Aspects of heart failure development and prevention in women

Anna-Karin Halldin

Department of Primary Health Care, Institute of Medicine at
Sahlgrenska Academy, University of Gothenburg

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anna-karin.halldin@gu.se

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To my family

Abstract

Background:
Heart failure (HF) is a severe progressive condition with physical and cognitive suffering for the patient. There are differences in the HF spectrum, as HF is not a homogeneous condition, but rather is heterogeneous and differs between men and women. Women more often are older and suffer from heart failure with preserved ejection fraction (HFpEF), in contrast to men who more often are younger and suffer from heart failure with reduced ejection fraction (HFrEF). There are differences between male and female cardiac responses to various underlying conditions resulting in the different phenotypes of HF. As most previous research was conducted on male HF patients and in a hospital setting, the results may not be fully applicable for the care of women with HF in the primary care context.

Aim:
The overall aim of the thesis was to investigate aspects of risk factors for the development of heart failure in women.

Methods:
Two population studies conducted in Gothenburg Sweden, "The Prospective Population Studies of Women" (PPSWG) and "The Gerontological and Geriatric Population Studies in Gothenburg" (H70), were used. Women were longitudinally followed with questionnaires, laboratory tests and physical examinations on several occasions from 1968 to 2016. Paper I prospectively studied the impact of obesity/overweight on the risk of developing HF in women of different ages. Paper II was a prospective study, investigating whether a change in the level of physical activity or Body Mass Index (BMI) had any impact on risk of developing HF in women. Paper III was a prospective cohort study, investigating the impact of triglycerides and cholesterol levels on the future risk of HF development in 50-year-old women. Paper IV studied secular trends in important cardiovascular risk factors for HF by comparison of five representative cohorts of 38- and 50-year-old women over a period of 48 years.

Results:
Obesity in younger and middle ages proved to be a risk factor for later HF, but not so for older women. Being physically active in both younger and older ages protected against development of HF. Increased level of physical activity in older ages was protective. Increased triglyceride levels but not cholesterol in 50-year-old women were associated with the development of later HF. Most risk factors for HF in women showed a decreasing pattern for later born cohorts, but BMI, mental stress and frequency of depressive symptoms increased in some of the cohorts.

Conclusion:
A healthy lifestyle is of great importance for reducing the risk of developing HF in women. Different preventive measures have different impacts on HF development in women of different ages. It is important to focus on the most effective primary prevention means, especially since there is a lack of medical treatment proven to reduce mortality and morbidity in the heart failure phenotype most prevalent in women.

Keywords:
Women, heart failure, obesity, physical activity, population study, risk factor, prevention, mental stress, serum triglycerides, serum cholesterol.

Sammanfattning på svenska

Hjärtsvikt är ett allvarligt progredierande tillstånd som orsakar fysiskt och kognitivt lidande för patienten. Det finns skillnader i hjärtsviktsspektrumet mellan män och kvinnor. Hjärtats kompensatoriska mekanismer skiljer sig åt hos kvinnor och män vilket resulterar i olika fenotyper av hjärtsvikt. Kvinnor är oftare äldre och utvecklar fenotypen hjärtsvikt med bevarad pumpförmåga, till skillnad från män, som oftare utvecklar hjärtsvikt i yngre åldrar med fenotypen hjärtsvikt med nedsatt pumpförmåga. Eftersom de flesta tidigare studier avseende hjärt-kärl sjukdomar har gjorts med manliga deltagare som vårdats på sjukhus, vilka skiljer sig från patientgruppen kvinnor i primärvården, kanske de resultaten inte är relevanta för hjärtsvikt hos kvinnor i primärvården.

Syftet med denna avhandling var att undersöka olika riskfaktorers samband med hjärtsviktsutveckling hos kvinnor.

Detta arbete är baserat på två befolkningsstudier som genomförts i Göteborg, Sverige, ”The Prospective Study of Women in Gothenburg” (PPSWG), och ”The Gerontological and Geriatric Population Studies in Gothenburg” (H70). Kvinnor följdes över tid från 1968 till 2016 med frågeformulär, laboratorieundersökningar och läkarundersökningar, vilket ger en stabil bas på vilken denna avhandling vilar.

Studie I: I denna studie undersökte vi samband mellan övervikt / fetma och utveckling av hjärtsvikt hos kvinnor av olika åldrar.

Studie II: Denna studie utröner samband mellan fysisk aktivitet, förändring i fysisk aktivitetsnivå och Body Mass Index (BMI) å ena sidan, och utveckling av hjärtsvikt hos kvinnor i olika åldrar.

Studie III: I denna studie undersöks samband mellan triglycerid- och kolesterolvärden hos 50-åriga kvinnor och senare utveckling av hjärtsvikt.

Studie IV: Denna studie belyser sekulära trender av kardiovaskulära riskfaktorer genom att jämföra fem kohorter av 38- och 50-åriga kvinnor under en tidsperiod av 48 år.

Resultat:
Förekomst av fetma hos yngre och medelålders kvinnor visade sig vara en riskfaktor för utveckling av hjärtsvikt men hos äldre kvinnor kunde detta samband inte ses. Att vara fysiskt aktiv genom hela livet både hos yngre och äldre kvinnor visade sig skydda mot framtida utveckling av hjärtsvikt, likaså ökad nivå från stillasittande till att vara fysiskt aktiv var associerat med minskad risk för utveckling av hjärtsvikt hos äldre kvinnor. Triglycerider, men inte kolesterol hos 50-åriga kvinnor var associerat med framtida utveckling av hjärtsvikt. Flera viktiga riskfaktorer för hjärtsviktsutveckling har minskat över tid. Däremot ses en ökning av stress, depression och BMI hos några grupper.

Slutsatser:
Sammanfattningsvis är hälsosam livsstil av stor betydelse för att minska risken för framtida hjärtsviktsutveckling hos kvinnor. Olika förebyggande aktiviteter har olika effekt på risken att utveckla hjärtsvikt hos kvinnor i olika åldrar. Det är därför viktigt att fokusera på de mest effektiva förebyggande faktorerna för respektive person. Detta är speciellt angeläget eftersom det saknas farmakologisk behandling som minskar dödlighet och sjuklighet för fenotypen av hjärtsvikt som är vanligast förekommande hos kvinnor.

List of papers

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

I. Halldin A-K, Schaufelberger M, Lernfelt B, Björk L, Rosengren A, Lissner L, Björkelund C.

Obesity in Middle Age Increases Risk of Later Heart Failure in Women - Results from the Prospective Population Study of Women and H70 Studies in Gothenburg, Sweden.

J Card Fail. 2017;23(5):363-369

II. Halldin A-K, Lernfelt B, Lissner L, Björkelund C.

Impact of changes in physical activity or BMI on the risk of heart failure in women - the prospective population study of women in Gothenburg.

Scand J Prim Health Care. 2020; 38(1): 56-65.

III. Halldin A-K, Lissner L, Lernfelt B, Björkelund C.

Cholesterol and triglyceride levels in midlife and risk of heart failure in women, a longitudinal study - the Prospective Population Study of Women in Gothenburg.

Submitted to BMJ open 28 Dec 2019

IV. Halldin A-K, Lissner L, Hange D, Lernfelt B, Björkelund C.

Secular trends in cardiovascular risk factors with particular regard to heart failure in 38-and 50-year-old women - The Prospective Population Study of Women in Gothenburg.

In Manuscript.

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Abbreviation

List of abbreviations

ACE-inhibitors	Angiotensin converting enzyme inhibitors
AHA	American Heart Association
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EPIC	European Prospective Investigation into Cancer and Nutrition
GP	General Practitioner
HF	Heart Failure.
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HFSA	The Heart Failure Society of America
HR	Hazard Ratio
H70	Gerontological and Geriatric Population Studies in Gothenburg.
ICD	International Classification of Diseases
IHD	Ischaemic Heart Disease

HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
MET	Metabolic Equivalent
NO	Nitric Oxide
NT-ProBNP	N-Terminal-prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PPSWG	Prospective Population Study of Women in Gothenburg.
RAAS	Renin-Angiotensin-Aldosterone system
RALES	Randomized Aldosterone Aldactone Evaluation Study
RCT	Randomized Clinical Trials
ROS	Reactive oxygen species
SCORE	Systematic Coronary Risk Estimation
SES	Socioeconomic Status
UCG	Ultrasonic Cardiography (echo cardiography)
WHO	World Health Organization
WHR	Waist Hip Ratio

1. Introduction

The lifestyle of today plays an important role in the development of various health conditions, such as diabetes type 2, mental health disorders, some cancers and cardiovascular disease. In health care, great advances have been made in the medical treatment of cardiac diseases, resulting in individuals living longer with their cardiovascular condition (1-7). Another approach is to focus on prevention in order to reduce the incidence of these conditions on the population level. A healthy lifestyle reduces the risk of developing ischaemic heart disease in women, and recent studies on heart failure in women show similar results (8, 9).

Women are often inadequately represented in heart failure studies. Women are also, compared to their male counterparts, to a lesser extent diagnosed correctly by means of echocardiography (10-13), which is the most preferable method to diagnose and assess heart failure (5, 14). Furthermore, it appears that heart failure in women differs somewhat from heart failure in men.

We thus find it important to study heart failure in women, to better understand the condition, and to better provide the best possible primary and secondary prevention and treatment within health care, and particularly in primary care, where most non-acute onset heart failure patients are diagnosed and treated. Approximately 20% of patients with heart failure are diagnosed and treated exclusively in primary care (15, 16). Most older people are cared for by primary care physicians, and heart failure is common among older people. In addition to this, primary care physicians carry out follow-ups of patients who have been hospitalised for heart failure and also heart failure patients who have been referred from cardiology wards to primary care. Moreover, in the general population, a proportion of individuals are at risk of developing heart failure and these individuals are most often seeking primary health care. Summing up, the general practitioner encounters a wide spectrum of heart failure patients, and it is of utmost importance to possess the best knowledge and competence to meet their needs and to give the best possible care.

This thesis focuses on identifying important modifiable risk factors for future development of heart failure in women, as well as which changes in the lifestyle-related risk factors are the most important for reducing future risk of heart failure.

In addition, we study secular trends in these risk factors for heart failure, in order to understand the shift in these risk factors over time, thereby laying the groundwork for taking appropriate health care measures.

1.1 Definition of heart failure

Heart failure is a condition of structural or functional abnormality of the ventricular filling- or ejection capacity, resulting in an inability to provide sufficient amount of oxygenated blood needed by the body. The clinical syndrome of heart failure comprises typical symptoms of breathlessness and fatigue. Furthermore, the clinical symptoms may be accompanied by objective findings such as swelling of the ankles and elevated jugular venous pressure. The 2016 European guidelines for the diagnosis and treatment of acute and chronic heart failure acknowledge three subgroups of heart failure.

I. Heart failure with reduced ejection fraction (HFrEF), with an ejection fraction < 40%.

I. Heart failure with midrange ejection fraction (HFmrEF), with an ejection fraction between 40-49%.

II. Heart failure with preserved ejection fraction (HFpEF), with an ejection fraction ≥50%.

The ejection fraction (EF) equals the volume of blood ejected from the left ventricle divided by the total left ventricular end diastolic volume.

$$EF(\%) = \frac{Volume\ ejected\ by\ left\ ventricle\ (ml)}{Total\ left\ ventricular\ end\ diastolic\ volume\ (ml)} \times 100$$

1.2 Pathophysiology and prevalence of heart failure.

Pathophysiology of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)

The most common aetiology of HFrEF is previous myocardial infarction with scarring of the myocardium resulting in reduced ejection fraction, reducing cardiac output. Reduced cardiac output will activate the Renin-Angiotensin-Aldosterone system (RAAS) and levels of angiotensin II and aldosterone increase. This in turn results in vasoconstriction by angiotensin II, and increased sodium retention by aldosterone as compensatory mechanisms. When this situation is prolonged, as in chronic heart failure, a vicious circle occurs, in which vasoconstriction increases the blood pressure and the afterload, and fluid retention increases the preload. The result is a total increase in the workload on the heart, further reducing the cardiac output, feeding the vicious circle, and finally pulmonary oedema may occur (Figure I).

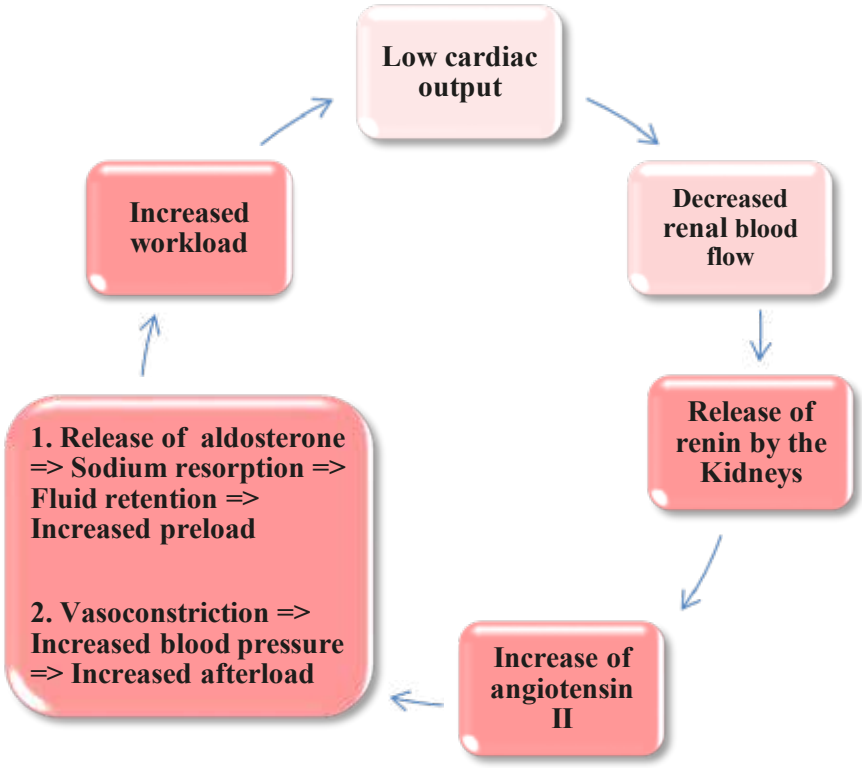

Figure I. Vicious circle of heart failure with reduced ejection fraction.

The aetiology of HFpEF is more complex, with several underling possible conditions such as obesity, diabetes, age, microvascular dysfunction and endothelial dysfunction. The ultimate result will be stiffening of the left ventricle, increased left ventricular filling pressure, reduced filling of the left ventricle and enlarged left atrium, all signs of diastolic dysfunction, finally resulting in low cardiac output and possibly pulmonary oedema (Figure II)

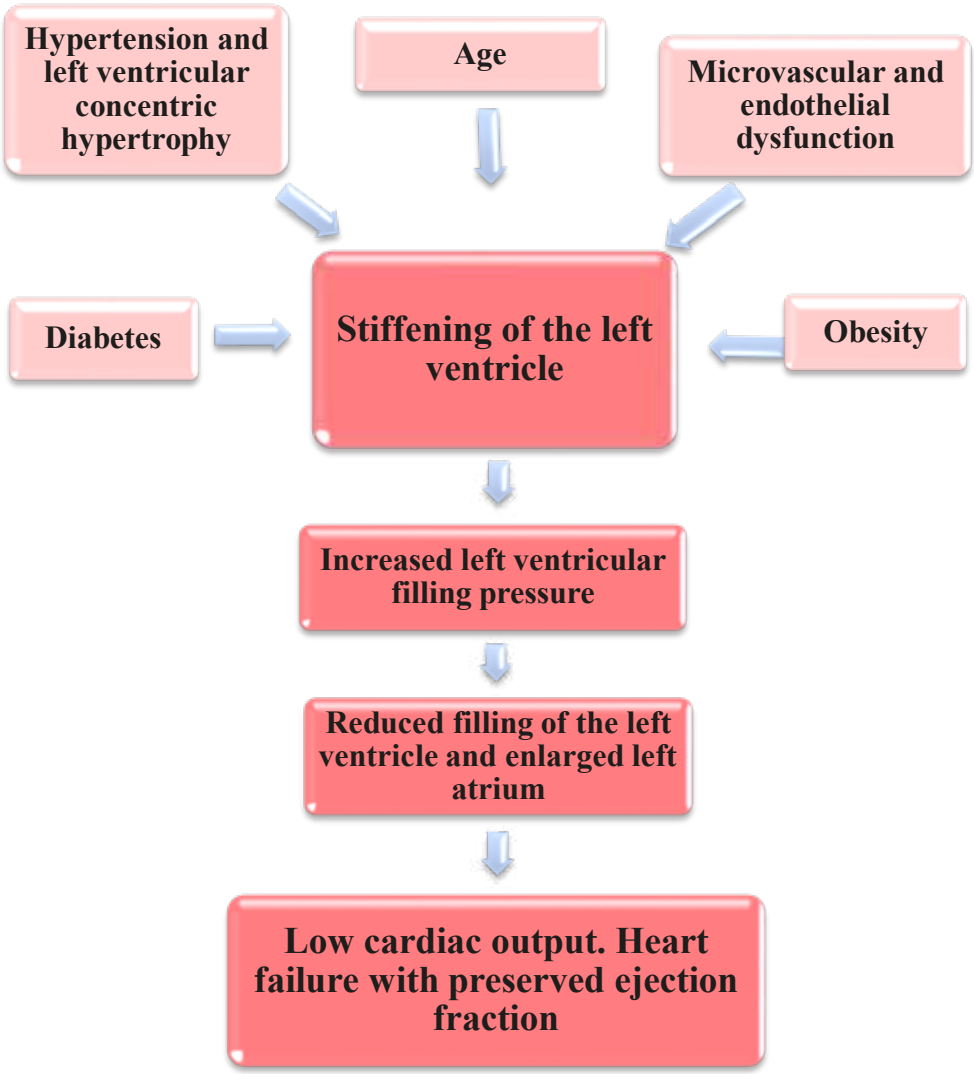

Figure II Pathophysiology of HFpEF

Severity of symptoms is most commonly classified according to the classification of the New York Heart Association (NYHA).

NYHA 1: No limitation of physical activity. No experience of dyspnoea, fatigue or palpitation during ordinary physical activity.

NYHA 2: Slight limitation of physical activity. Slight experience of dyspnoea, fatigue or palpitation during ordinary physical activity. No symptoms at rest.

NYHA 3: Moderate limitation of physical activity. Experience of dyspnoea, fatigue or palpitation during less than ordinary physical activity. No symptoms only at rest.

NYHA 4: Severe limitation of physical activity. Experience of dyspnoea, fatigue or palpitation at rest. Increase of symptoms at minimal physical activity.

Prevalence of heart failure

Heart failure is a progressive condition, which over time will affect the patient´s physical and cognitive capacity. The prognosis is poor, even worse than some of the most common cancers (17-22). In developed countries, the prevalence of heart failure is estimated to be 2% (23). Because of lack of population-based studies, there are difficulties in estimating the prevalence of heart failure in developing countries (24). According to The European Society of Cardiology, at least 15 million people in Europe suffered from heart failure in 2008 (25). In a policy statement from the American Heart Association (AHA), heart failure prevalence is predicted to increase from 2.42% in 2012 to 2.97% in 2030, meaning that in 2030 there will be over eight million heart failure patients in the United States (26). The Rotterdam study demonstrated an overall prevalence of heart failure of 3.9% in the general population of 55 years or above (27). A Swedish study showed a heart failure prevalence of 2.2% in the Stockholm area (15). Heart failure is a very age-dependent condition, and the prevalence increases with age up to 8.4% for people who are 75 years or older (28). It is estimated that about 50% of all heart failure patients have HFpEF (29). A meta-analysis of 28 articles including community dwelling people 60 years of age or older showed that the median prevalence rate

of all type heart failure was 11.8%, while the median prevalence rate of HFpEF and HFrEF was 4.9% and 3.3% respectively. The prevalence trends were rising for HFpEF and declining for HFrEF (30). One important reason for this is the demographic shift in the population towards older ages. There have also been great advances in the treatment of cardiovascular diseases, both invasive and non-invasive treatment during the last decades, and, as a result of this progress, people are now living longer with their cardiovascular conditions (1-6, 31). There may also be epidemiological changes in risk factors that affect and increase the incidence and prevalence of heart failure.

1.3 Lifestyle and cardiac disease

The lifestyle of today plays an important role in the development of various health conditions, such as diabetes type 2, mental health disorders, such as depression and anxiety, some cancers and cardiovascular disease. Primary prevention should be the area to focus upon to reduce the incidence of these conditions for the benefit of the population. It is well known that a healthy lifestyle reduces the risk of developing ischaemic heart disease (IHD), and recent studies on heart failure show similar results (8, 9).

1.3.1 Overweight and obesity

In the general population, obesity is a known risk factor for mortality (32, 33). Obesity has also been reported to be a risk factor for mortality in the older population for both men and women, but especially in obese men (34). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, severe obesity but not overweight was associated with increased mortality in women above 65 years of age (35). On the other hand, one meta-analysis reported an association between first grade obesity and no increased mortality, both for people above 65 years of age and for mixed ages, 25-64 years of age or 40-80 years of age (32). This may be an example of the so called “obesity paradox” where

overweight and mild obesity are more advantageous concerning mortality as compared to having a normal weight.

In both men and women, there is an association between obesity and overweight and an increased risk of heart failure (36), and causality between obesity and heart failure has been reported (37). Women in the early stages of obesity but free of any other pathological condition showed evidence of subclinical ventricular diastolic dysfunction that was correlated to BMI (38). There are also several studies describing a heart failure obesity paradox where mortality of obese patients with established heart failure is lower than mortality of lean patients with heart failure (39, 40).

Obesity is increasing in the general population in Sweden. Results from the Public Health Agency of Sweden concerning overweight and obesity trends between 2006 and 2018 published in 2019 revealed an increase in obesity frequency in the population from 5% to 7% in women and from 6% to 10% in men aged 16-29 years, and from 11% to 14% for both men and women aged 30-44 years (41).

There is a gap in knowledge concerning the relationship between overweight/obesity and the development of heart failure in women of different ages, since older individuals tend to have higher fat mass for a given BMI (42). Therefore, it is of great importance to study the significance of obesity and overweight in relation to the development of heart failure in women of different ages.

1.3.2 Physical activity

Low physical activity has been shown to be a risk factor for heart failure in both men and women (43-45). Further, the risk of developing heart failure in women has been shown to be reduced by physical activity (9). A dose-dependent relationship of higher levels of leisure time physical activity and lower risk of HFpEF, but not for HFrEF has been demonstrated (46). Heart failure patients with a high cardiorespiratory fitness do not exhibit the obesity paradox, in which obese and overweight heart failure patients have a lower mortality than heart failure

patients with normal weight. That is, regardless of BMI, heart failure patients with a high cardiorespiratory fitness demonstrate a very good survival compared to heart failure patients with low cardiorespiratory fitness (47). Reduced risk of all-cause mortality or hospitalisation is present for women with heart failure who exercise compared to women with heart failure and no exercise, and women also had more benefit of exercise training compared to men (8). Thus, physical activity plays an important role in the spectrum of heart failure in women, but whether a change in physical activity over time has an impact on the risk of developing heart failure in overweight or obese women without a previous history of cardiac disease or heart failure has not been thoroughly studied.

1.4 Use of biomarkers for diagnosis and prevention

The use of biomarkers is a very important component in the daily work of the general practitioner. With the help of biomarkers, the general practitioner can often distinguish between disease and non-disease, estimate the risk of developing a certain disease or follow the progression of a disease or its treatment. Systematic Coronary Risk Estimation (SCORE) is an instrument developed for risk stratifying, which estimates the 10-year mortality risk of cardiovascular disease, and is based on blood pressure level, serum cholesterol level, age, gender and smoking. Low Density Lipoprotein (LDL) level is a well-known biomarker for the risk of IHD as well as a tool to evaluate the effect of lipid lowering treatment. N-Terminal-prohormone of B-type natriuretic peptide (NT-ProBNP) is a biomarker which is easily accessible by blood sample and therefore useful for the general practitioner to evaluate whether a patient may suffer from heart failure or not. A normal level of NT-ProBNP may be used to rule out the heart failure diagnosis because of its high negative predictive value, whereas an elevated level indicates a possible heart failure diagnosis and calls for further assessment (5). However, there are some conditions that need to be considered when evaluating the NT-ProBNP level. NT-ProBNP increases with age, with renal dysfunction and may also be slightly elevated in patients with chronic obstructive pulmonary disease (COPD) and in patients with atrial fibrillation. This is especially important in the primary care setting where the cut off level of NT-ProBNB is lower than in an acute decompensated situation in the emergency setting at the hospital. Primary care patients are often elderly and have some degree of renal dysfunction. Patients with COPD and patients with atrial fibrillation are also common in primary care,

and thus, evaluating the slightly elevated NT-ProBNP becomes a delicate task. The prevalence of atrial fibrillation is at least 2.9 % of the Swedish adult population (48). A cross-sectional study in a primary care setting in Stockholm including individuals 70-74 years old showed a prevalence of 12% (49). The prevalence in the general population of COPD stage I in the Uppsala region in Sweden was reported to be 16% (50). On the other hand, obese patients often have a lower value of NT-ProBNP and therefore a lower cut off value may be considered for these patients. Patients with HFpEF also generally show a lower value of NT-ProBNP than patients with HFrEF, which makes it difficult to accurately recognise the condition. In the primary, non-acute setting, a NT-ProBNP level of 125 pg/ml is considered the cut off value; in the acute setting the cut off value is 300 pg/ml. Results below these cut off levels exclude the heart failure diagnosis (5).

According to current knowledge, there is no acknowledged suitable specific biomarker for estimating the risk of heart failure comparable to LDL levels and the risk of IHD. In one study, based on the Framingham Heart Study, dyslipidemia was correlated with an increased risk of heart failure (51), and another study showed that in patients hospitalised for HFrEF, low triglycerides at discharge predicted worse outcome than hospitalised heart failure patients with higher levels of triglycerides at discharge (52). The same results were also reported in a study of heart failure outpatients; low levels of serum triglycerides compared to higher levels predicted higher risk of mortality (53). Whether there is a correlation between serum triglycerides or serum cholesterol and future risk of heart failure in healthy women without previous cardiac disease has not been thoroughly investigated.

1.5 Aging population

The population of Sweden is growing older. According to the Swedish Central Bureau of Statistics, the average life expectancy in Sweden may increase around seven years for men and five years for women until 2060, with the average life expectancy for men almost 87 years and for women almost 89 years at that time (54). As we grow older, we are more prone to illness and disease. Because of the advances in the medical treatment of cardiovascular diseases, patients now grow older with their cardiovascular condition (1-7). On the other hand, there are indications of improvements in general health over time. Physical activity habits

have improved (55, 56). However, an assessment of cardiac function with various techniques and in-hospital treatment is costly. Heart failure imposes a great burden on hospitalisation (57) and on the economy (58), thus highlighting the importance of the condition.

1.6 Primary care

Primary care is the first line of health care. Patients seek their general practitioner because of diffuse, and not very distinguishable symptoms. It is the role of the primary care general practitioner to evaluate these symptoms and either diagnose and treat the patient correctly or to refer the patient to the secondary care level for further evaluation. Often, early symptoms of heart failure in women are non-specific and may mimic other conditions, for example pulmonary disorders, or just feeling out of shape. Sometimes the patients adjust their daily life to their reduced physical capacity and the heart failure diagnose is delayed. With greater knowledge about heart failure and risk factors for heart failure in women, the general practitioner will be better equipped and have greater opportunities to help their female patients, whether it concerns reducing the risk of future development of heart failure with lifestyle improvements, or to treat her with the best medical treatment available. Primary care is involved in many phases of a woman´s life – already from early childhood at the children's welfare clinic, through antenatal and postnatal care, besides ordinary health care consultations. Thus, there are numerous personal meetings and great possibilities for preventive as well as diagnostic work. All inhabitants in Sweden have around 42 million personal contacts with primary care every year, whereof around 32% (14 million) are visits to general practitioners (59).

1.7 Gender differences in heart failure

1.7.1 Differences in cardiovascular pathophysiology in men and women

UCG when performed in women with heart failure shows that they tend to have preserved left ventricular ejection fraction and a smaller left ventricular end diastolic volume compared to men, even after adjusting for body size (10, 60, 61).

Structure and function of the left ventricle differ between men and women. This may be caused by different remodeling of the left ventricle in men and women, as a response to elevated systolic blood pressure. Women´s hearts develop concentric hypertrophy as opposed to men´s hearts, where eccentric hypertrophy prevails (62). Hence, stroke volumes in women are smaller compared to stroke volumes in men. Women on the other hand have a slightly higher heart rate than men, resulting in an adequate cardiac output.

With increasing age, the diastolic and systolic stiffness increases in both men and women, but the increase is steeper in women compared to men (63). This is also true for the relationship between arterial stiffness and left ventricular diastolic dysfunction shown by a stronger correlation between augmentation index and left ventricular diastolic dysfunction in women than in men (64).

Because of the smaller left ventricle, further enhanced by concentric remodelling, in addition to the higher ventricular stiffness and higher degree of diastolic dysfunction in women (65), they are more dependent on heart rate to maintain an adequate cardiac output. Maximal heart rate decreases with age, and this chronotropic effect enables heart failure symptoms to emerge, especially during exercise where the combination of reduced ventricular volume, reduced contractile and chronotropic reserve together result in a cardiac output too low to

meet the demands of exercise, revealing exercise intolerance, a hallmark of HFpEF.

There are also differences in coronary artery disease between men and women. Men are more likely to suffer from obstructive coronary artery disease in the larger epicardial coronary vessels (66, 67), with subsequent myocardial infarction and subsequent HFrEF, while women predominantly show microvascular dysfunction. Microvascular dysfunction is highly prevalent in patients with HFpEF (68) and contributes to the pathophysiology of HFpEF. One important factor is impaired endothelial function that is driven by low grade systemic inflammation (69). Non-cardiac comorbidities especially prevalent in women with HFpEF such as hypertension, obesity, diabetes, and iron-deficiency are all associated with low-grade systemic inflammation. This low-grade inflammation induces oxidative stress in the vascular system where the microvascular endothelial system of the heart increases the production of endothelial reactive oxygen species (ROS). Increased levels of ROS lead to reduced available levels of endothelial nitric oxide (NO). Low NO availability leads through additional signalling pathways to cardiomyocyte hypertrophy and conversion of fibroblast to myofibroblasts and the deposition of collagen in the interstitial space, ultimately resulting in hypertrophic myocardium interspersed with fibrotic tissue giving a thick stiffened left ventricular wall (69). Reduced levels of endothelial NO also affect the vasodilatory capacity of the arteries negatively.

On the other hand, even though coronary artery disease is less common in women, when it is present, it poses a greater risk for heart failure in women than hypertension (43). Diabetes is one of the most important risk factors for coronary artery disease in women and may thereby indirectly increase the risk of heart failure in women (70, 71).

1.7.2 Representativeness of women in heart failure studies

Enrolment of women in randomized clinical trials (RCT) of cardiovascular disease has increased over time but is still not sufficient to correspond to the proportion of women in the population with the condition of interest. This is especially true for

heart failure, where women's participation only amounts to approximately 30% of the study population, whereas women account for about 50% of all patients with heart failure (72, 73). In more recent studies of heart failure, the overall representation of women in heart failure clinical trials remains at ~30% and has not increased further. In studies of HFpEF solely, the participation of women was higher, i.e. in clinical trials 56% and in epidemiological studies 62% (74). Some of the contributing reasons for the underrepresentation of women in most clinical trials may be inadequate strategies for recruiting women to heart failure studies, or the investigators may not ask the questions, or study the variables relevant to women's cardiac health due to the history of focusing on male cardiac disease. One study pointed out that women perceived higher risk of harm than benefit from participating (75). Heart failure studies that were conducted on HFrEF automatically excluded women with HFpEF. Elderly heart failure populations where women are prevalent also carry more comorbidities which exclude these women from clinical trials. In addition, since cardiovascular disease, including heart failure, affects women later in life compared to men, earlier studies with specific younger age cut offs result in exclusion of women (76).

1.7.3 Heart failure in men and women

Women represent 50% of the total heart failure population, but the aetiology of heart failure differs somewhat in men and women, resulting in the two major phenotypes of heart failure, HFrEF and HFpEF. Depending on the setting and cut-off value of EF for HFpEF, most studies report that HFpEF accounts for approximately 50% of the total heart failure population (18, 29, 77, 78).

A large body of epidemiological studies report that HFpEF patients are more likely to be older and to be female than male (18, 29, 77-84), but previous studies also have reported equal cumulative incidence of HFpEF and HFrEF (85-88) in women. The gender differences in HFpEF and HFrEF prevalence are mainly driven by age and the dominance of male cumulative incidence of HFrEF. HFrEF is more prevalent in males, and the main underlying aetiology is ischaemic

heart disease with obstructive coronary artery disease and previous myocardial infarction (85, 89).

However, men and women with heart failure present with similar symptoms. Nevertheless, for both HFpEF and HFrEF, women tend to experience higher burden of symptoms with more dyspnea, peripheral oedema, orthopnea, rales, fatigue and worse quality of life compared to men (61, 89-91).

1.7.4 Comorbidities in men and women with heart failure

Men and women have similar numbers of comorbidities, but patients with HFpEF have on the average one more comorbidity compared to patients with HFrEF.

In women with heart failure compared to men with heart failure, hypertension is more prevalent both in HFpEF and HFrEF (61, 89, 92). A history of valvular disease is more associated with heart failure in women than in men (93, 94), and also thyroid disease is more prevalent in women than in men with heart failure (93, 95). Compared to men, anaemia is more prevalent in female heart failure patients (93), and iron deficiency is more prevalent in women than men with acute decompensated heart failure both in HFpEF and in HFrEF (96, 97). Arthritis is more prevalent in women than in men, and findings have shown an increase in incident rate ratio in heart failure which was slightly more pronounced for women than for men (98). Obesity has been shown to be associated with heart failure in both women and men (99, 100), and obesity is more prevalent in women with heart failure than in men with heart failure for both HFpEF and HFrEF (61, 89). Depression is more common in women than in men and more common in HFpEF compared to HFrEF (101). Atrial fibrillation has a stronger association with new-onset HFpEF in women compared to men (88).

In men, important comorbidities are coronary artery disease and atrial fibrillation, both for HEpEF and HFrEF (61, 89, 92). Idiopathic dilated cardiomyopathy is more associated with heart failure in men than in women (102-106).

A large register study of heart failure found the prevalence of COPD to be ~29% in both men and women, another register study reported COPD prevalence of 29% in men and 26% in women, and the Euro Heart Failure Survey II reported higher prevalence in men, i.e. 22% compared to women 15% (93, 107).

Diabetes is more frequently reported in heart failure register studies compared to prospective randomized trials (107) and is more prevalent in hospitalised patients than in outpatients, but shows no consistent gender differences or differences between HFpEF and HFrEF (61, 89, 92).

1.7.5 Diagnosis, management and medical treatment of heart failure

The management of heart failure patients differs depending on the setting, and there are also gender differences in the management of the patients. In many cases, women are not diagnosed correctly, i.e. by means of echocardiography (UCG). UCG is included in the European and the United States guidelines (5, 14) as the most preferable method to diagnose and assess heart failure. One Swedish study of heart failure patients in primary care showed that echocardiography was performed in only 31% of the patients and that it was performed to a lesser extent in women than in men. This study also showed that women received less effective medical treatment compared to men, both concerning choice of medical treatment and dosage (11). Studies in the primary care setting in Poland and Italy reported that among patients with chronic heart failure, women were not as frequently assessed by echocardiogram as men (12, 13). Another study, based on heart failure patients participating in the Euro Heart Survey on Heart Failure, confirmed that women to a lesser extent compared to their male counterparts were evaluated with echocardiogram, were less frequently referred to cardiology wards, and were less optimally medically treated (10). More recent studies show that women and men are more equally treated with the recommended medications (13, 89, 108).

For patients with HFrEF, angiotensin converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARB), aldosterone antagonists, and beta blockers have all shown mortality and morbidity benefits and are recommended to all patients with HFrEF, if not contraindicated or not tolerated,

according to present ESC and AHA guidelines for pharmacological treatment. However, the benefits for women concerning ACE-inhibitors are unclear due to underrepresentation of women in clinical heart failure trials. Two large meta-analyses reported a trend towards reduction in hospitalisation and improved survival, but the results did not reach statistical significance (109, 110). Aldosterone antagonists seem to be favourable for women based on subgroup analyses of the EMPHASIS-HF trial, the EPHESUS trial and the RALES trial (111-113). Diuretics should be used to relieve symptoms but the effect on morbidity and mortality has not been studied in randomized controlled trials (5). Digoxin may be considered to reduce hospitalisation risk in patients with sinus rhythm and symptomatic HFrEF (5). Also newer therapies are available, such as ivabradine, which selectively inhibits the voltage gated If channel in the sinus node, reducing the heart rate, and angiotensin-neprilysin inhibitors which combine the effect of ARB on RAAS and also slow down the degradation of natriuretic peptides and bradykinin. These therapies seem to be equally efficient in men and women and are recommended in selected groups of patients with HFrEF (5, 114).

Traditional heart failure treatment with ACE-inhibitors, ARB and beta blockers has not proven efficient enough to reduce mortality or morbidity in HFpEF patients (5, 114). Diuretics improve symptoms of congestion. Aldosterone receptor antagonists may reduce hospitalisation in appropriately selected patients (115). Angiotensin-neprilysin inhibitors may also have some beneficial effect on hospitalisation in women and selected groups of patients, but further research is necessary (116).

1.7.6 Prognosis and cause of death

European data report of a 12-month all cause mortality rate for hospitalised heart failure patients to be 17% and for outpatients to be 7% (5). Five-year all cause mortality rate after first hospitalisation is poor, mounting to 60% for heart failure patients overall, 75 % for acute decompensated chronic heart failure and 44% for new onset acute heart failure (117).

HFpEF compared to HFrEF

Mortality estimates for patients with HFpEF differ among clinical trials, observational studies and meta-analyses, with higher mortality rates in observational studies than in clinical trials, most likely because of selection of younger patients with less burden of comorbidities in clinical trials compared to observational studies. The reported 5-year mortality rate has ranged from 43% to 74% (18, 84, 118) for HFpEF patients in observational studies. Mortality risk increased with higher age and comorbidity burden. One large meta-analysis including seven RCTs and 24 observational studies reported that patients with HFpEF have about 32% lower mortality risk compared to patients with HFrEF (119). Patients who have been hospitalised for HFpEF have high mortality rates, i.e. 16% for the first six months after hospitalisation, which was equivalent to HFrEF patients according to one community-based study (29). One register-based study showed a 5-year mortality rate of ~75% for both HFpEF and HFrEF patients above 65 years of age after hospitalisation for heart failure (120).

The primary cause of death both in HFpEF and HFrEF patients in clinical trials is cardiovascular. A systematic review of 8 clinical trials and 24 epidemiological HFpEF studies revealed a cardiovascular cause of death in 60-70% of total deaths in the RCTs and 14-83% with a median of 59% in the epidemiological studies. The non-cardiovascular causes of death amounted to 20-30% in the RCTs and ~40 % in the epidemiological studies (121). In HFrEF studies, cardiovascular cause of death accounted for ~80% (122, 123).

In RCT studies of HFpEF patients, the most prevalent mode of cardiovascular death was sudden cardiac death in ~40%, followed by heart failure death in ~20-30%, and the most prevalent non-cardiovascular mode of death was cancer, ~35-40% (121). In epidemiological studies of HFpEF, heart failure death accounted for ~60% of the cardiovascular deaths and sudden cardiac death ~20-30%. Cancer was the most prevalent mode of death of the non-cardiovascular deaths, accounting for ~20-30%.

In RCT HFrEF studies of mode of death, the most prevalent mode of cardiovascular death was sudden cardiac death, ~40%, and heart failure death accounted for ~20-30%. Among the non-cardiovascular deaths, cancer was the most prevalent and accounted for ~35-40% (122, 123).

Women compared to men

In HFrEF clinical trials, women compared to men had lower risk of first hospitalisation for heart failure, lower risk of sudden death and death due to heart failure as well as lower risk of non-cardiovascular death. Women also had lower risk of fatal and non-fatal myocardial infarction, but a higher rate of stroke. Women had lower rate of hospital admissions both for all-cause, cardiovascular, non-cardiovascular and heart failure compared to men (89).

In HFpEF clinical trials, women compared to men had significantly lower risk of cardiovascular and non-cardiovascular hospitalisation, but similar risk of first hospitalisation for heart failure. The risk of cardiovascular death, including sudden death and death because of aggravated heart failure, and non-cardiovascular death was also lower for women than for men. Women were less likely to have a fatal or non-fatal myocardial infarction than men, but the risk of stroke was similar between men and women (61). One prospective observational study conducted at an outpatient clinic reported that in HFpEF, male gender was a predictor for cardiac death and that failure of the right ventricle was an important underlying cause. In women, right heart failure accounted for 37% of deaths and of non-cardiac death, infection accounted for the largest proportion, i.e. 23% (124).

As there are differences in cardiac disease between men and women, we find it important to study heart failure in women, to better understand the condition, and hence to better provide the best possible prevention and treatment.

2. Aims

The overall aim of this thesis was to study the risk of developing heart failure in women from different perspectives, with focus on obesity, change in physical activity and BMI and serum levels of triglycerides and cholesterol, and to investigate secular trends of these and other risk factors for heart failure.

The specific aims of the studies were:

I. To investigate if overweight and/or obesity is a risk factor for the development of heart failure in women of different ages.
II. To study whether a change in physical activity or BMI over time may influence the risk of heart failure development.
III. To investigate the association between serum-triglycerides and cholesterol and risk of heart failure development in four cohorts of 50-year-old women.
IV. To study secular trends in heart failure related risk factors in five different Swedish cohorts of 38- and 50-year-old women.

3. Study population and Methods

3.1 Study population

The Prospective Population Study of Women in Gothenburg, Sweden, 1968-69 to 2016-17. Paper I-IV

The Prospective Population Study of Women in Gothenburg (PPSWG), Sweden was initiated in 1968 with a cross-sectional examination and included 1462 women aged 38, 46, 50, 54, and 60 years. The women were representative of the women in Gothenburg at the time of study. They were recruited from the Swedish Population Registers, with recruitment based on birth dates (125). The women were then invited to participate in subsequent follow-up examinations with the same examination protocol at each examination.

At the follow-up examination 1980-1981, two additional groups aged 26 and 38 years were included. Further, to ensure representativeness of the women aged 38 and 50 years, women who had moved into Gothenburg and fulfilled the inclusion criteria were invited to the examination 1980-1981 (126).

In the examination 1992-1993, women born 1922 who had moved into the study area since the initial examination 1968-1969, and who fulfilled the inclusion criteria were invited to ensure representativeness. The participation rates were high in all of the examinations. About one-fifth of the participants in 1968-1969 had died before the follow-up 1992-1993, which gave a participation rate of 70% of those who participated in 1968-1969 and who were alive in 1992-1993 (127).

In the 2000-2001 follow-up examination, all women who had participated in 1968-1969 and who were alive in 2000-2001 were invited; 494 women participated.

Home visits were made to those women who declined participation due to old age, frailty or physical impairment and who were not able to travel to the examination site (n= 167). The total participation rate was 71% (women who died before the examination period ended were excluded, n=533) (128).

In 2004-2005, an additional follow-up examination was conducted. Newly invited women 38 years old and born in 1966 were examined for the first time. In total, 343 women were invited and 207 accepted to participate, resulting in a participation rate of 60%. The majority of the women born in 1954 who were 50 years old at the examination 2004-2005 were newly invited and the remaining part had participated in the examination 1992-93. 503 women were invited, and 293 women accepted to participate, yielding a participation rate of 58% (55).

Yet another examination was conducted in 2016-2017. Women born in 1978 were examined for the first time. Additional women born in 1966 were newly recruited to fulfil representativeness, and the remainder of the women had participated in 2004-2005, which resulted in a sample of 415 women 38 years old and 430 women 50 years old. From this sample, a total of 263 women, 38 years old, and 310 women, 50 years old, participated with a participation rate of 63% and 73%, respectively (129). Table I.

Table I. Year of birth and age at examination (years), number of participants (N) and participation rates (%) in the examinations 1968-1969, 1980-1981, 1992-1993, 2000-2001, 2004-2005 and 2016-2017.

	Year of birth									
	1908	**1914**	**1918**	**1922**	**1930**	**1942**	**1954**	**1966**	**1978**	**total**
Year of examination										
1968-1969										
age	60	54	50	46	38					38-60
N	81	180	398	431	372					1462
1980-1981										
Age	72	66	62	58	50	38	26			26-72
N	49	140	325	332	308	122	85			1362
%	60	78	82	77	83	85[1]	66[1]			
1992-1993										
Age	84	78	74	70	62	50	38			38-84
N	19	79	213	270	249	93	61			984
%	23	44	54	63	67	76[2]	72[2]			57[3]
2000-2001										
Age	92	86	82	78	70					70-92
N	8	44	176	202	231					661
%	66[8]	64[7]	75[6]	67[5]	74[4]					71[9]
2004-2005										
Age							50	38		38+50
N							293	207		500
%							58[11]	60[10]		
2016-2017										
Age								50	38	38+50
N								310	263	573
%								73	63	

[1] Of those sampled in 1980-1981, [2] Of those participating in 1980-1981, [3] Of women born in 1908-1930. [4] Of the women born in 1908 and who were alive in 2001. [5] Of the women born in 1914 and who were alive in 2001. [6] Of the women born in 1918 and who were alive in 2001. [7] Of the women born in 1922 and who were alive in 2001. [8] Of the women born in 1930 and who were alive in 2001. [9] Of the women born in 1908-1930 and who were alive in 2001. [10] Of the 503 women invited in 2004-05. [11] Of the 343 women invited in 2004-05.

The Gerontological and Geriatric Population Studies in Gothenburg (H70). Paper I

The Gerontological and Geriatric Population Studies in Gothenburg (H70) were initiated in 1971-72. The study included six cohorts of men and women who were representative of the population. The participants were followed longitudinally from the age of 70 years (130). Only the women were included in paper I, with the exception of the women born in 1901-02.

The second population sample of 70-year-olds was invited in 1976-77, and 562 women were examined with a participation rate 81 %. In 1981-82, the survivors were re-examined at age 75, and 429 women participated, giving a participation rate of 85% (131).

The third population sample of 70-year-olds was invited in 1982, and 317 women were examined as a part of the Intervention Study of Elderly in Gothenburg (132). A control group identified at age 70, who were 76 years old in 1987, was invited together with the survivors from the original sample. In total, 356 women aged 76 years were investigated, with a participation rate of 74%. 96 women were investigated for the first time in 1987.

In 1990, at the age of 75 years, 180 women were examined in The Nordic Comparative Study. The participation rate was 72%, and the sample was shown to be representative (133).

A fifth population sample of 70-year-olds was examined in 1992 (134). A majority of the women in this cohort also participated in the PPSWG and had reached 70 years of age. To achieve representativeness, 102 women were included for the first time at the age of 70 years.

In 2000, a sixth population sample of 70-year-olds was invited (135). This examination was performed together with the PPSWG, and to achieve

representativeness 114 women were included for the first time at age 70. In total 345 women born in 1930 participated in the examination 2000.

Sampling and procedural details as well as participation rates at all examinations have been presented elsewhere (55, 125-135).

3.2 Methods

Table 1. Summary of design, material and method of the included studies.

	Design	Study group	Data gathering	Data analysis
Paper I	Longitudinal Prospective Observational study	Participants in the PPSWG and women participating in the H70 studies	Baseline data 1980. NPR and Swedish Register of causes of death and death certificates 1980-2006	Hazard Ratio of risk of heart failure development in obese or overweight women of different ages.
Paper II	Longitudinal Prospective Observational study	Participants in the PPSWG	Baseline data 1968 + 1980 NPR and Swedish Register of causes of death 1980-2012	Hazard Ratio of risk of heart failure development in women with regards to change in physical activity or change in BMI

Paper III	Longitudinal Prospective Observational study of four cohorts of women	Participants in the PPSWG	Baseline data 1968, 1980, 1992, 2004. NPR and Swedish Register of causes of death 1980-2012	Hazard Ratio of heart failure development in women. Association of levels of triglycerides and cholesterol in 50- year-old women.
Paper IV	Cohort comparison study of five cohorts of women	Participants in the PPSWG	Baseline data 1968, 1980, 1992, 2004 and 2016	Secular and linear trends for cardiovascular risk factors of five cohorts of 38- and 50-year-old women

PSWG [1] : Population Study of Women in Gothenburg. NPR[2] : Swedish Hospital Discharge Registry.

Paper I:

Obesity in Middle Age Increases Risk of Later Heart Failure in Women – Results From the Prospective Population Study of Women and H70 Studies in Gothenburg, Sweden.

In total, 2574 women from the PPSWG and H70 studies were included; 1243 women were aged 26-65 years and 1331 were aged 66-76 years at baseline. The examination methods used in both PPSWG and H70 studies were the same and included the same protocol and questionnaires on factors relating to social and lifestyle variables, information on drug consumption and medical history, as well

as a physical examination by a physician, and also blood pressure measurements, electrocardiogram and laboratory assessments.

Socioeconomic status was classified into low, medium and high, based on marital status and education, occupation and income of the woman or her husband. Blood pressure was measured in the sitting position, in the right arm after 5 minutes of rest and to the nearest 2 mmHg. Using a balance scale, body weight was measured to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm. BMI was calculated, weight/height^2. The women were allowed to drink water but not to eat during the night before the blood sample was collected. In accordance with WHO criteria, overweight vas defined as 25≤ BMI <30 and obesity as BMI ≥30.

Data on mortality and hospital discharge diagnoses were collected over a period of 26 years, 1980 to 2006. Heart failure diagnoses were classified according to the International Classification of Diseases, 9th and 10th revision (ICD-9) 428A, B or X, and ICD-10 I50.

Statistical analyses

For descriptive data, t-tests for continuous variables were used for differences between groups. Cox regression models were used to test associations between BMI and heart failure as well as for interaction between BMI and heat failure. Hazard ratio of heart failure was calculated for each BMI group within two age groups. The models were adjusted for age, blood glucose, smoking, alcohol consumption, serum triglycerides and systolic blood pressure.

Paper II:

Impact of changes in physical activity or BMI on the risk of heart failure in women - the Prospective Population Study of Women in Gothenburg.

The study population originated from the PPSWG and included 1749 women. All women went through similar examination procedures at baseline and at follow-up

examinations. The examinations included registration of socioeconomic status, lifestyle habits such as smoking and alcohol consumption and levels of physical activity. Also, information on medical history, consumption of medication and family history of diseases was gathered.

Body weight and body height were measured at all examinations, and BMI was calculated. Blood samples were drawn, and urinary samples were collected in the fasting state in the morning. Blood pressure was measured in the sitting position after 5 minutes of rest.

The women were categorised according to reported levels of physical activity into non-active (inactive or almost inactive) and active (at least 4 hours per week of moderate activity such as walking, gardening, bicycling, dancing or similar activities or regular intense training during the last year).

According to WHO classification, overweight was classified as $25 \leq$ BMI < 30 and obesity as BMI ≥ 30.

Diagnoses were set according to the International Classification of Diseases, 9th and 10th revision (ICD-9) 428A, B or X, and ICD-10 I50.

Mortality data and hospital care data on heart failure were collected from 1980 to 2012, a period of 32 years.

Statistical analyses

Tests of Schoenfeld residuals were calculated for the total model for assumption of proportional hazard. The significant result from this test motivated a follow-up analysis with a division of the time period into the first and second decade, and separate effect was demonstrated. Cox regression model was used to calculate the effect in each category of activity-change and BMI-change. Multivariable models controlled for age, serum triglycerides, serum cholesterol, smoking and hypertension.

Only women free of previous history, signs or diagnosis of heart failure were included in this study.

Paper III

Cholesterol and triglyceride levels in midlife and risk of heart failure in women, a longitudinal study - the Prospective Population Study of Women in Gothenburg.

1143 women, in four cohorts aged 50 years, from the PPSWG were included in this study and all women participated in follow-up investigations with the same examination procedures. The examinations included a questionnaire comprising information on socioeconomic status. Information on medical history both in participants as well as a family medical history was collected. Information on lifestyle related variables including smoking and alcohol consumption and level of physical activity was reported.

Physical examination included measurements of body weight and body height and BMI was calculated. Blood pressure measurements were conducted after 5 minutes of rest in the sitting position. Blood samples and urinary samples were collected in the morning after a fasting night.

According to Carlsson´s standard occupations grouping system, socioeconomic position was classified into low, medium and high, based on marital status, education, and occupation of the woman or her husband.

Physical activity was reported as leisure time physical activity and classified into non-active (inactive or almost inactive) and active (at least four hours per week of

moderate physical activity such as walking, bicycling, dancing, playing golf, or regular highly intensive exercise several times a week for the past year).

The women were categorised as smokers if they smoked one cigarette or more per day or had stopped smoking during the previous year, and as non-smokers if they had stopped smoking more than a year before the examination or had never smoked.

Diagnoses were set according to the International Classification of Diseases, 9th and 10th revision (ICD-9) 428A, B or X, and ICD-10 I50.

Mortality data were collected until 2012 and data on hospital discharge data on heart failure were collected between 1980 to 2012. Serum triglycerides and serum cholesterol were assessed at baseline between 1968 to 2004.

Statistical analyses

Four population-based cohorts of 50-year-old women participated. Only women without previous heart failure or myocardial infarction were included. Differences between groups were tested with t-test for continuous variables and by Pearson´s chi square test for categorical variables. Cox regression model was used to calculate the association between serum triglycerides and serum cholesterol as continuous variables and heart failure. Multivariable models were adjusted for age, BMI, smoking and physical activity.

Paper IV:

Secular trends in cardiovascular risk factors with particular regard to heart failure in 38- and 50-year-old women - The Prospective Population Study of Women in Gothenburg.

Five representative cohorts of 38- and 50-year-old women from the PPSWG participated in this study. All women were followed according to the same examination procedures at each follow-up examination. The examinations included questionnaire-based variables concerning lifestyle habits, symptoms of depression, mental stress and perceived overall health and also information on medication.

Physical examinations included blood pressure measurements to the nearest 2 mmHg. Body weight and body height were measured, and BMI was calculated. Blood and urinary samples were collected in the morning in the fasting state.

Classification of questionnaire-based variables

Mental stress: High level of stress was present if the woman experienced feelings of nervousness, irritability, tension, fearfulness or suffered from sleep disturbances for more than one month at a time, on multiple occasions during the last five years, or experienced permanent stress during the last year or during the five last years.

Depressive mood: Depressive mood was present if the women experienced feelings of depression during the last three months.

Perceived overall health: Good or very good perceived overall health was present if the woman reported her situation as “exceptionally good”, “excellent”, “good” or “neither good nor bad”. Bad overall health was present if the women assessed her situation as “not quite good”, or “bad”.

Physical activity: Physically active women reported at least four hours per week for the last year of walking, bicycling, running, dancing, playing tennis or similar activities or regular strenuous exercise several times per week.

Smoking: Women who smoked one or more cigarettes per day during the last year were identified as smokers.

Statistical analyses:

To test for trends over time for continuous variables, linear regression models were used, and for trend over time in prevalence of dichotomous variables, logistic regression models were used.
Significance level was set at $p<0.05$ and reported as either n.s., <0,05 or <0,01.

3.3 Ethical approval

The ethical review board of the University of Gothenburg approved of the Prospective Population Study of Women in Gothenburg and the Gerontological and Geriatric Population Studies in Gothenburg. Informed consent has been obtained from the subjects and the studies comply with the *Declaration of Helsinki.*

4. Results

Paper I:

Obesity in Middle Age Increases Risk of Later Heart Failure in Women – Results From the Prospective Population Study of Women and H70 Studies in Gothenburg, Sweden.

After excluding 12 women with heart failure at baseline, 22 women with missing data on BMI in the younger group and 54 women with missing data on BMI in the older group at baseline, a total of 2574 women were included in the present study. 1243 women were aged 26-65 years at baseline and 1331 women were aged 66-76 years at baseline.
In the younger group, 14.6% of the women developed heart failure by 2012 and 9% were obese at baseline. In the older group, 31.9% of the women developed heart failure by 2012 and 16% were obese at baseline. In the entire population, 23.4% developed heart failure by 2012. In the older group, mean BMI of 26 exceeded the upper limit of overweight. In the unadjusted analysis, we found a significantly higher risk of heart failure in the younger group in the overweight and obese BMI categories, but not in the older group. In the analyses adjusted for age, blood glucose, smoking, alcohol, systolic blood pressure and serum triglycerides, the significantly higher risk of future heart failure remained strong for obese women in the younger group, 26-65 years of age. There was no association between BMI categories and risk of heart failure in the older group, 66-76 years of age. Figure I shows the association between BMI and risk of heart failure across the BMI groups and the two age groups.

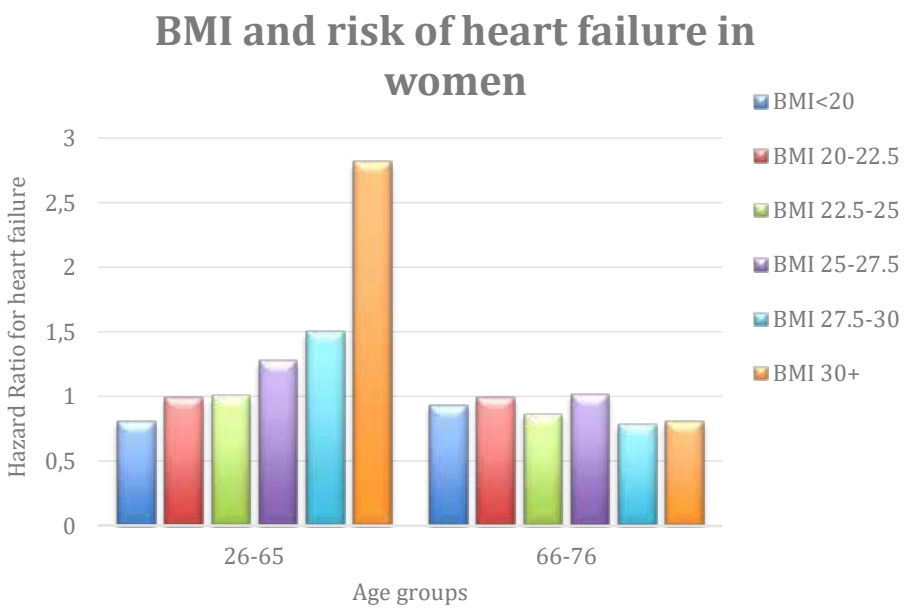

Figure I. BMI and risk of heart failure in women adjusted for age, blood glucose, smoking, alcohol, systolic blood pressure and serum triglycerides.

Paper II

Impact of changes in physical activity or BMI on risk of heart failure in women - the Prospective Population Study of Women in Gothenburg.

Periods 1968-1980 and 1980-1992:

Mean age at baseline in the earlier period 1968-1980 was 48 years for overweight women and 49 years for obese women, and mean age at baseline for the later period was 58 years both for overweight and obese women. Thus, women examined in the later period were around ten years older than the women in the earlier period.

Observations from 1968 to 1980

BMI could be followed from 1968 to 1980 in 1132 women, and 23.9% developed heart failure by 2012. The majority of women were non-overweight in both examinations. In the examination 1968, 26% of the women were overweight, and in the examination 1980, 36% of the women were overweight. 6.5% of the women in the examination 1968 were obese, and 10% of the women in the examination 1980 were obese.

The women who increased their BMI from overweight to obesity had a significantly increased risk of heart failure, i.e. HR 1.93 (95% CI 1.18-3.14) compared to the reference group of women who remained at BMI <25 both in 1968 and 1980. A decrease in BMI from obese to overweight and a constant BMI of obesity from 1968 to 1980 did not significantly show any association with risk of heart failure compared to the reference group.

Level of physical activity could be followed in 1132 women between 1968 and 1980. In 1968, 17% of the women were non-active, and in 1980, 29% of the women were non-active. Neither an increase in activity level from non-active to active nor a decrease from active to non-active showed any significant change in risk of later heart failure compared to the reference group of non-active women both in 1968 and 1980. The women who stayed active throughout the entire period had a significantly reduced risk of heart failure compared to the reference group, HR 0.66 (95%CI 0.44-0.99).

Observations from 1980 to 1992

BMI could be followed in 932 women between 1980 to 1992, and 20% developed heart failure by 2012. In the examination 1980, 61% of the women were non-overweight, and in the examination 1992, 48% of the women were non-overweight. In the examination 1980, 31% of the women were overweight compared to 35% in the examination 1992. 8% of the women in the examination 1980 were obese, and 17% of the women in the 1992 examination were obese. There was no significant change in the risk of later heart failure development in any of the BMI-change categories compared to the reference group with BMI <25 at both examinations 1980 and 1992.

Level of physical activity could be followed in 932 women in both examinations 1980 and 1992. In the examination 1980, 27% of the women were non-active as compared to 21% in the 1992 examination. 73% of the women in 1980 were active, and 79% of the women were active in 1992. The women who increased their level of activity from non-active to active and the women who continually stayed active

between 1980 to 1992 significantly reduced their risk of later development of heart failure with HR 0.40 (95% CI 0.22-0.72) and HR 0.47 (95% CI 0.29-0.74), respectively.
Figure II shows risk of heart failure with change in BMI and change in physical activity.

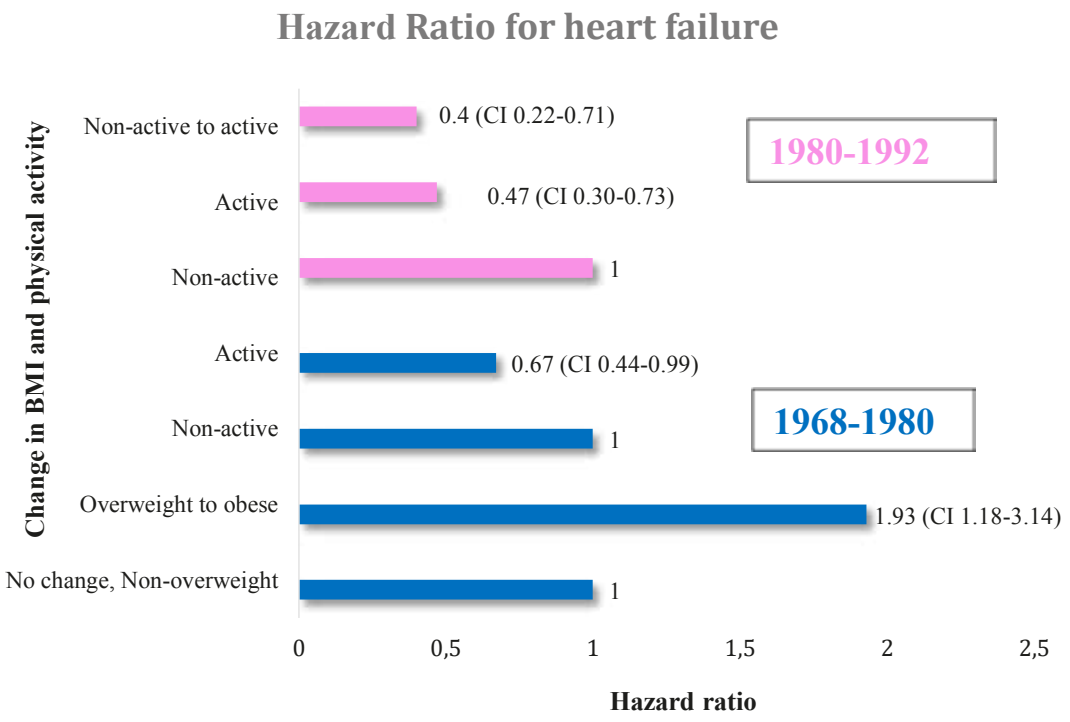

Figure II. Change in physical activity or BMI and risk of heart failure

Paper III

Cholesterol and triglyceride levels in midlife and risk of heart failure in women – a longitudinal study - the Prospective Population Study of Women in Gothenburg.

The study included 1143 women 50 years old in four cohorts, among whom 155 developed heart failure. In the youngest cohort born in 1954, no women developed heart failure and were therefore excluded from the final analyses. Women in the oldest cohort, born in 1918 and examined at age 50 years old in 1968, had slightly higher systolic blood pressure compared to the younger cohorts and also slightly higher levels of serum triglycerides and serum cholesterol. There was no significant difference in BMI among the cohorts. In the cohort born in 1930 and examined at 50 years old in 1980, more women were smokers compared to the other cohorts. Blood glucose and waist-hip-ratio were higher in the cohort born in 1954 and examined at 50 years old in 2004, compared to the earlier cohorts. More women were physically active in the cohorts examined in 1968 and 2004 compared to the other cohorts, and there were more women belonging to socioeconomic position III in the oldest cohort compared to the other cohorts. In the pooled analysis of the cohorts examined in 1968, 1980 and 1992, there was a significantly increased risk for heart failure development associated with serum triglycerides (HR 1.49; CI 1.10-2.03), but not with serum cholesterol. Adjustments were made for age, smoking, physical activity and BMI. When analysing serum triglycerides as a continuous variable in the cohort examined in 1968, there was a significant and independent association between levels of serum triglycerides and increased risk of heart failure (HR 1.8; CI 1.16-2.80, for each increment of 1.0 mmol/l of serum triglycerides), but not for serum cholesterol. Also, this analysis was adjusted for age, smoking, physical activity and BMI.

Paper IV

Secular trends in cardiovascular risk factors with particular regard to heart failure in 38- and 50-year-old women - The Prospective Population Study of Women in Gothenburg.

Questionnaire based results:

Around 25% of the 38- and 50-year-old women in the cohorts examined in 1980-81, 1992-93, 2004-05 and 2016-17 reported bad perceived overall health. Occurrence of depressive mood significantly increased in 38-year-old women, from 42% in 1980-81 to 55% in 2016-17 ($p = 0.03$), but not in 50-year-old women. Also, the proportion of women experiencing stress significantly increased for both 38- and 50-year-old women, for 38-year-old women from 19% in 1968-69 to 64% in 2016-17 ($p < 0.0001$), and for 50-year-old women from 17% in 1968-69 to 49% in 2016-17 ($p < 0.0001$). More women of both age groups in the later cohorts were physically active compared to the earlier cohorts, and the proportion of smoking women decreased in both age groups, in the 38-year-old women, from 46% in 1968-69 to 9% in 2016-17 ($p < 0.0001$) and in the 50-year-old women from 37% in 1968 to 12% in 2016 ($p<0.0001$). No statistically significant difference between the cohorts was found for reported use of anti-hypertensive medication.

Results from physical examination with anthropometric- and laboratory assessments:

There was a significant decrease in trends in both systolic and diastolic mean blood pressure for both 38- and 50-year-old women between the examinations 1968-69 to 2016-17. Levels of serum triglycerides were also significantly lower for both age groups between the examinations 1968-69 to 2016-17. HDL-analyses were available from 1992 and onward, and there was significant trends of higher mean level of HDL for both age groups in the examination 2016-17 compared to 1992-93. A significant trend in increase in BMI between 1968-69 to 2016-17 was seen for women 38 years old but not for women 50 years old.

5. Discussion

5.1 Major findings

Heart failure is not a homogeneous condition. There are two main phenotypes, and differences between men and women exist. Consequently, it is essential to increase our knowledge in order to provide the best care possible. Heart failure causes a considerable amount of suffering and treatment, and hospital care is costly (58). Therefore, a focus on prevention is imperative for the benefit of the population. Lifestyle factors have major impact on our health, and the importance of a healthy lifestyle is crucial for a broad spectrum of diseases as well as for our overall wellbeing. Obesity is a known risk factor for heart failure in both men and women (36). Furthermore, a sedentary, inactive lifestyle has been associated with increased risk of heart failure in women, and an active lifestyle has shown to be protective (9, 44). Biomarkers are valuable tools for the general practitioner to verify or to exclude various diseases and also to follow the effect of treatment. Biomarkers are also widely used for risk estimation of cardiovascular diseases. Finally, living conditions have changed during the past decades and may influence cardiovascular risk factors.

5.1.1 Obesity and risk of heart failure.

We found obesity in younger and middle-aged women to be an especially strong risk factor for later development of heart failure, whereas obesity in older age did not increase the risk of heart failure development. This finding is of major importance since obesity in young women is increasing in Sweden (41). Obesity has a direct and independent effect on the heart, apart from the risk of ischaemic heart disease, as obesity is associated with left ventricular diastolic dysfunction (38). Higher BMI is more strongly related to HFpEF than HFrEF (46) and HFpEF is the phenotype most prevalent in women (18, 29, 77-84). Obesity is also related to low grade inflammation, which has been shown to play a central part in heart failure development, especially of the HFpEF phenotype (69, 136). Another

potential mechanism of HFpEF is myocardial lipotoxicity, where increased myocyte uptake of fatty acids and storage of triglycerides results in cellular dysfunction, apoptosis, microvascular dysfunction followed by structural wall abnormalities, diffuse fibrosis and impaired cardiac function (137).
We also found increased risk of later heart failure in young women who increased their BMI from overweight to obesity, but not in older women who increased their BMI. We could not show significant association between a reduction in BMI from obese to overweight and reduction of risk of heart failure in any of the two examination groups. This may be explained by the small number of women who reduced their weight. However, studies conducted in Sweden reported reduced risk of heart failure in severely obese patients who had bariatric surgery (138, 139). All together our findings strongly implicate that gaining weight and obesity in young and young middle-aged women, with increased risk of living with obesity from midlife and onwards, is more harmful than weight gain or obesity in older women.

5.1.2 Physical activity and risk of heart failure

There is strong evidence of the protective effect of physical activity on the risk of cardiovascular disease and heart failure, and a stronger association with lower risk of HFpEF than HFrEF (46). There is also strong evidence that patients diagnosed with heart failure benefit from exercise, women even more than men (8). In our study of impact of change in physical activity on the risk of heart failure in healthy women, we showed a significant reduction in risk of heart failure in women who were regularly physically active over time, compared to non-active women in both younger and older women. This is in accordance with previous studies. We also showed a risk reduction in heart failure development in older women who increased their level of physical activity from non-active to active. Similar results were found by Pandey et al, showing that for each metabolic equivalent (MET) improvement in midlife fitness, the risk of later heart failure was reduced by 17% (140). This finding is valuable as it implies that it is more important to focus on fitness and physical activity than weight loss in elderly women. MET is a measure of the amount of oxygen consumed during various physical work. One MET equals the amount of oxygen consumed sitting at rest. During a light walk with the speed of three km/h and almost no perspiration and only a slight increase in breathing, the energy expenditure equals 3 METs (141). We could not demonstrate any significant association with increased physical activity and change of risk of

heart failure in the younger women and this may be explained by the small number of women in this category.

5.1.3 Cholesterol and triglyceride levels in midlife and risk of heart failure

In this study of four cohorts of 50-year-old women, we demonstrated a significant association between serum triglycerides and an increased risk of later heart failure. For the oldest cohort followed for 44 years, the hazard ratio for heart failure was 1.8, for each increment of 1.0 mmol/l of serum triglycerides. There was no association between serum cholesterol and risk of heart failure. Similar results were also recently found in a Danish population-based observational study where the authors showed a stepwise increase in risk of heart failure with stepwise increase in non-fasting serum triglycerides, but no association between LDL concentration and risk of heart failure (142). Cholesterol and LDL are strongly associated with ischaemic heart disease and especially obstructive coronary heart disease and HFrEF. However, this condition is far more prevalent in middle-aged men than middle-aged women (67), whereas in middle-aged women, microvascular dysfunction prevails (143), which is closely linked to systemic inflammation and HFpEF (68). Triglycerides are associated with inflammation (144) and may thus influence heart failure risk. Physical exercise has been reported to reduce the concentration of serum triglycerides for both younger and older men and women, and women with metabolic syndrome exhibited improvement in more risk factors than comparable men (145, 146).

5.1.4 Secular trends in cardiovascular risk factors and heart failure

Our study of secular trends in 38- and 50-year-old women reveals an improvement over time in traditional cardiovascular risk factors, which is also seen in previous observational cohort studies (55, 147), but BMI significantly increased over the years in the cohorts of younger women. This is unfortunate as we know from previous studies that obesity in young women increases the risk of heart failure

(99). Also, stress increased over the years in both 38- and 50-year-old women, as did depressive mood in the younger cohort. A dose-response association has been shown between depression and heart failure with a significantly increased risk for incident heart failure (148), and there is abundant evidence of chronic mental stress causing endothelial dysfunction (149). There is also a connection between inflammation, endothelial dysfunction, atherosclerosis and depression (150). Major depression is associated with increased inflammatory cytokines (151), which may be a possible pathway for heart failure development. Takotsubo cardiomyopathy is a special condition strongly related to predominantly acute stress, sometimes superimposed on chronically elevated stress or anxiety levels, and manifests with acute onset of transient myocardial dysfunction with reduced ejection fraction and chest pain. This condition is mostly prevalent in women and may clinically mimic myocardial infarction. In the acute setting, the condition may be complicated with acute decompensated heart failure and even cardiogenic chock or arrhythmias (152, 153).

5.2 General discussion

Heart failure is not a homogeneous condition, but rather is heterogeneous with differences in men and women, as well as different phenotypes where the two major types are HFpEF and HFrEF. In our studies we did not have the possibility to differentiate between HFpEF and HFrEF.

According to current knowledge, no medical treatment has been shown to reduce mortality and morbidity in patients with HFpEF, in contrast to HFrEF. Mortality is high in HFpEF. Therefore, prevention must be the area to focus upon to reduce the incidence and development of heart failure with preserved ejection fraction, which is the most common phenotype of heart failure in women in primary care. We have in our studies shown that obesity in younger and middle-aged women, but not in older women, increases the risk for heart failure. This result is consistent with another Swedish register study in which obesity in middle-aged men was associated with a higher risk of heart failure development (154). In this study, the authors reported that increased midlife BMI increased the risk of heart failure regardless of presence or absence of myocardial infarction or coronary revascularisation. Therefore, it is most concerning that the BMI of men and women has been increasing in Sweden (41).

We have shown that several of the known cardiovascular risk factors have improved during the last decades, but BMI, depressive mood and mental stress have increased, which may through the inflammatory pathway lead to heart failure development. Measures should be taken to break this trend.

Being physically active throughout life, and also an increased physical activity in older women reduces the risk of heart failure development. Physical activity reduces systemic inflammation and oxidative stress and improves endothelial function (155). This has earlier been demonstrated in obese women (156) and could thus be a feasible way of reducing the risk of heart failure development in women with obesity and should be considered the first line of heart failure prevention. It may also prevent obesity development, which is important for heart failure prevention in younger women.

Furthermore, depression and high chronic mental stress are associated with systemic low grade inflammation and endothelial dysfunction (157, 158). Thus in this perspective, physical activity could be a possible pathway for reducing risk of heart failure in women with depression or high level of mental stress.

Primary health care is one of the most appropriate settings for this preventive work, in terms of clarifying associations between increased BMI, lack of physical activity, stress and health issues such as heart failure. Through the numerous meetings with women, primary health care has the opportunity to support women and strengthen them in making favourable decisions concerning a healthy lifestyle.

But primary health care cannot act alone. The living environment must also promote and facilitate a healthy lifestyle, including available recreation areas, playgrounds for children, possibilities to move around safely by bike or walking. To promote and establish playful physical activities in schools could be a possible way of introducing and hopefully incorporating physical activity as a natural part of life. Also, avoiding vending machines with unhealthy snacks, sweet drinks and candy in schools should be considered. Women´s working environment is another important aspect to consider, particularly concerning mental stress and depression, as these conditions are highly associated with illness and sick leave in women (159).

5.2.1 Methodological considerations

In this thesis we have combined data from large prospective population studies of women and data from high quality national registers. This provided an opportunity for long-term follow-up periods, spanning over decades. The populations studied were highly representative of women in the area, and thus the results may be applicable to the general female population of the study area.

The Prospective Population Study of Women in Gothenburg is a large population study of women initiated in 1968, and it is still active. The Gerontological and Geriatric Population Studies in Gothenburg (H70) consisted of both men and women, but for the purpose of this thesis, only the women were included.

All women were followed longitudinally with regular follow-up examinations over several years. All follow-up examinations were conducted according to the same basic examination protocol. The protocol included both a questionnaire component, a physical examination component and laboratory analyses. The protocol covered lifestyle habits, socioeconomic status, physical and psychological medical history of the woman and medical history of her family, ongoing medications, present physical and medical conditions and a broad blood and urinary analysis.
Thus, the examination protocol covered most of the areas concerning the women´s health, living conditions and psychosocial situation, providing an almost complete basis and robust grounds for further research in many areas.
Combining data from these population studies and the high quality national registers gives a solid basis for this thesis.

Paper I was based on both the Prospective Population Study of Women in Gothenburg and the women from the Gerontological and Geriatric Population Studies in Gothenburg (H70) study.

Papers II-IV were based solely on the Prospective Population Study of Women in Gothenburg.

Observational studies have inherent limitations, such as the fact that detection of association does not inevitably indicate causation. The association may be explained by another factor related to both the exposure and the outcome, a confounding factor. Selection bias and information bias also need to be considered.

Association-Causation. Our results regarding obesity, physical activity and heart failure are consistent with a large number of previous studies. Very plausible explanations for a causative relationship between obesity and heart failure development have been reported in abundance (137, 160). Likewise, there are many studies elucidating the possible mechanisms underlying the favourable impact of physical activity for reducing risk of heart failure development (155, 161, 162). There is also earlier work on triglycerides and potential mechanisms for heart failure development (137, 144), as well as plausible mechanisms for heart failure development in psychological disorders such as depression and chronic mental stress (150, 157).

Confounders. Confounders or other possible risk factors must be considered, and we adjusted for well-known cardiovascular risk factors. In Paper I, we adjusted for age, blood glucose, smoking, alcohol consumption, serum triglycerides and systolic blood pressure. In Paper II, we adjusted for age, serum triglycerides, serum cholesterol, smoking and hypertension. We also excluded women with a previous history or signs of heart failure or myocardial infarction. In Paper III, we adjusted for age, BMI, smoking and physical activity, and we also excluded women with a previous history or signs of heart failure or myocardial infarction.

Selection bias. In observational studies, selection bias must be taken into account. The study population may not be representative of the entire target population due to the selection procedure of the study population or factors that affect the study population. Paper I was based on women participating in two large population studies (PPSWG and H-70), and Papers II-IV were based on women participating in PPSWG. The women were recruited from the Swedish population register and based on birth dates, ensuring that the invited sample was representative of the women in Gothenburg (125). Furthermore, during the follow-up periods, women who had moved into the study area and who fulfilled the inclusion criteria were invited to the follow-up examinations. Also, non-participation analyses have been conducted, and non-participants were interviewed by telephone or by letter (127). At 32-year follow-up, home visits were made to non-participants, mainly including women of the earlier born cohorts and women who had moved out of the study area. In this way, participation rate increased, and participation bias decreased. As well known in observational studies, invited individuals who decline participation have higher morbidity and mortality than participating individuals, and this is also true for the PPSWG (128). Taking into account all of the procedures and actions that were performed to ensure the representativeness

of the study populations on which this work is based, the selection bias and participation bias must be regarded as relatively low.

Information bias. In observational studies, information bias is important to evaluate. The participant information most sensitive to this bias in Paper I concerned smoking and level of alcohol consumption, but information on alcohol consumption was obtained using a standardised structured interview by a physician, and smoking habits were obtained by a standardised questionnaire. These procedures somewhat attenuated the risk of information bias. In Paper II, the participant information most sensitive to information bias was level of physical activity, as it is common to overestimate the level of physical activity. The fact that we clearly defined only two levels of physical activity, non-active and active, with a line drawn at four hours per week of physical activity, and that the standardised questionnaire defined what would be considered physical activity, in some way reduced the risk of this information bias. The possible information bias concerning alcohol and smoking habits would be subject to the same evaluation as in Paper I. Paper III was also susceptible to information bias on alcohol consumption, smoking habits and level of physical activity but the same procedures were performed as in Papers I and II, which may diminish the information bias. In Paper IV, the information concerning level of stress and feelings of depression was the information most susceptible to bias, but also for these measures, a standardised questionnaire was used with defined frequency levels of stress and feelings of depression, which reduced the risk of this information bias.

5.2.2 Strengths and limitations

Strengths

Strengths of all papers (I-IV) are the sampling procedure, the repeated uniform examinations at follow-up examinations, the long follow-up periods and also the representativeness of the study population. The participation rate was also generally high throughout the examinations.
In Paper IV, a great strength is not only the long observation period, 48 years, but also the study design with five different generations and the possibility to compare trends for both younger and older cohorts.

The high quality national registers in Sweden are a treasure for research, and the possibility to link these registers to each other and to population-based studies is a huge strength for population-based research in Sweden and enables long follow-up periods.

Limitations

In Paper I, a limitation is that only a hospital diagnosis of heart failure or heart failure as a cause of death were possible to use as endpoints. On the other hand, most heart failure patients will be hospitalised at some point and will thus be registered with a hospital diagnosis of heart failure. Another limitation may be the large age span in the younger group, 26 to 65 years. We performed all analyses with the youngest women 26 years of age excluded, and the results were not affected.

A most important limitation in Paper II is the low number of women who reduced their BMI and the few women in the younger group who increased their level of activity. This could be the explanation for the non-significant outcome for these categories.

In Paper III, one limitation is the relatively small number of women in the respective cohorts. Despite this fact, we still found that serum triglycerides were significantly and independently associated with increased risk of later heart failure development. Another limitation is that HDL and LDL analyses were not available at the time.

A limitation in Paper IV is the declining participation rates over time, which may be explained by changes in living conditions for women, where women in the later cohorts often were employed outside home and thus had little spare time to participate in research studies. Nevertheless, participation rates in the latest born cohorts were as high as 63-73%.

6. Conclusion

The main findings of these studies on risk of heart failure in women are:

- Obesity in younger age is highly associated with increased risk of later heart failure development. In contrast, obesity in older age does not seem to increase the risk of heart failure development.

- Weight gain from overweight to obesity in younger middle age increases the risk of future heart failure, whereas weight gain in later age is not associated with increased risk of heart failure.

- Staying physically active throughout life is protective and reduces the risk of heart failure development.

- Increased level of physical activity is associated with reduced risk of heart failure development, especially for previously sedentary women in later middle age.

- Levels of serum triglycerides but not serum cholesterol in middle-aged women are associated with increased risk of later heart failure.

- Some of the traditional risk factors for cardiovascular disease have improved over the years. However, other factors also associated with cardiovascular disease and heart failure development such as BMI, blood glucose, mental stress and depression show negative trends.

In summary, the results of the studies highlight risk factors for heart failure in women that are highly modifiable by lifestyle. This is of particularly great importance since there are no medical treatments yet available for the HFpEF phenotype of heart failure, which is the phenotype most common in women and elderly. It is also the heart failure phenotype that is increasing in prevalence. One

of the most important lifestyle factors is physical activity. We show that continuous physical activity is beneficial at all ages, and also that increased level of physical activity is especially beneficial for older sedentary middle-aged women. Primary health care is an important setting with many possibilities to influence and to support women to choose an active healthy lifestyle. Primary health care is also often the first line of help for women with stress disorders and depression, which are shown to be increasing in society and are associated with heart failure. All in all, primary health care has a primary role in caring for women´s cardiac health.

7. Clinical implications

This thesis contributes increased knowledge on risk factors for heart failure development in women. It also highlights that preventive actions and measures have different effects on women of different ages. This is important knowledge and may be useful for caregivers seeking to provide women with the most appropriate and effective preventive actions. This thesis also provides an understanding of the secular trends of risk factors for heart failure development, knowledge that is important for directing health care actions in the right direction.

As this work has shown, factors that increase risk of heart failure in women are factors that are largely influenced by today´s society and lifestyle. Therefore, primary care cannot act alone but must cooperate with other actors and societal institutions such as schools, workplaces, societal planners, and the Public Health Institute to facilitate a healthy lifestyle and to reduce symptoms of stress and depression in women. It is my hope and conviction that primary health care can stand strong in supporting women to make wise health decisions and can provide them with the best treatment available, as well as advise and help our policymakers and health planners to contribute to the best possible environment to prevent the development of heart failure in women.

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