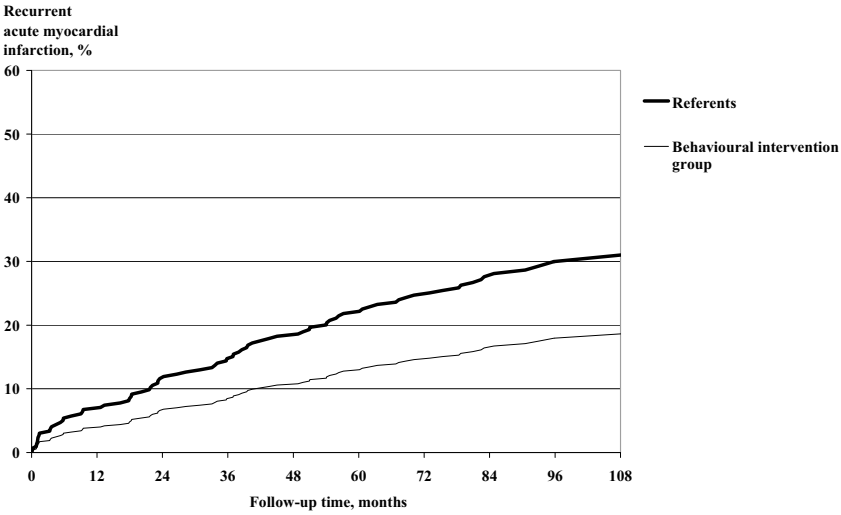


Figure 12. Cumulative first recurrent fatal and non fatal acute myocardial infarction, during 9 years (108 months) from baseline, adjusted for the influence of age, sex, marital status, education, smoking habits, co-morbidity (number of previous acute myocardial infarctions, angina pectoris, hyperlipidemia, hypertension, congestive heart failure, diabetes, asthma/congestive pulmonary disease, stroke), and peripheral artery disease, among those subjected to behavioural intervention group and referents

In the intervention group 69 (35.9%) subjects had a non-fatal and 1 (0.5%) a fatal CVD. The corresponding numbers in the reference group were 77 (45.3%) and 3 (1.8%). In a Cox analysis, adjusted for covariates and presented in Figure 11, the intervention group had 41% fewer fatal or non-fatal CVD events than the referents (HR 0.59, 95%CI 0.42-0.83, p=0.003).

The number of first recurrent non-fatal AMIs was 41 (21.4%) in the intervention group and 51 (30.0%) in the reference group. Two subjects had a fatal first recurrent AMI, both in the reference group. In a Cox analysis, adjusted for covariates and presented in Figure 12, the intervention group had 45% fewer fatal and non-fatal recurrent AMIs than the referents (HR 0.55, 95%CI 0.36-0.85, p=0.007), Table 9. There were no sex differences in any of the outcome analyses.

There was a strong dose-response effect between attendance rate at the group sessions and outcome rate. The first recurrent CVD proportion decreased from 73% among those not attending, to 53% for those attending fully. The corresponding proportions for recurrent AMI were 49% and 27%, respectively (data not shown).

Discussion

Study design and methodological consideration

Risk of recurrent AMI

To the best of our knowledge, this AMI registry study is the largest in the world to date. The WHO MONICA study, in comparison, with 166,000 AMI events [6, 19], is only one quarter the size. The study on risk of a recurrent AMI was based on data from the Swedish Acute Myocardial Infarction Statistics covering 775,901 events of fatal and non-fatal first and recurrent AMIs between 1972 and 2001 in Swedish men and women aged 20-84. The register permits the possibility of studying incidence of recurrent AMI, mortality and case fatality rates and, because of the possibility of linkage to the National Population Database, also incidence of first AMI. The register has been shown to be valid and reliable, the coverage is almost 100%, and a number of analyses based on it have previously been reported [5, 17, 130-134].

The individual personal identification number (PIN) given to all Swedish residents, whether citizens or not, allows a unique opportunity for follow-up studies and comparison in registers, for example, studies of time trends, regional differences and so forth. This can be used in national quality registers, and is facilitated by the fact that large parts of the databases of Statistics Sweden are available in a public statistical database, and on the Internet [103], as are databases at The National Board of Health and Welfare [135] (Swedish Acute Myocardial Infarction Statistics) database.

Co-morbidity data were based on the national Hospital Discharge register, also shown to be reliable and with almost 100% coverage [131, 136]. The demography data used were obtained from official sources, the National Land Survey [104] and the National Bureau of Statistics [103]. Since these data may change over time, the longitude and latitude coordinates referred to the location of the residential area at the time of the incident, and the population size and density data were set to the midpoint of the study period.

Psychosocial and Quality of life measures

The response rate was moderate among the referents, approximately 60%. However, within the matched quadruples more than 90% had at least one

referent responder, and the result of the matching procedure was satisfactory. The potential bias caused by a differential number of responding referents in the matched quadruples was handled by conditional analyses, in which cases were compared only with their own referents. The number of referents per case in this type of analysis is of minor importance as long as there is at least one, since randomly sampled referents per case are interchangeable by definition. The frequency of missing data in returned questionnaires was low. Some of the questionnaires have been validated in their English version and some in their Swedish version. However, all questionnaires have been used extensively in previous studies. Moreover, in our study measurements among the cases were compared with those of matched referents.

Effects of behavioural intervention on cardiovascular outcome

The randomization procedure produced fairly equal groups regarding background variables. In the analyses the intention to treat approach was used, regardless of attendance rate. For obvious reasons no complete blinding could be used. However, all "hard" outcome data were obtained from official registries, and the follow up was complete until death or end of follow up, minimizing the bias risk. The follow-up time was long enough to avoid conclusions to be based on temporary group differences.

Summing up methodological issues, we have no reason to believe that the data are affected by selection or other bias to such an extent that the conclusions have been affected.

Findings

Hazard function for recurrent event

The shape of the risk curve during follow up (hazard function) may have several determinants. The high initial risk may represent the underlying patho-physiological process with still unfinished but slowly regressing plaque or embolus production, or other trigger mechanisms. At any rate, the predisposing factors behind the infarction appear to become less active over the first few years. Since the hazard function after the fifth year, with a slow risk increase, is largely proportional to the hazard function for a first ever event, the risk increase from this time on is probably attributable to the ageing process. Since the shape of the hazard function appears to have been stable across the study period it surely represents the natural history of the risk of a recurrent AMI. The highly variable recurrence risk during the first few years after a previous event should be taken into account when discussing recurrence risk with patients.

The 28-day rule may have affected the estimation of the risk of a recurrent event. Since recurrent AMIs occurring within 28 days after the previous event were included in the latter, and were not included as exposure time in the analyses, the risk decrease for a recurrent AMI is probably underestimated. This means that the initial slope in Figure 2 may be underestimated, making the risk decrease even larger than shown.

The strength of this study is the very large size of the database that includes all reported AMI events in Sweden over 30 years. To the best of our knowledge it is the largest and most long-term register in the world. The data used in this study have high validity and an almost 100% coverage. Moreover, modern analysis techniques were used, which was not available when several previous studies in the area were performed, making detailed analyses with high precision possible. One limitation of the study is the relatively limited information on individual background variables, such as direct measures of infarction severity, risk factor profile and medical treatment. However, some of these limitations were overcome by the access to the Hospital Discharge Register, from which co-morbidity data could be accessed.

Other possible outcome affecting conditions may be variability of coronary care quality, changes in diagnostic AMI criteria, and change of case fatality rate during the study period. However, in Sweden, almost all AMI patients during the study period were admitted to government run regional hospitals with a coronary care unit (there are fewer than ten private hospitals in the country and none of them treat AMI patients), each with a catchment area population of about 250,000 residents. All hospital admissions are free of charge. The hospitals are supervised by the National Board of Health and Welfare, which regularly collects and publishes data on hospital care outcome for all these hospitals, promoting the adoption of new techniques. This means that the vast majority of the patients received the state of the art treatment available at the time. Moreover, calendar time was used as a proxy for such changes in the analyses.

The main diagnostic criteria change (inclusion of unstable angina) occurred in 2001, *i.e.*, in the last study year. The effect appears to have been small. Moreover, there is evidence that AMI damage volume size decreased during the study period, which may have contributed to the decreasing case fatality and AMI recurrence rates [10]. The potential effects of changing case fatality rate were at least partially taken into account in the analyses by calendar time.

Previous presented trends of AMI in Sweden are calculated with a definition of a first AMI event as no registered AMI in the National AMI Register for an individual during the previous seven years [18]. Our use of a 3 year time window makes possible a more precise statistical calculation of recurrent rate.

Secular effects in relation to the risk of recurrent events

The change of risk over calendar years is a secular effect. This means, for instance, that 60-year-olds in the 1990s had a lower risk of recurrent AMI than 60-year-olds in the 1980s. In this study we estimated the secular effect by using the average risk during the first year in the hazard function for events during specific years. It is well known that the risk factor panorama affecting the risk of a recurrent AMI is the same as that for a first AMI, as reviewed in the European and US guidelines on cardiovascular disease prevention in clinical practice, the only difference being the greater incentive for action in secondary prevention [57, 59]. It has also been shown that a risk factor change is followed by a change in incidence [6, 19, 137]. In this study the secular effects were parallel and appeared at about the same time for a first AMI and for recurrent AMI. This is an indication that the risk factor change in the population has affected both types of incidents in the same way.

Primary and secondary prevention of coronary heart disease was initiated in the 1960s, a few years after the initiation of the first population-based studies. The effects of such prevention in Sweden became evident in the early 1980s, *i.e.* later than in Finland and the USA [10, 22, 29, 31, 32]. The risk factor pattern in the general Swedish population has changed dramatically during the past 35 years, with a drop in tobacco smoking among men from 55% and among women from more than 30% to less than 20% in both sexes [137], a considerable drop in blood pressure not only among treated but also in the non-treated segments of the population [138], and a drop in total cholesterol by 1 mmol/L in the middle-aged general population to 5.5 mmol/L [137]. Moreover, more than 60% of patients on lipid-lowering treatment reach the treatment goal of a serum cholesterol level less than 5 mmol/L [68].

The decrease in the incidence of a first time AMI has stimulated interest in determining whether there is a similar decrease in the incidence of recurrent AMIs. A number of studies have analyzed time trends in recurrent AMI events. For example, The FINMONICA MI Register Study reported a that a decline in recurrent coronary events contributed greatly to the decline in coronary mortality in Finland in 1983-97 [31, 32], The Minnesota Heart Survey presented a falling recurrence rate of 20-30% between 1985 and 1997 among men but not among women [16, 29], and the NHANES I follow-up study covering trends during 1971-1992 in the US, showed a decreasing AMI recurrence in all sex and race groups, except for white women [22]. A decreasing trend was also described in the Northern Sweden MONICA area in 1985-98 for patients surviving the initial 28-day period [30]. We found a considerable decrease of recurrent AMI among both men and women beginning in the early 1980s. The large dataset permitted the extraction of detailed novel information on secular trends. There is no doubt

that secondary prevention efforts since the late 1970s have been effective enough to reverse the increasing recurrent AMI incidence rate trend.

Risk of new events in relation to co-morbidity and demography

It is well known that the risk of a first AMI or a mixture of first and recurrent AMIs varies between and within countries. However, the situation regarding risk of recurrent AMI is less clear. To the best of our knowledge this is the first study of geographical variation of recurrent AMI risk. There may be many reasons for geographical variation.

First, there may be a variation in diagnosis reliability. However, in Sweden almost all AMI patients during the study period were admitted to government run regional hospitals (there are fewer than ten private hospitals in the country and none have AMI patients), each with a catchment area population of about 250,000 residents, and a coronary care unit. All hospital admissions are free of charge, which means that there is no cost incentive against hospital admission. The hospitals are supervised by the National Board of Health and Welfare [135], which regularly collects and publishes data on hospital care outcome for all these hospitals, promoting the adoption of new techniques and care according to guidelines.

Secondly, there may be geographical differences in disease severity among AMI patients. Subjects living in small, peripheral communities with outward migration of young people may then be older and more ill than subjects living in more densely populated areas. However, in our analyses we adjusted for the influence of differences in the age and sex distribution between communities. The influence of disease severity could not be adjusted for directly, since we had no access to direct measures of disease severity. For this reason, two proxy variables were constructed, AMI number and attained co-morbidity at the time of the event. Both these proxy variables were closely related to the recurrent AMI risk, catching a considerable part of the total outcome variation in terms of the chi-square test level. It is therefore unlikely that the geographical differences are explained by age, sex or disease severity difference.

Thirdly, there may be geographical differences in the risk factor panorama or psycho-socio-economic factors. It may be that people living in sparsely populated areas are less likely to change their behaviour or way of life. Moreover, there may be a higher degree of social control in such areas as compared with more densely populated areas. If so, these areas may lag behind in the lifestyle changes that have taken place nationwide. To date, we have no firm evidence that the geographical risk differences may be explained by this factor. This remains to be investigated.

A fourth possible explanation to the geographical risk differences may be geographical differences in general stress level. If the risk differences could be explained by differences in stress level, one would anticipate an increas-

ing risk with population density, given the general belief that life in small, rural communities is less stressful than life in big cities. The curve-linear shape of the risk function indicates that more than one factor is at work. It may be that the social control and low likelihood of lifestyle change affects the risk level in areas with low population density, whereas the presumably high stress level in densely populated areas affects the risk in such places. At any rate, the factor or factors underpinning the geographical risk differences seem to be linked to population density rather than to geographical location. The analyses were stratified by sex, but the results were similar in the two sexes, and therefore the final analyses were performed in the total study population using sex as a covariate. This means that the results are equally valid for men and women.

Psychosocial and Quality of life measures

The results regarding sick leave, perceived health, fitness, activity, and complaint score were all in accordance with expectations based on interpretations of findings in previous studies [139-141], although these studies were uncontrolled. The cases generally had less favourable situations than the referents with more objective and subjective illness, and more symptom reporting.

Unexpectedly, no significant differences between cases and referents were found with respect to everyday life stress (a measure of self-rated stress behaviour), stressful life events, vital exhaustion or depressive mood. The proportion of individuals with a clinically recognizable depression is somewhat difficult to assess. According to Beck's and Hamilton's criteria a score of 20 or more indicates depression. This may mean that half of the study population, cases as well as referents are depressed. This is unlikely, rather, the cut-off level might be affected by cultural factors. Estimated from one of our databases about 2% of the Swedish population are diagnosed with clinical depression, which would mean that approximately 2% of our cases, too, were depressed. However, the proportion with sub-clinical depression may be larger or much larger.

Previous research indicates that severe life events may be more common in CHD cases [78, 142], although stressful life events as a CHD risk factor is controversial [143]. Although the effects of stressful life events are supposed to be long-term, we found no significant differences between cases and referents as we measured it within the first year after the incident. One possible explanation might be that the referent group included individuals with a past history of CHD or other illnesses and therefore were more similar to the cases than a "healthy" group would have been. We have no data on the referents' medical history. However, the referents were sampled from the general population and the proportion of CHD cases in the group might be expected to be 5% or less. The probability that this proportion of CHD cases caused

the non-significant case-referent difference in our study is small. Another possibility might be that differences in marital status between men and women and cases and referents affected our results. However, such differences were accounted for in the analyses. To our knowledge no other studies have addressed these issues. The large study population and the high statistical power of the present study indicate that it is unlikely that the differences were small only by chance. It is much more likely that they mirror a reality. The limitations of the study include its cross-sectional nature, which restricts the interpretations of cause and effect relationships.

The evidence for stress as a CHD risk factor is more consistent [78, 143]. The questionnaire on everyday life stress in our study had no specified time limit, but the wording is such that it can be interpreted as dealing with the present situation. The vital exhaustion questionnaire in this study covers the past three months and the depression questionnaire the past week. The cases may have reduced their stress related behaviour after the event, perhaps because they felt the need to be more relaxed, or they may have withdrawn from stress-provoking situations. It may be that the situation regarding stress, depression or vital exhaustion was quite different before the event, while during the first year after the event the cases' situations were more similar to those of the referents. This issue has not been addressed specifically in previous studies, but some support for an improvement of physical and social function and mental health (depression) over time was reported by Kristofferzon *et al*. [141]. Again, the sample size and statistical power favour the idea that our findings mirror a reality.

The cases reported a better social support situation than referents, significant for the Social Support Scale and the two subscales. This was an unexpected finding but may have the same explanation as for stress related behaviour above, *i.e.*, things may have calmed down during the first year after the event, the family and other social support providers may have increased their support as a result of the event. It may also reflect the short hospital based rehabilitation programme preceding the present programme and offered to the cases in the sample, in which family members were actively involved. This may to some extent have improved their psychological well-being, as well as involving their families in the rehabilitation process. The possible change of social support over time after a CHD event has not previously been addressed explicitly, although some evidence of perceived support have been presented [144]. We have no reason to believe that our findings are a matter of chance.

The Ladder of Life instrument offers strong evidence that the cases' life situations changed dramatically from pre-event to post-event. This change lends support to our speculation that several of the psychosocial measures we used may have improved considerably from before to after the event and reached or even surpassed the referent level. There were main sex differences in the responses. Female referents and female cases scored signifi-

cantly worse on complaints (physical and psychological symptoms), depressive mood, coping, stressful life events affecting others, optimism (LOT) and vital exhaustion than all men. This is in accordance with other studies showing that women tend to report (significantly) more health problems than do men after a CHD event [139-141, 145-148]. Quality of life, assessed using the Ladder of Life, was significantly lower in both female cases and female referents than in men. Male referents rated the best quality of life, and female cases the worst. These results are supported by Agewall *et al*., who found that self-assessed quality of life after an MI was significantly lower in women than among men despite similar age, treatment and haemodynamic and laboratory data [148].

Effects of behavioural intervention on cardiovascular outcome

A number of psychologically oriented treatment programs for patients with CHD have been reported in the literature [79]. The results from small randomized controlled trials testing rehabilitation programs post-AMI have shown conflicting results. Rahe *et al*. found reduced coronary mortality and recurrent events [149]. In the Recurrent Coronary Prevention Project, Friedman *et al*. reported a lower cardiac recurrence rate and a reduction in cardiac morbidity and mortality in post-AMI subjects who received type A counselling [150]. In two meta-analyses of psychosocial educational programs, (health education and stress management) for coronary disease patients, 34% reduced cardiac mortality and 29% reduction in recurrent AMI [151] and a reduction of mortality and morbidity during the first two years with some weakening thereafter was presented [152].

In contrast, Jones *et al.*, found no effects of stress management intervention on mortality, clinical sequel or clinical complications [153]. In the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study and in the Montreal Heart Attack Readjustment Trial (M-HART) the primary endpoints were mortality and recurrent events, but no beneficial effects were found [144, 154]. In a 2004 Cochrane review of the effects of psychological interventions on coronary heart disease, no evidence of effects of psychological interventions on total or cardiac mortality, but a reduction in non-fatal recurrent AMI has been shown [79], and intervention trials focused on stress management alone showed similar results. Few trials could report effects on traditional risk factors or quality of life.

There are several explanations for the positive results of our trial. The study population size was large enough to provide sufficient power (90% given 360 participants and 15% difference in outcome). The intervention programme was constructed so that patients would be involved, which kept adherence to the programme high [128]. The monitoring of the trial was intensive. All participants who did not show up for an examination were contacted by phone and offered a second chance (which most of them took).

All returned questionnaires were scrutinized for missing data, and if such were detected the patient was contacted by phone and offered a chance of completion (which most of the respondents took). We were able to adjust for a large number of outcome affecting variables other than the CBT program, which increased analysis and conclusion drawing precision. The results cannot, for instance, be explained by differences in traditional risk factor levels. Finally, the outcome registration was complete, at least as far as admission to hospital is concerned. Since all hospital admissions in Sweden are free of charge for the patients (paid by the National Social Insurance system) there are no financial impediments to hospital admission.

CHD prevention in the past and in the future

Primary health care plays an increasingly important role as the cornerstone of the health care system in treating major diseases, including CHD. Today we see a multifactorial combination of risk factors in the risk of developing CHD. A treating physician considers the whole individual, not the isolated risk factors, with a good overall picture of the patient and individualized treatment. Still, our high-risk patients tend not to receive optimum treatment [68, 155]. The question is: Is the reason for this that we administer unsatisfactory treatment, that our aims are too high?

Post-CHD care can be improved and lives saved. This poses a challenge to the health care system as a whole and especially to primary health care. CHD is both a personal and a national disability, causing production losses and contributing greatly to the growing societal costs of health care [7]. Sweden specifically and Europe generally have among the oldest populations in the world, and the proportion of the elderly is set to increase [7].

It is shown that social isolation/absence of personal networks, low socioeconomic status, job stress and stress in the family as well as negative emotions, including anger, depression and hostility affect the risk of a CHD event and may also impede the prognosis for patients with already established CHD [143, 156] There is growing evidence that psycho-social interventions, result in improved coping abilities, reduce anxiety and depressive feelings, and can also reduce stress and evoke healthier behaviour and a lifestyle that could diminish the progression of CHD [157].

Future concerns in CHD prevention

Despite the positive health trends in Sweden there are some future concerns. Compared with 30 years ago, women today smoke more than men. The proportion of smokers older than 15 years among men in 1977 was 41% and, in women 32%, while in 2006 the corresponding proportions were 12%, and 17% [7]. Among young women (16-24 years), 16% smoke today. Is this fact

a ticking time bomb that will change AMI incidence/mortality for men/women? Lung cancer is the most common cause of cancer death among Swedish women, with an increase of 81% between 1987 and 2007 [4].

The proportion of smokers is decreasing but the proportion of obesity (Body Mass Index (BMI) >30 kg/m^2) has increased steadily from 6% in 1989 to 10% in 2007, (self-reported data from OECD) [7]. These figures are probably underestimated. Excessive caloric intake, increased refined carbohydrate consumption and lack of regular, sustained, brisk physical activity have led to a steady increase in the incidence of abdominal obesity among children and adolescents, with an emerging epidemic of insulin resistance and increased risk of inactivity, development of diabetes, hypertension, *etc*., all well-known risk factors for CVD [158]. People with metabolic syndrome are more likely to die from CHD than others. The positive trends for CHD in AMI incidence, case fatality and mortality have not been seen in diabetics [159]. The good news, however, is that changes in lifestyle can reduce the risk of developing type 2 diabetes by 58% in subjects with impaired glucose tolerance as shown by Tuomilehto *et al*. [160].

Exercise has been shown to reverse metabolic syndrome, and diagnosed with this disorder greatly decreases these patients' risk of developing or dying from an AMI. Currently, experts recommend >30 minutes of moderate exercise about five times a week [59]. These 30-minute sessions can be done all at once, or they can be done in many short bursts, such as walking up the stairs instead of taking the elevator. Moderate exercise involves increasing one's heart rate to 50%-70% of its maximum level or walking at about three miles per hour (an easier way to determine moderate exercise levels is to make sure you can have a conversation comfortably while exercising).

Two recent meta-analyses on adherence to Mediterranean diet and health status point out a significant improvement in health status as seen by reduction in overall mortality and in mortality from CVD [161], and that only a Mediterranean dietary pattern is related to CHD in randomized trials [162].

We need to find strategies to reduce the costs associated with prevention. The quality-of-life improvement costs are not unreasonable as compared with other medical interventions we perform on a routine basis, *e.g.* PCI or CABG. The question is whether the population would be willing to comply with prevention to prevent CVD. Prevention does not need to be complicated or costly.

Implications for practice

The management of patients with CHD has evolved from a strategy of watchful waiting and use of supportive therapies to active treatment interventions. Still, the art of medicine is more than just medications. Our findings show that the secondary preventive work in Sweden has been successful

resulting in a decreasing trend in AMI recurrence in recent decades. Furthermore, for the first time the hazard function has been investigated in recurrent AMI. It is good news for coronary patients with a high initial risk of recurrent AMI after the last event changing into a slightly elevated risk as compared with individuals in the general population at equivalent ages. This stands in contrast to previous risk estimations based on survival data, and may result in revision of present risk estimations. Prevention efforts and coronary rehabilitation should be more focused on CHD patients with increased risk, especially female coronary patient. Confidence in the future is higher among CHD patients at the time they are discharged from hospital to follow-up in primary health care than in the general population. Why not take advantage of this great opportunity? Addition of CBT to secondary preventive programmes in CHD patients can further improve outcome in relation to the risk of recurrent CVD and AMI events. If a health intervention is being used, there should be evidence that it has an impact on health status. Attention should then be paid to the way in which the intervention is delivered and the characteristics of a secondary prevention programme to promote implementation. Further research is needed to elucidate the mechanisms of reducing risk and to develop and test the efficacy and effectiveness of similar interventions.

Conclusions

The risk of a recurrent AMI event was highly dependent on time from the previous event, a novel finding which may affect risk scoring. In addition, sex, age, and AMI number influenced the general risk level. There were strong secular trends in age-sex-AMI-number specific risk of a recurrent AMI towards diminishing risk in later years, indicating successful cardiovascular prevention, mainly secondary prevention.

There were considerable geographical differences in the risk for a recurrent AMI event, even when other outcome affecting variables are controlled for. These differences are best explained by residential area population density, with a high recurrent AMI risk in areas with the lowest and the highest population densities and the lowest risk in areas with moderate population density, the same way men and women. The mechanism or mechanisms underpinning these findings is as yet unclear.

Both sex and disease status are determinants of psychological well-being after a CHD event. However, sex seems to be the stronger determinant, since women generally do worse than men, and the high risk person in terms of low psychological well-being is the female cardiac patient. Readily measured demographic and psychosocial risk factor data may assist in the identification of post-coronary event patients who are at increased risk of poor clinical outcomes. Prevention efforts and cardiac rehabilitation should be targeted to those with increased psychosocial stress, specifically women, who experience greater disparities in recovery from cardiac events.

Intensified CBT intervention focused on stress management for one year in subjects with CHD, within a year from the index event, significantly improved outcome in the intervention group during nine years of follow-up on fatal or non-fatal recurrent CVD, and fatal and non-fatal recurrent AMI. A dose-response effect relationship was demonstrated in attendance rate at intervention group meetings, the higher the rate the better the outcome. The benefit was equivalent for men and women. The intervention group had significantly better credence in the future and lower systolic blood pressure, but there were no difference between the intervention and control group regarding psychosocial self-rated scores or in traditional risk factors. This demonstrates the potential of adding CBT to secondary preventive programmes post-AMI for better patient compliance and better outcome.

Summary in Swedish: svensk sammanfattning

Artikel I

Det är känt att risken för insjuknande i en första hjärtinfarkt har minskat under de senaste decennierna men det har hittills varit okänt om denna trend även gällt risken för ett återinsjuknande i en ny hjärtinfarkt. Data från åren 1969- 2001 insamlades från det nationella hjärtinfarktregistret vid Epidemiologiskt centrum, Socialstyrelsen, totalt drygt 1,1 miljoner hjärtinfarktinsjuknanden. Efter exkludering av de allra yngsta och äldsta åldersgrupperna, samt hjärtinfarkter med okänt infarktnummer återstod 775 901 infarkter för slutlig analys. Analyser visade att återinsjuknanderisken i en ny hjärtinfarkt är starkt beroende av tiden från föregående infarkt. Risken minskar brant och planar ut efter ca 2 år och når ett minimum efter 5 år varefter den sakta stiger. Denna stigning löper därefter parallellt med risken för ett förstagångsinsjuknande i motsvarande ålder men på en något högre nivå. Risken ökar med stigande ålder och antal tidigare infarkter. Trenden sågs i alla åldersgrupper och bland både män och kvinnor. Detta är en nyhet som kan komma att påverka framtida risk bedömning efter hjärtinfarkt. Återinsjuknanderisken visar även en sjunkande trend över kalendertid, med en statistiskt signifikant minskning från sent 70-tal och framåt. Denna trend sågs i alla åldersgrupper och bland både män och kvinnor och oavsett antal tidigare hjärtinfarkter. Detta tyder på ett framgångsrikt hjärtpreventivt arbete framför allt inom sekundärprevention.

Artikel II

Det finns geografiska skillnader i risken att insjukna i en första hjärtinfarkt i Sverige. Tidigare studier har påvisat att det finns en nord-sydlig respektive öst-västlig riskgradient med en ökande risk för hjärtinfarktinsjuknande med stigande nordlig latitud och ökande västlig longitud. Om dessa skillnader även gäller för risken för ett återinsjuknande i en ny hjärtinfarkt har hittills inte undersökts. Data från det nationella hjärtinfarktregistret, Lantmäteriverkets register och Befolkningsregistret bearbetades. Analyser visade på betydande geografiska skillnader i återinsjuknanderisk. Som mått på geografiska skillnader användes mantalsskrivningsortens longitud och latitud, befolkningsstorlek och befolkningstäthet. Efter justering för ålder, kön, insjuknan-

deår, hjärtinfarktnummer och annan samtidig sjuklighet (komorbiditet) kvarstod befolkningstätheten (invånarantal/km^2) som den enda statistiskt signifikanta förklaringen till den geografiska variationen i återinsjuknanderisk i en ny hjärtinfarkt. Orter med den lägsta och den högsta befolkningstätheten uppvisade högst återinsjuknanderisk, lika för män och kvinnor. Mekanismerna bakom dessa fynd är fortfarande inte klarlagda.

Artikel III

Få studier har undersökt den psyko-sociala situationen för hjärtpatienter under det första året efter ett insjuknande i kranskärlssjukdom, och ingen av dessa har varit kontrollerad. Totalt inkluderades 346 patienter, 75 år eller yngre, utskrivna från Akademiska sjukhuset, Uppsala efter en kranskärlshändelse för fortsatta kontroller i primärvården. Alla inkluderade patienter fick besvara en omfattande enkät om bl.a. psyko-socio-ekonomiska data. För var och en av dessa patienter valdes 3 kontrollpersoner (referenter) ur befolkningsregistret, matchade efter kön, ålder och bostadsort som fick besvara en motsvarande frågeenkät per post. Som väntat angav fallen en sämre rapporterad hälsa och aktivitets grad men de rapporterade överraskande ett bättre socialt stöd och en större framtidstro än referenterna.

Kvinnor rapporterade överlag en mindre gynnsam situation än män vad gäller stressande livshändelser som drabbar andra, utmattning, depression, copingförmåga, självförtroende, sömnbesvär och rapporterade symptom. Den minst gynnsamma situationen rapporterade kvinnliga fall. Under det första året efter en kranskärlshändelse förefaller både sjukdom och kön ha betydelse för psykologiskt välbefinnande, där könet förefaller vara det starkaste. Kvinnor angav generellt sett lägre välbefinnande än män, och den verkliga högriskpersonen, i form av lågt psykiskt välbefinnande, är den kvinnliga hjärtpatienten. Med hjälp av uppgifter från mätning av demografiska och psykosociala riskfaktorer skulle patienter kunna identifieras som löper en ökad risk för ett dåligt klinisk svar på rehabiliteringsresultat efter insjuknande i en hjärtsjukdom. Förebyggande insatser och hjärtrehabilitering bör riktas till dem med ökad psykosocial belastning, speciellt kvinnor, som upplever större skillnader i återhämtning efter hjärtsjukdom. Detta kan få betydelse för utformningen av framtida hjärtrehabilitering.

Artikel IV

Det finns starka indicier att psykosociala faktorer på ett oberoende sätt bidrar till risk för insjuknande i kranskärlssjukdom även efter statistiskt hänsynstagande till inverkan av traditionella riskfaktorer. SUPRIM-studien är en randomiserad kontrollerad klinisk prövning av optimerad beteende- och riskfak-

tor intervention jämfört med traditionell riskfaktor hantering för risken att återinsjukna i kranskärlssjukdom. Totalt ingick 362 patienter (varav 342 från artikel III), 75 år eller yngre, utskrivna efter kranskärlshändelse från Akademiska sjukhuset för fortsatt kontroll hos sin distriktsläkare i primärvården. Alla patienter fick efter utskrivning besvara en omfattande enkät, (samma som delarbete III), om bl.a. psyko-socio-ekonomiska data och genomgick antropometrisk mätning, blodtryckskontroll samt blodprovstagning. Dessa mätningar samt besvarande av enkäter upprepades månad 6, 12, 18 och 24, totalt vid 5 tillfällen. Hälften av deltagarna randomiserades i starten till särskild beteendeintervention, den andra hälften var kontrollgrupp.

Beteendeintervention bestod i gruppbehandling av kognitiv beteendeterapi (KBT) med fokus på stresshantering, totalt 20 tillfällen under 1 år under ledning av en psykolog eller psykologassistent.

Efter 2 år hade interventionsgruppen en signifikant ökad framtidstro och ett något lägre systoliskt blodtryck men i övrigt fanns ingen skillnad mellan grupperna med avseende på psykosocial självskattning eller traditionella riskfaktorer. Efter drygt 9 års uppföljning hade interventionsgruppen signifikant lägre återinsjuknande i cirkulationsorganens sjukdomar och färre återinsjuknanden i akut hjärtinfarkt jämfört med kontrollgruppen även efter statistisk justering för andra påverkansfaktorer. Död oavsett orsak var även ovanligare i interventionsgruppen, men skillnaden var inte statistiskt signifikant.

Effekten av beteendeintervention var också dosberoende då en hög deltagarfrekvens i KBT-programmet gav lägre risk för återinsjuknande över kalendertid än ett lågt deltagande. KBT i grupp förefaller påverka kranskärlssjuka på ett positivt sätt genom minskad återinsjuknanderisk i kardiovaskulär sjukdom trots att ingen påverkan på traditionella riskfaktorer kunde påvisas. Detta kan få betydelse för framtida sekundärpreventiva hjärtrehabiliteringsprogram genom att stärka patientens egenförmåga och därigenom förbättra patientens följsamhet till given behandling.

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