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To my family

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Abbreviations

AMI	Acute myocardial infarction
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CABG	Coronary artery by pass grafting
CHF	Chronic heart failure
CI	Confidence interval
CIBIS	Cardiac Insufficiency Bisoprolol Study
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CPX	Cardiopulmonary exercise test
Creat	Creatinine
CVD	Cardiovascular disease
DIG	Digitalis Investigation Group
ELITE	Evaluation of Losartan in the Elderly Study
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
fb-	Fasting blood
FH	Family history
Hb	Hemoglobine
HDL	High density lipoprotein
HF	Heart failure
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
LAD	Left atrium diameter
LDL	Low density lipoprotein
Lp	Lipoprotein
LVEF	Left ventricular ejection fraction
LVD	Left ventricular diameter
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MDRD	Modification of Diet in Renal Disease
MERIT-HF	Metoprolol Randomised Intervention Trial in Heart Failure
MI	Myocardial infarction
MPP	Malmö Preventive Project
MR	Mitral regurgitation
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
PASIS	Computerised patient administrative system
PCI	Percutaneous coronary intervention
Peak HR	Peak heart rate
Peak RER	Peak respiratory exchange ratio
Peak VO2	Peak oxygen uptake

RALES	Randomised Aldactone Evaluation Study
RVD	Right ventricular diameter
SAP	Stable angina pectoris
SD	Standard deviation
SOLVD	Studies of Left Ventricular Dysfunction
s	Serum
TG	Triglycerides
V-HeFT	Veterans administration Heart Failure Trial
UAP	Unstable angina pectoris

List of papers

I Tasevska-Dinevska G, Kennedy LM, Nilsson P, Willenheimer R. Gender aspects on heart failure incidence and mortality in a middle-aged, urban, community-based population sample: the Malmö Preventive Project. *Submitted European J of Epidemiology.*

II Tasevska-Dinevska G, Kennedy LM, Anevski D, Nilsson P, Christensson A, Willenheimer R. Gender differences in predictors of heart failure morbidity and mortality in an urban Swedish population: the Malmö Preventive Project. *Open Heart Failure Journal 2008; 1:1-8.*

III Tasevska-Dinevska G, Kennedy LM, Cline-Iwarson A, Cline C, Erhardt L, Willenheimer R. Gender aspects on survival among patients admitted to hospital with suspected or diagnosed heart failure. *Scand Cardiovasc J 2008; 10: 1-9.*

IV Tasevska-Dinevska G, Kennedy LM, Cline-Iwarson A, Cline C, Erhardt L, Willenheimer R. Gender differences in B-natriuretic peptide, left ventricular ejection fraction and mass, and peak oxygen consumption, in patients with heart failure. *In manuscript.*

Abstract

Heart failure (HF) is a common condition that often leads to hospitalisation. There is an increasing amount of data suggesting that there are inherent epidemiological and pathophysiological, as well as psychosocial differences between men and women with heart failure. These differences may be so profound that they warrant differences in management and treatment. Furthermore women have been greatly underrepresented in clinical HF treatment trials.

The major aim of the studies in the present thesis was to investigate gender aspects on heart failure in the urban population of Malmö. This thesis is based on two different studies, a retrospectively study I – Malmö Preventive Project (papers I and II) – and a prospective study II - Heart failure and women (papers III and IV), both carried out at Malmö University Hospital.

Paper I: We retrospectively examined gender differences in HF incidence and mortality during approximately 22 years of follow-up, in a middle-aged, community-based population sample. We found that women had lower risk for HF, all-cause death and HF-related death. Women were on average 65.6 ± 6.1 years and men were 65.4 ± 7.3 years old at the time of the HF diagnosis. Female and male HF patients had similar mortality risk. Causes of mortality among these relatively young, unselected HF patients differed from those previously described among older HF patients.

Paper II: We retrospectively examined gender differences in predictors of HF morbidity and mortality in a middle-aged, community-based population sample. We followed the subject for approximately 22 years. Although women and men shared many predictors of HF, there were several important differences between sexes.

Paper III: We prospectively assessed gender differences in survival among 930 consecutive patients (464 [49.9%] women, mean age 76.1±10.1 years), admitted to hospital with suspected or diagnosed HF. We followed the patients for approximately 4 years. Prognosis was poor among these elderly patients hospitalised with suspected or diagnosed HF. Among all patients, women had better survival, whereas both sexes had similar survival when the HF diagnosis was certified.

Paper IV: We prospectively assessed gender differences in factors related to Brain-natriuretic peptide (BNP), left ventricular ejection fraction (LVEF) and mass (LVM), and peak oxygen consumption (Peak VO2). The original patient sample consisted of 930 consecutive patients (464 [49.9%] women), admitted to hospital with suspected or diagnosed HF. Among these patients, we assessed all those who underwent echocardiography (408; 189 women and 219 men), and especially those with certified HF (221; 90 women and 131 men) according to predetermined clinical and echocardiography criteria.
Among these elderly HF patients, women had lower BNP, LVM and Peak VO2, but higher LVEF, and there were some important gender differences in factors independently related to these variables.

In conclusion, our findings support previous studies showing a multitude of gender differences among HF patients. In Paper I, many of our observations differ from those of other epidemiological studies, probably at least partly because of the relatively young mean age of our patients. However, the mean age was similar to that of most clinical HF trials, whereas the causes of mortality differ quite substantially from these trials. Our observations may be important for the interpretation and extrapolation of clinical trial results.

Few studies have examined predictors of HF. In Paper II we found that, while independent predictors of developing HF were similar to the classical predictors of cardiovascular diseases among men, women differed quite substantially in this regard. This was also largely true for independent predictors of combined HF or all-cause death.

In Paper III, our findings suggest that women and men with a valid in-hospital HF diagnosis based on contemporary criteria have similar long-term survival, irrespective of LVEF, medication and all other relevant baseline variables.

In Paper IV our results show that, among elderly patients with suspected or confirmed HF, there were some important differences between genders in BNP, LVEF, peak-VO2 and LVM, and in factors independently related to these variables. To our knowledge, this is the first study assessing gender differences in variables related to BNP, LVEF, peak-VO2 and LVM among HF patients. Our findings add further knowledge about gender differences in elderly HF patients.

Introduction

Chronic heart failure (CHF) is a common condition that often leads to hospitalisation [1-4]. CHF is the most common cause for hospitalisation among elderly people and the prognosis is poor despite improved treatment [5] An increasing amount of data suggests inherent epidemiological, pathophysiological and psychosocial differences between men and women with CHF [6, 7].

Definition of heart failure

HF is usually described as a syndrome, caused by cardiac dysfunction, and recognized by a constellation of signs and symptoms. Several clinical scoring systems for the diagnosis of HF have been developed for use in population-based epidemiological studies [8] and the most well-known is the Framingham scoring system [9]. Especially drug intervention trials have used echocardiography to examine the left ventricular (LV) systolic function in individuals with suspect HF. Individuals who have LV systolic dysfunction without symptoms should not be classified as cases of HF. Asymptomatic LV systolic dysfunction is also common [10, 11] and so is the condition so called diastolic heart failure, with typical HF symptoms but without LV systolic dysfunction [12, 13, 14].

The European Society of Cardiology (ESC) has proposed a definition of HF [15], which is used in Sweden today. It is based on:

- Having symptoms of HF
- Objective evidence of cardiac dysfunction at rest
- In cases were the diagnosis is in doubt, the response to treatment could be useful for confirming the diagnosis.

Gender and heart failure

Epidemiology

Incidence rates of HF are lower in women than in men in every age group.
Much of the information on incidence of HF comes from the Framingham Study [1, 5]. This study is based on a follow-up of a cohort assembled in 1948; therefore even later updates of the Framingham data (up to more than 40 years of follow up) may not be entirely contemporary. In this study, the average annual incidence of HF per 1000 subjects among individuals 45 years or older was 4.7 in women and 7.2 in men. Incidence rates increased with age in both men and women, approximately doubling with each decade of age, and women lagged slightly behind men in incidence at all ages. Other community samples in the US [4, 7] and in Europe [16, 17] have

also found lower incidence rates in women. Prevalence rates of HF are in general similar in women and men across different study populations [1, 4, 7, 11]. Women, however, have a lower prevalence of HF than men below the age of 70 to 75 years, and a higher prevalence at older ages. In absolute numbers, there are slightly more women than men with HF in the population [4]. Male predominance in incidence of HF appears to be due to the higher rate of coronary heart disease in men [17]. However, once coronary heart disease has become manifest with a myocardial infarction (MI), the risk of developing HF is higher in women than in men [18, 19, 20, 21]. The reasons are therefore unclear. The available incidence and prevalence data are based mostly on clinical criteria [9], occasionally with aid of echocardiograms.

Table 1.The incidence of HF in three epidemiological studies.

	Framingham		**Eastern Finland**		**Hillingdon (London)**	
Age, years	Men	Women	Men	Women	Men	Women
25-34					0.0	0.04
35-44					0.2	0.2
45-54	2.0	1.0	1.5	1.02	0.3	0.1
55-64	4.0	3.0	3.8	2.5	1.7	0.7
65-74	8.0	6.0	9.1	4.2	3.9	2.3
75-84	14.0	13.0	4.7	2.4	9.8	5.9
85-74	3.7	2.5				
85+					16.8	9.6

Risk factors and etiology

Coronary heart disease and hypertension are the most common predisposing conditions for HF both in men and women, given the high prevalence of these risk factors [5].
Our current understanding of risk factors for HF specific for women is limited and largely derived from the Framingham Study [5, 17, 22, 23]. Major conditions predisposing to HF include coronary heart disease, hypertension, valvular heart disease, diabetes mellitus and left ventricular hypertrophy [5, 23, 24, 25]. These factors overall predict HF equally in men and in women. However, diabetes [23] and hypertension [26] are stronger risk factors for HF in women than in men. The risk of HF associated with diabetes is more than threefold higher in women than in men [23], and the risk associated with hypertension also appears higher in women, about 50 % higher [26] than in men, although this has not been an entirely consistent finding [23].

When present alone, coronary heart disease is a more common etiology of HF in men, while hypertension is a more common etiology in women [5]. Although ischemic heart disease is less common as a contributing factor to HF in women than in men, women who sustain a myocardial infarction (MI) are more likely to develop HF as a post-infarction complication [18, 20, 21, 27] an observation that is independent of their older age [18]. The reasons for these gender differences in susceptibility to HF after myocardial infarction have not been elucidated.

In EuroHeart failure survey [28], ischemic heart disease was the most common reason for HF, while more than 50% had hypertension alone or in combination with ischemic heart disease and 27% had diabetes. In a retrospective study seeking to assess differences in graft patency

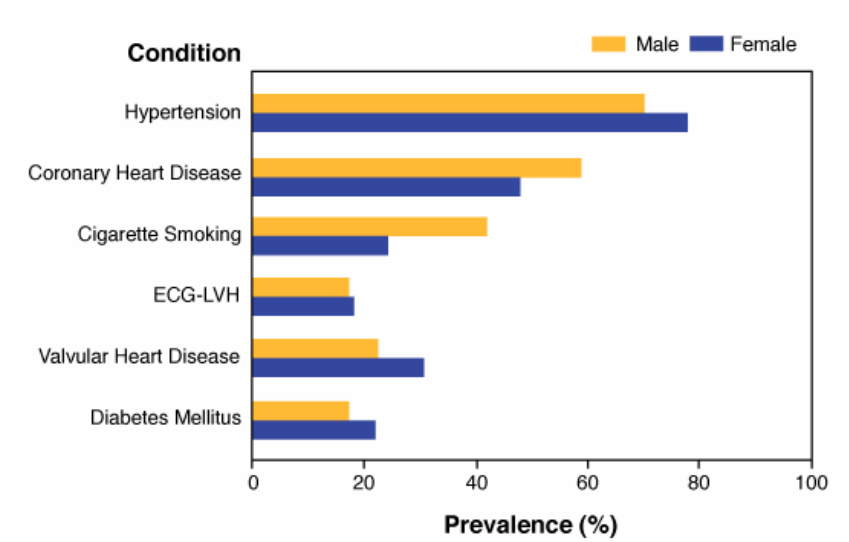
and clinical outcome between women and men after coronary artery bypass grafting surgery (CABG), the investigators found a worse clinical outcome but similar graft patency in women versus men one year after CABG, due to an excess exposure to risk factors in women [29].

The Framingham study from 1993 showed that left ventricular hypertrophy was a condition with high relative risk for CHF, both in men and women. In younger men cigarette smoking increased the likelihood of CHF but not in women or older men. That study did not find any association between high serum cholesterol levels and CHF [1].

Obesity has been reported to be among the strongest predictors of HF. In a Framingham analysis [30], moderate overweight (body mass index (BMI) 25-30 kg/m^2) was an independent predictor of developing HF among women but not among men. However, those who had BMI over 30 kg/m^2 had twice the risk of developing HF among both sexes, compared to those with normal BMI. A similar risk increase associated with obesity was seen in a Swedish study of middle-aged men [31]. Previous studies have shown that diabetes mellitus is an important predictor of CVD (cardiovascular disease) and HF among both men and women, although more important among women [32] .

The Study of men born 1913 found that smoking and high body weight were the strongest risk factor for CHF apart from hypertension [33]. No relationship with cholesterol was found, but another study showed an association between HDL (high density lipoprotein) cholesterol and risk for CHF in both sexes [5]. Ingelsson et al showed that insulin resistance and inflammation are strong independent risk factors for developing CHF, but the study included only men [34, 35].

Fig 1. Most common causes of HF etiology, by sex (the Framingham Study). JACC 1993; 22:6-13A.



Pathophysiology

Although data are limited, women are thought to be more likely than men to have diastolic dysfunction as the main underlying pathophysiological abnormality of HF [36]. This notion is mostly suggested by the finding, in those few studies of HF were not restricted to patients with impaired left ventricular systolic function, that women have higher LVEF and lower prevalence of LV systolic dysfunction compared with men [37, 38]. The lower prevalence of LV systolic dysfunction in women with heart failure compared with men may be mostly, but not entirely, due to gender differences in the etiology of HF, with hypertension and diabetes being more common antecedents of HF in women and ischemic heart disease more common in men [23, 26].

Animal studies in rats show gender differences in the remodelling process after myocardial infarction, which leads us to suspect that it might be similar in humans [39].
Due to the influence of estrogens the female heart responds differently to volume and pressure overload compared to the male heart. Males tend to develop ventricular dilation whereas females tend to develop ventricular hypertrophy. LVM increases with aging [40]. This pattern of response may be associated to oestrogen although other possible explanations exist. Androgenic hormones have an anabolic effect on myocytes while oestrogen is thought to have antiproliferative effects. Low oestrogen levels may lead to similar results as high androgenic hormone levels.

It has been suggsted that high levels of androgenic hormones may be the reason for the higher prevalence of hypertension and CVD after menopaus [40].

BNP is known for its very good negative predictive value in the diagnosis of LV systolic dysfunction, and can also be used among cardiovascular high risk patients to detect those with LV systolic dysfunction [41]. Prior studies have observed higher BNP levels in healthy women compared with healthy men and concluded that interpretation of natriuretic peptide levels should take into consideration gender and possibly age [42].

Peak VO2 is a known predictor of mortality among HF patients. Data on gender differences are rare, but in 150 patients with HF, Daida et al. showed that, women were characterized by shorter exercise time, lower peak-VO2 and lower peak oxygen pulse than men, after adjustment for age, peak heart rate (HR) [43], respiratory exchange ratio (RER), LVEF and HF etiology [44]. Pardaens et al. showed that, among 122 (99 male) adult heart transplant candidates, peak-VO2 was higher in male than in female patients, both before and after adjustment for body weight [45].

Diagnosis

The diagnosis of HF is difficult and may be somewhat unsure in clinical epidemiological studies. Incorrect diagnosis is common, especially in primary care were the examination resources are limited, e.g. echocardiography [46, 47]. Remes et al. showed in a study from Finland, that a HF diagnosis based on clinical signs/symptoms was more frequently incorrect among women than in men [48]. Among men the diagnosis of HF was correct in 57% and among women only in 14%

Despite a lower prevalence of LV systolic dysfunction, women with HF present with more symptoms and signs of decompensation than men, such as elevated respiratory rate, pulmonary

rales and edema, and higher New York Heart Association (NYHA) functional class [18, 49]. Even in studies that included only patients with LV systolic dysfunction, such as the Studies of Left Ventricular Dysfunction (SOLVD) [50] and the Cardiac Insufficiency Bisoprolol Study (CIBIS II) [51], women had symptoms and signs indicating a more advanced disease stage than men. This included more often dyspnea at rest, fatigue, peripheral edema, third heart sound and signs of elevated jugular venous pressure, and higher NYHA functional class. This tendency towards more symptoms and greater functional limitations among women was seen both in the treatment and prevention arms of SOLVD.

Similarly, among patients with idiopathic dilated cardiomyopathy, women were shown to report more symptoms, shorter exercise duration, and presented more frequently with signs of HF [52]. Although some of these differences in presentation might be due to the older age of the women, these findings overall indicate that women with HF suffer more limitations and lower quality of life compared with men.
In the study by Burns et al. [53], female and male HF patients surviving at one year had similar and substantial impairments in functional outcomes. However, in another patient series, [54] women had lower quality of life scores at one year after hospital discharge, and less improvement in physical function relative to baseline, compared with men.

In addition, women with HF are less likely to be referred to a hospital and more likely to be treated by general practitioners than men. Furthermore, once admitted to the hospital, women are less likely to be managed by a cardiologist than men [55, 56]. Women are also less likely than men to undergo cardiac catheterization and other diagnostic tests for HF [55]. Mejhert et al. showed that women were less frequently diagnosed using echocardiography [25]. These gender differences in referral and in evaluation may also contribute to the lower enrolment rates of women in HF failure trials.

Prognosis

Despite a general consensus on the poor prognosis of HF, there is considerable variability on mortality estimates across studies, and data on gender differences in mortality risk are conflicting. The Framingham Study has indicated that the prognosis of HF in women is significantly better than in men; the median survival after diagnosis of HF was 1.7 years in men and 3.2 years in women, and one-year mortality rate was 43 % in men and 36 % in women [57]. Also analyses of NHANES and the CIBIS II trial suggested that women have better prognosis than men [4, 51], whereas an analysis of the SOLVD trial showed the opposite [58]. However, also Scandinavian HF studies have shown better survival in women [25, 59].
A study from Texas, USA, in patients with HF and preserved LVEF, showed that, although the clinical manifestation of HF appeared to be more severe in women, HF hospitalisations were not increased and survival was better for women [60]. A pooled analysis of five randomized controlled HF trials showed that also among patients with LV systolic dysfunction women had better survival, despite similar LVEF, and hospitalisation over time was influenced more by etiology than gender [61].

Treatment

Pharmacological treatment

There are few studies that have specifically examined the treatment of HF in women. Most clinical trials have enrolled only 20-30 % women (Table 2), despite a similar prevalence of HF in men and women. The large-scale HF trials have included only patients with reduced LVEF, typically 35-40 % or less [62, 63, 64, 65, 66, 67, 68], which may account for the lower enrolment of women, who are more likely than men to have preserved systolic function, as described above.

According to previous and current guidelines on the treatment of HF, men and women should receive the same pharmacological treatment [69, 70] . However this can be questioned with regard to women. These guidelines are based on clinical trials conducted during the last decade. In these trials only approximately 30% or less of the subjects were women (Table 2). Some of the trials have performed subgroup analyses with regard to gender differences, but the trials were not designed for analyzing gender. The V-HeFT trials, investigating the effect of vasodilatators, were performed at the Veteran hospitals and did not include women [43, 71].

In the CONSENSUS-I trial [72] evaluating the effect of ACE (angiotensin converting enzyme)-inhibitors in patients with severe heart failure, sub-analysis showed that women had no survival benefit, while men had 51% reduction in mortality. In the SOLVD studies [65], women treated with ACE-inhibitors showed reduced morbidity and mortality, but to a lesser extent compared to men. A meta-analysis of 30 ACE-inhibitors trials showed similar reduction in morbidity and mortality, in both sexes. [73]

In the Carvedilol Heart Failure Study and MERIT-HF trial [62, 63], betablockers reduced mortality similarly in both sexes. There are other large betablockers trials that did not compare women and men [74, 75]. The DIG trial did not compare differences in mortality between women and men treated with digoxin [76]. The ELITE trials [77, 78] showed similar effects on mortality in women and men treated with either the angiotensin receptor blocker losartan or the ACE-inhibitor captopril. In the RALES study, there were no differences in mortality between sexes treated with spironolactone. [68].

Table 2. Proportion of women in some clinical pharmacological intervention trials.

Trial	No of patients (n)	Percent women (%)
V-HeFT-II	804	0
CONSENSUS I	253	30
SOLVD prevention	4228	11
ELITE II	3152	30
CIBIS II	2647	19
DIG	6800	22
RALES	1663	27

Estrogen replacement therapy

Estrogens have numerous effects on the cardiovascular system that may have potential clinical implications for the treatment of arteriosclerosis, hypertension and HF. Oral intake of conjugated estrogens is associated with an increase in angiotensinogen and decreased ACE activity [79]. Postmenopausal women taking estrogen therapy have lower renin levels than men and postmenopausal women not taking estrogens therapy. This decrease may be related to estrogen-mediated suppression of beta-adrenergic activity, although lower circulating androgens in women might also play a role. These observations suggest that there may be gender-related differences in response to ACE inhibition and beta-blocker therapy.

Estrogens have effects on lipid profiles, coagulation and fibrinolytic systems, nitric oxide and prostaglandin, all of which are important in the development of arteriosclerosis and coronary syndromes. Estrogen therapy in postmenopausal women decreases total cholesterol, low density lipoprotein (LDL) cholesterol, increases high density lipoprotein (HDL) cholesterol and decreases Lp (a) [80]. There is conflicting information regarding the benefits of estrogens on clinical cardiovascular events. There are no studies examining the role of estrogen replacement therapy in women with heart failure, although there may be theoretical benefits of estrogen replacement therapy.

Sequential biventricular pacemaker (resynchronization) and cardioverter defibrillator

There is evidence that biventricular resynchronization therapy reduces hospitalisation, improves quality of life and improves survival in patients with severe HF [81]. This effect was similar among women and men, but even here the proportion of women was low (approximately 30 %). Adding an ICD (implantable cardioverter defibrillator) the mortality was reduced slightly more [81]. Cleland et al. showed that cardiac resynchronization improves

symptoms and quality of life and reduces complications and the risk of death. These benefits in addition to those by standard pharmacologic theraphy. The proportion of women were low (approximately 25 %) and gender was not analyzed [82].

Heart transplantation

Transplantation has now become an accepted treatment option for patients with end stage CHF. This is primarily due to improved immunosuppressant therapy, which has lead to an improvement in post transplant survival. Currently the expected one-year survival for orthotopic heart transplant is approximately 85 %. However, the number of women undergoing transplantation remains lower than men. Although women represent approximately 40 % of cadaver donors, only approximately 25 % of heart transplant recipients are female [83] . The reasons for this disparity have not been well studied.

Few studies have looked at the survival of women after heart transplant. Most of these studies noted no difference in survival between women and men. However, Wechsler et al found a worse survival in women than in men up to three years after transplant [84]. The data on rejection post transplant in women are more consistent. Female transplant recipients have more episodes of rejection and are less likely to be successfully weaned off steroids than their male counterparts. After transplantation there is no gender difference in quality of life [85].

In conclusion, there are an increasing amount of data suggests inherent epidemiological, pathophysiological and psychosocial differences between men and women with HF. While the pathophysiology behind these differences remains to be elucidated, these differences indicate the need to develop trials designed to study the efficacy of clinical therapies in women and trials to study the pathophysiology. Until these data become available, the existing evidence from large-scale clinical trials suggests that women benefit from the currently recommended therapies of HF, and these therapies therefore should be offered to women. There is a need to prospectively study women with HF in both selected and unselected populations to learn more about the diagnosis and treatment of women with HF.

Aims

General aims

The general aim of the present thesis was to investigate the urban population in Malmö with regards to gender aspects on HF. We aimed to increase the knowledge about any gender differences in patients with HF and on how to investigate, examine, treat and take care of patients of both sexes.

The overall **hypothesis** was that there are important gender differences in incidence, prognosis and predictors of HF, as well as in factors related to HF.

Specific aims

The studies presented in this thesis were undertaken in order to investigate:

I. Long-term incidence, morbidity and mortality of HF in women and men of an urban Swedish population - the Malmö Preventive Project.

II. Baseline predictors of HF morbidity and mortality, in women and men of an urban Swedish population - the Malmö Preventive Project.

III. Gender differences in survival among 930 consecutive patients admitted to a central hospital and treated with intravenous diuretics because of suspected or confirmed HF.

IV. Gender differences in BNP, LVEF, LVM, peak VO2, and in variables related to these factors, among 930 consecutive patients admitted to a central hospital and treated with intravenous diuretics because of suspected or confirmed HF.

Subjects and methods

Malmö Prevention Project (Papers I and II)

In the first two papers, subjects were originally invited to participate in an observational longitudinal population study; The Malmö Preventive Project (MPP), in Malmö, Sweden [86]. The MPP was launched in 1974 at the Section of Preventive Medicine, Department of Medicine, University Hospital in Malmö, the only hospital for somatic care in a city of around 280 000 inhabitants. The project was based on a preventive case-finding programme with the aim to screen for cardiovascular risk factors, alcohol abuse and breast cancer in the population. A secondary aim was to implement health promotion for these conditions in selected subgroups of the cohort [86, 87].
In the present sub-study we wanted to describe subjects who got a HF diagnosis during approximately 22 years of follow-up and investigate gender aspects in this cohort.

Subjects

Between 1974 and 1992, 12,142 women and 30,818 men were invited to participate in the MPP. Men were mostly screened in the first half of the period (1974-1982) and women in the latter half (1981-1992), resulting in shorter follow-up time for women. The women were invited when a preventive programme for screening with mammography was launched. In all 33,346 subjects were included, of which 10,902 were women and 22,444 were men.
The overall attendance rate was 71% (range 64%-78%) [86].

Interviews and examinations

The screening at baseline included a physical examination for height (m) without shoes, and weight (kg) in light indoor clothing. The BMI was calculated (kg/m²). Blood pressure (BP, mmHg) was measured twice in the supine position after 10 min rest by use of a sphygmomanometer with a modifiable cuff width, and a mean figure was recorded.
Blood samples were drawn after an overnight fast. Serum- (s) cholesterol, s-triglycerides, fasting blood (fb)-glucose, s-hemoglobine and s-creatinine were analysed using routine methods at the Department of Clinical Chemistry, Malmö University Hospital. All subjects answered a detailed 260-item self-administered questionnaire on various aspects of lifestyle, medical history and family history [86].

The present study

Subjects who were hospitalised with a diagnosis of HF or died of HF during follow-up were considered HF patients. In all, 764 (2.3%) subjects were categorized as HF patients and 120 (1.1%) were women (Fig 2). The following ICD-codes in the first position were used to classify subjects as HF patients: ICD9, 428; ICD10, I500, I501 and I509, based on national register linkage analysis. A HF diagnosis was made by the treating physicians, based on a clinical assessment, X-ray examination and, to various extents, echocardiography, according to the clinical standards and recommendations of the different time periods during follow-up.

Physicians applied the recommendations for HF diagnosis from The Medical Products Agency (www.lakemedelsverket.se) and The National Board of Health and Welfare (www.socialstyrelsen.se) of Sweden. During the latter years, the criteria of the ESC were applied [69]**.** In some cases the diagnosis was based on autopsy. Death and hospitalisation diagnoses were continuously obtained from the Swedish national registries (National Board of Health and Welfare). There was no other formal follow-up of the HF patients within the MPP and the patients were referred to different physicians for treatment and follow-up.

An internal validation of the HF diagnosis was done among 5.5% of the HF patients and 1% of the non-HF subjects. The results are presented in papers I and II. Four patients (two of each gender) had a diagnosis of HF at baseline and were excluded from all analyses.

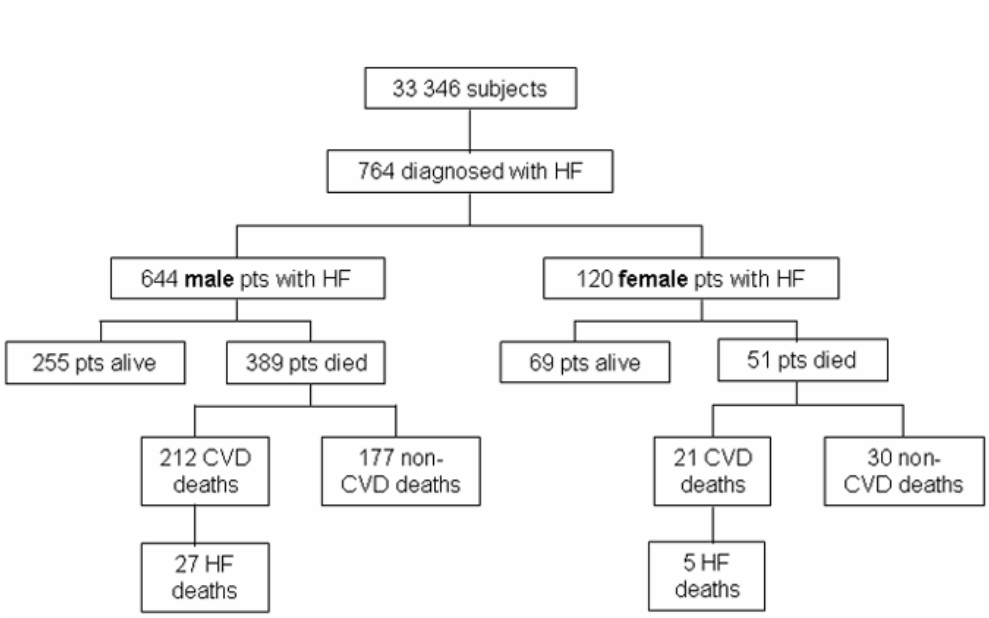
Patients were categorised according to BMI; underweight <22.00, normal-weight 22.00-24.99, overweight 25.00-29.99, and obesity ≥30.00 kg/m^2 [88]. Hypertension was defined as baseline BP ≥140/90 mmHg. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) study formula [89].

The 31st of December 2002 was the study end and subjects being alive were censored on this date. Subjects were censored on the day of the last available reliable data on morbidity and mortality if that occurred before the 31st of December 2002, e.g. if patients moved to another country. In such patients, the censor date constituted the study end. Subjects were included on average 21.7 ± 4.3 years before study end; 18.2 ± 4.3 years for women and 23.3 ± 3.0 years for men.

In Paper I, we assessed HF incidence and mortality among these subjects for approximately 22 years of follow-up, and compared HF patients with non HF subjects, and women with men.

In Paper II, we analysed baseline predictors for developing HF or combined HF or death among these subjects, during approximately 22 years of follow-up.

Fig 2: Flow chart of study participants



Heart Failure and women study (Papers III and IV)

In papers III and IV, study subjects were included from a prospective study performed at the Department of Cardiology, Malmö University Hospital.

The study was initiated as a part of the first Euro Heart Survey [90]. After concluding that inclusion, additional patients entered the present study. Assisted by a physician, a study nurse consecutively screened all patients admitted to the departments of Medicine, Cardiology, and Emergency at Malmö University Hospital in southern Sweden. The nurse first made an assessment of all computerized hospital admission records, in order to identify patients who were likely to fulfil the study criteria. Patients admitted after 5 p.m. during weekdays or anytime during weekends, were screened on the following weekday.

The patients were consecutively included during four periods; April 3rd – May 5th and May 17th – June 22nd 2000, January 18th – March 25th and June 7th – December 22nd 2002. Between May 17th and June 22nd 2000, patients were also included at the nearby Trelleborg Hospital (catchment area of around 50,000 subjects).

For all patients who fulfilled the inclusion criteria in accordance to criteria in Euro Heart Survey [90], data were extracted from hospital records and from the computerized patient administrative system (PASIS). No patient declined participation in this part of the study, where only already existing data was collected. The Patients were followed-up until December 31st 2005 (approximately four years), and data regarding mortality and morbidity were reliably extracted from PASIS. Patients were prospectively grouped based on whether they were diagnosed with HF at discharge or not, according to the ICD-10 code in any of the first three positions, and whether they had any hospital chart record of displaying signs and/or symptoms of HF at any time during the admission, not taking into account signs/symptoms prior to the admission**.** Data are presented in Paper III.

Patients were included in accordance with the following criteria:

1. A clinical diagnosis of HF during the index admission.
2. A HF diagnosis recorded in the hospital records at any time in the last 3 years.
3. Treatment with a loop diuretic for any other reason than renal failure during the 24 hours prior to death or discharge.
4. Treatment for HF or major ventricular dysfunction within 24 hours prior to death or discharge.

Patients were excluded for the following reasons:

1. Already participating in this study.
2. Difficulties to read and write or understand the questionnaires. This includes patients who do not speak Swedish, have mental disorders, and those who have drug or alcohol addiction.
3. Those who do not live in the Malmö/Trelleborg area.
4. The patient cannot or does not want to participate in the study.

Surviving patients who were willing to attend an echocardiography examination, a cardiopulmonary exercise test (CPX) and blood sampling, were given an out-patient appointment date approximately 12 weeks after discharge (Paper IV). The patients received verbal and written information, and provided written informed consent before proceeding to participate in the study. Data are presented in Paper IV.

Echocardiography

All echocardiography examinations were performed by one investigator using a Hewlett Packard 5500 (Andover, Mass, USA Sonos 2000) with a 2 to 4 MHz probe. The examinations were recorded and saved on an optical disk for later measurements.
Parasternal and apical views were obtained with the patient in a left lateral recumbent position. Measurements were performed blinded to all other information about the patients. The same investigator who performed the examination made all measurements. cardiac dimensions were measured in the parasternal long axis view in 2 D.
End diastolic measurements were performed at the onset of QRS according to the leading-to-leading edge rule. LV dilatation was considered present if the LV end diastolic diameter was at least 29 mm/m^2 body surface. Right ventricular (RV) dilatation was considered present if the end diastolic diameter was at least 18 mm/m^2 and left atrium (LA) dilatation was present if LA diameter was at least 22 mm/m^2. Assessment of mitral regurgitation (MR) was

performed using visual estimation of colour flow and continuous wave Doppler signals, measurement of proximal isovelocity surface area (PISA), assessment of pressure half time (PHT), and was considered significant if at least grade 2-3 of 4 possible [91].
Also LVM was calculated according to American Society of Echocardiography rule [91]. LVEF was visually assessed [92], and wall motion score index were evaluated in the long-axis, short-axis and apical four- and two-chamber views. The diastolic parameters were measured according to traditional diastolic function classification, based on pulsed Doppler assessment of the early to atrial transmitral flow ratio (E/A), the E-wave deceleration time (Edt) and the systolic to diastolic (S/D) pulmonary venous inflow ratio [93].

CPX - cardiopulmonary exercise test

A symptom-limited incremental exercise test was performed on a treadmill and with a spirometer, according to the modified Naughton protocol [94]. Oxygen uptake (VO2), carbondioxid uptake (VCO2) and respiratory exchange ratio (VCO2/VO2) were measured continuously with an automatic gas exchange system (MedGraphics CardioO2 ™ Combined VO2/ECG Exercise System, Medical Graphics Corporation, St Paul, Minnesota, USA). The values were obtained with 15 seconds intervals. The test was finished when maximum exertion was achieved, or due to significant arrhythmia, ischemia, or blood pressure fall. During the test there were repeated measurements of blood pressure and heart rate, as well as continuous 12 lead ECG (electrocardiogram) monitoring. The examinations were performed by the same nurse and physician.

Blood samples

Blood samples were obtained in the supine position after 30 minutes rest and were analysed by standard methods at the local laboratory. For analysing BNP we used one 5 ml pre-chilled EDTA vacutainer. The samples were immediately placed on ice and centrifuged at 4 º C before plasma aliquots were frozen at –70 º C for later analysis. The plasma BNP concentration was measured by an immunoradiometric (IRMA)-kit for human BNP (Shinoria BNP, Shionogi & Co., Ltd) [121]. The reference interval is < 6 pmol/L [95].

Blood pressure

BP was measured in the right arm in the seated position after 15 min rest. Korotkoff sounds corresponding to “phase I” was used to define the systolic and “phase V” the diastolic blood pressure. Anthropometric measurements (height and weight) were also carried out at the same time. BP was recorded by a nurse.

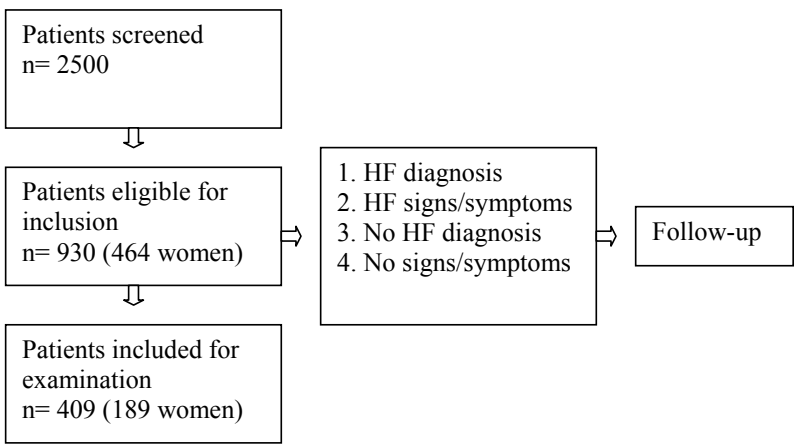
Among all 930 patients, 409 (189 women, 46.2 %) accepted to undergo follow-up examinations after discharge, and these constitute the total patient sample of Paper IV. Among patients who underwent a post discharge echocardiography examination (n=408), those who fulfilled pre-specified echocardiographic and clinical criteria were considered HF patients. They were compared with all those undergoing echocardiography and also women and men were compared.

Echocardiography criteria for heart failure were:

1. Ejection fraction (EF%) ≤50%
2. E/A >1 and LA diameter >21 mm/m^2
3. E/A <0.8
4. E/A >1 and E/É ≥15
5. E/É ≥15 and LA diameter >21 mm/m^2
6. EF% >50 and LA diameter >21 mm/m^2 and no significant MR (mitral regurgitation), (less than grade 2)

At least one criterion had to be fulfilled for a HF diagnosis.

Figure 3. Flow chart of study participants



The Regional Ethics Committee of Lund/Malmö approved study protocols. The studies were conducted in accordance with the Helsinki Declaration. Pathological findings during the examinations were taken care off through referral of the patients to different physicians.

Statistical methods

In **Paper I**, total mortality and mortality from different causes are described as the number (percentage) of deaths. Between-group differences with regard to morbid and mortal events were assessed by uni- or multivariable time-to-event analysis according to Cox, expressed as hazard ratio (HR) and 95% confidence interval (CI). Analyses of between-gender differences in risk of having an event were also performed with stratification for inclusion period, thus adjusting for differences in time of inclusion between women and men. We used five 5-year time periods of inclusion as stratification variable, from the first five years of the 70-ties through the first five years of the 90-ies. Differences in normally distributed continuous variables were tested with the unpaired t-test. Data are presented as means ± standard deviation. $P<0.05$ denotes statistical significance.

In **Paper II,** baseline variables (separately in women and men) were analysed in univariable Cox regression models with the diagnosis of HF and combined HF or all cause death as dependent endpoint variables, respectively. The basic time variable used at the time of endpoint was age and data was treated as left-truncated to adjust for time. The results are expressed as HR and 95% CI.
HRs data for continuous variables are given per unit increase, except for body mass index, blood pressure and eGFR, where HRs are per 10 units increase. $P<0.05$ denotes statistical significance.
All variables were further tested for inclusion in multivariable analysis using multivariable Cox regression models and using backward stepwise deletion of variables. The final models were tested using likelihood ratio test.
Bootstrap analyses were performed to validate the final model [122]. The bootstrap analyses were performed by 100 resamplings from the original sample, and for each resampled data set a stepwise backward deletion of variables analysis was performed in a multivariable Cox regression model.
The results of the bootstrap analyses are presented as the frequency of inclusion of covariates in a final multivariate regression model. Covariates with frequency > 90% were considered as strong independent predictors and >30% but <90% as weak independent predictors [123].
Final multivariable Cox regression models including only strong and as well as both weak and strong independent predictors, respectively, are presented.
The proportional hazards assumption was tested using residuals based test [124]. All survival analyses were performed using the package Survival in R, www. R-project.org.

In **Paper III,** data are presented as mean and standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. Student´s t-test was used to compare continuous variables, and the X^2 test for categorical variables.
Mortality hazard in relation to gender was first assessed in time-to-event Cox univariable analysis and expressed as HR and 95% CI for all groups.
All variables showing significant ($P<0.05$) association with mortality in univariable analysis were tested further for internal correlation, using Spearman rank correlation test for categorical and linear regression analysis for continuous variables.
In all analyses, $R> 0.3$ denoted significant internal correlation, and only the variable with the greatest association with mortality in univariable analysis was qualified as covariate in the Cox multivariable analysis.

In **Paper IV,** data for continuous and categorical variables were presented as in Paper III. Baseline variables showing significant association (using a criterion of $P<0.05$) with BNP, LVEF, peak VO2 and LVM (dependent factors), respectively, in univariable ANOVA, were tested further in multivariable ANOVA, using backwards stepwise deletion of variables. Variables remaining with a P-value <0.05 were considered independently related to the dependent factor. Associations were expressed using F-value.

StatView for Windows version 5.0.1 was used for statistical analyses in Paper I, III and IV and the package Survival in R, www. R-project.org., for paper II.

Results

Paper I

In this study we investigated gender-specific long-term HF incidence and mortality in an urban community-based sample of middle-aged subjects.
Between 1974 and 1992, 33,342 HF-free subjects (10,900 [32.7%] women, mean age 45.7±7.4 years) were included in the Malmö Preventive Project, on average 21.7±4.3 years before study end. Patients hospitalised for or dying of HF were categorised as HF patients, and 120 (1.1%) women versus 644 (2.9%) men experienced HF, (HR 0.61; 95% CI 0.50-0.74; P<0.0001), (Fig 4). Adjustment for baseline age further decreased the risk of HF, in women (HR 0.39, 95% CI 0.32-0.48; P<.0001) and when analysis was performed with stratification for inclusion period, the HR for women versus men was 0.46, 95% CI 0.35-0.59, P<.0001.

HF patients had higher mortality risk than non-HF subjects (HR 3.58; 95% CI 3.24-3.97; P<0.0001), (Fig 5).
Among all subjects, women had lower all-cause (HR 0.68, 95% CI 0.64-0.73, P<0.0001) and HF-related (HR 0.50, 95% CI 0.37-0.67, P<0.0001) mortality risk. When adjusting for age differences at baseline the risk for women versus men further decreased: HR 0.46; 95% CI 0.42-0.49; P<.0001 for all-cause mortality and HR 0.32; 95% CI 0.24-0.43; P<.0001 for HF related mortality risk. When stratifying for inclusion period, the HR for women versus men was 055, 95% CI 0.50-0.61, P<.0001 for all-cause mortality risk and HR 0.41, 95% CI 0.28-0.59, P<.0001 for HF related mortality risk.

Female and male HF patients had similar age-adjusted mortality risk (HR 0.78; 95% CI 0.58-1.07; P=0.12). The results were quite similar when stratifying for inclusion period (HR 0.95, 95% CI 0.64-1.39, P=0.77)
Among HF patients, 171/404 (42.3%) deaths were non-cardiovascular, 26/47 (55.3%) in women and 145/357 (40.6%) in men and only 32/404 (7.9%) deaths were due to HF (Figure 6).
Fig 7, shows different causes of death by sex among non-HF subjects. The most apparent differences compared to HF patients are that non-HF subjects had much lower mortality and predominantly died of non-CVD causes.

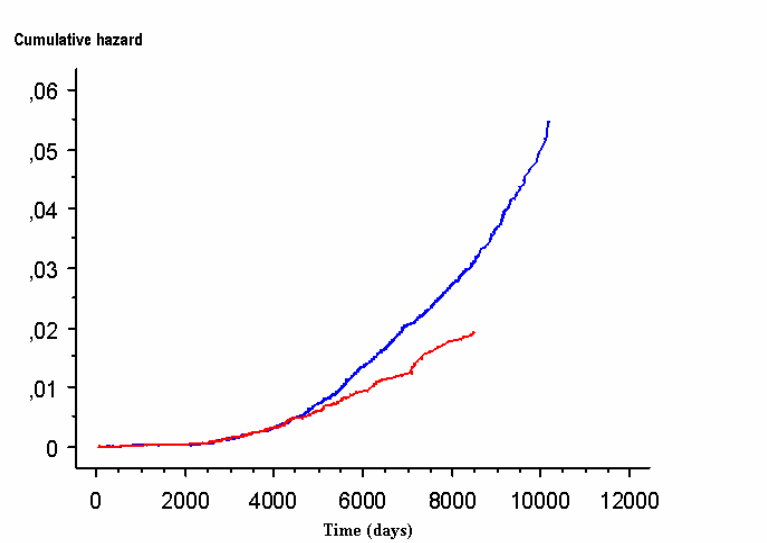


Fig 4. Cumulative HF incidence hazard in women (red) and men (blue) over the entire study period. Women versus men: HR 0.61; 95% CI 0.50-0.74; P<0.0001.

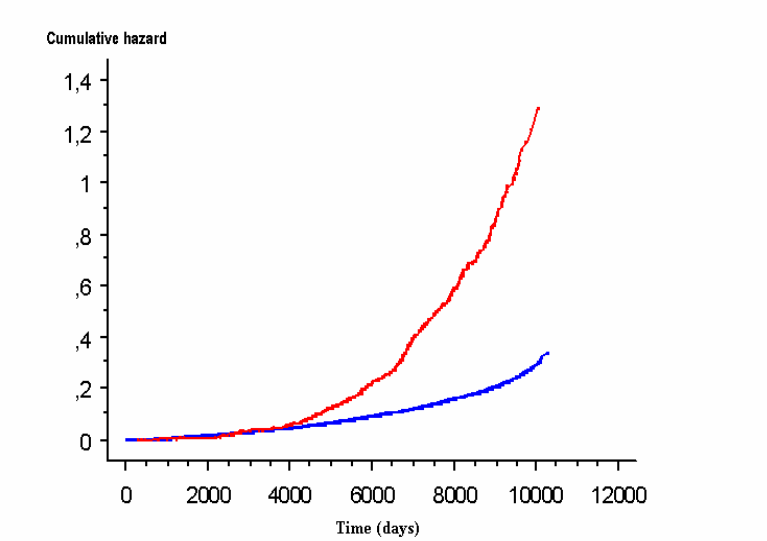
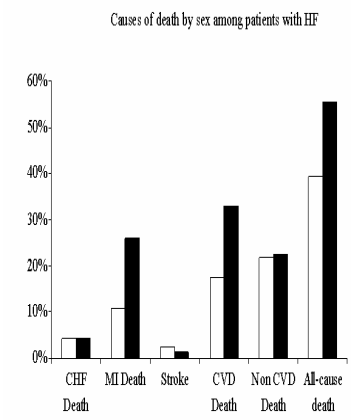


Fig 5. Cumulative all-cause mortality hazard in HF patients (red) and non-HF subjects (blue): HR for death 3.58; 95% CI 3.24-3.97; P<0.0001.



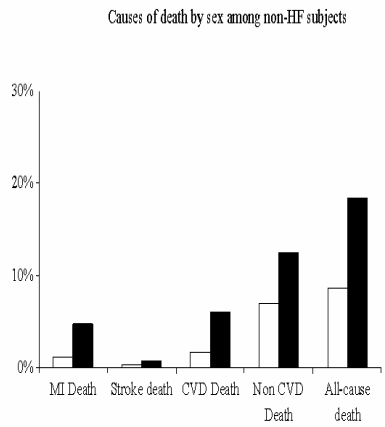


Fig 6.HF patients: Bars indicate the percentages of HF patients of each gender (120 women, 644 men) who died of the respective cause: HF, heart failure (5 women, 27 men); MI, myocardial infarction (13 women, 167 men); stroke (3 women, 8 men); CVD, cardiovascular disease (21 women, 212 men); non-CVD (26 women, 145 men); all-cause death (47 women, 357 men). **White: women, black: men**

Fig 7.Non-HF patients: Bars indicate the percentages of non-HF subjects of each gender (10,780 women, 21,798 men) who died of the respective cause: MI, myocardial infarction (125 women, 1051 men); stroke (47 women, 164 men); CVD, cardiovascular disease (180 women, 1324 men); non-CVD (751 women, 2711 men); all-cause death (931 women, 4035 men). **White: women, black: men**

Paper II

In this study we assessed gender specific baseline predictors for HF and combined HF or death. Subjects were included as in Paper I. During 21.7±4.3 years of average follow-up, 764 (2.3%) subjects were diagnosed with HF, 120 (1.1%) women and 644 (2.9%) men. Following bootstrap analysis, the only strong independent predictor of HF among women was smoking. Strong independent predictors of HF among men were diastolic blood pressure (BP), fasting blood (fb)-glucose, smoking, family history of myocardial infarction (FHMI), and previous CVD. During follow-up, 5,370 (16.1%) subjects died, 978 (9.0%) women and 4,392 (19.6%) men. Among both women and men, strong independent predictors of combined HF or all-cause death were high serum (s)-triglycerides, fb-glucose and estimated glomerular filtration rate (eGFR), smoking, and previous CVD. Among men, also underweight as well as high BMI, and systolic and diastolic BP, were strong independent predictors of HF or death (Table 3).

Table 3. Multivariable analysis of strong independent predictors of heart failure and combined heart failure or death, according to bootstrap analysis, in women and men (adjusted for age).

	Predictors of HF						**Predictors of HF or death**					
	Women			**Men**			**Women**			**Men**		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
BMI kg/m²	-	-	-	-	-	-	-	-	-	1.04	1.03-1.05	**<.0001**
Underweight	-	-	-	-	-	-	-	-	-	1.36	1.23-1.50	**<.0001**
Overweight	-	-	-	-	-	-	-	-	-	-	-	-
Obesity	-	-	-	-	-	-	-	-	-	-	-	-
Systolic BP Mm Hg	-	-	-	-	-	-	-	-	-	1.01	1.00-1.01	**<.0001**
Hypertension	-	-	-	-	-	-	-	-	-	-	-	-
Diastolic BP Mm Hg	-	-	-	1.04	1.04-1.05	**<.0001**	-	-	-	1.01	1.01-1.02	**<.0001**
Hemoglobin g/L	-	-	-	-	-	-	-	-	-	-	-	-
eGFR ml/min	-	-	-	-	-	-	1.01	1.01-1.02	**<.0001**	1.001	1.001-1.003	**<.0001**
Cholesterol mmol/L	-	-	-	-	-	-	-	-	-	-	-	-
Triglycerides mmol/L	-	-	-	-	-	-	1.27	1.17-1.39	**<.0001**	1.05	1.03-1.07	**<.0001**
Glucose mmol/L	-	-	-	1.18	1.13-1.23	**<.0001**	1.15	1.11-1.20	**<.0001**	1.10	1.08-1.12	**<.0001**
Sex: Women	-	-	-	-	-	-	-	-	-	-	-	-
Smoking	2.52	1.72-3.69	**<.0001**	1.92	1.62-2.27	**<.0001**	2.05	1.80-2.34	**<.0001**	2.16	2.03-2.31	**<.0001**
FH of MI	-	-	-	1.40	1.15-1.70	**<.0001**	-	-	-	-	-	-
Prior CVD	-	-	-	4.14	2.44-7.00	**<.0001**	2.21	1.41-3.45	**<.0001**	2.28	1.81-2.88	**<.0001**

HF, heart failure; BMI, body mass index; BP, blood pressure; Smoking, current and previous smokers versus never smokers; FH of MI, family history of myocardial infarction; CVD, cardiovascular disease, eGFR (estimated glomerular filtration rate).HRs for continuous variables are per unit increase, except for BMI, BP and eGFR, where HRs are per 10 units increase. HRs for the baseline BMI categories are for the respective categories versus the normal weight category. HRs for all other categories are compared to the opposite category.

Final multivariable Cox regression models including both weak and strong independent predictors, respectively, are presented in table 4b.

Table 4. Multivariable analysis of weak and strong independent predictors of heart failure and combined heart failure or death, according to bootstrap analysis, in women and men (adjusted for age).

	Predictors of HF						**Predictors of HF or death**					
	W			**Men**			**Women**			**Men**		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
BMI kg/m²	1.06	0.99-1.13	0.0610	1.11	1.08-1.13	**<.0001**	1.01	0.99-1.03	0.1400	1.03	1.01-1.05	**0.0074**
Underweight	-	-	-	1.33	0.99-1.79	0.0620	-	-	-	1.30	1.23-1.50	**<.0001**
Overweight	-	-	-	-	-	-	-	-	-	0.96	0.86-1.06	0.4100
Obesity	1.71	0.81-3.59	0.1600	-	-	-	-	-	-	1.12	0.89-1.41	0.3200
Systolic BP mm Hg	-	-	-	1.01	1.00-1.02	**0.0110**	1.01	1.00-1.01	**<.0001**	1.01	1.00-1.01	0.0870
Hypertension	-	-	-		-	-	-	-	-	1.09	0.99-1.21	**0.0087**
Diastolic BP mm Hg	-	-	-	1.02	1.01-1.03	**0.0002**	-	-	-	1.01	1.01-1.02	**<.0001**
Hemoglobin g/L	-	-	-	-	-	-	-	-	-	-	-	-
eGFR ml/min	-	-	-	-	-	-	1.01	1.006-1.01	**<.0001**	1.003	1.002-1.003	**<.0001**
Cholesterol mmol/L	-	-	-	1.10	1.02-1.19	**0.0120**	-	-	-	1.04	1.01-1.07	**0.0065**
Triglycerides mmol/L	1.45	1.16-1.82	**0.0013**	-	-	-	1.21	1.11-1.33	**<.0001**	1.04	1.02-1.07	**0.0004**
Glucose mmol/L	1.09	0.97-1.23	0.1500	1.15	1.09-1.20	**<.0001**	1.14	1.10-1.19	**<.0001**	1.10	1.08-1.12	**<.0001**
Sex: Women	-	-	-	-	-	-	-	-	-	-	-	-
Smoking	2.63	1.77-3.92	**<.0001**	1.97	1.66-2.33	**<.0001**	2.19	1.91-2.50	**<.0001**	2.15	2.02-2.29	**<.0001**
FH of MI	1.95	1.14-3.34	**0.0150**	1.39	1.14-1.68	**0.0001**	-	-	-	1.10	1.01-1.18	**0.0210**
Prior CVD	3.81	1.38-10.53	**0.0099**	4.07	2.40-6.89	**<.0001**	2.21	1.41-3.45	**0.0005**	2.29	1.82-2.89	**<.0001**

HF, heart failure; BMI, body mass index; BP, blood pressure; Smoking, current and previous smokers versus never smokers; FH of MI, family history of myocardial infarction; CVD, cardiovascular disease, eGFR (estimated glomerular filtration rate).
HRs for continuous variables are per unit increase, except for BMI, BP and eGFR, where HRs are per 10 units increase. HRs for the baseline BMI categories are for the respective categories versus the normal weight category. HRs for all other categories are compared to the opposite category.

Paper III

In this study we prospectively assessed gender differences in survival among 930 consecutive patients (464 [49.9%] women, mean age 76.1±10.1 years), admitted to hospital with suspected or diagnosed HF. Patients were prospectively grouped based on whether they were diagnosed with HF at discharge or not, according to the ICD-10 code in any of the first three positions, and whether they had any hospital chart record of displaying signs and/or symptoms of HF at any time during the admission, not taking into account signs/symptoms prior to the admission**.**

We found that overall, women had lower unadjusted mortality hazard ratio than men: HR 0.83; 95% CI 0.69-0.99; p=0.040, (Fig 8). Adjusted HR was 0.79; 95% CI 0.60-1.03; p=0.079. Unadjusted mortality was significantly higher among patients with a discharge HF diagnosis, compared to those without: HR 1.33; 95% CI 1.11-1.60; p=0.002; adjusted p=0.29. Women and men with a discharge HF diagnosis had similar survival: unadjusted HR 1.05; 95% CI 0.83-1.34; p=0.67 (Fig 9); adjusted HR 0.88; 95 % CI 0.63-1.23; p=0.44. Women had lower mortality risk among patients without a discharge HF diagnosis: HR 0.63, 95 % CI 0.48-0.83, p=0.001; adjusted HR 0.61, p=0.036.

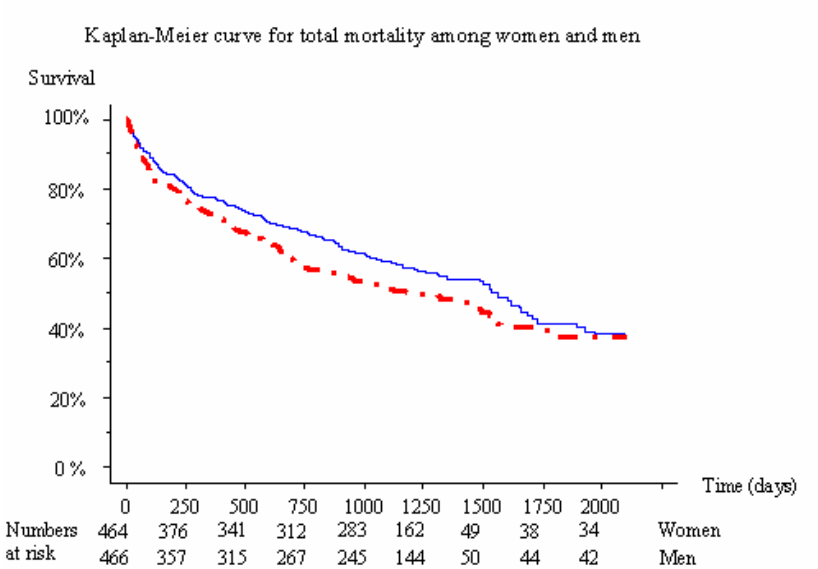


Fig 8. Kaplan-Meier curve for total mortality among all women and men. Log rank p=0.04. Solid (blue) line, women; dotted (red) line, men.

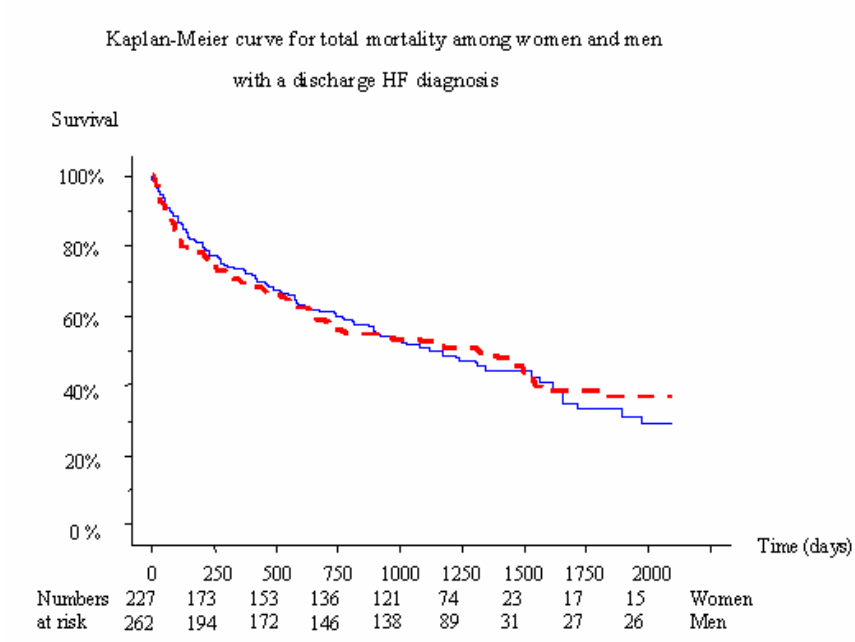


Figure 9. Kaplan-Meier curve for total mortality among women and men with a discharge HF diagnosis. Log rank p=0.67. Solid (blue) line, women; dotted (red) line, men.

Patients with signs/symptoms of HF had significantly higher unadjusted mortality hazard compared to those without (HR 1,56; 95% CI 1.25-1.94; P<.001), but borderline-significant when adjusted (HR 1.38:95% CI 0.99-1.91; P=0.056
Similar to patients with a HF diagnosis, female patients with signs/symptoms of HF had equal survival to male patients with signs/symptoms of HF: unjusted HR; 0.96; 95% CI 0.78-1.17; P=0.67; adjusted HR 0.81; 95% CI 0.60-1,09; P=0.16.

Paper IV

In this study, among 930 consecutive patients admitted to hospital for suspected HF, 409 (189 women, 46.2%) accepted follow-up after discharge (total patient sample). According to pre-specified echocardiographic and clinical criteria, 221 of these had definite HF (90 women, mean age 74.5 [9.8] years).

We found that women had lower BNP, Peak VO2, LVM but higher LVEF in both the entire patient sample and in patients with HF.

Women versus men among HF patients: BNP; (43.9 [38.1] versus 76.3 [88.9] pmol/L, P=0.0193), peak-VO2, (13.9 [4.3] versus 16.3 [4.2] ml/kg/min, P=0.0093), LVM index, (130.4 [46.5] versus 171.7 [57.6] grams/m^2, P<0.0001), LVEF, (49.8 [13.4] versus 42.4 [13.9] %, P=0.0004).
Women versus men among total patient sample: BNP; (40.2 [50.6] versus (65. [3 82.2] pmol/L, P=0.0031), peak- VO2, (14.4 [4.1] versus (16.3. [4.4] ml/kg/min, P=0.0004), LVMI, (125.2 [42.4] versus (165.6. [56.8] grams/m^2 , P<0.0001), LVEF, (52.2 [12.3] versus (44.5. [14.4] %, P<0.0001).

Among patients in the total sample, baseline variables independently related to BNP were BMI, LVEF, LVM, RV diameter and MR among women, and BMI, LVEF and peak-VO2 among men. Variables independently related to LVEF were BNP, LV diameter and smoking among women, and BNP, resting heart rate and LV diameter among men. Variables independently related to peak-VO2 were BMI, peak respiratory exchange ratio and age among women, and RV diameter, peak respiratory exchange ratio, peak heart rate, systolic BP, age and BNP among men. Variables independently related to LVM were BMI, LA diameter, systolic BP and LV diameter among women, and LA diameter and LV diameter among men (Table 5).

Among HF patients, baseline variables independently related to BNP were LVEF and MR among women, and creatinine, BMI, LVEF and peak-VO2 among men. Variables independently related to LVEF were LV diameter among women, and BNP, resting heart rate and LV diameter among men. Variables independently related to peak-VO2 were BMI, LVM and age among women, and RV diameter, age, BNP and resting heart rate among men. Variables independently related to LVM were BMI and LV diameter among women, and LA and LV diameter among men (Table 6).

Table 5 Variables independently related to BNP, LVEF, peak-VO2 and LVM, in patients with a hospitalisation for suspected HF (total patient sample), in multivariableANOVA**.**

	Sodium	BMI	LAD	LVEF%	Peak-VO2	LVM	RVD	MR	Peak RER	Peak HR	Syst BP	Age	BNP	Rest HR	LVD	Current smoking
BNP																
All	F=4.0 P=.0472	*F=25.2* P<.0001	F=16.3 P<.0001	*F=14.0* P=.0003	F=21.4 P<.0001											
Women		F=8.0 P=.0060		F=7.2 P=.0092		F=11.1 P=.0014	F=7.7 P=.0069	F=6.5 P=.0130								
Men		F=13.7 P=.0005		F=14.3 P=.0002	F=29.4 P<.0001											
LVEF%																
All													*F=28.7* P<.0001		*F=93.3* P<.0001	
Women													F=16.0 P<.0001		F=23.8 P<.0001	F=6.7 P=.0051
Men													F=13.2 P=.0005	F=11.8 P=.0009	F=33.0 P<.0001	
Peak VO2																
All		F=30.7 P<.0001							F=9.5 P=.0024	F=9.5 P=.0024	F=10.9 P=.0012	F=16.6 P<.0001	F=13.5 P=.0003			
Women		F=25.1 P<.0001							F=10.6 P=.0017			F=10.0 P=.0022				
Men							F=5.1 P=.0262		F=44.9 P<.0001	F=24.9 P<.0001	F=11.4 P=.0011	F=12.2 P=.0006	F=10.5 P=.0017			
LVM																
All		F=7.9 P=.0054	*F=36.0* P<.0001												F=155.7 P<.0001	
Women		F=7.7 P=.0072	F=4.7 P=.0335								F=4.5 P=.0369				F=24.1 P<.0001	
Men			F=42.1 P<.0001												F=75.3 P<.0001	

Variables above were independently related to respective endpoints (BNP, Peak VO2, LVEF%, LVM): P<0.05.
BNP,B- natriuretic peptide; Peak VO2, peak oxygen consumption; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; Na, sodium; BMI, body mass index; La, left atrium diameter; RVD and LVD, right and left ventricular diameter; MR, mitral regurgitation; Peak RER, peak respiratory exchange ratio; HR, heart rate; syst BP, systolic blood pressure.

Table 6 Variables independently related to BNP, LVEF, peak-VO2 and LVM, in patients with confirmed HF, in multivariable ANOVA**.**

	Creat	BMI	LAD	LVEF%	Peak-VO2	LVM	RVD	MR	Peak RER	Age	BNP	Rest HR	LVD
BNP													
All		F=20.6 P<.0001			F=29.3 P<.0001								F=14.0 P=.0004
Women				F=6.6 P=.0132				F=23.3 P<.0001					
Men	F=4.1 P=.0460	F=8.8 P=.0047		F=4.6 P=.0366	F=23.4 P<.0001								
LVEF%													
All											F=8.3 P=.0047		F=51.0 P<.0001
Women													F=35.4 P<.0001
Men											F=8.4 P=.0054	F=11.9 P=.0011	F=15.4 P=.0003
Peak VO2													
All		F=30.5 P<.0001							F=4.5 P=.0380	F=11.6 P=.0011	F=24.1 P<.0001		
Women		F=12.1 P=.0001				F=4.9 P=.0346				F=12.7 P=.0013			
Men							F=5.8 P=.0194			F=11.2 P=.0016	F=10.5 P=.0021	F=11.5 P=.0013	
LVM													
All		F=7.0 P=.0091	F=21.6 P<.0001										F=86.0 P<.0001
Women		F=15.2 P=.0003											F=29.8 P<.0001
Men			F=20.9 P<.0001										F=39.5 P<.0001

Variables above were independently related to respective endpoints (BNP, Peak VO2, LVEF%, LVM): P<0.05
BNP,B- natriuretic peptide; Peak VO2, peak oxygen consumption; LVEF, left ventricular ejection fraction; LVM, left ventricular mass;
Creat, creatinine; BMI, body mass index; La, left atrium diameter; RVD and LVD, right and left ventricular diameter; MR, mitral regurgitation;
Peak RER, peak respiratory exchange ratio; HR, heart rate.

Discussion

An increasing amount of data suggests inherent epidemiological, pathophysiological and psychosocial differences between men and women with HF. Prior studies reporting on gender aspects of HF epidemiology have mostly been performed in elderly subjects, have often included small cohorts, have usually had short observation time, and/or have included selected patients. HF is relatively uncommon in younger age groups [5] and there is a little epidemiological data in younger HF patients. Therefore, the findings of the present thesis expand the pre-existing knowledge.

Risk for heart failure

The incidence rates of HF are lower in women than in men in every age group.

Most of the information about incidence of HF comes from the Framingham Study[1], but also other community samples in the US [4, 7] and in Europe [16] have found lower incidence rates in women.

In Paper I, we observed that women had a lower risk than men of being hospitalised for or dying of HF. Women in this study were mostly included in later time periods than men, but when analyses were stratified for inclusion period the results were similar to non-stratified results. The shorter time of follow-up among women was adjusted for by the use of time to event analysis.

Prior studies have shown that women are generally diagnosed with HF at older ages compared to men [11, 96, 97]. Our results could have been influenced by to the relatively low mean age at the time of the HF diagnosis among both sexes, but when adjustment for baseline age was done, the risk of HF among women further decreased compared with men.

Also in Paper III, we observed a lower percentage of women than men having a HF diagnosis. These patients were elderly, consecutively included, and there was no selection of these patients. In Paper I, few patients had a history of CVD and MI at baseline, and any between-gender differences in this regard cannot explain the higher incidence of HF among men. In Paper III, men more frequently had a history of MI and CABG compared with women, which may contribute to the higher risk of developing HF among men.

Thus, the present thesis included both younger and elderly HF patients, and the results suggesting that women have lower risk of developing HF compared with men, as supported by previous studies.

Validity of heart failure

HF is a disease defined by a constellation of different clinical signs and symptoms and the diagnosis also demands a measurement of cardiac function. Some physicians may feel insecure about the HF diagnosis when echocardiographic LV systolic function is normal, which is especially common in women [14, 96, 98, 99]. The validity of a HF diagnosis may be affected by the complexity of the disease.

Data from previous diagnosis validation studies of CVD, like myocardial infarction and stroke, have shown a diagnostic validity of approximately 95% in the hospital discharge registers in different countries, Sweden included [100, 101, 102, 103].

There are a few studies investigating the validity of a HF diagnosis in a national hospital discharge register. Ingelsson et al. examined the validity of the diagnosis of HF in the Swedish hospital discharge register [104]. Eighty-two percent of HF cases in the hospital discharge register were classified as having definite HF using the ESC definition as gold standard. The validity of a hospital discharge register HF diagnosis was higher in patients treated at an internal medicine (86 %) or cardiology (91 %) clinic, or when it was the primary diagnosis (95 %). Echocardiographic examination only slightly increased the validity of the diagnosis.

In our studies (Papers I and II) we carried out an internal validation of the HF diagnosis in 42 (5.5%) HF patients, 5 women and 37 men, randomly selected over the entire follow-up period.

Among these, 39 (93%) had data on LVEF and 35 (83%) had a record of symptoms of HF. Mean LVEF was 34% (range 10-60%). Those who had no record of an echocardiogram (n=3), all had typical HF symptoms.

An internal validation was made also among 300 (0.9%) non-HF subjects, 90 women and 210 men. Among these, 269 (90%) had no hospitalisation during the follow up. We did not find any subject having a diagnosis of CHF during follow-up in this sample.

To be more confident of a correct HF diagnosis, we used only HF diagnosis codes in the first position in paper I and II, but HF codes in the first 3 positions in paper III and IV, according to the inclusion criteria of the Euro Heart Survey study. However, slightly more than half were in the first position [90].

Our internal validation suggests that a HF diagnosis was largely correct. Thus, it is pointing in a similar direction to the findings by Ingelsson et al.

Heart failure mortality/survival

HF is associated with poor prognosis and frequent hospitalisation, and it is the most common cause for hospitalisation among elderly people [1, 2, 3, 4, 5]. There is considerable variability in mortality estimated across HF studies, and data on gender differences in mortality are conflicting.

Most prior data from HF studies indicate that women have better survival than men. The Framingham Heart Study indicated better prognosis in women [57], as did NHANES [4] and CIBIS II [51], whereas an analysis of the SOLVD trial showed the opposite [58].

Also Scandinavian HF studies have shown better survival in women [25, 59]. Among patients with systolic HF, it has been indicated that women may have more advanced symptoms of HF despite similar or even better LVEF than men [50, 52], which may be relevant in this context.

A study from Texas, USA, in patients with HF and preserved LVEF, showed that, although the clinical manifestation of HF appeared to be more severe in women, HF hospitalisations were not increased and survival was better for women [60]. However, a study including patients hospitalised for HF showed better survival in women, independent of LVEF [105], and a pooled analysis of 5 randomized controlled HF trials showed that also among patients with LV systolic dysfunction women had better survival, despite similar LVEF, and hospitalisation over time was influenced more by etiology than gender [61].

In Paper I, we found that the prognosis among HF patients was poor with about 25% one-year mortality for both sexes. This is supported by previous studies [2, 3, 4, 5, 57]. Women had 20 % lower mortality hazard following the diagnosis of HF, but the difference was not statistically significant, nor without, neither with adjustment for age at the time of HF diagnosis and not when stratifying for the inclusion period.

Our conclusion is that age is not explaining this finding and that female and male HF patients in a middle-aged, community-based sample had similar mortality risk following the diagnosis of HF. However the risks of CVD and MI mortality were significantly lower among female HF patients.

We did not have access to data on treatment after the diagnosis of HF and could not adjust for any possible between-sex differences in this regard. However, prior studies [4, 25, 51, 57, 59, 60, 61, 105] have not indicated that women with HF receive better treatment than men. We also did not have data on LVEF in all patients and between-sex differences may in this regard at least partly explain differences in CVD and MI mortality risk, although a prior study showed better survival in women independent of LVEF [105]. Men with HF suffered more often from severe coronary artery disease than women with HF and this could be an important reason for the worse CVD and MI mortality risk in male HF patients.

In Paper III, we prospectively investigated patients hospitalised for suspected or confirmed heart failure. Prognosis was generally poor among patients hospitalised with suspected or diagnosed HF. Women had better unadjusted but not adjusted survival than men among all hospitalised patients. In patients with a discharge HF diagnosis, as well as among those with signs/symptoms of HF, survival was similar between sexes, both in unadjusted and adjusted analysis. Inversely, women had better survival among patients without a discharge HF diagnosis, both in unadjusted and in adjusted analysis.
Our findings suggest that women and men with a valid in-hospital HF diagnosis based on contemporary criteria have similar long-term survival, irrespective of LVEF, medication and all other relevant baseline variables.

This finding is not generally supported by findings in previous studies. The discharge diagnosis of HF in our study was mostly based on the recommendations of the European Society of Cardiology [69] and generally based on at least an evaluation of sign/symptoms of HF prior to and during the hospital stay, and an echocardiographic examination or some other method for evaluation of cardiac function. We included a HF diagnosis in any of the first three positions according to the standards of the Euro Heart Survey, of which slightly more than half were in the first position. Thus, an invalid diagnosis of HF should not be the reason for this discrepancy.

In our study, in accordance with the European Society of Cardiology criteria [69], we did not require a low LVEF for the diagnosis of HF, but some evidence of a disturbed cardiac function, although the mean LVEF was clearly reduced among patients with a discharge HF diagnosis and among those with signs/symptoms of HF.
A possible reason for the different finding in our study, as compared with most others, may be different age groups. Patients in our study were elderly. In most clinical trials patients have been considerably younger [4, 51, 58, 60], although other studies have included elderly patients [25, 57 59, 105].

Women with a discharge HF diagnosis as well as women with signs/symptoms of HF were discharged with less angiotensin-converting enzyme inhibitors, compared with corresponding

men. In addition, women more often had hypertension treatment, whereas men more often had a history of AMI and prior coronary surgery, more often were current/ previous smokers, and had more depressed LVEF. All of these factors may influence survival after a hospitalisation for HF. However, also in adjusted analysis, taking all medication and other relevant covariates into account, women and men did not have significantly different mortality risk, although HRs were numerically better for women versus men in adjusted as compared to unadjusted analysis.

Women were less likely to be examined by echocardiography, despite the fact that all included patients were hospitalised with suspected HF. Although this might in part have been due to the older age of the women, this is clearly not in line with current recommendations [69], and suggests a need for further improvement in diagnosing HF.

The validity of our observations, with regard to the comparison between women and men, is likely to be improved by the fact that we included around 50% women, whereas many other studies, especially the early ones [4, 51, 58], included relatively few women.

Causes of death

The main findings in Paper I are that almost half of the deaths among HF patients were attributable to non-CVD causes, and that only around 10% of the deaths were due to HF. Our HF patients of both genders were on average 65.5 years of age at the time of the HF diagnosis and the causes of death among our HF patients contrast substantially to the causes of death seen in the major clinical HF trials, performed in similar age groups, which are mainly HF related [51, 65, 66, 72, 78.]. More than 50% of the deaths among female HF patients and more than 40% of deaths among male HF patients were attributable to non-CVD causes.

In some cases HF patients might have been judged to die of causes that were actually secondary to HF, such as various infectious diseases, constituting 15% of the non-CVD causes of death. However, this is unlikely to explain more than a very small part of the non-CVD mortality. It is also unlikely that this high frequency of non-CVD death was due to incorrect HF diagnoses; our internal validation showed that, all of both the HF and the non-HF diagnoses were correct in the random subsample examined.
It is obvious that our relatively young HF patients of both sexes had substantial non-CVD co-morbidity, which often was judged the cause of death.

Interestingly, few HF patients of both sexes died of HF. This could be explained by a propensity to provide MI or other coronary artery disease as cause of death in patients with HF and coronary artery disease. This is supported by the fact that MI was the cause of death in 45% of the HF patients who died during follow-up, being especially common in male HF patients.

In conclusion, Paper I showed that in a community-based sample of middle-aged subjects, during 22 years of observation, more than 50% of deaths among female and more than 40% in male HF patients were attributable to non-CVD causes, indicating substantial important co-morbidities in these relatively young HF patients. We found relatively low HF mortality among HF patients of both sexes. MI was the single most common cause of death, significantly more prevalent in male than in female HF patients. There were significant gender differences with regard to incidence of HF and HF-related mortality; women were less likely to be diagnosed with HF and had substantially lower risk of all-cause and HF-related death. The prognosis among HF patients was poor, with around 25% one-year mortality for

both sexes. Women and men were of similar mean age at the time of the diagnosis of HF, but female HF patients had significantly lower CVD mortality risk compared to male HF patients, although all-cause mortality risk did not differ significantly.

Many of our observations differ from those of other epidemiological studies, probably at least partly because of the relatively young mean age of patients. However, the mean age was similar to that of most clinical HF trials, whereas the causes of mortality differ quite substantially from these trials and women and men had similar mortality risk and survival. Our observations may be important for the interpretation and extrapolation of clinical trial results in practice.
Our findings in paper III, suggest that women and men with a valid in-hospital HF diagnosis based on contemporary criteria have similar long-term survival, irrespective of LVEF, medication and all other relevant baseline variables.

Predictors of heart failure

Few studies have examined predictors of HF. In the American study, NHANES I [106], male sex, low education, physical inactivity, smoking, overweight, hypertension, diabetes, valvular disease and ischemic heart disease were independent predictors of developing HF, whereas high s-cholesterol was not. Obesity has been reported to be among the strongest predictors of HF. In recently published analyses from Framingham [30], moderate overweight (BMI 25-30 kg/m^2) was an independent predictor of developing HF among women but not among men. However, those who had BMI over 30 kg/m^2 had twice the risk of developing HF among both sexes, compared to those with normal BMI. A similar risk increase associated with obesity was seen in a Swedish study of middle-aged men [31].

In Paper II of the present thesis, we assessed predictors of HF and, for the sake of competing risks, the combined endpoint of HF or all-cause death. The predictors of HF in Paper II compare reasonably well with those of prior studies, although with some noteworthy differences [30, 106] . Thus, we found that, besides age, strong independent predictors of developing HF among men were high diastolic BP and fb-glucose, as well as smoking, family history of MI and previous CVD. However, among women, the only strong independent predictor of HF was smoking. Interestingly, and in contrast to the Framingham study [30], neither overweight, nor obesity were independent predictors of HF in either sex. However, obesity was a weak independent predictor among women and high BMI (as a continuous variable) was a weak independent predictor of HF among both sexes, and almost qualified as a strong independent predictor among men. Further, in contrast to men, high diastolic BP and s-cholesterol were not independent predictors of HF among women.

Previous studies have shown that diabetes mellitus is an important predictor of CVD and HF among both men and women, although more important among women [32]**.** In contrast, in the present study, high fb-glucose was a strong independent predictor of HF only among men, whereas it was only a weak independent predictor among women, not even independent in the final multivariable model. This could potentially be explained by the relatively young mean age of subjects in our study.

Underweight, high BMI, systolic BP, diastolic BP, eGFR, s-triglycerides and fb-glucose, as well as smoking and previous CVD, were strong independent predictors of combined HF or death among men. In contrast, underweight, high BMI, and systolic and diastolic BP, were not strong independent predictors among women.

Many studies have shown a relationship between decreased eGFR and increased risk of CVD and CVD death [107]. In the present study, eGFR was not at all an independent predictor of HF alone, whereas increasing eGFR was a strong independent predictor of combined HF or death among both women and men. This rather surprising finding may be due to other reasons than actual renal function. S-creatinine poorly reflects renal function in individuals with normal to slightly decreased renal function. Using the MDRD formula, a low s-creatinine results in a high eGFR. However, a low s-creatinine may be due to reduced muscle mass, which may be the true reason for the poor prognosis, e.g. if it is caused by chronic disease. We believe that a low s-creatinine was predominantly a sign of reduced muscle mass in our study. Furthermore, the method of calculating eGFR by the MDRD formula was developed from a study of 1628 patients with chronic renal disease [89]. The appropriateness of this equation to estimate renal function in large groups of patients to study the effect of renal function on cardiovascular risk factors has, however, been debated. Because the MDRD equation was developed from a study that did not include healthy subjects it has raised concern of underestimating GFR in healthier populations.

In a study by Rule et al, of 320 patients with chronic kidney disease and 580 healthy kidney donors, it was reported that the MDRD equation underestimated GFR by 6.2% in patients with chronic kidney disease and by 29 ml/min/1.73 m^2 in the healthy group [108]. Since our patients had normal or close to normal renal function according to the s-creatinine values, it is wise not to draw any firm conclusions regarding the relationship between eGFR and the outcome endpoint of HF or death.

In conclusion, while independent predictors of developing HF were similar to the classical predictors of CVD among men, women differed quite substantially in this regard. This was also largely true for independent predictors of combined HF or all-cause death.
Increasing eGFR was a strong independent predictor of combined HF or death among both women and men. This rather surprising finding may be due to other reasons than actual renal function.

Factors related to heart failure

There exist substantial differences between women and men with HF in the clinical presentation of the disease, as well as in the important HF-related factors B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), peak oxygen consumption (peak-VO2), and LV mass (LVM) [36, 37, 38, 40, 44, 45, 48, 109, 110].

In Paper IV, we investigated these factors separately for women and men. We compared all patients undergoing echocardiography with only those having definite HF according to prespecified echocardiography and clinical criteria

As commonly found in HF studies [23, 26, 36, 37, 38], men more often than women had a history of AMI and CABG, and were more often previous smokers, whereas women had higher LVEF, and more often had treatment for hypertension and a history of respiratory disease, both in the total patient sample and in patients with definite HF. In the total sample as well as among HF patients, women had lower BNP, peak-VO2 and LVM.

Prior studies have observed a higher BNP in healthy female compared with healthy men and concluded that interpretation of natriuretic peptide levels should take into consideration gender and possible age [42].
Our observation that women had lower peak-VO2 than men is supported by previous research [44, 45]. In our study, women had lower LVM than men. This might not be expected, since our patients were elderly and we know that LVM increases in women with aging [40]**.** Thus, LVM tends to become similar in elderly women and men with HF.
The female heart might respond differently to volume and pressure overload compared to the male heart [40]**.** Among rats with HF, males tend to develop dilation whereas females tend to develop myocardial hypertrophy [39]**.** This pattern of response may be related to estrogen, although other possible explanations exist. Androgenic hormones have an anabolic effect on myocytes while estrogen is thought to have antiproliferative effects [39, 40]**.**

In both patient samples, variables independently related to BNP were partly different in women and men. Previous studies have shown that BMI, LVEF, peak-VO2, creatinine and MR are related to BNP [42, 111, 112, 113, 114, 115, 116, 117, 118, 119]**,** but there are no prior studies reporting on gender differences in this regard. We found that LVEF was independently related to BNP in both women and men, irrespective of whether the HF diagnosis was confirmed or not. However, in both samples, peak-VO2 was independently related to BNP only in men. Possibly, women reach their true peak-VO2 to a lesser extent than men. This is somewhat supported by the observation that women had had lower peak-VO2 than men, despite higher LVEF and lower BNP, suggesting less severe HF. A lower muscle mass in women might also be relevant in this regard. In both samples, MR was independently related to BNP only in women and in the total sample, LVM was independently related to BNP only among women. Thus, variations in BNP are strongly related to LVEF in both genders. However, the degree of MR and LVM seem to be more important to the BNP variability in women, whereas peak-VO2 is more important to variations in BNP in men.

In both samples, LV diameter showed an independent relationship to LVEF in both genders. Previous studies have shown that BNP is related to LVEF, and we observed this relationship among both genders in the total patient sample, but not in women with definite HF. This could be partly explained by the observation that women more often had preserved LVEF [36]**.** In both samples, resting heart rate was independently related to LVEF in men, but not in women. This could at least partly be explained by the lower prevalence of atrial fibrillation in women, although not statistically significant.

Not surprisingly, age was independently related to peak-VO2 among both women and men in both samples. Interestingly, peak respiratory exchange ratio was independently related to peak-VO2 among both sexes in the total patient sample, but in neither sex among HF patients. This might be partly due to a different relationship between ventilation and CO2 production in patients with and in those without HF, i.e. different VE/VCO2 slopes [120]. In neither sex, in neither sample, LVEF was independently related to peak-VO2. However, among men in both samples, RV diameter was independently related to peak-VO2, whereas LVM was independently related to Peak VO2 only among female HF patients. Also BMI was independently related to peak-VO2 only among women, and this was observed in both samples. Heart rate was independently related to peak-VO2 only among men; resting heart rate among male HF patients and peak heart rate among men in the total sample.

For both genders, LVM was independently related to LV diameter in both samples and to LA diameter in the total sample. However, among female HF patients LA diameter was not

independently related to LVM. Instead, BMI was independently related to LVM only among women, in both samples. Interestingly, systolic BP was related to LVM only among women in the total sample. This might be related to the greater prevalence of treated hypertension among women, as compared with men. Notably, age was not related to LVM in either sex in either sample. Since women's LVM increases with age, possibly due to the estrogenic and androgenic effects, one might have expected age to be associated with LVM among women [40].

In conclusion, there were several important between-gender differences with regards to BNP, LVEF, peak-VO2 and LVM, both among patients with and among those without confirmed HF. Variables that were independently related to these HF factors, differed importantly between women and men. These findings may help to explain differences between women and men with HF.

Study limitations and strengths

Malmö Preventive Project (MPP) (Papers I and II)

Possible limitation of this study may be that patients with HF without any hospitalisation or death during follow-up were not identified as HF patients. However, it is unlikely that a patient with HF will survive for many years without any hospitalisation. The MPP was launched at the University Hospital in Malmö, which is the only hospital for somatic care in a city of around 280,000 inhabitants .The HF diagnosis, as well as a lack of a HF diagnosis, may not be entirely correct. However, our internal validation suggests that it is largely correct. Furthermore, most patients were diagnosed with HF during the latter years of the study, when the ESC diagnostic criteria were applied and echocardiography
was used almost invariably to verify the HF diagnosis. We did not have general access to data on cardiac function, e.g. LVEF, which also is a limitation. Lastly, we do not know if there was any selection bias of our subjects at the time of inclusion.
Among the strengths of the study are the high attendance rate of 71%, the relatively high number of participating subjects and the relatively long period of follow-up. In addition, the records on hospitalisation and death during follow-up are based on national registers and, therefore, solid and reliable. Another strength is the high internal validity of a HF diagnosis and of a lack of a HF diagnosis. Even if there was a long follow-up, the subjects were still quite young witch is illustrated by the observation that only around 16% of all subjects died during follow-up, 9% of the women and 20% of the men. The predictors may change during life and may be different at a later stage in life. Further, predictors may be different among subjects of a mean age of around 65 years at the time of endpoint assessment, as in the present study, as compared with subjects of a more advanced age. Therefore, our results may not be universally applicable. We have not assessed social, ethnic or educational background of the subjects, which may be regarded as a limitation.

Heart Failure and women study (Papers III and IV)

The validity of our observations, with regard to the comparison between women and men, is likely to be improved by the fact that we included around 50% women, whereas many other

studies, especially the earlier ones, included relatively few women. Furthermore, patients in our study were unselected and consecutively included during the four inclusion periods and they were prospectively followed. Thus there was no selection. However, we applied the inclusion criteria used in the Euro Heart Survey, which may be a limitation. The presence of signs and/or symptoms of HF did not take into account any signs/symptoms prior to the admission. Additionally, this assessment was limited to hospital records and may, therefore, be somewhat imprecise. However, the categorisations of the patients into those with/without a discharge HF diagnosis and into those with/without signs/ symptoms of HF were predefined, prior to study start. Some of the patients, more commonly women, did not undergo an echocardiography examination, which might have affected diagnostic accuracy and outcome analyses, and this is a limitation of the study. In Paper IV, one important limitation is the limited patient sample. Thus, any lack of a significant association between two variables might be due to insufficient statistical power. However, the primary use of F-values to describe associations is one way of reducing this possible error. Another limitation may be that we did not have data on BNP and peak-VO2 in all patients. This was due to practical problems, e.g. some patients could not perform CPX and some BNP samples could not be analysed due to technical problems in the laboratory.

Conclusion

The conclusions of this thesis are:

In a community-based sample of middle-aged subjects, during 22 years of observation, more than 50% of deaths among female and more than 40% in male HF patients were attributable to non-CVD causes, indicating substantial important co-morbidities in these relatively young HF patients. We also found relatively low HF mortality among HF patients of both sexes. MI was the single most common cause of death, significantly more prevalent in male than in female HF patients.

There were significant gender differences with regard to incidence of HF and HF-related mortality; women were less likely to be diagnosed with HF and had substantially lower risk of all-cause and HF-related death. The prognosis among HF patients was poor, with around 25% one-year mortality for both sexes. Women and men were of similar mean age at the time of the diagnosis of HF, but female HF patients had significantly lower CVD mortality risk compared to male HF patients, although all-cause mortality risk did not differ significantly.

These observations differ from those of other epidemiological studies, probably at least partly because of the relatively young mean age of patients. However, the mean age was similar to that of most clinical HF trials, whereas the causes of mortality differed quite substantially from those trials. Our observations may be important to the interpretation and extrapolation of results from clinical trials.

Independent predictors of developing HF in a community-based sample of middle-aged subjects were similar to the classical predictors of CVD among men, but women differed quite substantially in this regard. This was also largely true for independent predictors of combined HF or all-cause death.

Our findings in the sample of patients admitted to hospital for suspect or confirmed HF suggest that women and men with a valid in-hospital HF diagnosis based on contemporary criteria have similar long-term survival, irrespective of LVEF, medication and all other relevant baseline variables. The validity of our observations in this sample, with regard to the comparison between women and men, is likely to be improved by the fact that we included around 50% women and the study was prospectively designed.

Among patients admitted to hospital for suspected or confirmed HF, there were several important between-gender differences with regards to BNP, LVEF, peak-VO2 and LVM, both among patients with and among those without confirmed HF. Variables that were independently related to these HF factors, differed importantly between women and men. These findings may help to explain differences between women and men with HF.

Ethical considerations

In this thesis, the first study primarily involved healthy subject, who were invited to participate in a screening study. These subjects were volunteers and received written information, but they did not have to sign informed consent. At this time (1974), this was not needed for ethical approval.
In the second study the patients were hospitalized at Malmö University Hospital and at Trelleborg Hospital, and received both verbal and written information during the admission. These patients provided written informed consent before proceeding to participate in the study. Also the staff at the departments was informed about the study and the heads of the departments approved the study.
All studies have been conducted according to the Declaration of Helsinki, which states that the patients must be volunteers and well informed of the study and that they can withdraw their consent without any explanation or reprisal.
All data were kept in a secure office and no unauthorised person had access to the data. Every patient received a screening number and data was kept without the patient's personal identification number.
Patients were informed about all abnormal findings during the examinations and were offered different preventive programs according to MPP, and in the Heart failure and women study a physician had responsibility to inform the patients and refer them to different physicians depending on the abnormal findings. The Regional Ethics Committee of Lund/Malmö approved the study protocols.

Future perspectives

Our findings suggest that HF patients included in clinical trials are highly selected and poorly representative to HF patients in general of that age group. There is a need to include a wider range of patients and the proportion of women needs to be increased in large HF studies. If HF studies were to include less selected patients, this could also result in increased knowledge about men, and not only about women. There is also a need to improve the validity of the HF diagnosis, based on contemporary criteria. We need more knowledge about gender differences in the HF pathophysiology and definitely more knowledge about risk factors and other HF related factors. There is a need to increase the proportion of women in large, randomised intervention studies in HF, which might contribute to improved treatment of women with HF. The contemporary understanding is that women should be offered the same diagnostic work up and treatment as men. However, maybe additional knowledge can contribute to an even better care for women and reduce the mortality further, which among HF patients in general is poor. The findings of the present thesis have contributed to improved knowledge in this area.

Summary in Swedish - Sammanfattning på svenska

Hjärtsvikt är ett vanligt förekommande sjukdomstillstånd som drabbar 2-3% av befolkningen och som uppvisar en ökande prevalens. Hjärtsvikt förekommer lika ofta hos män och kvinnor. Trots detta är kunskaperna om detta sjukdomstillstånd till övervägande del baserade på studier av sjukdomen hos män. I kliniska studier utgör kvinnor i regel högst 20-30 % av de studerade individerna. En växande mängd publicerad data antyder att det finns basala skillnader mellan män och kvinnor med hjärtsvikt. Dessa skillnader kan delvis vara betingade av utrednings- och handläggningsolikheter inom sjukvården. Huruvida hjärtsvikt hos män och kvinnor har grundläggande patofysiologiska skillnader är oklart. Det är mycket angeläget att kunskapen om eventuella skillnader mellan könen ökas, för att på ett tillförlitligt sätt kunna erbjuda dessa patienter ett säkert och tillfredsställande omhändertagande samt adekvat behandling.

Denna avhandling bygger på två olika studier. Den första är baserad på ett stort befolkningsmaterial från studien Malmö Förebyggande Medicin, bestående av 33,342 medelålders friska frivilliga individer, varav 10,900 (32.7%) är kvinnor.

De två första artiklarna baseras på detta material.

Arbete I beskriver könsaspekter på incidens av och mortalitet i hjärtsvikt med en uppföljningstid på ca 22 år. Vi fann att kvinnor hade lägre hjärtsviktsincidens och lägre risk för död samt hjärtsviktrelaterad död jämfört med män. Bland de 764 (120 kvinnor) individer som utvecklade hjärtsvikt under uppföljningstiden var dödligheten hög för bägge könen, med ca 25 % 1-årsdödlighet. Hjärtinfarkt var den vanligaste enskilda orsaken till död, speciellt vanlig hos män. Kvinnor hade lägre kardiovaskulär dödlighet jämfört med män, men det var ingen signifikant skillnad mellan könen för död totalt sett. Orsaken till död hos dessa hjärtsviktspatienter var till stor del icke kardiovaskulär; mer än 50 % av kvinnorna och mer än 40 % av männen dog av icke-kardiovaskulära orsaker.

Arbete II beskriver könsskillnader i prediktorer för insjuknande i hjärtsvikt och kombinerad hjärtsvikt eller död. Vi fann att oberoende prediktorer för utveckling av hjärtsvikt hos män liknande de klassiska prediktorerna för utveckling av kardiovaskulär sjukdom, men hos kvinnorna var det inte så.

Den andra delen av avhandlingen bygger på ett material av patienter med redan befintlig hjärtsvikt, antingen misstänkt men obekräftad hjärtsvikt, eller bekräftad hjärtsvikt s.k. Hjärtsvikt och kvinnor-studien.

De två sista artiklarna baseras på detta material.

Arbete III beskriver skillnader i överlevnad mellan män och kvinnor som vårdats på sjukhus för misstänkt eller verifierad hjärtsvikt. Dessa 930 patienter varav 465 kvinnor, delades upp i fyra grupper; (1) de som hade en verifierad hjärtsviktsdiagnos i epikris vid utskrivningen, (2) de som hade symptom/tecken på hjärtsvikt, (3) de som inte hade hjärtsviktdiagnos, samt (4) de som inte hade symtom/tecken på hjärtsvikt. Vi fann att prognosen var dålig för alla patienter, men kvinnor och män med hjärtsviktsdiagnos eller symptom/tecken på hjärtsvikt hade likvärdig överlevnad under ca fyra års uppföljning. Diagnosen baserades på nutida hjärtsviktskriterier (Europeiska Cardiologföreningens kriterier för hjärtsvikt) och resultatet

avseende överlevnad var oberoende av vänster hjärtkammares ejektionsfraktion, farmakologisk behandling och alla uppmätta variabler vid studiestart som kunde påverka överlevnaden.

Arbete IV, beskriver skillnader mellan könen avseende viktiga faktorer relaterade till hjärtsvikt, samt variabler relaterade till dessa faktorer, dels bland patienter med misstänkt hjärtsvikt, dels bland patienter med säkerställd hjärtsvikt. Patienterna genomförde ultraljudsundersökning av hjärtat, arbetsprov med mätning av maximal syreupptagningsförmåga och tog blodprover där bl a Brain natriuretisk peptid (BNP) ingick. Dessa patienter delades i två grupper; (1) alla de som utförde ultraljudsundersökning av hjärtat och (2) endast de som hade hjärtsvikt enligt förutbestämda kriterier baserade på kliniska iakttagelser och ultraljudsundersökning av hjärtat. Vi undersökte vilka variabler som var oberoende relaterade till BNP, maximal syreupptagningsförmåga, vänster hjärtkammares massa samt vänster hjärtkammares ejektionsfraktion (ett mått på pumpförmåga).
Vi fann att kvinnor i bägge grupperna hade lägre BNP, maximal syreupptagningsförmåga och massa för vänster hjärtkammare, men att de hade högre ejektionsfraktion för vänster hjärtkammare. Vi fann också att variabler som var oberoende relaterade till dessa hjärtsviktsfaktorer skiljde sig signifikant mellan könen.

Sammanfattningsvis redovisar avhandlingen potentiellt viktiga fynd vad gäller könsaspekter på hjärtsvikt. Detta område är högaktuellt för närvarande men vi har lite kunskap inom fältet. Arbete I och II bidrar med potentiellt viktig kunskap om epidemilogi bland individer som är yngre än den genomsnittliga hjärtsviktspopulationen, men som är i samma ålder som patienter ingående i de flesta större vetenskapliga studier av behandling av hjärtsvikt. Flera fynd har inte tidigare varit kända. Arbete III och IV redovisar flera potentiellt viktiga fynd avseende skillnader mellan könen i prognos vid hjärtsvikt, samt ger ny kunskap om möjliga orsaker till könsskillnader i den kliniska presentationen av hjärtsvikt.

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