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Incidence of heart failure in an urban population

–Reference to immigrant status, biological, life style and
socioeconomic risk factors

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Doctoral Dissertation

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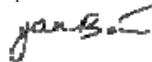
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Abstract The overall aim of the thesis was to study heart failure (HF) in an urban population, with reference to immigrant status, biological, life style and socioeconomic risk factors. The thesis is based on four papers. Paper I included inhabitants (N=114,917; aged 40-89 years) in the city of Malmö, Sweden, followed from November 1 st , 1990 until December 31 st , 2007. Paper II-IV used the population-based Malmö Diet and Cancer cohort (n=28,449; aged 45-73 years), followed from 1991-1996 until December 31 st , 2008 or June 30 th , 2009. Cases of HF were retrieved through the Swedish Hospital Discharge Register. Information on background characteristics in paper I was retrieved from the Population and Housing Census and the Swedish total population register. Participants in paper II-IV underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire. The risk of HF hospitalization was significantly higher among immigrants from Finland, Former Yugoslavia and Hungary compared to Swedish natives, after taking marital status, annual income and housing conditions into account. Furthermore, foreign-born had a significantly higher risk for HF hospitalization independently of hypertension, socioeconomic and several life-style risk factors. A significant interaction was seen between waist circumference and immigrant status on incident HF hospitalization; the increased HF risk was limited to immigrants with high waist circumference. Elevated body mass index, waist circumference, waist-hip ratio, body fat percentage and weight increased the risk of HF hospitalization in both sexes, independently of several sociodemographic, life style and biological factors. The joint exposure of high body mass index and high waist-hip ratio, or waist circumference, further increased the risk for HF hospitalization. In addition, the top quartile compared to the bottom quartile of red cell distribution width had a significantly higher risk for HF hospitalization after adjusting for other risk factors. In conclusion, there are substantial differences in risk of hospitalization due to HF among immigrants from different countries. Immigrant status was associated with risk of HF hospitalization independently of hypertension, socioeconomic and several life-style risk factors. Obesity is a risk factor for HF hospitalization, and the joint exposure to high body mass index and high waist-hip ratio or waist circumference further increased the HF risk. Red cell distribution width was found to be associated with long-term incidence of first hospitalization due to HF among middle-aged subjects.		
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–Reference to immigrant status, biological, life style and
socioeconomic risk factors

Yan Borné



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Doctoral thesis

2012

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Cover: Photo of Malmö by Nils Borné and Heart by Tina Borné

To

My mother Professor **陳懋湘**

My father Professor **章文洪**

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Abstract

The overall aim of the thesis was to study heart failure (HF) in an urban population, with reference to immigrant status, biological, life style and socioeconomic risk factors.

The thesis is based on four papers. Paper I included inhabitants (N=114,917; aged 40-89 years) in the city of Malmö, Sweden, followed from November 1st, 1990 until December 31st, 2007. Paper II-IV used the population-based Malmö Diet and Cancer cohort (n=28,449; aged 45-73 years), followed from 1991-1996 until December 31st, 2008 or June 30th, 2009. Cases of HF were retrieved through the Swedish Hospital Discharge Register. Information on background characteristics in paper I was retrieved from the Population and Housing Census and the Swedish total population register. Participants in paper II-IV underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire.

The risk of HF hospitalization was significantly higher among immigrants from Finland, Former Yugoslavia and Hungary compared to Swedish natives, after taking marital status, annual income and housing conditions into account. Furthermore, foreign-born had a significantly higher risk for HF hospitalization independently of hypertension, socioeconomic and several life-style risk factors. A significant interaction was seen between waist circumference and immigrant status on incident HF hospitalization; the increased HF risk was limited to immigrants with high waist circumference. Elevated body mass index, waist circumference, waist-hip ratio, body fat percentage and weight increased the risk of HF hospitalization in both sexes, independently of several sociodemographic, life style and biological factors. The joint exposure of high body mass index and high waist-hip ratio, or waist circumference, further increased the risk for HF hospitalization. In addition, the top quartile compared to the bottom quartile of red cell distribution width had a significantly higher risk for HF hospitalization after adjusting for other risk factors.

In conclusion, there are substantial differences in risk of hospitalization due to HF among immigrants from different countries. Immigrant status was associated with risk of HF hospitalization independently of hypertension, socioeconomic and several life-style risk factors. Obesity is a risk factor for HF hospitalization, and the joint exposure to high body mass index and high waist-hip ratio or waist circumference further increased the HF risk. Red cell distribution width was found to be associated with long-term incidence of first hospitalization due to HF among middle-aged subjects.

List of original papers

- I. **Borné Y**, Engström G, Essén B, Sundquist J, Hedblad B.
Country of birth and risk of hospitalization due to heart failure: a Swedish population-based cohort study. *European Journal of Epidemiology* 2011, 26(4):275-283.
- II. **Borné Y**, Engström G, Essén B, Hedblad B.
Immigrant status and increased risk of heart failure: the role of hypertension and life-style risk factors. *BMC Cardiovasc Disord* 2012, 12(1):20.
- III. **Borné Y**, Hedblad B, Essén B, Engström G.
Anthropometric measures in relation to risk of heart failure hospitalization: a Swedish population-based cohort study. Accepted (October 2012) for publication in *European Journal of Public Health*
- IV. **Borné Y**, Smith JG, Melander O, Hedblad B, Engström G.
Red cell distribution width and risk for first hospitalization due to heart failure: a population-based cohort study. *European Journal of Heart Failure* 2011,13(12):1355-1361.

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Abbreviations

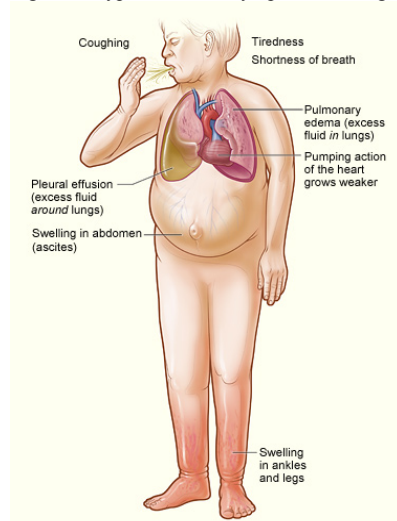
BMI	Body mass index
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
EF	Ejection fraction
ESC	European Society of Cardiology
HF	Heart failure
HR	Hazard ratio
hsCRP	high-sensitive C-reactive protein
ICD	International Classification of Diseases
IHD	Ischemic heart disease
LV	Left ventricular
MDC	Malmö Diet and Cancer study
MDC-CC	Malmö Diet and Cancer cardiovascular cohort
MI	Myocardial infarction
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NHANES I	The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous coronary artery intervention
RDW	Red cell distribution width
RAAS	Renin angiotensin-aldosterone system
SEK	Swedish Kronor
WC	Waist circumference
WHR	Waist to hip ratio

Introduction

Definition and clinical characteristics of heart failure

Heart failure (HF) can be defined as a complex clinical syndrome secondary to abnormality of cardiac structure or function which impairs heart to deliver oxygen at a rate commensurate with the metabolizing tissues requirements [1]. Typical clinical symptoms and signs of HF are: shortness of breath or trouble breathing, swelling in the ankles, feet, legs and fatigue (tiredness); elevated jugular venous pressure, pulmonary crackles, and displaced apex beat [1], figure 1.

Figure 1. Typical clinical symptoms and signs of heart failure.



(Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services)

There are many different terminologies used to describe HF. HF with a reduced left ventricular (LV) ejection fraction (EF) or “systolic HF” refer to the patients with an $EF \leq 35\%$, the normal LVEF generally considered to be $>50\%$ [1]. HF with preserved LVEF or “diastolic HF”, referring to patients with an LVEF in the range of 35-50%, is more complex and requires information from several echocardiographic measures and natriuretic peptides or invasive haemodynamic measures [1, 2]. Thus, the HF with preserved LVEF patients, including 1) those with isolated diastolic LV dysfunction; and 2) those with isolated right ventricular dysfunction, do not have a dilated heart. However, cardiac output may be reduced and many have an increased

LV wall thickness and increased left atrial size [1]. HF is also categorized according to the New York Heart Association (NYHA) function classification of cardiac disease based on the symptomatic severity, Table 1. Another terminology is based on the time-course, i.e. “chronic HF” vs. “acute HF”.

Table1. New York Heart Association (NYHA) function classification of cardiac disease

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity and no symptoms.
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but mild symptoms (fatigue, palpitation, or dyspnea) during ordinary physical activity.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, symptoms during less than ordinary activity.
Class IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. Mostly bed bound patients.

(Modified from The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256)

Aetiology and pathophysiology of heart failure

Most cases of HF are caused by hypertension and coronary heart disease (CHD) [3-7]. The NHANES I (First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study) in the United States reported that CHD attribute to more than 60% of the HF in the general population [8]. The Framingham Heart Study found that hypertension contributes to 75% of HF, account for 39% of HF events in men and 59% in women [7]. Hypertension is usually accompanied by CHD, diabetes, LV hypertrophy or valve disease. Myocardial infarction (MI) account for 34% in men and 13% in women and valvular heart disease account for 7-8% [7].

HF begins as initial decline in pumping capacity of the heart related to an index event such as a coronary event or onset of atrial fibrillation. The ventricle remodeling with dilatation and impaired contractility leads to reduced EF. The adrenergic nervous system, the renin angiotensin-aldosterone system (RAAS) and the cytokine system are activated to compensate the decline in pumping capacity of the heart. In the short-term, the HF remains asymptomatic since these systems are able to restore cardiovascular function to a normal homeostatic range. However, in the long-term, the compensatory mechanisms of these systems can lead to increasing enlargement of LV and decline EF, worsening LV remodeling and subsequent cardiac decompensation, and the HF goes from asymptomatic to symptomatic [9].

Diagnosis of heart failure

Diagnosis of HF begins with assessment of symptoms and signs, patients’ medical history. Echocardiographic examination to evaluate cardiac structure and LVEF is today considered an obligate cornerstone in the diagnosis of HF, although magnetic resonance imaging and invasive hemodynamic examinations are regarded as more

exact methods [1]. Other recommendations for the diagnostic investigation of HF are: electrocardiogram to determine heart rhythm, heart rate, QRS duration and other abnormalities; a complete blood count, measurements of blood chemistry, thyroid function and natriuretic peptides (B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP) or Mid-regional pro-atrial natriuretic peptide (MR-proANP)); and eventually an X-ray to identify pulmonary congestion/oedema, but also for differential diagnosis purposes regarding lung diseases [1].

Epidemiology of heart failure

HF is one of the leading causes for morbidity and mortality, particularly in elderly [10, 11] because of the increased aging populations and the prolongation of the lives of cardiac patients by modern therapy. Worldwide, HF affects 23 million people [12]. Approximately 1-2% of the adult population in the developed countries has HF [13]. HF affects approximately 4.7 million people in the United States [13]. In Europe, European Society of Cardiology (ESC) estimated that 10 million out of 900 million people had HF [14]. About half million cases of HF are diagnosed annually in both the US or Europe [15]. In North America and Europe, the lifetime risk to develop HF is 1 in 5 for a 40 year-old [12].

The overall mortality for HF patients is high. A Task Force for the diagnosis and treatment of chronic HF of the ESC reported 2005 that half of HF patients will die within four years, and more than half of the patients with severe HF will die within 1 year [14]. In the Framingham study, median survival after HF diagnosis was 1.7 years for men and 3.2 years for women, and only 25% of men and 38% of women survived 5 years [13]. There is a trend of improved survival in HF, and women seem to have better overall prognosis than men, but women have worse functional capacity [16].

Heart failure in Sweden

In Sweden, there are 200 000-300 000 patients with HF symptoms and a similar amount of patients have significant LV dysfunction [6]. The mean age for diagnosed HF is 75 years [17]. HF is the most common hospitalization diagnosis in patients aged 65 years and over, and the total annual costs for HF management are approximately 2% of the Swedish health care budget [18]. In the Swedish Heart Failure Registry one-year mortality rate among HF patients was 19-21% [19, 20]. In a national study, during 1998 and 2004, 59% of HF patients hospitalized due to HF had died within 5 years [21]. However, the HF mortality rate varies with age, one-year mortality rate for those aged below 65 years was 6% [20]. The corresponding figures for those aged 65-74 years, 75-84 years and 85 years or older were 11%, 20% and 38%, respectively [20].

Risk factors for heart failure

HF is a multifactorial process involving several risk factors. Traditional risk factors that have been associated with incidence of HF includes age, male sex, diabetes,

hypertension, inflammation, overweight/obesity, smoking, high alcohol consumption, low physical activity, socioeconomic factors, valvular heart disease (especially aortic stenosis and mitralis insufficiency) and CHD [7, 8, 10, 11, 22-31]. Incidence of HF increases with age, most cases occur in the elderly, and incidence is higher in men than women [3, 8, 10, 27, 32]. Diabetes is one of the most common risk factors for HF [8, 13, 25, 32, 33]. Diabetes increases the risk of HF by inducing myocardial structural and functional change or attributes to hypertension, obesity and dyslipidemia. Obesity per se is associated with diabetes, hypertension, inflammation, dyslipidemia and LV hypertrophy [8, 27, 34-38]. Low-graded inflammation, in terms of raised levels of various biomarkers in the blood (e.g. acute phase proteins, erythrocyte sedimentation rate, leucocytes), has also been shown associated to the development of HF [24, 39-42]. Low socioeconomic status increases the risk of HF [23, 43]. Low level of education has been shown associated with high biologic and behavior risk factors for HF, e.g. smoking, overweight, hypertension, diabetes, alcohol consumption [44-46].

Current knowledge on heart failure and reference to immigrant status, biological, life style and socioeconomic risk factors

Heart failure and immigrant status

People move for various reasons, e.g. war, starvation, environmental disasters, persecution, poverty or social circumstances [47]. Today, with increased globalization, migration becomes a growing phenomenon throughout the world, including Europe and Sweden. Migrants' health reflects influences from many factors, e.g. country of birth, genetic and social heritage, the reason for migration, as well as effects of migration and acculturation. Migrants with diverse cultural background would likely impact health status in the host country.

Marmot et al investigated, almost 40 years ago, prevalence and incidence of hypertension and CHD among Japanese men living in Japan, and those who had migrated to Hawaii and California [48, 49]. The rate of CHD was found lowest in Japan, intermediate in Hawaii (i.e. large Japanese community) and highest in California (i.e. more "westernized" Japanese). In Britain, mortality risk in cardiovascular disease (CVD) has been found lower in immigrants from France, Italy and Spain and higher in immigrants from the India compared to British natives; mortality in respiratory disease and cancer were generally low among immigrants compared to British natives [50]. However, a recent review of data sources for studies of ethnic groups reported that high-quality routine data on the health status of migrants and ethnic minority populations are generally not available in Europe. For several EU Member States, no relevant data could be identified [51].

Immigration to Sweden has increased markedly during the last decades, especially of refugees during the Balkan wars in the 1990s, from the Middle East in the first decade of this millennium, and of labour immigrants from the European Community. Previously the labor immigration has been very restricted with exception from the Nordic countries, which have been without barriers, dominated by the Finns. The

proportion of foreign-born people in Sweden increased from 9.2% in 1990 to 13.8% in 2008 [52]. The corresponding figures in Malmö, the third largest city in Sweden, were 16% and 28%, respectively [52]. It has been reported that foreign-born compared to Swedish-born people have higher risk for and higher mortality rate from CVD [53-55]. Previous studies from Malmö have shown that there are substantial differences in risk of CVD between residential areas with high and low proportion of immigrants [56-58]. In addition, in a study of the whole middle-aged Malmö city population in 1990, immigrants from Yugoslavia and Hungary had higher, and immigrants from Romania had lower risk for incident stroke during a 10 year follow-up compared to Swedish natives [59]. These associations were not explained by age, sex, income or marital or house status. Whether similar association exists between immigration status and risk of HF is largely unknown.

Heart failure and different anthropometric measures

Obesity is a major risk factor for CVD [60-64], including an increased risk of HF [8, 26, 65]. The underlying causal links between obesity and cardiac dysfunction are complex [66]. It is still controversial which anthropometric measure is most useful for assessment of the cardiovascular risk [61, 67-70]. Body mass index (BMI), being the marker for general fat, is the most practical and commonly used. However, the INTERHEART study, a multinational case-control study of MI, reported substantially stronger relationships for the waist to hip ratio (WHR) than for BMI [62]. Since visceral fat is more metabolically active than other fat tissues, it has been proposed that WHR or waist circumference (WC) is preferable [61, 71].

Heart failure and red cell distribution width

Red cell distribution width (RDW) is a measure of anisocytosis or variation in the volume of circulating erythrocytes. Recent studies have established RDW as a strong independent predictor of prognosis in HF patients [72-77], and for new symptomatic HF in subjects with a history of MI [78]. Felker et al. first reported higher RDW as a novel predictor of morbidity and mortality among chronic HF patients in a large clinical trial [72]. Subsequent studies have validated this observation, and demonstrated that high RDW is associated with worse long-term outcome and adding to other prognostic variables such as natriuretic peptides (e.g. NT-proBNP) [77], independently of haemoglobin levels and anaemia status [73]. Inflammation, ineffective erythropoiesis, undernutrition, and impaired renal function have been suggested as potential mechanisms linking RDW to outcome [74], however results have not been consistent [77]. Furthermore, all these studies (60-65) included subjects with previous HF or CVD, circumstances which potentially could confound the relationship between RDW and HF.

Scope of the thesis

Incidence of HF among immigrants in Sweden is largely unknown, and it is unclear whether it could be associated with biological, life style and socioeconomic risk factors. In addition, few have studied the relationships between different anthropometric measures and incidence of HF, and the results are not consistent. Furthermore, to the best of our knowledge, there are no studies on the association between RDW and risk of HF in subjects from the general population without a history of HF or MI.

Aims of the thesis

General aim

The general aim of this thesis has been to investigate the incidence of HF in an urban population, with special reference to immigrant status, biological, life style and socioeconomic risk factors.

Specific aims

The purposes of this thesis were to explore:

In Paper I; the relationship between country of birth and risk of HF hospitalizations after taking age, sex and socioeconomic indicators into account.

In Paper II; 1) the association between immigration status and risk of HF hospitalization and to what extent the relationship is explained by conventional cardiovascular risk factors; and 2) whether immigrant status is related to case-fatality (i.e. one-month mortality and one-year mortality) after HF.

In Paper III; 1) the relationship between risk of HF hospitalization and different anthropometric measurements, weight, BMI, WC, WHR, body fat percentage and height,; and 2) if there is any combined effect of the different anthropometric measurements on the risk of HF.

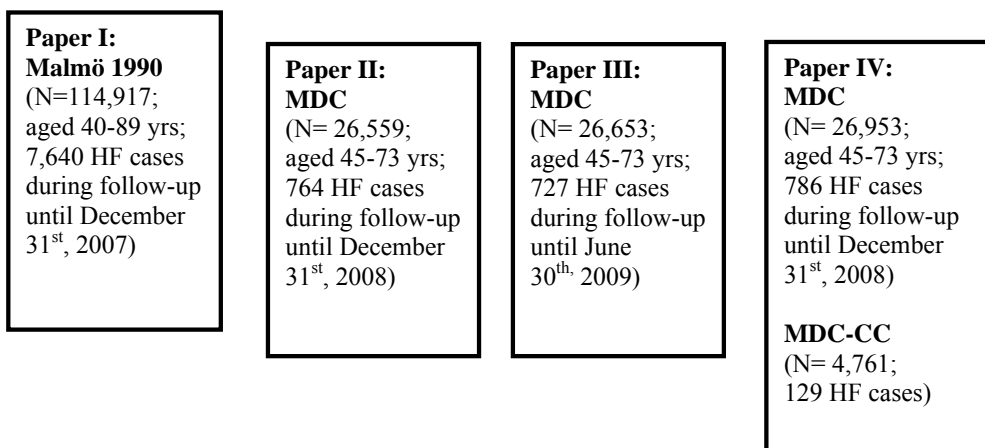
In Paper IV; 1) the relationships between RDW and risk of hospitalization due to HF in asymptomatic middle-aged subjects; and 2) if this relationship was modified by novel biomarkers, including hemodynamic stress (NT-proBNP), renal function (cystatin C) and inflammation markers (leukocyte count and high-sensitive C-reactive protein (hsCRP)).

Materials and Methods

The population of Malmö is the material for the paper I-IV of this thesis. Malmö is a city in southern Sweden, with approximately 230,000 inhabitants in the 1990, and 280,000 inhabitants in 2007 [52]. In 1990 around 16% of the Malmö population was born outside of Sweden. The corresponding figure in 2008 was 28% [52]. Immigrants mainly came from Denmark, Former Yugoslavia, Finland, Germany, Poland and Hungary [52].

Study population

Description of study materials in the present thesis



Paper I

The Malmö 1990 cohort

The study population consisted of a total of 118,134 subjects, aged 40 to 89 years, all registered as residents in the city of Malmö November 1st, 1990. After excluding subjects with history of MI (n=2,133) or those who were hospitalized due to HF (n=1,714) before November 1st 1990, 114,917 (50,981 men and 63,936 women) subjects remained. All subjects were followed from November 1st, 1990 until first

hospitalization attributable to HF, MI, death, emigration from Sweden, or December 31st, 2007, whichever came first.

Population Registers

Information about the background characteristics was retrieved from the Population and Housing Census (“Folk- och bostadsräkning”) in 1990 [79]. This survey is a total register of the Swedish population November 1st, 1990, and includes information on marital status, rented and self-owned homes, annual income and country of birth. This database consists of information from a mailed self-administered questionnaire and data from other population registers. Failure to complete and return the questionnaire was associated with a financial penalty. Information on annual income was retrieved from the Swedish income register, i.e. assessment of taxes in 1991 (for the income year 1990). Information on country of birth and marital status were retrieved from the Swedish total population register. Information on education, occupation and housing condition were based on self-reported questionnaires. The response rate of the questionnaire was 97.5%. Information about migration and deaths during the follow-up period was retrieved from the Swedish population register and the Swedish Cause of Death Register.

Paper II-V

The Malmö Diet and Cancer study (MDC)

MDC is a prospective cohort study from the city of Malmö in southern Sweden. In all, 28,449 men (N=11,246, born 1923-1945) and women (N=17,203, born 1923-1950) aged 45- to 73-years attended the baseline examination between March 1991 and September 1996. Participants underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire [80]. Participation rate and representativity in the MDC study has been described in detail elsewhere [81].

The MDC cardiovascular cohort (MDC-CC)

Between October 1991 and February 1994, a randomly selected subgroup was invited to take part in a study of the epidemiology of carotid artery disease, the MDC-CC [28, 82]. This subcohort includes 6,103 subjects, of whom 5,533 subjects donated blood after fasting conditions [83]. Data on NT-proBNP, cystatin C and hsCRP were available for 4,761 subjects (aged 46-68 years, 60% women). This subcohort in the MDC-CC with data on biomarkers did not differ from the whole MDC cohort in terms of age, sex, biological, lifestyle and socio-economic factors [83].

Case retrieval and definition of endpoints

HF cases were retrieved by record linkage with the Swedish Hospital Discharge Register [84]. Subjects with a hospital discharge diagnosis of HF (International

Classification of Diseases, ICD, 8th code 427.00, 427.10, 428.99; ICD, 9th code 428; and ICD, 10th code I50, I11.0, respectively) as the primary diagnosis were considered to have HF.

Cases of acute MI were retrieved by record linkage with registers of hospital discharges and deaths in accordance to diagnosis criteria used in the National MI register [85]. Non-fatal MI was defined as 410 (ICD-8 and 9) or I21 (ICD-10). Information about percutaneous coronary artery intervention (PCI) was retrieved from the national Swedish Coronary Angiography and Angioplasty Register [86]. Information on coronary artery bypass graft surgery (CABG) was retrieved from the Swedish Hospital Discharge Register. Information on mortality was obtained through the Swedish Cause of Death Register.

A validation study has shown that a primary diagnosis of HF in the Swedish Hospital Discharge Register has a validity of 95% [84]. The corresponding figure for MI is 94% [87].

Heart failure risk factors definitions and measurements

Paper I

Country of birth

Information about country of birth was available for 99.96% of the population (51 missing). Immigrants from countries (i.e. USA, Iraq, Ghana, etc) for which the total follow-up time was less than 2,500 person years were excluded. As in a previous study from this cohort, the Peoples Republic of China and Vietnam were grouped into one category [59]. Thus, selected countries in the analysis contained 98.1% of the cohort.

In an additional analysis, country of birth was also categorized into low income countries (i.e. \leq \$610), middle income countries (i.e. \$611-\$7,620) and high income countries (i.e. $>$ \$7,620) based on 1990 Gross national income per capita in \$ [88].

Socioeconomic status

Socioeconomic indicators used for the analysis were marital status, total annual income and housing status as previous studies have shown their association with HF [23, 43, 89-92].

Marital status was categorized into married, single, divorced, or widowed [59]. The total annual income 1990 (in Swedish Kronor (SEK)) was categorized into 6 categories: 0 to 50,000; 50,100 to 100,000; 100,100 to 150,000; 150,100 to 200,000; 200,100 to 250,000; and $>$ 250,000. November 1st, 1990, \$1 corresponded to 5.62 SEK.

Annual income might not fully reflect the socioeconomic differences among people, i.e. retired people or women with low income in the high income household. Rented home was associated with cardiovascular mortality in a Swedish study [92]. Therefore, the results were also adjusted for housing status. Housing status was grouped into self-owned home (house or apartment) or rented home. Among the population, 55.6% owned their house or apartment, and 40.5% rented their apartment first or second hand. Subjects with missing data on housing status (3.9%) were in the analysis coded in a separate category.

Paper II-IV

Information on current use of nitroglycerin, blood pressure-lowering, lipid-lowering or anti-diabetic medications, smoking habits, alcohol consumption, leisure time physical activity, educational level, marital status and country of birth were obtained from a self-administered questionnaire [83].

Measurement and definition of biological factors

- History of coronary artery disease (CAD) at baseline was defined as either current treatment with nitroglycerin or previous PCI or CABG revascularization.
- Blood pressure was measured using a mercury-column sphygmomanometer after 10 min of rest in the supine position.
- Hypertension was defined as blood pressure equal or above 140/90 mm Hg or current use of blood pressure-lowering medication.
- Diabetes mellitus was defined as fasting whole blood glucose level greater than 109 mg/dL (i.e. 6.0 mmol/L), self-reported physician's diagnosis of diabetes or use of anti-diabetic medications.
- WC (in cm) was measured midway between the lowest rib margin and iliac crest. WC was stratified into normal WC and high WC (≥ 94 cm for men and ≥ 80 cm for women) [93].
- WHR was defined as the ratio of circumference of waist to hip.
- BMI was calculated as weight (kg) divided by the square of the height (m^2).
- BF% was calculated using an algorithm, according to procedures provided by the manufacturer (Bioelectrical impedance analysis 103, RJL systems, single-frequency analyser, Detroit, USA) [94].
- Leucocyte concentrations was analysed consecutively in fresh heparinized blood.
- RDW, haemoglobin were analysed consecutively in fresh heparinized blood. Erythrocyte diameter was measured using a fully automated assay (SYSMEX

K1000). RDW was calculated as the width of the erythrocyte distribution curve at a relative height of 20% above the baseline.

Definitions of lifestyle factors

- Subjects were categorized into current smokers (i.e. those who smoked regularly or occasionally) or non-smokers (i.e. former smokers and never smokers).
- High alcohol consumption was defined as >40 g alcohol per day for men and >30 g per day for women.
- Low level of physical activity was defined as the lowest tertile of a score revealed through 18 questions covering a range of activities in the four seasons. The evaluation of the questionnaire has been previously reported [95]

Definition of socioeconomic factors

- Immigrant status was grouped as Swedish-born and foreign-born.
- Educational level was defined as low education (up to grade 9) and high (> 9 years) [85].
- Marital status was categorized into married or unmarried [85].

Measurement of cardiovascular biomarkers in the MDC-CC

NT-proBNP, Cystatin C and high-sensitive C-reactive protein in the MDC-CC were analysed in fasting plasma samples that had been frozen at -80°C immediately after collection without previous thawing [83].

Statistics

SPSS version 15.0 and PASW version 18 were used in the statistical analysis. A p -value <0.05 was considered as statistically significant.

In paper I hazard ratios (HR), with 95% confidence interval (CI) were calculated using Cox proportional hazards regression models. Sweden was used as the reference group in all analysis in terms of country of birth. HRs were first adjusted for baseline age and sex, then additionally adjusted for marital status (4 categories), annual income (6 categories) and housing status (3 categories). Possible interaction between age and income, and between country of birth and sex, respectively, on risk of HF was explored by introducing interaction terms in the multivariate models.

In paper II Cox proportional hazards regression and the Kaplan-Meier curve was used to examine the association between selected immigrant status and risk of HF hospitalization. Age and sex were included as covariates in the basic model. Secondly, we also adjusted for other possible confounders. Case-fatality rates were calculated as the proportion of those with a HF hospitalization that died within one- month and one-year, respectively. Cox proportional hazards regression was used and adjusted for age, sex and year of HF event.

In paper III Cox proportional hazards regression was used to examine the association between anthropometric measures (in sex-specific quartiles) and incidence of HF hospitalization. The Harrell's C statistics were calculated to assess the HF prediction efficiency. The log likelihood ratio was calculated to assess whether the model was improved by adding anthropometric measures to the explanatory variables. Possible interaction between anthropometric measures and age, sex and cardiovascular risk factors on incident HF was explored.

In paper IV cross-sectional relations of RDW quartiles to cardiovascular risk factors were assessed using one way ANOVA for continuous variables and logistic regression for dichotomous variables. P-values from trend tests across quartiles were used. Cox proportional hazards regression was used to examine the association between RDW (in sex-specific quartiles) and incidence of HF. Time axis was time from screening to follow-up until death, emigration, incident HF, or end of follow-up. HRs with 95% CIs were calculated. Possible interaction between RDW and age, sex and cardiovascular risk factors on HF was explored by introducing interaction terms in the multivariate model.

Ethical approvals

The studies comply with the Declaration of Helsinki. The Malmö 1990 cohort was approved by the Lund University Ethics review Committee (LU 78-02 and 2009/46). The MDC cohort was approved by the ethics committee at Lund University, Lund, Sweden (LU 51/90). The MDC is registered in the US Library of Medicine as trial number NCT 01216228. All participants provided written informed consent.

Results and conclusions of paper I-IV

I. Country of birth and risk of hospitalization due to heart failure: a Swedish population-based cohort study.

Results

Risk of hospitalization due to HF in relation to country of birth

During a mean follow-up of 13.5±5.3 years, a total of 7,640 individuals (3,624 men and 4,016 women) were discharged from hospital with first time HF as primary diagnosis. The incidence of hospitalized HF per 10,000 person-years was 53 in men and 46 in women, respectively. Incident HF increased significantly and linearly by age, in 5-year age groups from 3 per 10,000 person-years in subjects aged 40-44 years to 267 per 10,000 person-years in subjects aged 85-89 years (p for trend <0.001).

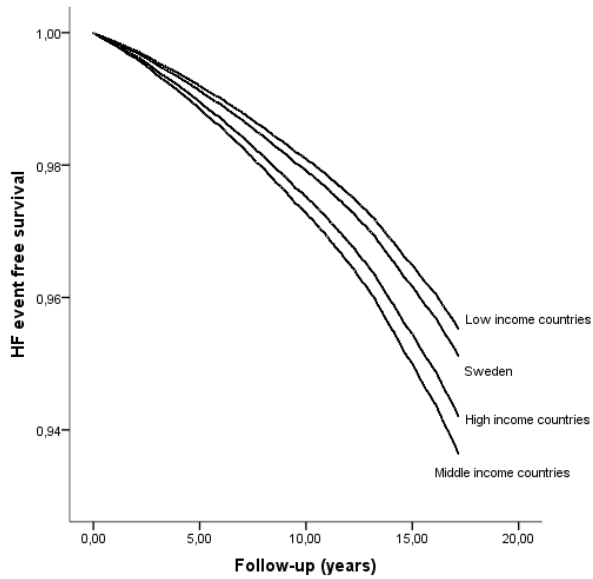
The overall analysis showed substantial differences in risk in terms of hospitalization due to HF between countries of birth (p <0.001, 19df). The risk of HF was significantly higher among immigrants from Finland (HR, 1.40; 95% CI, 1.10 to 1.81), Former Yugoslavia (HR, 1.45; 1.23 to 1.72) and Hungary (HR, 1.48; 1.16 to 1.89) compared to Swedish natives, after taking marital status, annual income and housing conditions into account.

Risk of hospitalization due to HF in relation to age, sex and socioeconomic indicators

Age and male sex were, independently of marital status, housing condition and annual income, related to an increased risk of HF hospitalization. Single, divorced and widowed compared to married subjects were also independently associated with increased risk for hospitalization due to HF. In addition, renting house and low annual income were associated with higher risk for HF.

Additional analyses were performed by categorizing country of birth for immigrants into high, middle and low income countries. A significant higher risk, compared to Swedish natives, was observed among immigrants from high-income countries (HR, 1.12; 1.01 to 1.25) and middle-income (HR, 1.14; 1.02 to 1.26). This risk increase was independent of age, sex, marital status and socioeconomic indicators, Figure 2.

Figure 2. Age and sex-adjusted risk for hospitalization due to HF in relation to country of birth of immigrants and annual income based on 1990 GNI (Gross National Income).



Conclusion

There were substantial differences in risk of HF hospitalization among immigrants from different countries that cannot be explained by selected socioeconomic factors.

II. Immigrant status and increased risk of heart failure: the role of hypertension and life-style risk factors.

Results

Overall, mean age at baseline was 58 ± 7.6 years and 61.5% were women. A total of 23,430 subjects were born in Sweden and 3,129 (11.8%) were born outside Sweden. Of those born outside Sweden, the majority came from Denmark (10.5%), Former Yugoslavia (8.3%), Finland (7.6%), Germany (8.8%), Poland (5.0%) and Hungary (4.3%).

Risk of HF hospitalizations in relation to immigrant status

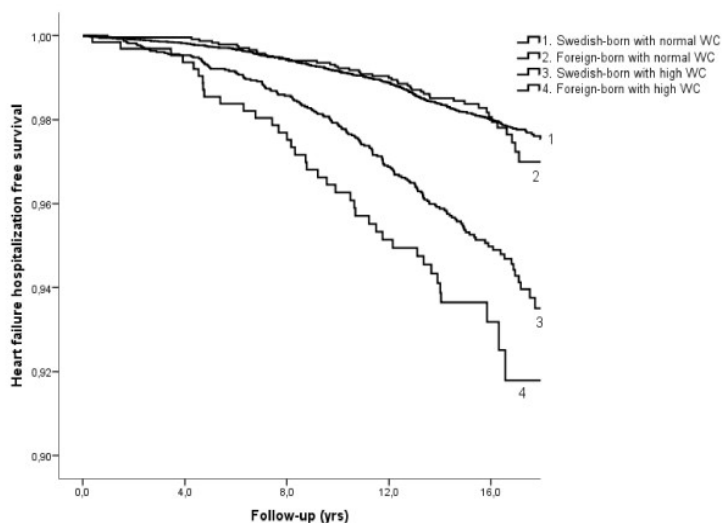
During a mean follow-up of 15 years, a total of 764 individuals (421 men and 343 women) were hospitalized with HF as primary diagnosis. Of them, 166 (96 men and 70 women) had an incident MI before or concurrent with HF hospitalization during follow-up.

Foreign-born had a significantly higher risk for HF (HR: 1.37; 1.08-1.73), after adjustment for other possible confounders. Age and male sex, increased WC, leukocyte count, systolic blood pressure, use of blood pressure-lowering medication, diabetes, smoking, high alcohol consumption, low physical activity, low educational level were independently associated with an increased risk for HF.

Interaction between immigrant status and other risk factors on incidence of HF

There was a statistically significant interaction between immigrant status and WC ($p < 0.001$) on incidence of HF. To further explore the interaction between country of birth and WC, WC was stratified into normal and high WC in men and women, respectively, figure 3. After stratification for WC, a significant higher risk of HF was only observed in foreign-born with high WC (HR: 2.11; 1.62-2.76), while foreign-born with normal WC had similar risk (HR: 1.17; 0.85-1.60) as compared to Swedish natives with normal WC.

Figure 3. Heart failure hospitalization free survival in relation to immigration status and high/normal waist circumference.



Case fatality

Thirty-two (4.2%) subjects died within one month after the HF hospitalization and 95 (18.9%) had died within one year after the hospitalization due to HF. Although not significant, foreign-born subjects tended to have lower one-month and one-year mortality (HR: 0.20; 95% CI: 0.03-1.44, $p=0.109$ and HR: 0.47; 0.22-1.01, $p=0.053$, respectively), after adjustment for age, sex and year of the HF hospitalization.

Conclusion

Immigrant status was associated with long-term risk of HF hospitalization, independently of hypertension and several life-style risk factors. There was a significant interaction between WC and immigrant status on incident HF; the increased HF risk was limited to immigrants with high WC.

III. Anthropometric measures in relation to risk of heart failure hospitalization: a Swedish population-based cohort study.

Results

Risk of HF hospitalizations in relation to anthropometric measures

During a mean follow-up of 14 years, a total of 727 individuals (398 men and 329 women) were hospitalized with HF as primary diagnosis. Of them, 157 (91 men and 66 women) had an incident MI before or concurrent with HF hospitalization during follow-up.

Overweight and obesity increased the risk of HF hospitalization independently from several sociodemographic, lifestyle and biological factors. BMI, WC, WHR and body fat percentage were significantly related to an increased risk of HF in both sexes. Taking potential confounding factors into account, the HR of all HF hospitalization (4th vs 1st quartile) were 1.88 (1.50-2.34) for WC, 1.80 (95% CI: 1.45-2.24) for BMI, 1.75 (1.42-2.16) for WHR, and 1.36 (1.09-1.69) for body fat percentage, figure 4.

C-statistics and p-value for model improvement was calculated. In model 1 all anthropometric measures significantly added information above risk factors. WC and WHR, but not body fat percentage, significantly added to the model on top of BMI. C-statistic results were marginally increased compared to a model including risk factors and BMI.

Risk of HF hospitalization in relation to combined pattern of different anthropometric measures

Significant interaction was observed between BMI and WHR ($p=0.004$), waist ($p=0.005$), weight ($p=0.010$) and height ($p=0.035$), respectively, on hospitalization due to HF. There were no significant interactions between age and any of the anthropometric measures. The joint exposure of high BMI (e.g. the top quartile) and high WHR (e.g. the top quartile) further increased the risk in an additive way, Table 2.

Figure 4. Adjusted hazard ratio (HR, 95% confidence interval) for different anthropometric measures (in sex-specific quartiles, Q1 to Q4) in relation to the risk of hospitalization due to heart failure.

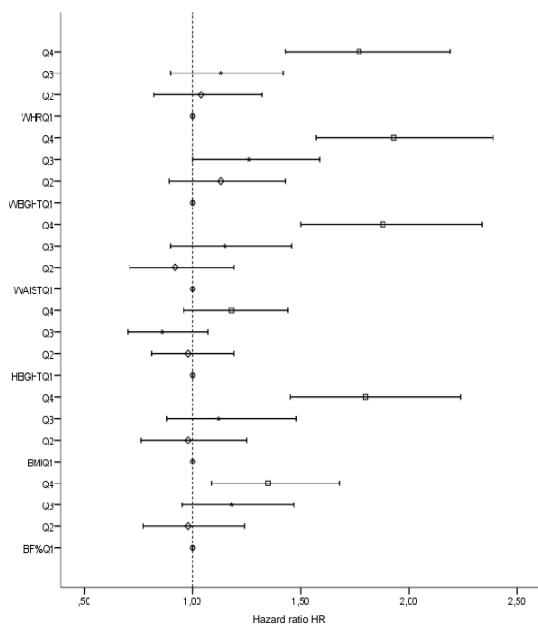


Table 2. Risk of HF hospitalization in relation to combined pattern of different anthropometric measures.

MDC (N=26,653)	Heart failure, n (per 1000 p-y)	Adjusted HR (95% CI)
BMI Q1-3, WHR Q1-3 (n=16,851)	316 (1.30)	1.00
BMI Q1-3, WHR Q4 (n= 3,138)	103 (2.34)	1.58 (1.26-1.98)
BMI Q4, WHR Q1-3 (n= 3,158)	119 (2.65)	1.66 (1.34-2.06)
BMI Q4, WHR Q4 (n= 3,506)	191(3.99)	2.13 (1.77-2.58)
BMI Q1-3, WC Q1-3 (n=18,460)	351 (1.32)	1.00
BMI Q1-3, WC Q4 (n= 1,529)	66 (3.11)	1.62 (1.24-2.11)
BMI Q4, WC Q1-3 (n= 1,638)	47 (1.99)	1.44 (1.06-1.95)
BMI Q4, WC Q4 (n= 5,026)	263 (3.80)	1.97 (1.67-2.34)

Hazard ratio HR adjusted for age, sex, civil status, education level, immigrant status, smoking habits, alcohol consumption, physical activities, blood pressure-lowering medication, lipid-lowering medication, systolic blood pressure, leukocyte count and diabetes mellitus. CI, confidence interval. p-y, person-years.

MDC, Malmö Diet and Cancer. BMI, body mass index. WHR, waist-hip ratio. WC, waist circumference.

Conclusion

Our results support the view that raised BMI, WC, WHR or body fat percentage increases the risk of HF hospitalization. The joint exposure of high BMI and high WHR or high WC further increased the risk in an additive way.

IV. Red cell distribution width and risk for first hospitalization due to heart failure: a population-based cohort study.

Results

Incidence of first hospitalizations due to heart failure in relation to red cell distribution width

During a mean follow-up of 15 years, a total of 773 individuals (423 men and 350 women) were diagnosed with HF. Of these, 166 (96 men and 70 women) had an incident MI before or concurrent with HF during follow-up.

Subjects in the top compared to the bottom quartile of RDW had a significantly higher risk for HF (HR: 1.47, 1.14–1.89), (*p* for trend 0.005), adjusting for all covariates, Table 3. If cases with MI before or concurrent with HF were included, the risk increase was rather similar (1.33, 1.07–1.66), (*p* for trend 0.020).

In the final model, age, male sex, history of CAD, systolic blood pressure, use of blood pressure-lowering medication, diabetes, WC, smoking, high alcohol consumption, low physical activity, low educational level, being unmarried, and leucocyte count were independently associated with an increased risk of HF. No significant interaction was observed between RDW and other risk factors on incidence of HF.

Table 3. Incidence of first hospitalization due to HF in relation to sex-specific quartiles (Q1–Q4) of RDW in the MDC cohort.

Sex-specific quartiles of RDW	Incident HF without prior MI			All incident HF		
	HF (N)	HR ^a	HR ^b	HF (N)	HR ^a	HR ^b
Q1 (<i>n</i> = 6685)	103	Reference	Reference	141	Reference	Reference
Q2 (<i>n</i> = 6640)	146	1.29 (1.00–1.66)	1.33 (1.03–1.71)	186	1.20 (0.96–1.49)	1.23 (0.99–1.53)
Q3 (<i>n</i> = 6732)	163	1.32 (1.03–1.70)	1.37 (1.07–1.77)	199	1.18 (0.95–1.46)	1.21 (0.97–1.51)
Q4 (<i>n</i> = 6727)	195	1.57 (1.23–2.00)	1.47 (1.14–1.89)	247	1.44 (1.17–1.77)	1.33 (1.07–1.66)
Total (<i>n</i> = 26 784)	607			773		
<i>p</i> for trend		<0.001	0.005		0.001	0.020

^aHazard ratio (HR) adjusted for age and sex.

^bHR adjusted for age, sex, history of coronary revascularization, use of nitroglycerin treatment, SBP, use of blood pressure-lowering medication, diabetes mellitus, waist circumference, smoking, high alcohol consumption, low physical activity, marital status, low education level, haemoglobin, and leucocyte count. CI, confidence interval.

Subgroup analysis with adjustment for other biomarkers

In the MDC-CC (n= 4761), the HR (95% CI) in the top compared to the bottom quartile of RDW was 1.85 (1.04–3.31, *p* for trend 0.039) taking all covariates included in the final model of the whole MDC into account. This risk was relatively unchanged (1.82; 1.01–3.31, *p* for trend 0.049), by adding hsCRP and cystatin C to the model; however, it became slightly reduced and non-significant (HR: 1.65; 0.90–3.00, *p* for trend 0.114) when NT-proBNP was also taken into account.

Conclusion

RDW was found to be associated with long-term incidence of first hospitalization due to HF among middle-aged subjects. The possible mechanism underlying the association between RDW and incident HF needs further investigation.

General discussion

Heart failure and immigration status

We found that immigrants in Sweden have higher risk for HF hospitalization compared to Swedish natives. Our results are consistent with previous studies on immigration status and cardiovascular risk in the city of Malmö, in Sweden, as well as from other countries [11, 53, 55, 57, 58, 96-98].

Paper I showed that there were substantial differences in risk of HF hospitalization among foreign-born subjects in the Malmö population, Sweden. Increased incidence of HF hospitalizations was found among immigrants from Finland, Former Yugoslavia and Hungary. However, in that paper it was still unclear to what extent the observed increased risk in these groups could be explained by major biological and lifestyle risk factors for HF, e.g., hypertension, overweight, and smoking.

As retrieving individual data from a complete urban population is not feasible, we used the MDC cohort to further explore the association of immigration status and risk of HF hospitalization. In paper II, we found a wide range of biological and life-style risk factors independently associated with risk for HF. In that study the increased HF risk in foreign-born subjects remained after taking age, gender, blood pressure, treatment for hypertension or hyperlipidemia, WC, leucocyte count, diabetes, smoking, alcohol consumption, physical activity, marital status and education into account. It was concluded that being foreign-born is associated with significantly higher risk for HF hospitalization, independent of several biological, lifestyle and socioeconomic risk factors. Furthermore, the results from the MDC cohort also showed that the increased risk among immigrants is modified by the presence of other risk factors. There was a significant interaction between WC and immigrant status on risk of HF hospitalizations, and the increased incidence was mainly observed in those with high WC.

Possible explanations

International migrants are not a homogeneous group in terms of health risk. One possible explanation for the observed increased risk of HF hospitalization in foreign-born compared to Swedish-born might be influences from their country of birth. The proportion of foreign-born was 15.2 in whole Malmö population (aged 40-89 years) and 11.8% in the MDC cohort (aged 45-73 years). This group mainly came from Denmark, Former Yugoslavia, Finland, Germany, Poland and Hungary. The majority of these countries have higher incidence of CVD compared to Sweden [99, 100]. Since most cases of HF are caused by hypertension or CHD, the high CVD risk in

their country of origin might partly explain the increased risk of hospitalization due to HF.

Another possible explanation could be different circumstances and reasons to migrate to Sweden. During 1965–1973 former Yugoslavians were often recruited by Swedish companies as labour immigrants with low skilled jobs, and from 1973 to 1990s, when the labour immigration was stopped, they often immigrated to Sweden for family reunion and as asylum. After the politic instability in Hungary 1956, many Hungarian immigrants came to Sweden as refugees. Finnish immigrants came to Sweden as labour migrants from 1945 to 1970s. This suggests that immigrants from the above mentioned countries to Sweden could be regarded as selected groups. To what extent this might influence risk of HF is unclear. A study of mortality of immigrants in England and Wales, found that all-cause standardized mortality ratio of immigrants are mostly lower than in their countries of origin, with an exception of male Irish immigrants [50]. This might suggest that first-generation immigrants are health selected and healthier than the population which they came, and male Irish immigrants reflected selection of disadvantage group and adverse effect of acculturation. In a Swedish study all-cause mortality risk was lower in the majority of immigrant groups compared to their country of birth [54].

A third explanation could be associated with low socioeconomic status of immigrants compared to Swedish natives. It has been shown that Former Yugoslavians had disadvantage into the labour markets compared to native Swedes [101]. In addition, it also matters where you live as substantial socioeconomic differences between residential areas in cities have been demonstrated. Studies have shown that residential areas in Malmö with high proportion of immigrants and low socioeconomic status have high incidence of CVD [56, 102]. However, when several socioeconomic indicators were adjusted for in paper I, the observed difference in risk of HF among immigrants from Finland, former Yugoslavia and Hungary still remained. This suggests that the increased risk of HF in immigrants from these countries is not completely mediated by the socioeconomic indicators. However, the significantly increased risk of HF for Danish immigrants was reduced and became non-significant when adjusted for SES, which suggest that socioeconomic circumstances still play a role. In the MDC cohort, foreign-born had higher education level than native Swedes and the results remained significant after adjustments for education and marital status. Thus, socioeconomic differences seem to be an insufficient explanation for the increased incidence of HF hospitalizations among foreign-born subjects.

In addition, before the baseline examination in 1990 the majority of these three immigration groups have lived in Sweden at least 20 years or more. One could assume that the high risk for hospitalization due to HF in the present study might also be the result of stress from cultural and psychosocial change to acculturate and integrate into the Swedish society. Immigrants with their own distinctive culture would undergo some degree of acculturation to incorporate culture attributes from the host countries in the process of migration, which often pose physical and psychological stress on migrants as they deal with changes and integration into different social and economic systems [103-105]. In a Swedish study, a low sense of coherence, poor acculturation (men only), poor sense of control, and economic

difficulties were strong risk factors for psychological distress [105]. However, another Swedish study has shown that Finnish labour migrants had higher risks for MI compared to Swedish natives, and that this increased risk still remained after 20 years in Sweden [106].

The highest risk for HF observed among foreign-born with high WC in the MDC cohort might provide some possible explanation to the higher risk of HF among immigrants from Finland, former Yugoslavia and Hungary. As a heterogeneous group there are substantial differences among immigrants to Sweden by country of birth [94, 107]. A previous cross-sectional study, based on the MDC cohort, found that women born in Hungary, Poland and Germany had higher WHR compared to Swedish-born women, after taking age, height, smoking, physical activity, occupation and percentage of body fat into account [94]. In men, WHR was increased in participants from Yugoslavia, Germany and Finland [94]. Although we, due to limited number of HF events, were unable to study immigrants by country of birth in the MDC cohort, several other studies have shown that increased abdominal adiposity is strongly associated with cardiovascular risk [26, 70, 108]. Inadequate exercise, over-intake of food or alcohol, metabolic imbalance and genetic abnormalities could cause high WC. A high WC could influence known cardiovascular risk factors, e.g., dyslipidemia, hypertension, glucose intolerance, inflammation markers [109-111], that increase the risk of developing HF.

In the MDC cohort, foreign-born tended to have lower one-month and one-year mortality after HF compared to Swedish-born subjects, but the difference did not reach statistical significance. This finding might be explained by the so-called "obesity paradox" [112], foreign-born had higher WC than Swedish-born in the MDC cohort, and overweight and high WC have paradoxically been shown associated with improved outcome among HF patients [112, 113]. It has also been reported that immigrants and native Swedish HF patients are quite similar in terms of symptoms, health care seeking, the distress level, physical function, emotional state and self-care [114, 115]. In addition, more immigrants than Swedes are referred to HF clinic after discharge for follow-ups [114], which could reduce mortality in this group.

It could also be speculated whether competing deaths could explain the lower case fatality rates in immigrants. Ischemic heart disease (IHD) is associated with high mortality and IHD has often been developed prior to HF. However, one study reported that immigrants in Sweden in general do not seem to have a higher mortality after a first MI than native Swedes, in particular when differences in socioeconomic status are accounted for [116]. Competing IHD mortality is therefore a less likely explanation for our results.

Heart failure and different anthropometric measures

In paper III, focusing on obesity and its association with HF risk, we found that overall weight, BMI, WC and WHR, respectively, were anthropometric measures significantly associated to the risk of HF hospitalization with largely the same effect sizes for all measures. Although statistically significant, body fat percentage showed

weaker relationships with HF. The relationships were independent of potential confounders, including multiple biological, lifestyle, and socio-economic factors.

Possible explanations

The underlying mechanism between obesity and HF is complex. Obesity is associated with a higher risk of hypertension, insulin resistance and diabetes mellitus [36, 65, 117, 118], which result in neurohormonal change and MI; obesity can also cause renal sodium retention, higher leptin [119] and inflammation oxidative stress [24, 37]. All of these circumstances can contribute to a haemodynamic overload, lead to LV hypertrophy, which increase the risk of HF [66, 120, 121]. The joint exposure of high WHR or high WC and high BMI further increased the risk in an additive way, which indicate that the location of body fat add additional information about risk of HF [67]. Abdominal adipose tissue, particularly visceral-fat deposits, has metabolic effects, which are associated with insulin resistance, dyslipidemia and elevated levels of inflammatory markers [122].

In our study, overweight or obesity measured by BMI, WC, WHR or body fat percentage, respectively, emerged as significant independent predictors of HF in multivariate models, taking several potential confounders into account. This suggests that obesity by itself, or by its mediated mechanisms, is responsible for the development of HF. IHD is another major cause of HF. In our additional analysis, the risk for HF hospitalization was only marginally changed after censoring 157 patients with incident nonfatal MI during follow-up period.

Heart failure and red cell distribution width

We also established a graded association between RDW and risk of first hospitalization due to HF independent of potential confounders, including multiple biological, lifestyle, and socio-economic factors. In a randomly selected subcohort of the MDC, which included information on NT-proBNP, hsCRP, and cystatin C, additional adjustment for these risk markers only slightly decreased the HR.

Possible explanations

The mechanism underlying the relationship between RDW and HF is unclear. It has been shown that activation of the RAAS is associated with increased erythropoiesis [123, 124], which also increases the RDW. Increased neuroendocrine activation is also associated with cardiac arrhythmia, and it is an important feature of HF and atrial fibrillation [125]. Hence, one could speculate that a possible link between RDW and HF could be increased levels of angiotensin or adrenergic hormones [126], which could increase RDW and reduce cardiac function.

RDW has been associated with low-graded systemic inflammation [127]. In our study, RDW was associated with leukocyte counts and hsCRP, e.g. classic markers of inflammation, which have previously been shown associated with incidence of HF [39]. However, the relationship between RDW and risk of HF hospitalizations remained unchanged when leukocytes or hsCRP were taken into account. This

suggests that inflammation is not the major mechanism for the increased incidence of HF in the present study. RDW was associated with several other risk factors, e.g. age, WC, smoking, high alcohol consumption, diabetes, blood pressure, history of CAD, leukocyte count, and being unmarried. However, RDW remained significant after adjustment for these risk factors, and there was no interaction between RDW and other risk factors on incidence of HF. Malnutrition and deficiency of vitamin B₁₂ and folic acid are other factors that are associated with high RDW, because of their role in erythropoiesis [74]. We did not have information on plasma levels of these vitamins, and it therefore remains unclear as to whether these factors contributed to the relationship between RDW and incident HF in our study.

Natriuretic peptides, e.g. NT-proBNP, is produced mainly in the cardiac ventricles and is involved in body fluid homoeostasis and blood pressure control [128-131]. Cystatin C is a marker of renal function that predicts cardiovascular events [132-134]. In the present study, both NT-proBNP and cystatin C were significantly associated with RDW. Adjustment for cystatin C and hsCRP only marginally affected the RDW risk for hospitalization due to HF, when NT-proBNP was also taken into account; the point estimate of HR for individuals belonging to the top quartile of RDW decreased from 1.85 (1.04–3.31) to 1.64 (0.90–3.00). However, the analysis of the MDC-CC was based on a substantially smaller sample and it is likely that the absence of a significant relationship could be explained by low statistical power.

Methodological considerations

Representativeness and generalizations

The health care in Sweden is a public, tax financed health care insurance system, and everyone is covered to the same extent independent of the amount of tax each individual paid. According to recently published Swedish studies, the Swedish health care system has achieved equality in the care and treatment of patients with HF [114, 135]. In these studies symptom recognition and health care seeking were rather similar among immigrants and native Swedes who were hospitalized due to HF. In the city of Malmö there is only one hospital and patients from all residential areas can reach the hospital within 15 min, so the availability of the hospital could be regarded to be similar for all patients.

In paper I, the Malmö 1990 cohort included the total middle-aged population living in the city of Malmö in 1990, and information on country of birth was available for almost all study subjects. Those who during the follow-up emigrated were censored at the time of emigration. However, re-migration from Sweden without reporting to the authorities could possibly exaggerate the population at risk and cause low risk estimates for some immigrant groups. A report from Sweden Statistics estimated that ~25,000 to 50,000 foreign-born individuals who officially live in Sweden have left the country [136]. A previous study from the present cohort explored whether exclusion of individuals without income, according to the assessments of taxes, had any impact on the relationships between country of birth and incidence of disease [59]. No major influence on HRs for incident stroke was found in that study. Therefore, we believe that a re-migrant effect is a minor problem in our study and should not explain the observed increased risk for HF related to country of birth.

In paper II-IV, the MDC cohort included a large numbers of subjects with a long follow-up period and identified large numbers of HF events. The 40.8% participation rate in the MDC study questions the representativity of the population [81]. Mortality has been shown significantly higher in non-participants both during and following the recruitment period [81]. In that study, participants in the MDC study were also compared to participants in a mailed health survey performed in Malmö 1994, with regard to subjective health, lifestyle and sociodemographic characteristics. The proportion reporting good health was found higher in the MDC study than in the mailed health survey (where 75% participated), however socioeconomic structure and prevalence of smoking and overweight/obesity was similar [81]. In paper II, based on the MDC cohort, we were unable to study immigrants by country of origin due to limited number of HF events, and the study design required that participants could speak Swedish language. Thus, one question is whether this group of immigrants is representative to all immigrants in the city. Among all subjects aged 45-73 years in

the whole Malmö population, foreign-born had a significantly higher age and sex-adjusted risk for HF (HR: 1.27; 1.17-1.38) compared to Swedish-born after adjustment for age and sex in paper I. Corresponding HR in the MDC cohort was 1.44 (1.14-1.82), and we therefore believe that the results can be generalized.

Validity

Endpoints

The Swedish Hospital Discharge Register was used for case retrieval. A validation study has shown that a primary diagnosis of HF, irrespective of clinic type, in the Swedish Hospital Discharge Register has a validity of 95% [84]. The corresponding figure for MI is 94% [87]. A similar high HF diagnosis validity (94.3%) was found in a Canadian study using the Framingham criteria [137], and in a Danish study (99%) using ESC criteria [138]. However, a study from United Kingdom reported that only 77% of HF discharge diagnoses were correct [139]. There are underreporting of HF by using HF discharge diagnosis; in the EuroHeart Failure survey programme a sensitivity of 53-59% of HF diagnosis was found in northern European countries [140]. Low sensitivity has also been reported from studies in UK and in Denmark (66% and 29%, respectively) [138, 139].

We were lacking information on type and cause of HF. Thus, we can only speculate whether the increased risk of hospitalizations due to HF among immigrants in the present study was related to a reduced or preserved LVEF. In addition, total incidence of HF may be underestimated since we cannot make any conclusion about cases that were less severe or were treated outside hospital, e.g. in primary health care centers. The Swedish heart failure registry reported that 90% of HF diagnoses were made following a hospital visit and only 10% at primary health care setting and that the majority of HF patients were in NYHA II-IV, only 8 % were classified as NYHA I [19]. Therefore, since all cases in our study were treated in-hospital with a primary diagnosis of HF, we can assume that the diagnosis was valid and that the HF was quite severe in most cases. In paper I, we also included those 960 subjects who died outside hospital with HF as the underlying death cause as potential HF cases, however, this did only marginally affect the results.

Risk factors

The choice of risk factor variables introduced into a multivariate model can influence the results. Adjustments for risk factors that are mediators in the causal pathway of the disease could underestimate the relationship between exposure and a certain outcome, while leaving out genuine confounders could overestimate the result. In paper I, we lack information on cardiovascular risk factors, e.g. blood pressure, dietary habits, smoking habits and physical activity patterns. However, to collect these data from a complete urban population is not possible. Furthermore, it is also possible that chosen SES indicators (i.e. housing conditions, annual income and marital status) in the present study do not fully eliminate the effect of SES on

hospitalization due to HF. Information on annual income and marital status in the present study was based on data from the total population register; however, housing conditions was questionnaire-based and self-reported. Annual income might not fully reflect the socioeconomic differences for all people, e.g. retired people or women with low income in households with high income. However, we lacked information for example on household income and psychosocial stressors.

The variables used for adjustments in study II-IV, e.g., age, sex, smoking, hypertension, diabetes, hyperlipidemia, abdominal obesity, smoking, alcohol consumption, physical activity, educational level, marital status, immigrant status are well known cardiovascular risk factors [7, 8, 10, 25, 26, 62, 96, 141]. Although we adjusted our analysis for several biological, lifestyle and socio-demographic factors, and because of the observational nature of the study, we cannot exclude the possibility of residual confounding.

Lack of follow-up data regarding anthropometric measures and other risk factors is another issue to be discussed. It is possible that biological factors, e.g., blood pressure and WC changed during the follow-up. However, this is usually a slow process and one study found that adipose tissue distribution is stable through the lifespan [142]. Some subjects might change the status in terms of smoking, physical activity, alcohol consumption and marriage. It is unknown whether change of risk factors during the follow-up could be differential between immigrants and native Swedes.

Conclusions

There are substantial differences in risk of hospitalization due to HF among immigrants from different countries. Immigrant status was associated with risk of HF hospitalization independently of hypertension, socioeconomic and several life-style risk factors. Obesity is a risk factor for HF, and the joint exposure to high BMI and high WHR or WC further increased the HF risk. RDW was found to be associated with the HF risk. Further studies are required to provide knowledge about the underlying mechanisms and whether RDW is a potentially useful new biomarker for HF.

Summary in Swedish

(Populärvetenskaplig sammanfattning)

Bakgrund: Hjärtsvikt är en av de ledande orsakerna till sjuklighet och död, särskilt hos äldre beroende på ökad medelålder i befolkningen samt förlängd överlevnad hos hjärtpatienter via modern behandling. Genom att studera invandring, socioekonomiska och biologiska faktorerets betydelse för insjuknande av hjärtsvikt kan man öka förståelsen om riskpersoner och få fram rationella strategier för förbättrad prevention.

Syfte: Det övergripande syftet i avhandlingen har varit att studera riskfaktorer, i termer av invandring, socioekonomiska omständigheter, biologi och livstil, för sjukhusvård för hjärtsvikt i en storstadsbefolkning.

Metoder: Projektet utgår ifrån registerdata samt två befolkningsbaserade kohorter i Malmö: 1) "1990-kohorten" (delarbete I), som inkluderar alla individer (40-89 år) mantalsskrivna i Malmö 1990; samt 2) "Malmö Kost Cancer" (delarbete II-IV), som inkluderar män och kvinnor i åldersgruppen 45-73 år, boende i Malmö 1991-1996. Information om första vårdtillfälle på sjukhus för hjärtsvikt och hjärtinfarkt inhämtades via samkörning med det nationella patientregistret.

Delarbete I: Syftet var att undersöka sambandet mellan födelseland och risken för sjukhusvård för hjärtsvikt.

Studien inkluderar 114917 personer utan tidigare hjärtinfarkt eller hjärtsvikt, varav 15.2% är födda utomlands. Under 13 års uppföljning vårdades 764 individer på sjukhus för hjärtsvikt. Risken för hjärtsvikt jämfördes mellan invandrare från olika länder och svenskfödda. En signifikant ökad risk noterades för invandrare ifrån Finland, tidigare Jugoslavien och Ungern. Skillnaderna kunde inte förklaras av ålder, kön, civilstånd, årsinkomst och boendeform, samtliga i sig oberoende riskfaktorer för hjärtsvikt. Risken var generellt sett signifikant högre för invandrare ifrån länder med hög jämfört med låg medelinkomst per capita (enligt Gross National Index).

Delarbete II: Syftet var att undersöka: 1) sambandet mellan invandrarstatus och risken för sjukhusvård för hjärtsvikt och utforska till vilken grad sambandet kunde förklaras av skillnader i traditionella riskfaktorer för hjärtkärlsjukdom; samt 2) huruvida invandrarstatus är förenat med en ökad dödlighet (en och 12 månader) efter hjärtsvikt.

Studien inkluderar 26559 individer (61% kvinnor) utan tidigare känd hjärtkärlsjukdom, varav 11.8% födda utanför Sverige. Under 15 års uppföljning vårdades 764 individer på sjukhus för hjärtsvikt. Invandrare hade jämfört med svenskfödda en signifikant ökad risk (37%) för hjärtsvikt, oberoende av ålder, kön, högt blodtryck, flera livsstilsrelaterade faktorer och socioekonomiska omständigheter.

En signifikant interaktion noterades mellan invandrarstatus och bukomfång för hjärtsviktsrisken, där riskökningen var begränsad till invandrare med stort bukomfång. Inga signifikanta skillnader i korttids- eller långtidsöverlevnad sågs mellan svensk- och utlandsfödda individer.

Delarbete III: Syftet var att undersöka: 1) sambandet mellan risken för sjukhusvård för hjärtsvikt och olika kroppsmått; samt 2) huruvida det finns en kombinerad effekt av olika kroppsmått på risken för hjärtsvikt.

Studien inkluderar 26653 individer, utan tidigare känd hjärtkärlsjukdom. Sambandet mellan olika kroppsmått (längd, vikt, body mass index (BMI), bukomfång, midjastuss kvot samt impedansmått procent kroppsfett) och risken för sjukhusvårdad hjärtsvikt studerades. Samtliga kroppsmått var förenat med en signifikant ökad risk för hjärtsvikt, oberoende av flera sociodemografiska, livsstil och biologiska faktorer. Individer med kombinationen av högt BMI och en hög midja-stuss kvot, eller stort bukomfång, hade den högsta risken.

Delarbete IV: Syftet var att undersöka: 1) sambandet mellan variationen i volymen av cirkulerande röda blodkroppar (RDW) och risken för sjukhusvård för hjärtsvikt; samt 2) huruvida sambandet förklaras av andra biomarkörer relaterade till hämodynamisk stress, njurfunktion och låggradig inflammation.

Studien inkluderar 26784 individer utan tidigare känd hjärtkärlsjukdom. Efter 15 års uppföljning var sjukhusvård i hjärtsvikt för högsta jämfört med lägsta kvartilen av RDW förenat med en signifikant ökad risk (47 %). Riskökningen kvarstod efter man tagit hänsyn till potentiella störfaktorer som sjukhistoria för kranskärlsoperation, biologiska, livsstilrelaterade och socioekonomiska omständigheter. I en delkohort (n=4761) kvarstod riskökningen även efter man tagit hänsyn till cystatin C och hsCRP, emedan punkttestimatet sjönk något efter justering för biomarkören NT-proBNP, relaterad till hämodynamisk stress.

Slutsatser: Jämfört med svenskfödda finns det stora skillnader i risk för sjukhusvård för hjärtsvikt bland invandrare från olika länder. Riskökningen är oberoende av flera sociodemografiska, livsstilrelaterade och biologiska faktorer. En signifikant interaktion noterades mellan invandrarstatus och bukomfång för hjärtsviktsrisken, där riskökningen var begränsad till invandrare med stort bukomfång. Olika kroppsmått i sig är förenat med en ökad risk för hjärtsvikt efter man tagit hänsyn till potentiella störfaktorer. Dock individerna med en kombination av högt BMI och hög midja-stuss kvot, eller stort bukomfång, hade den högsta risken. I en individuell riskbedömning för hjärtkärlsjukdom, och dess komplikationer som hjärtsvikt, ger kroppsmåtten bukomfång eller midja-stuss värdefull information utöver BMI. RDW var förenat med en ökad risk för hjärtsvikt, dock ytterligare studier krävs för att ge kunskaper om bakomliggande mekanismer och huruvida RDW är en potentiell användbar ny biomarkör vid hjärtsvikt.

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Paper I

Country of birth and risk of hospitalization due to heart failure: a Swedish population-based cohort study

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Abstract To explore the relation between country of birth and risk of hospitalization due to heart failure (HF). All 40–89 year-old inhabitants in the city of Malmö, Sweden ($n = 114,917$, of whom 15.2% were born outside Sweden) were followed from November 1st, 1990 until December 31st, 2007. During a mean follow-up of 13.5 ± 5.3 years, a total of 7,640 individuals (47.4% men) were discharged from hospital with first-ever HF as primary diagnosis. Of them, 1,243 individuals had myocardial infarction (MI) before or concurrent with the HF hospitalization. The risk of HF was compared between immigrants from selected countries and Swedish natives. The overall analysis showed substantial differences among immigrant groups ($P < 0.001$). Compared to Swedish natives, significantly increased HF risk was found among immigrants from Finland (HR (hazard ratio): 1.40; 95% CI, 1.10–1.81), Former Yugoslavia (1.45: 1.23–1.72) and Hungary (1.48: 1.16–1.89), taking age, sex, marital status, annual income and housing condition into account. Analysis results were similar when cases with MI before or concurrent with the HF hospitalization were included in the analysis. In general, the risk of HF was significantly higher

among immigrants from high-income and middle-income countries. Marital status, annual income and housing condition were also significant independent risk factors for HF in this population. There are substantial differences in risk of hospitalization due to HF among immigrants from different countries that can not be explained by socioeconomic factors. To what extent these differences could be explained by biological risk factors remains to be explored.

Keywords Epidemiology · Cohort study · Heart failure · Immigration

Introduction

Heart failure (HF) is one of the leading causes for morbidity and mortality, particularly in elderly [1, 2]. In Europe, it is estimated that at least 15 million patients have HF [3]. In Sweden, HF is the most common hospitalization diagnosis in subjects aged 65 and over, and the total annual costs for HF management are approximately 2% of the Swedish health care budget [4]. HF can be the result of various cardiac diseases; however, most cases of HF are caused by hypertension or coronary heart disease (CHD) [1, 5–7].

Immigration to Sweden has increased markedly during the last decades, especially of refugees during the Balkan wars in the 1990s, from the Middle East in the first decade of this millennium and of labour immigrants from the European Community. Previously the labour immigration has been very restricted with exception from the Nordic countries, which have been without barriers, dominated by the Finns. The proportion of foreign-born people in Sweden increased from 9.2% in 1990 to 13.8% in 2008 [8]. The corresponding figures in Malmö, the third largest city in Sweden, were 16–28% [8]. It has been reported that

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foreign-born compared to Swedish-born people have higher risk for and higher mortality rate from cardiovascular disease (CVD) [9–11]. Incidence of HF among immigrants in Sweden is however, largely unknown.

Previous studies from Malmö have shown that there are substantial differences in risk of CVD between residential areas with high and low proportion of immigrants [12–15]. The purpose of the present population-based study is to explore the relationship between country of birth and risk of HF hospitalizations after taking age, sex and socioeconomic indicators into account.

Methods

Study population and follow up

November 1st, 1990, a total of 118,134 subjects, aged 40–89 years, were registered as residents in the city of Malmö. After excluding subjects with history of myocardial infarction (MI) ($n = 2,133$) or those who were hospitalized due to HF ($n = 1,714$) before November 1st 1990, 114,917 (50,981 men and 63,936 women) subjects remained. All subjects were followed from November 1st, 1990 until first hospitalization attributable to HF, MI, death, emigration from Sweden, or December 31st, 2007, whichever came first. Since HF is very uncommon in young subjects, the study was restricted to individuals aged 40–89 years [6].

Population registers

Information about the background characteristics was retrieved from the National Swedish Census Data (“Folkoch bostadsräkning, FoB”) in 1990 [16]. This survey is a total register of the Swedish population November 1st, 1990, and includes information on marital status, rented and self-owned homes, annual income and country of birth. This database consists of information from a mailed self-administered questionnaire and data from other population registers. Failure to complete and return the questionnaire was associated with a financial penalty. Information on annual income was retrieved from the Swedish income register, i.e. assessment of taxes in 1991 (i.e. for the income year 1990). Information on country of birth and marital status were retrieved from the Swedish total population register (TPR). Information on education, occupation and housing condition were based on self-reported questionnaires. The response rate of the questionnaire was 97.5%. Information about migration and deaths during the follow-up period was retrieved from the Swedish TPR and the Swedish Cause of Death Register.

HF cases were retrieved by record linkage with the Swedish Hospital Discharge Register (SHDR) [17]. Subjects

with a hospital discharge diagnosis of HF (International Classification of Diseases, ICD, 8th code 427.00, 427.10, 428.99; ICD, 9th code 428; and ICD, 10th code I50, I11.0, respectively) as the primary diagnosis were considered to have HF. As previously reported from this study population, cases of acute MI was retrieved by record linkage with registers of hospital discharges and deaths in accordance to diagnosis criteria used in the National MI register [18]. A validation study, at the National Board of Health and Welfare in Sweden, has shown that the diagnosis of MI in the SHDR is valid in 90–95% of the cases [19]. Subjects with non-fatal MI were followed until the day of infarction and censored thereafter. In addition, risk of HF was explored for all HF cases, including those with MI during the follow-up. Non-fatal MI was defined as 410 (ICD-9) or I21, I22 (ICD-10). The data from 1983–1990 prior to November 1st, 1990 were used to exclude subjects with previous hospitalization due to HF or MI. In a study that reviewed hospital records of patients with HF according to the Swedish hospital discharge register, it was shown that the validity was 95% if HF was the primary diagnosis, irrespective of clinical type [17]. In that study a review board examined the validity of the diagnosis according to European Society of Cardiology definition of HF [20]. No major difference in validity was found whether patients had been treated at an internal medicine or cardiology clinic (86 and 91%, respectively) [17].

Country of birth

Information about country of birth was available for 99.96% of the population (51 missing). Immigrants from countries (i.e. USA, Iraq, Ghana, etc.) for which the total follow-up time was less than 2,500 person years were excluded. As in a previous study from this cohort, the Peoples Republic of China and Vietnam were grouped into one category [21]. Thus, selected countries in the analysis contained 98.1% of the cohort.

In an additional analysis, country of birth was also categorized into high income countries (i.e. $\leq \$610$), middle income countries (i.e. $\$611$ – $\$7,620$) and low income countries (i.e. $> \$7,620$) based on 1990 GNI (Gross national income) per capita in US\$ [22], Table 1.

Socioeconomic status

Socioeconomic indicators used for the analysis were marital status, total annual income and housing status as previous studies have shown their association with HF [23–29].

Marital status was categorized into married, single, divorced, or widowed [21]. The total annual income 1990 (in Swedish Kronor (SEK)) was categorized into 6 categories: 0–50,000; 50,100–100,000; 100,100–150,000;

Table 1 Baseline characteristics of 40–89-years-old Swedish natives and selected immigrant groups by country of birth, living in Malmö, Sweden, 1990

	<i>N</i>	Men (%)	Mean age (years)	Married (%)	Self-owned home (%)	Mean income (1,000 SEK)	Mean years in Sweden (years)
<i>Country of birth</i>							
Sweden	96,674	44	62 ± 13	54	58	136	–
Denmark (1)	2,639	46	60 ± 11	48	46	118	20
Finland (1)	1,392	40	55 ± 10	42	52	121	21
Norway (1)	513	44	60 ± 12	43	43	113	20
Germany (1)	1,484	41	61 ± 12	52	57	125	22
Austria (1)	221	48	59 ± 12	57	57	123	21
Italy (1)	238	70	55 ± 10	63	52	120	21
Former Yugoslavia (2)	3,372	52	53 ± 9	63	34	111	19
Poland (2)	2,221	36	55 ± 13	45	41	94	14
Portugal (2)	236	51	53 ± 8	72	46	116	20
Romania (2)	392	50	55 ± 11	58	25	78	7
Hungary(2)	1,128	55	56 ± 11	52	48	115	19
Former Soviet Union (2)	475	40	62 ± 13	47	45	107	18
Czechoslovakia (2)	447	52	55 ± 11	46	45	107	17
Turkey (2)	213	55	53 ± 11	59	10	93	16
Greece (2)	284	56	53 ± 9	67	19	97	17
Iran (2)	237	57	50 ± 10	58	10	31	3
Chile (2)	337	46	51 ± 10	38	22	87	9
China, Vietnam (3)	284	46	57 ± 13	69	12	51	8
Countries with p-y < 2,500	2,130	58	53 ± 11	51	32	93	13
Total	114,917	44	61 ± 13	53	56	132	17
<i>Country according to income</i>							
Sweden	96,674	44	62 ± 13	54	58	136	–
High-income countries (1)	7,439	45	59 ± 12	48	49	118	20
Middle-income countries (2)	10,153	49	54 ± 11	55	35	100	16
Low-income countries (3)	600	61	52 ± 12	59	17	70	10
Not applicable ^a	51	61	61 ± 13	43	29	84	12
Total	114,917	44	61 ± 13	53	56	132	17

Figures are shown as mean (SD) or as proportions. Number attached to each specific country belonged to country classification according to GNI (Gross National Income)

SEK Swedish Kronor

^a Missing data on country of birth

150,100–200,000; 200,100–250,000; and >250,000 SEK per year. In November 1st, 1990, \$1 corresponded to 5.62 SEK.

Annual income might not fully reflect the socio-economic differences among people, i.e. retired people or women with low income in the high income household. Therefore, the results were also adjusted for housing status. Housing status was grouped into self-owned home (house or apartment) or rented home. Among the population, 55.6% owned their house or apartment, and 40.5% rented their apartment first or second hand. Subjects with missing data on housing status (3.9%) were in the analysis coded in a separate category.

Statistics

Hazard ratios (HR), with 95% confidence interval (CI) were calculated using Cox proportional hazards regression models. In terms of country of birth, Sweden was used as the reference group in all analysis. HRs were first adjusted for baseline age and sex, then additionally adjusted for marital status (4 categories), annual income (6 categories) and housing status (3 categories). Possible interaction between age and income, and between country of birth and sex, respectively, on risk of HF was explored by introducing interaction terms in the multivariate models. Analysis involved the computer software SPSS (15.0). This

study was approved by the Lund University Ethics review Committee (LU 78-02 and 2009/46).

Results

Baseline characteristics of study cohort

Baseline characteristics of Swedish natives and selected immigrant groups are presented in Table 1. Overall, mean (SD) age of participants at entry was 60.8 ± 13.2 years and 55.6% ($n = 63,936$) were women. A total of 99,976 subjects were born in Sweden and 15.9% outside Sweden, of whom 25% in other Nordic countries.

Incidence of MI in relation to immigration to Sweden

During the 16 year follow-up period 12,712 subjects (6,924 men and 5,788 women) had an acute MI. The incidence was 103 in men and 67 in women, respectively, per 10,000 person-years. Foreign born subjects had a higher risk for MI as compared to subjects born in Sweden (HR: 1.08; 95% CI: 1.02–1.14, $P = 0.008$), taking age, sex and socio-economic indicators into account.

Risk of hospitalization due to HF in relation to country of birth

During a mean follow-up of 13.5 ± 5.3 years, a total of 7,640 individuals (3,624 men and 4,016 women) were discharged from hospital with first time HF as primary diagnosis. The incidence of hospitalized HF per 10,000 person-years was 53 in men and 46 in women, respectively. Incident HF increased significantly and linearly by age, in 5-year age groups from 3 per 10,000 person-years aged 40–44 years to 267 per 10,000 person-years aged 85–89 years ($P < 0.001$). Of the 7,640 cases with HF, 1,243 (677 men and 566 women) had an MI before or concurrent with the hospitalization of HF. The latter group was censored at the time of the infarction in the first analysis.

The overall analysis showed substantial differences in risk in terms of hospitalization due to HF between countries of birth ($P < 0.001$, 19df), Table 2. Adjusted for age and sex, the risk of HF was significantly higher among immigrants from Finland, Denmark, Former Yugoslavia and Hungary compared to Swedish natives. This risk increase remained among immigrants from Finland (HR: 1.40; 95% CI, 1.10–1.81), Former Yugoslavia (HR: 1.45; 1.23–1.72) and Hungary (HR: 1.48; 1.16–1.89), after taking marital status, annual income and housing conditions into account, Table 2.

The results were only marginally changed when HF cases with incident MI before or concurrent with hospitalization for HF ($n = 1,243$) were included in the analysis, i.e. the risk increase for HF remained among immigrants from Finland (HR: 1.42; 1.13–1.78), Former Yugoslavia (HR: 1.34; 1.14–1.57) and Hungary (HR: 1.41; 1.12–1.77), Table 2.

In addition, 960 subjects died outside hospital with HF as the underlying death cause. These potential HF cases had no prior hospitalization due to HF; however, including them as cases in the multivariate analysis did only marginally affect the results and immigrants from Finland, Hungary and Former Yugoslavia has significantly increased risk for HF (data not shown).

Risk of hospitalization due to HF in relation to age, sex and socioeconomic indicators

Age and male sex were, independently of marital status, housing condition and annual income, related to an increased risk of HF hospitalization, Table 3. Single, divorced and widowed compared to married subjects were also independently associated with increased risk for hospitalization due to HF. In addition, renting house and low annual income were associated with higher risk for HF. Excluding subjects with missing information on housing conditions (i.e. 3.9%) did only marginally change the results, i.e. the significantly risk increase for HF remained among immigrants from Finland, Former Yugoslavia and Hungary.

There was a significant interaction ($P < 0.001$) between annual income and age on risk of HF hospitalizations. When stratifying the cohort under and equal or above 65 years the effect of income on risk for HF was higher for younger than elderly subjects (data not shown). No significant interaction ($P = 0.368$) between country of birth and sex on risk of HF hospitalization was observed.

Additional analysis

Additional analyses were performed by categorizing country of birth for immigrants into high, middle and low income countries. When the analysis was restricted to risk of HF hospitalization without previous or concurrent MI, a significant higher risk, compared to Swedish natives, was observed among immigrants from high-income countries (HR: 1.12; 1.01–1.25) and middle-income (HR: 1.14; 1.02–1.26). This risk increase was independent of age, sex, marital status and socioeconomic indicators. Including HF cases with MI ($n = 1,243$) before or concurrent with HF during the follow-up in the analysis did only marginally change the results, Table 2, Fig. 1.

Table 2 Incidence and risk of hospitalization due to heart failure in relation to country of birth

	HF excluding previous MI			HF including previous MI		
	n (per 10,000 p-y)	HR ^a (95% CI)	HR ^b (95% CI)	n (per 10,000 p-y)	HR ^a (95% CI)	HR ^b (95% CI)
<i>Country of birth</i>						
Sweden	5,589 (44)	Reference	Reference	6,677 (51)	Reference	Reference
Denmark	149 (43)	1.25 (1.07–1.48)	1.16 (0.99–1.37)	177 (51)	1.23 (1.06–1.43)	1.13 (0.98–1.32)
Finland	64 (32)	1.52 (1.19–1.94)	1.40 (1.10–1.81)	78 (39)	1.52 (1.22–1.91)	1.42 (1.13–1.78)
Norway	24 (35)	0.95 (0.64–1.42)	0.90 (0.61–1.36)	28 (41)	0.92 (0.63–1.33)	0.88 (0.61–1.28)
Germany	90 (45)	1.16 (0.94–1.43)	1.13 (0.92–1.39)	109 (55)	1.17 (0.97–1.42)	1.14 (0.94–1.38)
Austria	7 (23)	0.69 (0.33–1.45)	0.66 (0.31–1.38)	7 (25)	0.57 (0.27–1.20)	0.55 (0.26–1.15)
Italy	8 (23)	0.94 (0.47–1.87)	0.85 (0.42–1.69)	11 (31)	1.04 (0.58–1.88)	0.94 (0.52–1.69)
Former Yugoslavia	144 (29)	1.72 (1.45–2.03)	1.45 (1.23–1.72)	164 (33)	1.58 (1.35–1.85)	1.34 (1.14–1.57)
Poland	100 (31)	1.20 (0.99–1.46)	1.05 (0.86–1.28)	119 (37)	1.18 (0.98–1.41)	1.03 (0.86–1.24)
Romania	17 (30)	1.36 (0.84–2.19)	1.12 (0.69–1.80)	22 (38)	1.41 (0.93–2.15)	1.17 (0.77–1.78)
Hungary	65 (41)	1.65 (1.29–2.10)	1.48 (1.16–1.89)	76 (48)	1.57 (1.25–1.97)	1.41 (1.12–1.77)
Former Soviet Union	31 (47)	1.11 (0.78–1.57)	1.04 (0.73–1.48)	35 (56)	1.04 (0.75–1.46)	0.98 (0.70–1.37)
Czechoslovakia	14 (21)	0.85 (0.51–1.44)	0.76 (0.45–1.29)	20 (30)	1.01 (0.65–1.55)	0.90 (0.58–1.40)
Turkey	6 (19)	0.86 (0.39–1.92)	0.70 (0.31–1.55)	8 (25)	0.94 (0.47–1.883)	0.76 (0.38–1.53)
Greece	3 (8)	0.47 (0.15–1.45)	0.39 (0.13–1.20)	7 (17)	0.89 (0.42–1.86)	0.73 (0.35–1.54)
Iran	6 (16)	1.05 (0.47–2.34)	0.78 (0.35–1.74)	9 (24)	1.27 (0.66–2.45)	0.96 (0.50–1.85)
Chile	8 (16)	1.01 (0.50–2.01)	0.79 (0.39–1.58)	9 (18)	0.92 (0.48–1.78)	0.73 (0.38–1.40)
China, Vietnam	9 (22)	0.77 (0.40–1.48)	0.62 (0.32–1.20)	10 (24)	0.71 (0.38–1.32)	0.58 (0.31–1.07)
<i>P</i> value (<i>df</i> = 19)		<0.001	<0.001		< 0.001	<0.001
<i>Country according to income</i>						
Sweden	5,589 (44)	Reference	Reference	6,677 (51)	Reference	Reference
High-income countries	377 (37)	1.19 (1.07–1.32)	1.12 (1.01–1.25)	451(44)	1.18 (1.07–1.30)	1.11 (1.01–1.22)
Middle-income countries	415 (28)	1.31 (1.19–1.45)	1.14 (1.02–1.26)	493 (33)	1.28 (1.16–1.40)	1.10 (1.01–1.21)
Low-income countries	16 (18)	0.91 (0.56–1.49)	0.74 (0.45–1.22)	19 (21)	0.89 (0.57–1.39)	0.73 (0.46–1.14)
<i>P</i> value (<i>df</i> = 4)		<0.001	0.023		<0.001	0.035

HF heart failure, MI myocardial infarction, HR hazard ratio, CI confidence interval, *p*-y person-years

^a HR adjusted for age and sex

^b HR adjusted for age, sex, marital status, annual income and self-owned home

Discussion

Our analysis of prospective associations between country of birth and risk of hospitalization due to HF has yielded some novel and potentially important findings. First, we have demonstrated that immigrants from Finland, Former Yugoslavia, and Hungary, compared to Swedish-born subjects had significantly higher risk for hospitalization due to HF. These differences persisted when taking socioeconomic factors into account. Secondly, in an additional analysis we also found that the risk for HF among immigrants from high- and middle-income countries was significantly higher than their counter parts. These findings are in line with previous studies showing substantial differences in immigration, country of birth and incidence of CVD in other countries and in Sweden [2, 9–11, 30–32]. In Malmö, Sweden and in other cities, residential areas with

high proportion of immigrants are often characterized by high incidence of CVD [12–15]. The increased cardiovascular risk among immigrants in this population is consistent with what have been reported previously from other Swedish studies [9–11].

There are several possible explanations of the findings in the present study. First, the observed increased risk of HF hospitalizations among immigrants from Finland, Former Yugoslavia and Hungary might reflect influences from their countries of origin. Most cases of HF are caused by hypertension or CHD [1, 5–7]. There are substantial differences in CVD mortality between countries and regions, Eastern European countries generally have high rates of CVD or CHD mortality [33]. In Hungary an increasing CVD mortality have been reported from the early 1970s, with the highest mortality rate in 1985. [34]. Elevated body mass index, high intake of saturated fat and salt have been

Table 3 Risk of hospitalization due to heart failure in relation to age, sex and socioeconomic status at baseline

	HF excluding previous MI HR ^a (95% CI)	HF including previous MI HR ^a (95% CI)
<i>Age</i>		
Per year	1.11 (1.10–1.12)	1.11 (1.10–1.11)
<i>P</i> value	<0.001	<0.001
<i>Sex</i>		
Woman	Reference	Reference
Man	1.99 (1.88–2.11)	2.08 (1.98–2.20)
<i>P</i> value	<0.001	<0.001
<i>Marital status</i>		
Married	Reference	Reference
Single	1.16 (1.07–1.26)	1.10 (1.02–1.18)
Divorced	1.18 (1.09–1.28)	1.19 (1.10–1.27)
Widowed	1.20 (1.12–1.28)	1.19 (1.12–1.27)
<i>P</i> value	<0.001	<0.001
<i>Housing condition</i>		
Self-owned	Reference	Reference
Rented	1.16 (1.10–1.22)	1.16 (1.11–1.21)
<i>P</i> value	<0.001	<0.001
<i>Annual income (SEK)</i>		
0–49,000	Reference	Reference
50,000–100,000	0.99 (0.93–1.07)	1.01 (0.94–1.07)
100,100–150,000	0.85 (0.78–0.92)	0.86 (0.80–0.93)
150,100–200,000	0.66 (0.60–0.74)	0.67 (0.61–0.74)
200,100–250,000	0.53 (0.45–0.61)	0.52 (0.46–0.60)
>250,000	0.56 (0.48–0.66)	0.55 (0.48–0.63)
<i>P</i> value	<0.001	<0.001

HF heart failure, MI myocardial infarction, HR hazard ratio, CI confidence interval

^a HR adjusted for age, sex, and when appropriate for marital status, annual income and self-owned home

suggested as possible risk factors explaining the high risk for CVD among Hungarians [35]. High incidence of CVD has also been reported in Finland and former Yugoslavia [33]. Hence, we can not exclude the possibility that high CVD risk of their country of origin might explain, at least partly, the increased risk of hospitalization due to HF among immigrants from Finland, Former Yugoslavia, and Hungary in our study.

Secondly, another possible explanation could be different circumstances and reasons to migrate to Sweden. During 1965–1973 former Yugoslavians were often recruited by Swedish companies as labour immigrants with low skilled jobs, and from 1973 to 1990s, when the labour immigration was stopped, they often immigrated to Sweden for family reunion and as asylum. After the politic instability in Hungary 1956, many Hungarian immigrants

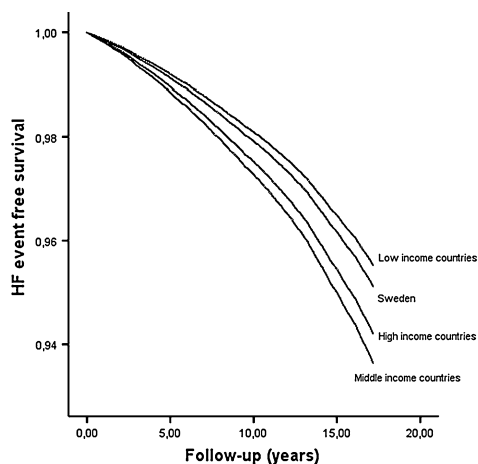


Fig. 1 Age- and sex-adjusted risk for hospitalization due to HF in relation to country of birth of immigrants and annual income based on 1990 GNI (Gross National Income)

came to Sweden as refugees. Finnish immigrants came to Sweden as labour migrants from 1945 to 1970s. This suggests that immigrants from the above mentioned countries to Sweden could be regarded as selected groups. To what extent this matter might influence risk of HF is unclear. In addition, before the baseline examination in 1990 the majority of all these three immigration groups have lived in Sweden for at least 20 years or more. One could assume that the high risk for hospitalization due to HF in the present study might also be the result of stress from cultural and psychosocial change to acculturate and integrate into the Swedish society. However, another Swedish study has shown that Finnish labour migrants had higher risks for MI compared to Swedish natives, and that this increased risk still remained after 20 years in Sweden [36].

Third, another explanation could be associated with low socioeconomic status of immigrants compared to Swedish natives. It has been shown that Former Yugoslavians had disadvantage in labour markets compared to native Swedes [37]. In addition it also matters where you live, as substantial socioeconomic differences between residential areas in cities have been demonstrated. In the city of Malmö, Sweden, residential areas with low socioeconomic circumstances and high proportion of immigrants have been characterized by high incidence of CVD [12–15]. International and national studies have reported that prevalence of cardiovascular risk factors is associated with socioeconomic status [12, 38–40]. In a Swedish study rented home was associated with cardiovascular mortality [40]. In the present study, risk of HF was related to

socioeconomic status. However, when several socioeconomic indicators were adjusted for in the analysis, the observed difference in risk of HF among immigrants from Finland, former Yugoslavia and Hungary still remained. This suggests that the increased risk of HF in these groups is not completely mediated by the socioeconomic indicators in this study. On the other hand, the significantly increased risk of HF for Danish subjects was reduced and non-significant when adjusted for SES, which suggest that socioeconomic circumstances still play a role.

Strength and limitation

It is important to be aware of strength but also limitations in the study design, measurement procedures, and methodological issues that might influence the interpretation of the results.

Rates of first hospitalizations due to HF, as presented in Table 2, were consistent with what have been reported by others [41]. In that study the crude incidence for different populations ranged from 1.0 to 5.0 per 1,000 person-years in the general population [41]. Some methodological issues should also be considered. Sweden has a health care system which is financed by the community, and no insurance is needed. According to recently published Swedish studies, the Swedish health care system has achieved equality in the care and treatment of patients with HF [42, 43]. In these studies symptom recognition and health care seeking were rather similar among immigrants and natives Swedes who were hospitalised due to HF [42, 43]. In the city of Malmö there is only one hospital and patients from all residential areas can reach the hospital within 15 min, so the availability of the hospital could be regarded to be similar for all patients.

Emigration, vital status and hospitalizations at the end of the follow-up were up-dated on all individuals by data linkage with regional and national registers. The completeness and validity of these registers have been documented in several other studies from the city [12, 21]. We were unable to include cases of HF which are diagnosed and treated as out of hospital patients. Thus, we cannot draw any conclusions about less severe cases. Since all cases were treated in-hospital with a primary diagnosis of HF, we can assume that the diagnosis was valid and that the HF was quite severe in most cases [44]. Furthermore, a validation study of cases retrieved from the Swedish hospital discharge register has shown that the validity of the diagnosis was 95%, irrespective of clinic type, if HF was the primary diagnosis [17]. We also included those 960 subjects who died outside hospital with HF as the underlying death cause as potential HF cases; however, this did only marginally affect the results. In addition, the large number of individuals and events, and the complete and

reliable data about the background population are considerable study strengths. The main limitation of the present study is that we lack information on cardiovascular risk factors, e.g. blood pressure, dietary habits, smoking habits and physical activity patterns. However, to collect these data from a complete urban population is not possible.

We did not observe any risk increase for hospitalization due to HF among immigrants from low-income countries. However, only 16 events was observed in this group ($n = 600$) limiting the statistical power due to few events.

Information on country of birth was available for almost all study subjects. Those who during the follow-up emigrated were censored at the time of emigration. However, re-migration from Sweden without reporting to the authorities could possibly exaggerate the population at risk and cause low risk estimates for some immigrant groups. A report from Sweden Statistics estimated that ~25,000 to 50,000 foreign-born individuals who officially live in Sweden have left the country [45]. A previous study from the present cohort explored whether exclusion of individuals without income, according to the assessments of taxes, had any impact on the relationships between country of birth and incidence of disease [21]. No major influence on hazards ratios for incident stroke was found in that study. Therefore, we believe that a re-migrant effect is a minor problem in our study and should not explain the observed increased risk for HF related to country of birth.

Finally, it is also possible that the chosen SES indicators (i.e. housing conditions, annual income and marital status) in the present study do not fully eliminate the effect of SES on hospitalization due to HF. Information on annual income and marital status in the present study was based on data from the TPR; however, housing conditions was questionnaire-based and self-reported. Annual income might not fully reflect the socioeconomic differences for all people, e.g. retired people or women with low income in households with high income. However, we lacked information for example on household income and psychosocial stressors. The latter is known to vary by social position [46]. It could also be discussed whether socio-economic circumstances are mediators, rather than confounders, in the relationship between country of birth and HF.

In conclusion, there are substantial differences in risk of hospitalization due to HF among immigrants from different countries that can not be explained by socioeconomic factors. Immigrants from Finland, Former Yugoslavia and Hungary had compared to Swedish natives significantly higher risk. To what extent these differences could be explained by biological risk factors remains to be explored.

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Conflict of interest None declared.

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Paper II

RESEARCH ARTICLE

Open Access

Immigrant status and increased risk of heart failure: the role of hypertension and life-style risk factors

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Abstract

Background: Studies from Sweden have reported association between immigrant status and incidence of cardiovascular diseases. The nature of this relationship is unclear. We investigated the relationship between immigrant status and risk of heart failure (HF) hospitalization in a population-based cohort, and to what extent this is mediated by hypertension and life-style risk factors. We also explored whether immigrant status was related to case-fatality after HF.

Methods: 26,559 subjects without history of myocardial infarction (MI), stroke or HF from the community-based Malmö Diet and Cancer (MDC) cohort underwent a baseline examination during 1991-1996. Incidence of HF hospitalizations was monitored during a mean follow-up of 15 years.

Results: 3,129 (11.8%) subjects were born outside Sweden. During follow-up, 764 subjects were hospitalized with HF as primary diagnosis, of whom 166 had an MI before or concurrent with the HF. After adjustment for potential confounding factors, the hazard ratios (HR) for foreign-born were 1.37 (95% CI: 1.08-1.73, $p = 0.009$) compared to native Swedes, for HF without previous MI. The results were similar in a secondary analysis without censoring at incident MI. There was a significant interaction ($p < 0.001$) between immigrant status and waist circumference (WC), and the increased HF risk was limited to immigrants with high WC. Although not significant foreign-born tended to have lower one-month and one-year mortality after HF.

Conclusions: Immigrant status was associated with long-term risk of HF hospitalization, independently of hypertension and several life-style risk factors. A significant interaction between WC and immigrant status on incident HF was observed.

Keywords: Immigrant status, heart failure, risk factors, cohort study, case-fatality, epidemiology

Background

Heart failure (HF) is one of the leading causes for morbidity and mortality, particularly in the elderly. Hypertension and myocardial infarction (MI) are the main causes of HF in the general population [1-5]. Other important risk factors that have been associated with incidence of HF include age, male sex, overweight, diabetes, smoking, physical inactivity, alcohol consumption, inflammatory and socioeconomic factors [2,6-13].

It has repeatedly been shown that immigrants in Sweden have higher risk of coronary heart disease and stroke compared to Swedish-born subjects [14-17]. In a previous study of the entire population of Malmö, Sweden, we found substantial differences in risk of HF hospitalization among foreign-born subjects [18]. In that study, increased incidence of HF hospitalizations was found in immigrants from Finland, Former Yugoslavia and Hungary. However, it is still unclear to what extent the increased risk in these groups could be explained by major biological and lifestyle risk factors for HF, e.g., hypertension, overweight, and smoking.

Thus, the purpose of the present study was to further explore the association of immigration status and risk of

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HF hospitalization in an urban population-based cohort and to what extent the relationship is explained by conventional cardiovascular risk factors. We also explored whether immigrant status was related to case-fatality (e.g. 1-month and 1-year, respectively) after HF.

Methods

Study population

The Malmö Diet and Cancer (MDC) cohort is a prospective cohort study from the city of Malmö in southern Sweden. Sample characteristics, data collection and clinical definitions for MDC have been described previously [19-21]. Briefly, 28,449 men ($n = 11,246$, born 1923-1945) and women ($n = 17,203$, born 1923-1950) attended a baseline examination between March 1991 and September 1996. Participants underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire.

Subjects with history of cardiovascular events (coronary events or stroke, $n = 970$ subjects) or HF ($n = 46$ subjects) at the baseline examination were excluded. In addition, subjects were also excluded due to missing information on blood pressure (BP), waist circumference (WC), smoking habits, alcohol consumption, physical activity, leukocyte counts, educational level, marital status and country of birth. Thus, the final study population in the analysis consisted of 26,559 (10,227, 38.5% men and 16,332, 61.5% women) subjects, aged 45-73 years. The study was approved by the ethical committee at Lund University Lund, Sweden, and all participants provided informed consent.

Measurements and definitions

Information on current use of BP lowering, lipid-lowering or anti-diabetic medications, smoking habits, alcohol consumption, leisure time physical activity, educational level, marital status and country of birth were obtained from a self-administered questionnaire [20]. WC (in cm) was measured midway between the lowest rib margin and iliac crest in the standing position without clothing. WC was stratified into normal WC and high WC (≥ 94 cm for men and ≥ 80 cm for women) [22]. Blood pressure was measured using a mercury-column sphygmomanometer after 10 minutes of rest in the supine position. Hypertension was defined as blood pressure equal or above 140/90 mm Hg or current use of blood pressure-lowering medication. Leukocyte concentrations were analysed consecutively in fresh heparinized blood. Diabetes mellitus was defined as fasting whole blood glucose level greater than 109 mg/dL (e.g. 6.0 mmol/L), self-reported physician's diagnosis of diabetes, or use of antidiabetic medications. Subjects were categorized into current smokers (i.e., those who smoked regularly or occasionally) or non-smokers (i.e., former smokers and

never smokers). High alcohol consumption was defined as > 40 gram alcohol per day for men and > 30 g/day for women. Leisure time physical activity was grouped as lowest quartile or other. As previously described educational level was defined as low education (up to grade 9) and high (> 9 years) [23]. Marital status was categorized into married or unmarried. Immigrant status was grouped as Swedish-born and foreign-born. We were unable to study immigrants from individual countries of birth due to limited numbers of HF cases.

Ascertainment of cardiovascular events and HF

The Swedish Hospital Discharge Register (SHDR) was used for case retrieval. Validation study has shown that a primary diagnosis of HF in the SHDR has a validity of 95% [24]. The corresponding figure for MI is 94% [25]. HF was defined as International Classification of Diseases- 8th revision (ICD-8) code 427.00, 427.10 and 428.99; 428 (ICD-9); and I50, I11 (ICD-10) as the primary diagnosis [24]. Non-fatal MI was defined as 410 (ICD-8 and 9) or I21 (ICD-10) [25]. Information on mortality was obtained through the Swedish Cause of Death Register. All subjects were followed from the baseline examination until a first diagnosis of HF, emigration from Sweden, death or December 31st, 2008, whichever came first.

Statistical analysis

Cox proportional hazards regression was used to examine the association between selected immigrant status and risk of HF hospitalization in the MDC cohort. Hazard ratios (HR), with 95% confidence interval (CI) were calculated. Age and sex were included as covariates in the basic model. Secondly, we also adjusted for systolic BP, use of BP-lowering medication, lipid-lowering medication, diabetes mellitus, WC, current smoking, high alcohol consumption, low physical activity and leukocyte counts. Possible interactions between immigrant status and age, sex and cardiovascular risk factors on incidence of HF were explored by introducing interaction terms in the multivariate model. The primary analysis was performed with censoring at first nonfatal MI during follow-up, i.e., cases with MI prior to HF were not counted. Secondary analysis included all HF incident cases, regardless of MI. Two-sided p values < 0.05 were considered significant. The Kaplan-Meier curve was used to illustrate incidence of hospitalization due to HF in relation to immigrant status and waist circumference.

Case-fatality rates were calculated as the proportion of those with a HF hospitalization that died within 1-month and 1-year, respectively. Cox proportional hazards regression was used and adjusted for age, sex and year of HF event. All analyses were performed using PASW version 18 (SPSS Inc., Chicago, Illinois).

Results

Overall, mean age (\pm standard deviation) at baseline was 58 ± 7.6 years and 61.5% were women. A total of 23,430 subjects were born in Sweden and 3,129 (11.8%) were born outside Sweden. Of those born outside Sweden, the majority came from Denmark (10.5%), Former Yugoslavia (8.3%), Finland (7.6%), Germany (8.8%), Poland (5.0%) and Hungary (4.3%). Baseline characteristics of Swedish-born and foreign-born in relation to conventional cardiovascular risk factors (WC, leukocyte count, systolic BP, use of BP-lowering and lipid-lowering medication, diabetes mellitus, current smoking, high alcohol consumption, low physical activity) and socioeconomic factors (educational level, marital status) are presented in Table 1. Foreign-born subjects were younger, more often current smokers, diabetics, high alcohol consumers, and had more often low physical activity than those born in Sweden. During a mean follow-up of 15 years, a total of 764 individuals (325 men and 273 women) were hospitalized with HF as primary diagnosis. Of them, 166 (96 men and 70 women) had an incident MI before or concurrent with HF hospitalization during follow-up. The latter group was censored at the time of the infarction in the primary analysis.

Risk of HF hospitalizations in relation to immigrant status

The overall analysis showed higher risk of HF hospitalization for foreign-born compared to Swedish-born. Adjusted for age and sex, foreign-born had a significantly higher risk for HF (HR: 1.44; 95% CI, 1.14-1.82)

compared to Swedish-born. This increased risk remained (HR: 1.37; 1.08-1.73) after adjustment for other possible confounders, Table 2. If cases with MI before or concurrent with HF hospitalization ($n = 166$) were included in the analysis, the risk for HF hospitalization among foreign-born (HR: 1.24; 1.01-1.54) was only marginally changed, Table 2.

In the final model, age and male sex, increased WC, leukocyte count, systolic BP, use of BP-lowering medication, diabetes, smoking, high alcohol consumption, low physical activity, low educational level were independently associated with an increased risk for HF, Table 2.

Interaction between immigrant status and other risk factors on incidence of HF

Interaction terms between covariates were added in the final Cox's proportional hazards model with adjustment for possible confounders. There was a statistically significant interaction between immigrant status and WC ($p < 0.001$) on incidence of HF. There were no other significant interactions between immigrant status and risk factors.

To further explore the interaction between country of birth and WC, WC was stratified into normal and high WC in men and women, respectively [22], Table 3 and Figure 1. After stratification for WC, a significant higher risk of HF was only observed in foreign-born with high WC (HR: 2.11; 95% CI, 1.62-2.76), while foreign-born with normal WC had similar risk (HR: 1.17; 0.85-1.60) as compared to Swedish natives with normal WC.

Table 1 Characteristics of subjects in the Malmö diet and cancer (MDC) cohort in relation to immigration status, at the baseline examination 1991-1996

MDC (N = 26,559)	Swedish-born (n = 23,430)	Foreign-born (n = 3,129)	P value
Mean age (years)	58.2 \pm 7.6	56.9 \pm 7.2	< 0.001
Men (%)	38.4	39.1	< 0.001
Waist circumference (cm)	84 \pm 15	85 \pm 10	< 0.001
SBP (mmHg)	141 \pm 20	140 \pm 20	< 0.001
DBP (mmHg)	86 \pm 10	85 \pm 13	0.426
Leukocytes (10^9 /L)	6.4 \pm 2.2	6.5 \pm 3.5	0.183
Hypertension (%)	40.5	38.6	< 0.001
Use of BP-lowering medications (%)*	41.1	40.1	< 0.001
Use of lipid-lower medications (%)	2.4	2.1	0.279
Diabetes (%)	2.8	3.3	< 0.001
Current smoker (%)	27.9	31.0	< 0.001
High alcohol consumption (%)	4.2	5.2	0.015
Low physical activity (%)	24.5	28.4	< 0.001
Low educational level (%)	42.1	35.3	< 0.001
Married (%)	65.7	62.3	< 0.001

All other values are mean \pm SD, unless otherwise stated. * Use of blood pressure (BP)-lowering medications is calculated as proportions of hypertensives in each group ($n = 9488$ and $n = 1207$, respectively).

Table 2 Final multivariate model for first hospitalization due to heart failure in the MDC cohort

	INCIDENT HF WITHOUT PRIOR MI HR† (95% CI)	p value	ALL INCIDENT HF HR† (95% CI)	p value
Foreign-born (yes vs no)	1.37 (1.08-1.73)	0.009	1.24 (1.01-1.54)	0.045
Age (per 1 year)	1.11 (1.09-1.12)	< 0.001	1.11 (1.09-1.12)	< 0.001
Male sex (yes vs no)	1.71 (1.44-2.03)	< 0.001	1.68 (1.45-1.95)	< 0.001
Waist circumference (per 5 cm)	1.03 (1.02-1.04)	< 0.001	1.03 (1.02-1.04)	< 0.001
Systolic blood pressure (per 10 mm Hg)	1.13 (1.09-1.18)	< 0.001	1.15 (1.11-1.20)	< 0.001
Leukocyte count (per 10 ⁹ /L)	1.02 (1.01-1.03)	0.005	1.02 (1.01-1.03)	0.001
Use of BP-lowering medications (yes vs no)	2.02 (1.69-2.41)	< 0.001	2.03 (1.74-2.37)	< 0.001
Use of lipid-lowering medications (yes vs no)	1.10 (0.73-1.63)	0.658	1.43 (1.06-1.94)	0.021
Diabetes mellitus (yes vs no)	2.78 (2.12-3.65)	< 0.001	2.80 (2.22-3.54)	< 0.001
Smoking (yes vs no)	1.94 (1.63-2.32)	< 0.001	2.11 (1.81-2.46)	< 0.001
High alcohol consumption (yes vs no)	1.53 (1.10-2.14)	0.012	1.40 (1.03-1.91)	0.032
Low physical activity (yes vs no)	1.27 (1.07-1.52)	0.008	1.26 (1.07-1.47)	0.004
Unmarried (yes vs no)	1.21 (1.02-1.44)	0.028	1.15 (0.98-1.34)	0.081
Low educational level (yes vs no)	1.18 (1.00-1.39)	0.050	1.23 (1.06-1.42)	0.005

Hazard ratio (HR)† in the final model. CI, confidence interval.

Case fatality

Thirty-two (4.2%) subjects died within 1-month after the HF hospitalization and 95 (18.9%) had died one year after the HF. After adjustment for age, sex and year of the HF hospitalization, the immigrants group tended to have lower one-month and one-year mortality (HR: 0.20; 95% CI: 0.03-1.44, $p = 0.109$ and HR: 0.47; 0.22-1.01, $p = 0.053$, respectively).

Discussion

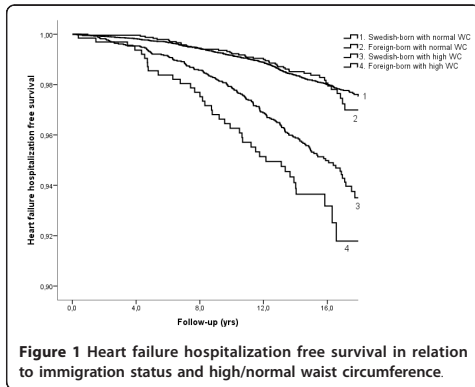
The present population-based cohort study shows that being foreign-born is associated with significantly higher risk for HF hospitalization, independent of several biological, lifestyle and socioeconomic risk factors. The results are in line with prior studies on immigration status and cardiovascular disease (CVD) in Sweden [14,16,18]. However, the present results also show that the increased risk among immigrants is modified by the presence of other risk factors. There was a significant interaction between WC and immigrant status on risk of HF hospitalizations, and the increased incidence was mainly observed in those with high WC.

One possible explanation for the increased risk of HF hospitalization in foreign-born compared to Swedish-born might be influences from their country of birth. Compared to 15.6% being foreign-born in whole Malmö [18], the proportion of foreign-born in the MDC cohort were 11.8% of all study subjects. This group mainly came from Denmark, Former Yugoslavia, Finland, Germany, Poland and Hungary. The majority of these countries have higher incidence of CVD compared to Sweden [26,27]. Since most cases of HF are caused by hypertension or CHD, the high CVD risk in their country of origin might partly explain the increased risk of hospitalization due to HF. It has often been suggested that socioeconomic differences could explain the high morbidity in immigrant groups. Studies have shown that residential areas in Malmö with high proportion of immigrants and low socioeconomic status have high incidence of CVD [28,29]. However, the immigrants in this cohort study had higher education levels than those born in Sweden and the present results remained significant also after adjustments for education and marital status. Socioeconomic differences therefore seem to be

Table 3 Interaction between immigration status and waist circumference (WC) on incidence of HF in the MDC cohort

	INCIDENT HF WITHOUT PRIOR MI HR† (95% CI)	ALL INCIDENT HF HR† (95% CI)
Interaction term Immigrant status*WC	$P < 0.001$	$P < 0.001$
Swedish-born with normal WC (reference)	1	1
Swedish- born with high WC	1.67 (1.38-2.02)	1.71 (1.45-2.03)
Foreign- born with normal WC	1.17 (0.85-1.60)	1.06 (0.79-1.42)
Foreign- born with high WC	2.62 (1.87-3.67)	2.45 (1.80-3.34)

Hazard ratio HR† adjusted for age, sex, civil status, education level, smoking habits, alcohol consumption, physical activities, BP-lowering medication, lipid-lowering medication, systolic BP, leukocyte count and diabetes mellitus. CI, confidence interval.



an insufficient explanation for the increased incidence of HF hospitalizations in foreign-born.

In the present study, a wide range of biological and life-style risk factors were independently associated with risk for HF. The increased HF risk for foreign-born still remained after adjustment for these risk factors. There was a significant interaction between immigrant status and WC on incidence of HF, which showed that the highest risk for HF was limited to foreign-born with high WC. As a heterogeneous group there are substantial differences among immigrants to Sweden by country of origin [30,31]. A previous cross-sectional study, based on the MDC cohort, found that women born in Hungary, Poland and Germany had higher WHR compared to Swedish-born women, after taking age, height, smoking, physical activity, occupation and percentage of body fat into account [31]. In men, WHR was increased in participants from Yugoslavia, Germany and Finland [31]. In that study length of residence in Sweden was found inversely associated with central adiposity in immigrants and it was concluded that immigrants may be at higher risk of obesity-related comorbidities [31].

Several studies have shown that increased abdominal adiposity is strongly associated with cardiovascular risks [10,32,33]. Inadequate exercise, over-intake of food or alcohol, metabolic imbalance and genetic abnormalities could cause high WC. The high WC influence known risk factors, e.g., dyslipidemia, hypertension, glucose intolerance, inflammation markers [13,34,35], that increase risk of developing HF.

Foreign-born tended to have lower mortality after HF compared to Swedish-born, but the difference did not reach statistical significance. This might be explained by the so-called "obesity paradox", since the foreign-born had higher WC than Swedish-born and overweight and high WC paradoxically have been associated with

improved outcome among HF patients [36,37]. It has been reported that immigrants and native Swedish HF patients are quite similar in terms of symptoms, health care seeking, the distress level, physical function, emotional state and self care [38,39]. More immigrants than Swedes are referred to HF clinic after discharge for follow-ups [40], which could reduce mortality in this group.

Strength and limitation

The study used large numbers of subjects with a long follow-up period and identified large numbers of HF events [19,21]. The cardiovascular endpoints were retrieved from national registers, and studies have showed high case validity for HF and MI in the register data [24,25].

A main limitation of the present study is lack of information on type and cause of HF. Previous studies have demonstrated that immigrants to Sweden have an increased incidence of CVD [16,17]. However, we can only speculate whether the increased risk of hospitalizations due to HF among immigrants in the present study was related to a reduced or normal ejection fraction. In addition, we were unable to include HF patients who only were treated as out-patients. The total incidence of HF is therefore underestimated and we cannot make any conclusion about less severe cases which often are treated as out-patients. The 40.8% participation rate in the MDC study questions the representativity of the population [41]. It was shown that non-participants had higher mortality rate than participants in the MDC cohort. However, there was no substantial difference when comparing baseline characteristics of subjects in the MDC study to a survey study from the Malmö city with participation rate of 75% [41]. Another short-coming is that we were unable to study immigrants by country of origin due to limited number of HF events, however in a previous study based on the whole Malmö city population we found an increased incidence of HF hospitalizations in immigrants from Finland, Former Yugoslavia and Hungary [18].

The MDC study required participants to be able to speak Swedish language. One question is whether this group of immigrants is representative to all immigrants in the city. Among all subjects aged 45-73 years in the whole Malmö population, foreign-born had a significantly higher risk for HF (HR: 1.27; 95% CL, 1.17-1.38) compared to Swedish-born after adjustment for age and sex. The corresponding HR in the MDC cohort was 1.44 (95% CI; 1.14-1.82), and we therefore believe that the results can be generalized.

The choice of risk factors variables in the multivariate model can influence the results since adjustments for risk factors that are mediators in the causal pathway will

underestimate of the relation, while leaving out genuine confounders will overestimate the result. The variables used for adjustments in the study, e.g., age, sex, smoking, hypertension, diabetes, abdominal obesity, alcohol consumption and physical activity are well known cardiovascular risk factors [2,4,5,9,10,12,42,43]. Educational level is a widely used measure of socioeconomic circumstances in epidemiologic studies, and is considered to be related to health outcome by its influence on lifestyle behaviors and value [44]. Low educational level has been reported to associate with higher cardiovascular risk [45,46]. Marital status has been found associated with HF [7,47].

The lack of follow-up data regarding anthropometric measures and other risk factors in the present study is another issue to be discussed. It is possible that biological factors, e.g., blood pressure and WC changed during the follow-up. However, this is usually a slow process and one study found that adipose tissue distribution is stable through the lifespan [48]. Some subjects might change the status in terms of smoking, physical activity, alcohol consumption and marriage. It is unknown whether change of risk factors during the follow-up could be differential between immigrants and native Swedes.

Conclusions

In conclusion, immigrant status is associated with long-term risk of HF hospitalization, independently of hypertension and several life-style risk factors. A significant interaction between WC and immigrant status on incident HF was observed.

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Authors' contributions

YB, GE and BH constructed the concept and design of the project; YB performed the analysis and drafted the manuscript; YB, GE, BE and BH participated in the analysis and interpretation of data and revised the manuscript critically. All authors approved the final manuscript to be published.

Competing interests

Gunnar Engström is employed as senior epidemiologist by AstraZeneca R&D.

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Paper III

**Anthropometric measures in relation to risk of heart failure hospitalization:
a Swedish population-based cohort study**

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Abstract

Background: It is unclear which anthropometric measure is most useful for assessment of the cardiovascular risk. We investigated the association between different anthropometric measures and risk of heart failure (HF) hospitalization.

Methods: Body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), body fat percentage (BF %), weight and height were measured among 26 653 subjects (aged 45-73 years) without history of myocardial infarction (MI), stroke or HF from the Malmö Diet and Cancer cohort at baseline in 1991-1996. Incidence of HF hospitalizations was monitored during a mean follow-up of 15 years.

Results: 727 subjects were hospitalized with HF as primary diagnosis, of whom 157 had an MI before or concurrent with the HF. After adjustment for potential confounding factors, the hazard ratios of HF hospitalization (4th vs 1st sex-specific quartile) were 1.80 (95% CI: 1.45-2.24) for BMI, 1.87 (1.50-2.34) for WC, 1.77 (1.43-2.19) for WHR, 1.35 (1.09-1.68) for BF%, 1.93 (1.57-2.39) for weight and 1.18 (0.96-1.44) for height. Significant interactions between BMI and WC and WHR, respectively, were observed, and the joint exposure of high BMI and high WC or high WHR further increased the risk. The results were similar in secondary analyses, i.e. excluding incident HF with previous MI during the follow-up.

Conclusion: Our results support the view that raised BMI, WC, WHR or BF% increases the risk of HF hospitalization. The joint exposure of high BMI and high WHR or high WC further increased the risk in an additive way.

Keywords: anthropometric measures, heart failure hospitalization; risk factors; population-based cohort study

Introduction

Obesity is a major risk factor for several cardiovascular diseases (CVD) (1-5), including an increased risk of heart failure (HF) (6-8). The underlying causal links between obesity and cardiac dysfunction are complex. Obesity is associated with a higher risk of hypertension (9), insulin resistance and diabetes mellitus (4), inflammation (10-12), socioeconomic status and lifestyle (13-15), all of which could increase the cardiovascular risk.

It is still controversial which anthropometric measure is most useful for assessment of the cardiovascular risk. Body mass index (BMI), being the marker for general fat, is the most practical and commonly used. However, the INTERHEART study, a multinational case-control study of myocardial infarction, reported substantially stronger relationships for the waist-hip ratio (WHR) than for BMI (3). Since visceral fat is more metabolically active than other fat tissues, it has been proposed that WHR or waist circumference (WC) is preferable (2, 16). However, few have studied the relationships with incidence of HF, and the results are not consistent. Some studies have shown that BMI, WC and WHR had similar prediction for incident HF (17). Others found that abdominal body fat distribution may be a stronger risk factor for HF than overall obesity (18, 19).

The aim of the study was to explore the relationship between risk of HF hospitalization and different anthropometric measures, i.e., BMI, WC, WHR, body fat percentage (BF %), weight and height, in a population-based cohort study. We also explored if there is any combined effect of the different anthropometric measures on the risk of HF.

Materials/subjects and Methods

Study population

The “Malmö Diet and Cancer (MDC)” cohort, from the city of Malmö in southern Sweden, was used for the present study. Detailed information for MDC has been described previously (20-22). In brief, all men and women, born between 1923 and 1950 in Malmö city were invited to the MDC study. During the period March 1991 to September 1996, 28 449 subjects (11 246 men and 17 203 women) underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire. Participation (rate of 41%) in the MDC study has been described in detail elsewhere (21). In short, mortality has been shown significantly higher in non-participants both during and following the recruitment period. The participants in the MDC study were also compared to participants in a mailed health survey in Malmö 1994, with regard to subjective health, lifestyle and sociodemographic characteristics. The proportion reporting good health was found higher in the MDC study than in the mailed health survey (where 75% participated), however socioeconomic structure and prevalence of smoking and overweight/obesity was similar (21).

In the present study, subjects with history of cardiovascular events (myocardial infarction (MI) or stroke, N=970 subjects) or HF (N= 46 subjects) before the baseline examination were excluded. In addition, subjects (n=780) were also excluded due to missing values of anthropometric measurements and other biological, life-style and socioeconomic variables. Thus, the final study population in the analysis consisted of 26 653 (10 223, 38.4% men and 16 430, 61.6% women) subjects, aged 45-73 years.

The ethics committee at Lund University Lund, Sweden, approved the study (LU 51/90) and all participants provided informed consent.

Baseline examinations

The examinations were performed by two trained nurses at the screening center. Standing height was measured with a fixed stadiometer calibrated in centimeters. Weight was measured to the nearest 0.1 kg using balance-beam scale with subjects wearing light clothing and no shoes. BMI was calculated as weight (kg) divided by the square of the height (m²). Waist was measured as the circumference (cm) between the lowest rib margin and iliac crest

and hip circumference (cm) as the largest circumference between waist and thighs. WHR was defined as the ratio of circumference of waist to hip. Bioelectrical Impedance Analyzers (BIA) was used for estimating body composition and BF% was calculated using an algorithm, according to procedures provided by the manufacturer (BIA 103, RJL systems, single-frequency analyser, Detroit, USA) (23). Weight, height, BMI, WC, WHR and BF % was categorized into sex-specific quartiles Q1–4.

Information on current use of lipid, blood pressure-lowering and anti-diabetic medications, smoking habits, alcohol consumption, leisure-time physical activity, education level, civil status and immigrant status were obtained from a self-administered questionnaire. Blood pressure was measured using a mercury-column sphygmomanometer after 10 minutes of rest in the supine position. Leukocyte concentrations were analysed consecutively in fresh heparinized blood. Diabetes mellitus was defined as self-reported physician's diagnosis of diabetes, or use of antidiabetic medications. Low level of leisure-time physical activity was defined as the lowest tertile of a score revealed through 18 questions covering a range of activities in the 4 seasons. The evaluation of the questionnaire has been previously reported (24). Subjects were categorized into current smokers (i.e. those who smoked regularly or occasionally) or non-smokers (i.e. former smokers and never smokers). High alcohol consumption was defined as >40 g alcohol per day for men and >30 g per day for women. Educational level was classified into three categories. "Primary education" included those who had less than 9 years of education, "Some/completed secondary education" included those who had 9-12 years of education, and "Education at college or university level" included those who had >12 years of education. Civil status was categorized into married or not. Immigrant status was grouped as Swedish-born and foreign-born.

Ascertainment of cardiovascular events and HF

All subjects were followed from the baseline examination until a first hospitalization due to HF as primary diagnosis, emigration, death or June 30st, 2009, whichever came first. The primary analysis included all HF hospitalization. Subjects were censored at first nonfatal MI in an additional analysis. HF was defined as code 427.00, 427.10, 428.99 (ICD-8); 428 (ICD-9) and I50, I11 (ICD-10) as the primary diagnosis. Non-fatal MI was defined as 410 (ICD-8 and 9) or I21 (ICD-10). The Swedish Hospital Discharge Register (SHDR) was used for case retrieval. Validation studies in the SHDR have shown a validity of 95% for a primary diagnosis of HF, and 94% for MI (25, 26)

Statistical analysis

Cox proportional hazards regression was used to examine the association between anthropometric measures (in sex-specific quartiles) and incidence of HF hospitalization. Time axis was follow-up time until death, emigration, incident HF or end of follow-up. Hazard ratios (HR), with 95% confidence interval (CI) were calculated. Age and sex were included as covariates in the basic model. Secondly, we also adjusted for systolic blood pressure, leukocyte counts, use of blood pressure or lipid-lowering medication, diabetes mellitus, current smoking, high alcohol consumption, low leisure physical activity, low education, marital status and immigrant status. In an additional analysis we also censored subjects with incident MI before or concurrent with HF during the follow-up period. The Harrell's C statistics (27) were calculated to assess the HF prediction efficiency. The log likelihood ratio was calculated to assess whether the model was improved by adding anthropometric measures to the explanatory variables. Possible interaction between anthropometric measures and age, sex and cardiovascular risk factors on incident HF was explored by introducing interaction terms in the multivariate model. All analyses were performed using PASW version 18 (SPSS Inc., Chicago, Illinois).

Results

Study cohort

The study population characteristics are presented in table 1. Overall, mean age at baseline was 58 ± 7.6 years, and 61.6% were women. Men compared to women were older, taller and heavier, had higher BMI, WC and WHR, and had a lower BF %. Men were more often hypertensive, high alcohol consumers and had more diabetes. Men were also more often married and had lower education as compared to women.

Risk of HF hospitalizations in relation to anthropometric measures

During a mean follow-up of 14 years, a total of 727 individuals (398 men and 329 women) were hospitalized with HF as primary diagnosis. Of them, 157 (91 men and 66 women) had an incident MI before or concurrent with HF hospitalization during follow-up. The latter group was censored at the time of the infarction in a secondary analysis.

The overall analysis showed that overweight and obesity increased the risk of HF hospitalization independently from several sociodemographic, lifestyle and biological factors. BMI, WC, WHR and BF % were significantly related to an increased risk of HF in both sexes, Table 2. Taking potential confounding factors into account, the HR:s of HF hospitalization (4th vs 1st sex-specific quartile) were 1.87 (95% CI): 1.50-2.34) for WC, 1.80 (1.45-2.24) for BMI, 1.77 (1.43-2.19) for WHR, and 1.35 (1.09-1.68) for BF %, Table 2, Figure 1. Interaction terms between sex and age, respectively, and different anthropometric indicators were added in the final Cox's proportional hazards model with adjustment for possible confounders. There was a statistically significant interaction between BMI with sex ($P=0.002$), however no interaction was observed between sex and other anthropometric measures (e.g. WC, WHR, BF%, weight or height). For BMI the HR for all HF hospitalization (4th vs 1st quartile) was 1.82 (1.37-2.42) among men and 1.80 (1.28-2.53) among women. There were no significant interactions between age and any of the anthropometric measures.

If cases with MI before or concurrent with HF hospitalization ($n=157$) were excluded in the analysis, the risk for HF hospitalization was only marginally changed (data not shown). Nor did the results change in an analysis including 28 cases without previous history of HF hospitalization, who had HF as underlying cause of death. (data not shown)

C-statistics and p-value for model improvement was calculated (online supplement, Table 1). In model 1 all anthropometric measures significantly added information above risk factors. WC and WHR, but not BF %, significantly added to the model on top of BMI. C-statistic results were marginally increased compared to a model including risk factors and BMI, online supplement, Table 1.

Risk of HF hospitalization in relation to combined pattern of different anthropometric measures

Significant interaction was observed between BMI and WHR ($P=0.004$), waist ($P=0.005$), weight ($P=0.010$) and height ($P=0.035$), respectively, on hospitalization due to HF. The joint exposure of high BMI (the top quartile) and high WHR (the top quartile) further increased the risk in an additive way. Overweight subjects with high BMI combined with high WHR had a two-fold higher risk compared to individuals with low or normal BMI (quartile 1-3) and low or normal WHR (quartile 1-3), Table 3. A similar additive effect was observed for BMI and WC. Table 3.

Discussion

Previous studies have established an association between overweight or obesity and an increased risk of HF. The present population-based cohort study extends these findings showing an independent association between overweight or obesity and risk of first HF hospitalization among middle-aged subjects. The relationships were independent of potential confounders, including multiple biological, lifestyle, and socio-economic factors. Overall weight, BMI, WC and WHR were anthropometric measures significantly associated to the risk of HF hospitalization with largely the same effect sizes for all measures. Although statistically significant, BF% showed weaker relationships with HF.

The underlying mechanism between obesity and HF is complex. Obesity is associated with a higher risk of hypertension (9), insulin resistance and diabetes mellitus (28, 29) which result in neurohormonal change and MI; obesity can also cause renal sodium retention, higher leptin (30) and inflammation oxidative stress (11, 12). All of these can contribute to haemodynamic overload, lead to left ventricular hypertrophy, which increase the risk of HF (31-33). The joint exposure of high WHR or high WC and high BMI further increased the risk in an additive way, which indicate that the location of body fat add additional information about risk of HF.

The main risk factors for HF include age, male sex, diabetes, hypertension, high levels of blood lipids, inflammation, smoking, high alcohol consumption, low physical activity and socioeconomic factors (7, 10, 34-39). In our study, overweight or obesity measured by BMI, WC, WHR or BF %, respectively, emerged as significant independent predictors of HF in multivariate models, taking these risk factors into account. This suggests that obesity by itself or its mediated mechanisms are responsible for HF. Ischemic heart disease is another major cause of HF. In our additional analysis, the risk for HF hospitalization was only marginally changed after censoring 157 subjects with nonfatal MI during follow-up period.

Strength and limitations

The strength of the study was the large numbers of subjects and events during a long follow-up period. Further, the cardiovascular endpoints, e.g. HF and MI, were retrieved from national registers with high case validity (25, 26).

A main limitation of the present study is lack of information on type and cause of HF. All HF cases were treated in-hospital as a primary diagnosis and we were unable to include less severe out-patient HF cases. Since we have no information on the less severe cases, we cannot make any conclusion about them. However, in the MESA (Multi-Ethnic Study of Atherosclerosis) study, including men and women aged 45-84 years without clinically apparent CVD, obesity based on different anthropometric measures was found associated with concentric left ventricular remodeling in men as in women (40). In that same cohort it has also been shown that overweight and obesity based on BMI were associated with differences in the right ventricular morphology, independent of left ventricular measures (41). This supports the view that obesity also is associated with less severe cases of HF.

Another question is if the study cohort was representative for the background population since the participation rate of MDC was 41%. A previous study found no substantial difference in terms of socio-demographic structure or in prevalence of smoking and overweight/obesity among participants in the MDC study compared to a mailed health survey (where 75% participated) from the city of Malmö (21). Additionally, we excluded 708 subjects due to missing data of anthropometric, lifestyle or socioeconomic circumstances. In that group there were 36 cases of HF hospitalization during the follow-up period. Mean BMI, waist circumference, body fat percentage was somewhat higher, and rate of hospitalization due to HF significantly higher, among cases with than without missing data (n=727), online supplement Table 2.

Change in exposure is an inherent problem in long-term cohort studies. We lack information on anthropometric measures during the follow-up period. It is possible that body fat distribution in some cases changed during the 15 years follow-up. However, this is usually a slow process and one study found that adipose tissue distribution is stable through the lifespan (42). Finally, although we adjusted our analysis for several biological, lifestyle and socio-demographic factors, and because of the observational nature of the study, we cannot exclude the possibility of residual confounding, however our data may indicate a link between anthropometric measures and an increased risk of HF hospitalization.

This study add to the previous knowledge (43) that both general adiposity and abdominal adiposity are associated with increased risk of CVD and death, and that use of waist circumference or waist-to-hip ratio in addition to BMI might be useful when assessing individual risk for CVD and its complications.

Conclusions

In conclusion, elevated BMI, WC, WHR, BF %, respectively, increase the long-term risk of HF hospitalization. The joint exposure of high BMI and high WHR or high WC further increased the risk in an additive way.

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Conflict of interest

Gunnar Engström is employed as senior epidemiologist by AstraZeneca R&D.

Key points

- There was an independent association between overweight or obesity and risk of first HF hospitalization among middle-aged subjects.
- Elevated BMI, WC, WHR, BF %, respectively, increase the long-term risk of HF hospitalization.
- The joint exposure of high BMI and high WHR or high WC further increased the risk.
- Additional information of WC and WHR to BMI might be useful when assessing individual risk for CVD and its complications.

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Table 1. Characteristics of the “Malmö Diet and Cancer (MDC)” cohort participants.

MDC (N=26 653)	Men (n=10 223)	Women (n=16 430)
Hospitalization due to HF, n (per 1000 p-y)	398 (2.78)	329 (1.39)
Age at screening (years)	59.0±7.0	57.4±7.9
BMI (kg/m ²)	26.2±3.4	25.4±4.2
WC (cm)	93.6±12.6	77.7±10.5
WHR	0.94±0.1	0.79±0.1
BF %	20.7±4.9	30.7±5.0
Weight (kg)	81.7±12.0	67.9±11.6
Height (cm)	176.5±6.6	163.7±6.0
Leukocyte count (10 ⁹ /L)	6.4±2.6	6.4 ±2.3
Systolic blood pressure (mmHg)	143.9±19.2	139.2±20.2
Diastolic blood pressure (mmHg)	88.0±9.8	84.0±9.7
Use of blood pressure-lowering medication (%)	17.9	15.5
Use of lipid-lowering medication (%)	3.3	1.8
Diabetes (%)	3.6	2.3
Current smoking (%)	28.8	27.9
High alcohol consumption (%)	7.5	2.4
Low physical activity (%)	25.3	24.8
Married (%)	72.6	60.8
Primary education (%)	45.2	39.0
Some/completed secondary school (%)	31.8	37.5
Education at college or university level(%)	23.0	23.5
Foreign-born (%)	12.0	11.8

Values are means ± standard deviation, unless stated otherwise. p-y, person-years.

MDC, Malmö Diet and Cancer; HF, heart failure. BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; BF%, body fat percentage

Table 2: Hospitalizations due to heart failure (HF) in relation to different anthropometric measures.

Sex-specific quartiles	Q1	Q2	Q3	Q4	p for trend
BMI	n= 6666	n= 6661	n= 6662	n= 6664	
Median, kg/m ² (men/women)	22.5/21.1	24.9/23.5	26.9/26.0	30.0/30.1	
HF , n (per 1000 p-y)	121 (1.27)	132 (1.38)	164 (1.72)	310 (3.34)	
Adjusted HR (95% CI)	1.00	0.98 (0.76 -1.25)	1.12 (0.88 -1.42)	1.80 (1.45-2.24)	<0.001
WC	n= 6766	n= 6103	n= 7229	n= 6555	
Median, cm(men/women)	82/67	90/73	96/79	105/90	
HF , n (per 1000 p-y)	112 (1.15)	112 (1.27)	174 (1.68)	329 (3.64)	
Adjusted HR (95% CI)	1.00	0.92 (0.71 -1.19)	1.15 (0.90 -1.46)	1.87 (1.50-2.34)	<0.001
WHR	n= 6661	n= 6698	n= 6650	n= 6644	
Median (men/women)	0.88/0.74	0.92/0.77	0.96/0.80	1.01/0.85	
HF , n (per 1000 p-y)	149 (1.34)	137 (1.42)	169 (1.78)	292 (3.18)	
Adjusted HR (95% CI)	1.00	1.04 (0.82 -1.32)	1.13 (0.90 -1.42)	1.77 (1.43-2.19)	<0.001
BF %	n= 6851	n= 6228	n= 7266	n= 6308	
Median, % (men/women)	15/25	19/29	22/32	26/37	
HF , n (per 1000 p-y)	133 (1.37)	135 (1.51)	205 (1.97)	254 (2.87)	
Adjusted HR (95% CI)	1.00	0.98 (0.77 -1.24)	1.18 (0.95 -1.47)	1.35 (1.09-1.68)	0.001
Weight	n= 6946	n= 6407	n= 6702	n= 6598	
Median, kg (men/women)	69/56	77/64	84/70	95/81	
HF , n (per 1000 p-y)	134 (1.36)	145 (1.58)	166 (1.73)	282 (3.05)	
Adjusted HR (95% CI)	1.00	1.13 (0.89 -1.43)	1.26 (1.00 -1.59)	1.93 (1.57-2.39)	<0.001
Height	n= 6821	n= 6375	n= 6328	n= 7129	
Median, cm(men/women)	169/157	175/162	178/165	184/170	
HF , n (per 1000 p-y)	236 (2.48)	179 (1.98)	140 (1.54)	172 (1.67)	
Adjusted HR (95% CI)	1.00	0.98 (0.81 -1.19)	0.86 (0.70 -1.07)	1.18 (0.96-1.44)	0.357

HR adjusted for age, sex, civil status, education level, immigrant status, smoking habits, alcohol consumption, physical activities, blood pressure-lowering medication, lipid-lowering medication, systolic blood pressure, leukocyte count and diabetes mellitus.

HR, hazard ratio; Q, quartile; CI, confidence interval; p-y, person-years; BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; BF %, body fat percentage.

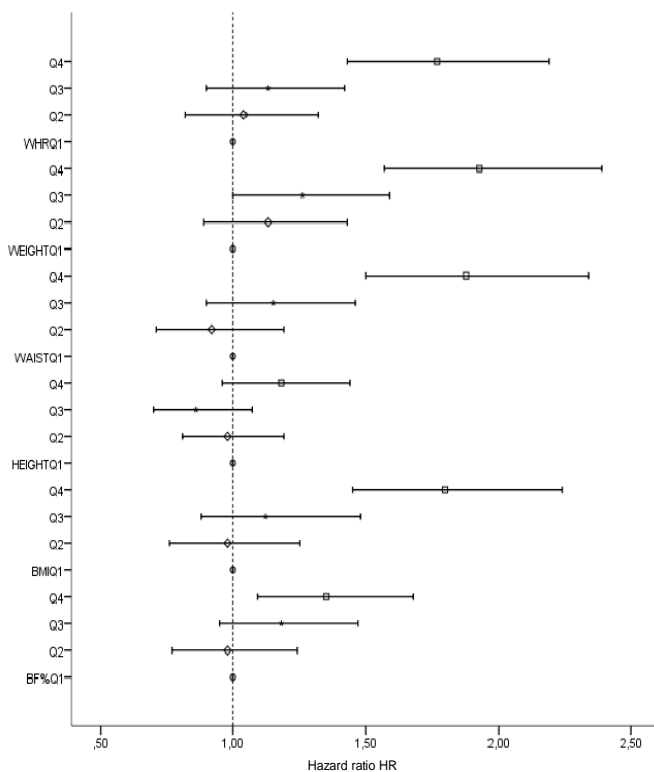
Table 3. Risk of hospitalization due to heart failure (HF) in relation to combined pattern of different anthropometric measures.

MDC (N=26,653)	HF, n (per 1000 p-y)	Adjusted HR (95% CI)
BMI Q1-3, WHR Q1-3 (n=16,851)	316 (1.30)	1.00
BMI Q1-3, WHR Q4 (n= 3,138)	103 (2.34)	1.58 (1.26-1.98)
BMI Q4, WHR Q1-3 (n= 3,158)	119 (2.65)	1.66 (1.34-2.06)
BMI Q4, WHR Q4 (n= 3,506)	191(3.99)	2.13 (1.77-2.58)
BMI Q1-3, WC Q1-3 (n=18,460)	351 (1.32)	1.00
BMI Q1-3, WC Q4 (n= 1,529)	66 (3.11)	1.62 (1.24-2.11)
BMI Q4, WC Q1-3 (n= 1,638)	47 (1.99)	1.44 (1.06-1.95)
BMI Q4, WC Q4 (n= 5,026)	263 (3.80)	1.97 (1.67-2.34)

HR adjusted for age, sex, civil status, education level, immigrant status, smoking habits, alcohol consumption, physical activities, blood pressure-lowering medication, lipid-lowering medication, systolic blood pressure, leukocyte count and diabetes mellitus. CI, confidence interval. p-y, person-years.

MDC, Malmö Diet and Cancer; HF, heart failure; HR, hazard ratio; Q, quartile; BMI, body mass index; WHR, waist-hip ratio; WC, waist circumference.

Figure 1. Adjusted hazard ratio (HR, 95% confidence interval) for different anthropometric measures (in sex-specific quartiles, Q1 to Q4) in relation to the risk of hospitalization due to heart failure.



Online supplements:

Table 1. Results from model likelihood ratio test and Harrell's C statistic

	<i>p</i> value for model improvement	C-statistic
Model 1#		0.7957
Model 1+BMI	<0.001	0.7992
Model 1+WC	<0.001	0.8004
Model 1+WHR	<0.001	0.7984
Model 1+BF%	0.007	0.7961
Model 1+BMI +WC	0.001	0.8008
Model 1+BMI +WHR	0.001	0.8001
Model 1+BMI +BF%	0.787	0.7991

*P value for -2 log likelihood ratio test.

Model 1: age, sex, civil status, education level, immigrant status, smoking habits, alcohol consumption, physical activities, blood pressure-lowering medication, lipid-lowering medication, systolic blood pressure, leukocyte count and diabetes mellitus. BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; BF %, body fat percentage.

Model 1+BMI WC, Model 1+BMI +WHR and Model 1+BMI +BF%, respectively, compared with Model 1+BMI

Table 2. Baseline characteristics and rate of hospitalizations due to heart failure (HF) among cases with and without missing data.

Characteristics	HF cases without missing data (n=727)	HF cases with missing data (n=36)
HF hospitalization per 1000 p-y	1.92	3.29
Age at screening (years)	63±6.7	62±5.4
Sex (male %)	54.7	52.8
BMI, body mass index (BMI)	27±4.6	28±4.6
Waist circumference (WC)(cm)	92±14.2	95±16.2
Waist-hip ratio (WHR)	0.9±0.1	0.9±0.1
Body fat percentage (BF %)	27±7.8	28±7.3
Weight (kg)	80±15.8	81±15.2
Height (cm)	170±9.3	168±7.2
Leukocyte count (10 ⁹ /L)	6.9±1.9	7.0 ±2.1
Systolic blood pressure (mmHg)	153±20.5	151±22.0
Blood pressure-lowing medication (%)	38.7	30.6
Lipid-lowing medication (%)	5.8	2.8
Diabetes (%)	11.4	13.9
Current smoker (%)	36.5	16.0
High alcohol consumption (%)	5.9	0
Married (%)	64.5	68.0
Primary education (%)	55.2	81.8
Foreign-born (%)	12.1	16.0

Among HF cases with missing data (n=36) data are depicted for variables with information for >20 subjects. Values are means ± standard deviation, unless stated otherwise. p-y, person-years. MDC, Malmö Diet and Cancer.

Paper IV

Red cell distribution width and risk for first hospitalization due to heart failure: a population-based cohort study

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Aims

Red cell distribution width (RDW) has been associated with cardiovascular disease, but the relation to heart failure (HF) is unclear. We investigated the association between RDW and incidence of first hospitalization due to HF in a population-based cohort.

Methods and results

Red cell distribution width was measured in 26 784 subjects (aged 45–73 years, 61% women), without history of myocardial infarction (MI), stroke or HF, who participated in the Malmö Diet and Cancer study during 1991–1996. Incidence of HF was identified from the national Swedish hospital discharge register during a mean follow-up of 15 years and studied in relation to RDW. During follow-up, 773 subjects (55% men) were hospitalized due to HF, of whom 166 had an MI before or concurrent with the HF. After adjustment for potential confounding factors (including history of coronary revascularization, biological, lifestyle, and socio-economic factors), the hazard ratios (HR) for HF were 1.47 (95% CI: 1.14–1.89) in the top compared with the bottom quartile of RDW (*P* for trend 0.005), censoring subjects with incident MI before HF. The results were similar when all hospitalized HF cases were included (HR: 1.33, 1.07–1.66), (*P* for trend 0.020). After additional adjustment for N-terminal pro-B-type natriuretic peptide, cystatin C and high-sensitive C-reactive protein in a randomly selected subcohort (*n* = 4761), HR was 1.64 (CI: 0.90–3.00) comparing the top vs. bottom quartile of RDW.

Conclusion

Red cell distribution width was found to be associated with long-term incidence of first hospitalization due to HF among middle-aged subjects.

Keywords

Red cell distribution width • Heart failure • Risk factors • Cohort study • Epidemiology

Introduction

Red cell distribution width (RDW) is a measure of anisocytosis or variation in the volume of circulating erythrocytes. Red cell distribution width is part of routine haematology laboratory tests and is a useful indicator for differentiation and classification of anaemia.^{1–3} Recent studies have established RDW as a strong independent predictor of prognosis in heart failure (HF) patients^{4–9} and for new symptomatic HF in subjects with a history of myocardial infarction (MI).¹⁰ Felker *et al.* first reported higher RDW as a novel predictor of morbidity and mortality among chronic HF patients in a large clinical trial.⁴ Subsequent

studies have validated this observation and shown association with worse long-term outcome to be additive to other prognostic variables such as N-terminal pro-B-type natriuretic peptide (NT-proBNP)⁹ and independent of haemoglobin levels and anaemia status.⁵ Other studies have suggested inflammation, ineffective erythropoiesis, undernutrition, and impaired renal function as potential mechanisms linking RDW to outcome,⁶ but results have not been consistent.⁹ Furthermore, these studies included subjects with previous HF or cardiovascular diseases. To the best of our knowledge, there are no studies on the association between RDW and risk of HF in subjects from the general population without a history of HF or MI.

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Thus, the purpose of the present study was to explore the relationships between RDW and risk of hospitalization due to HF in asymptomatic middle-aged subjects. We also sought to explore whether this relationship was modified by novel biomarkers, including haemodynamic stress (NT-proBNP), renal function (cystatin C), and inflammation markers [leucocyte count and high-sensitive C-reactive protein (hsCRP)].

Methods

Study population

The Malmö Diet and Cancer study (MDC) is a prospective cohort study from the city of Malmö in southern Sweden. Sample characteristics, data collection, and clinical definitions for MDC have been described previously.^{11–14} Briefly, 28 449 men ($n = 11\ 246$, born 1923–1945) and women ($n = 17\ 203$, born 1923–1950) attended a baseline examination between March 1991 and September 1996. Participants underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire. Information on RDW was available in 28 363 subjects. Subjects with previous admission for MI or stroke ($n = 970$ subjects) or HF ($n = 46$ subjects) at the baseline examination were excluded. In addition, 663 subjects were excluded due to missing information on blood pressure, use of blood pressure medication, history of diabetes mellitus, waist circumference, smoking habits, alcohol consumption, physical activity, education level, civil status, and leucocyte counts. Thus, the final study population in the analysis consisted of 26 784 (10 277 men and 16 507 women) subjects, aged 45–73 years.

Between October 1991 and February 1994, a randomly selected subgroup was invited to take part in a study of the epidemiology of carotid artery disease,¹⁴ the MDC cardiovascular cohort (MDC-CC). Of the 6103 invited subjects, 5533 participated in additional examinations to assess carotid atherosclerosis by ultrasound and donated blood after fasting conditions.¹³ Data on conventional cardiovascular risk factors, NT-proBNP, cystatin C, and hsCRP, were available for 4761 subjects (aged 46–68 years, 60% women). Participants in the MDC-CC with measurement of biomarkers did not differ from the whole MDC cohort in terms of age, sex, biological, lifestyle, and socio-economic factors.¹³

All participants provided written informed consent, and the study was approved by the ethics committee at Lund University, Lund, Sweden (LU 51/90). The MDC is registered in the US Library of Medicine as trial number NCT 01216228.

Measurements and definitions

Information on current use of nitroglycerin, blood pressure-lowering and anti-diabetic medications, smoking habits, alcohol consumption, leisure-time physical activity, education level, and civil status were obtained from a self-administered questionnaire.¹³ Waist circumference (in cm) was measured midway between the lowest rib margin and iliac crest. Blood pressure was measured using a mercury-column sphygmomanometer after 10 min of rest in the supine position. Diabetes mellitus was defined as fasting whole blood glucose level greater than 109 mg/dL (i.e. 6.0 mmol/L), self-reported physician's diagnosis of diabetes or use of anti-diabetic medications. Subjects were categorized into current smokers (i.e. those who smoked regularly or occasionally) or non-smokers (i.e. former smokers and never smokers). High alcohol consumption was defined as >40 g alcohol per day for men and >30 g per day for women. High education was defined as a degree from college, university or higher, e.g. 12 years

or more.¹⁵ Civil status was categorized into married or not.¹⁵ Low level of physical activity was defined as the lowest tertile of a score revealed through 18 questions covering a range of activities in the four seasons. The evaluation of the questionnaire has been previously reported.¹⁶ Information about percutaneous coronary artery interventions (PCI) was retrieved from the national Swedish Coronary Angiography and Angioplasty Register.¹⁷ Information on coronary artery bypass graft surgery (CABG) was retrieved from the Swedish Hospital Discharge Register (SHDR). History of coronary artery disease (CAD) at baseline was defined as either current treatment with nitroglycerin or previous PCI or CABG revascularization.

Red cell distribution width, haemoglobin, and leucocyte concentrations were analysed consecutively in fresh heparinized blood. Erythrocyte diameter was measured using a fully automated assay (SYSMEX K1000). Red cell distribution width was calculated as the width of the erythrocyte distribution curve at a relative height of 20% above the baseline. Reference values were 36.4–46.3 fL in women and 35.1–43.9 fL in men.¹⁸

Cardiovascular biomarkers in the MDC-CC were analysed in fasting plasma samples that had been frozen at -80°C immediately after collection without previous thawing.¹³ NT-proBNP was analysed using the automated Dimension Vista Intelligent Lab System method (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois).¹⁹ Levels of Cystatin C were measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Deerfield, Illinois).²⁰ High-sensitive C-reactive protein was analysed using the Tina-quant[®] CRP latex assay (Roche Diagnostics, Basel, Switzerland) on an ADVIA[®] 1650 Chemistry System (Bayer Healthcare, NY, USA).

Ascertainment of cardiovascular events and heart failure

All subjects were followed from the baseline examination until a first hospitalization due to HF as primary diagnosis, emigration, death or December 31, 2008, whichever came first. The primary analysis included only HF cases without preceding MI, before or on the same day as the HF hospitalization. In this analysis, subjects were censored at first non-fatal MI. Additional analysis included all incident HF cases, regardless of MI during follow-up. Heart failure was defined as International Classification of Diseases – 8th revision (ICD-8), code 427.00, 427.10, and 428.99; 428 (ICD-9); and I50, I11 (ICD-10) as the primary diagnosis.²¹ Non-fatal MI was defined as 410 (ICD-8 and 9) or I21 (ICD-10).²² The SHDR was used for case retrieval. A validation study has shown that a primary diagnosis of HF in the SHDR has a validity of 95%.²¹ The corresponding figure for MI is 94%.²²

Statistical analysis

Cross-sectional relations of RDW quartiles to cardiovascular risk factors were assessed using linear regression for continuous variables and logistic regression for dichotomous variables. *P*-values from trend tests across quartiles were used. Data from the whole MDC cohort were used to examine the association between RDW and incident hospitalizations due to HF. Cox proportional hazards regression was used to examine the association between RDW (in sex-specific quartiles) and incidence of HF. Time axis was time to follow-up until death, emigration, incident HF, or end of follow-up. Hazard ratios (HR) with 95% confidence interval (CI) were calculated. Age and sex were included as covariates in the basic model. Secondly, we also adjusted for history of CAD, systolic blood pressure (SBP), use of blood pressure-lowering medication, diabetes mellitus, waist circumference, current smoking, high alcohol consumption, marital status, low education, low physical activity, haemoglobin, and leucocyte

counts. The fit of the proportional hazards model was checked visually by plotting the incidence rates over time and by entering time-dependent covariates into the model. Possible interaction between RDW and age, sex and cardiovascular risk factors on HF was explored by introducing interaction terms in the multivariate model. Subsequently, the final model was repeated in the MDC-CC, taking also NT-proBNP, cystatin C, and hsCRP (as continuous variables) into account. N-terminal pro-B-type natriuretic peptide and hsCRP showed a right-skewed distribution and were logarithmically transformed. The HR for incident HF was also expressed per 1 SD for the RDW, cystatin C, NT-proBNP, and hsCRP. All analyses were performed using PASW version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

Median RDW (inter-quartile range, IQ) was 40.1 (38.2–42.5) in men and 40.6 (38.5–42.7) in women. Cardiovascular risk factors at the baseline examination in relation to the sex-specific quartiles

of RDW are presented in Table 1. Of haematological parameters, increased RDW was associated with increased mean corpuscular volume (MCV), leucocyte and platelet counts but decreased erythrocytes and mean corpuscular haemoglobin concentration (MCHC). Age, current smoking, high alcohol consumption, history of CAD, and being unmarried were positively associated and waist circumference, diabetes, diastolic blood pressure (DBP), and use of blood pressure-lowering medication were inversely associated with RDW. In the MDC-CC, cystatin C, hsCRP, and NT-proBNP were significantly associated with RDW (Table 1).

Incidence of first hospitalizations due to heart failure in relation to red cell distribution width and known cardiovascular risk factors

During a mean follow-up of 15 years, a total of 773 individuals (423 men and 350 women) were diagnosed with HF. Of these, 166 (96

Table 1 Baseline characteristics for MDC and MDC-CC in relation to sex-specific quartiles (Q1–Q4) of RDW

MDC (n = 26 784)	Quartiles of RDW				P for trend
	Q1 (n = 6685)	Q2 (n = 6640)	Q3 (n = 6732)	Q4 (n = 6727)	
Male sex (%)	38.4	38.3	38.1	38.6	
RDW range, men (fL)	<38.2	38.2–40.0	40.1–42.4	>42.4	
RDW range, women (fL)	<38.6	38.6–40.5	40.6–42.7	>42.7	
Erythrocytes (10 ¹² /L)	4.8 ± 0.40	4.7 ± 0.45	4.6 ± 0.46	4.5 ± 0.64	<0.001
Haemoglobin (g/L)	140 ± 26	141 ± 21	141 ± 18	141 ± 19	0.548
MCV (fL)	85 ± 17	88 ± 8.6	90 ± 7.6	93 ± 4.7	<0.001
MCHC (g/L)	341 ± 20	341 ± 39	340 ± 39	339 ± 20	0.028
Leucocytes (10 ⁹ /L)	6.1 ± 1.5	6.3 ± 2.0	6.4 ± 1.8	6.8 ± 3.7	<0.001
Platelet count (10 ⁹ /L)	227 ± 57	229 ± 58	231 ± 57	234 ± 66	<0.001
Age (years)	56.8 ± 7.0	57.8 ± 7.4	58.5 ± 7.8	59.1 ± 7.9	<0.001
Waist circumference (cm)	85 ± 13	85 ± 16	84 ± 13	83 ± 16	<0.001
SBP (mmHg)	141 ± 20	141 ± 20	141 ± 20	141 ± 20	0.475
DBP (mmHg)	86 ± 10	86 ± 10	85 ± 10	85 ± 10	<0.001
Blood pressure-lowering medication (%)	40.9	40.6	40.3	39.3	0.038
Diabetes (%)	4.4	2.9	2.1	1.9	<0.001
Current smoker (%)	14.3	21.6	29.6	47.3	<0.001
High alcohol consumption (%)	3.2	3.5	4.3	6.4	<0.001
Low physical activity (%)	25.3	24.2	24.1	26.3	0.195
Married (%)	69.1	66.3	64.5	61.2	<0.001
Low education (%)	32.5	33.6	32.0	30.7	0.228
History of CAD (%)	1.3	1.4	1.6	1.9	0.004
MDC-CC (n = 4761)	Q1 (n = 1319)	Q2 (n = 1218)	Q3 (n = 1141)	Q4 (n = 1083)	P for trend
RDW range, men (fL)	<38.1	38.2–40.0	40.1–42.4	>42.5	
RDW range, women (fL)	<30.8	38.6–40.5	40.6–42.7	>42.8	
NT-proBNP ^a (pg/mL)	55 (31–102)	63 (33–108)	61 (37–113)	66 (37–121)	<0.001 ^b
Cystatin C (mg/L)	0.77 ± 0.14	0.77 ± 0.15	0.78 ± 0.16	0.79 ± 0.16	0.001
hsCRP ^a (mg/L)	1.2 (0.9–56.0)	1.4 (0.9–37.9)	1.3 (0.9–58.1)	1.3 (0.9–60.2)	0.004 ^b

^aNT-proBNP and hsCRP are presented as median (interquartile range in brackets) due to skewed distributions.

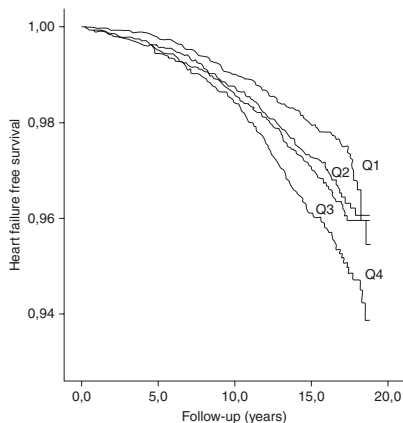
^bP value for log-transformed value for NT-proBNP and hsCRP. All other values are means ± SD, unless otherwise stated.

Table 2 Incidence of first hospitalization due to HF in relation to sex-specific quartiles (Q1–Q4) of RDW in the MDC cohort

Sex-specific quartiles of RDW	Incident HF without prior MI			All incident HF		
	No. of HF	HR ^a	HR ^b	No. of HF	HR ^a	HR ^b
Q1 (n = 6685)	103	Reference	Reference	141	Reference	Reference
Q2 (n = 6640)	146	1.29 (1.00–1.66)	1.33 (1.03–1.71)	186	1.20 (0.96–1.49)	1.23 (0.99–1.53)
Q3 (n = 6732)	163	1.32 (1.03–1.70)	1.37 (1.07–1.77)	199	1.18 (0.95–1.46)	1.21 (0.97–1.51)
Q4 (n = 6727)	195	1.57 (1.23–2.00)	1.47 (1.14–1.89)	247	1.44 (1.17–1.77)	1.33 (1.07–1.66)
Total (n = 26 784)	607			773		
P value for trend		<0.001	0.005		0.001	0.020

^aHazard ratio (HR) adjusted for age and sex.

^bHR adjusted for age, sex, history of coronary revascularization, use of nitroglycerin treatment, SBP, use of blood pressure-lowering medication, diabetes mellitus, waist circumference, smoking, high alcohol consumption, low physical activity, marital status, low education level, haemoglobin, and leucocyte count. CI, confidence interval.

**Figure 1** Heart failure hospitalization free survival in relation to sex-specific quartiles (Q1–Q4) of RDW.

men and 70 women) had an incident MI before or concurrent with HF during follow-up.

Subjects in the top compared to the bottom quartile of RDW had a significantly higher risk for HF (HR: 1.47, 95% CI: 1.14–1.89), (P for trend 0.005), adjusting for all covariates (Table 2 and Figure 1. If cases with MI before or concurrent with HF were included, the risk increase was rather similar (1.33, 1.07–1.66), (P for trend 0.020). In the final model, age, male sex, history of CAD, SBP, use of blood pressure-lowering medication, diabetes, waist circumference, smoking, high alcohol consumption, low physical activity, low educational level, being unmarried, and leucocyte count were independently associated with an increased risk of HF (Table 3). If RDW was entered as a continuous variable into

the final model the HR per SD (i.e. 3.55 fL) was 1.12 (1.05–1.19, $P < 0.001$). The corresponding HR was 1.11 (1.05–1.17, $P = 0.001$) if cases with MI before or concurrent with HF were included. No significant interaction was observed between RDW and other risk factors on incidence of HF (data not shown).

Incidence of first hospitalizations due to heart failure in relation to sex-specific quartiles of red cell distribution width adjusting for other biomarkers

In the MDC-CC ($n = 4761$), the HR (95% CI) in the top compared to the bottom quartile of RDW was 1.85 (1.04–3.31), (P for trend 0.039) taking all covariates included in the final model of the whole MDC into account (Table 4). This risk was relatively unchanged (1.82; 1.01–3.31), (P for trend 0.049), by adding hsCRP and cystatin C to the model; however, it became slightly reduced and non-significant (HR: 1.65; 0.90–3.00), (P for trend 0.114) when NT-proBNP was also taken into account (Table 4). In this model, the HRs for incident HF per 1 SD of cystatin C, hsCRP, and NT-proBNP were 0.57 (0.16–2.04, $P = 0.385$), 1.30 (1.06–1.59, $P = 0.012$), and 1.99 (1.61–2.48, $P < 0.001$), respectively.

Discussion

Previous studies have established the association of RDW with new congestive HF onset in people with prior MI, as well as poor prognosis in patients with clinical HF.^{4,5,10} The present large, population-based cohort study extends these findings to show a graded independent association between RDW and risk of first hospitalization due to HF among middle-aged subjects. This relationship was independent of potential confounders, including multiple biological, lifestyle, and socio-economic factors. In a randomly selected subcohort of the MDC, which included information on NT-proBNP, hsCRP, and cystatin C, additional adjustment for these risk markers only slightly decreased the HR. The results suggest that RDW is a new risk factor for incidence of first hospitalization due to HF.

Table 3 Final multivariable model for first hospitalization due to heart failure in the MDC cohort

	Incident HF without prior MI HR ^a (95% CI) ^b	P value	All incident HF HR ^a (95% CI) ^c	P value
RDW (Q4 vs. Q1)	1.47 (1.14–1.89)	0.003	1.33 (1.07–1.66)	0.011
Age (per 1 year)	1.10 (1.09–1.12)	<0.001	1.10 (1.09–1.12)	<0.001
Male sex	1.75 (1.45–2.12)	<0.001	1.74 (1.48–2.06)	<0.001
History of CAD ^d (yes vs. no)	2.02 (1.42–2.86)	<0.001	2.30 (1.72–3.07)	<0.001
SBP (per 10 mm Hg)	1.15 (1.10–1.20)	<0.001	1.17 (1.12–1.21)	<0.001
Blood pressure-lowering medication (yes vs. no)	1.89 (1.58–2.27)	<0.001	1.92 (1.63–2.25)	<0.001
Diabetes mellitus (yes vs. no)	2.97 (2.26–3.89)	<0.001	2.95 (2.34–3.73)	<0.001
Waist circumference (per 5 cm)	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	0.001
Smoking (yes vs. no)	1.84 (1.53–2.21)	<0.001	2.02 (1.72–2.38)	<0.001
High alcohol consumption (yes vs. no)	1.52 (1.09–2.12)	0.015	1.39 (1.02–1.90)	0.036
Low physical activity (yes vs. no)	1.25 (1.05–1.50)	0.012	1.24 (1.06–1.45)	0.007
Unmarried (yes vs. no)	1.21 (1.02–1.44)	0.025	1.14 (0.98–1.33)	0.084
Low educational level (yes vs. no)	1.21 (0.99–1.47)	0.059	1.26 (1.06–1.50)	0.010
Leucocyte count (per 10 ⁹ /L)	1.02 (1.01–1.03)	0.012	1.02 (1.01–1.03)	0.002
Haemoglobin (per 1 g/L)	0.99 (0.99–1.00)	0.267	0.99 (0.99–1.00)	0.186

^aHazard ratio (HR) in the final model.^bThe model was based on 607 HF events.^cThe model was based on 773 HF events.^dHistory of CAD includes information on current use of nitroglycerine or revascularization with PCI and CABG prior to baseline. CI, confidence interval.**Table 4** Incidence of first hospitalization due to HF in relation to sex-specific quartiles (Q1–Q4) of RDW in the MDC-CC

Sex-specific quartiles of RDW	Incident HF without prior MI				All incident HF			
	HF (n)	HR ^a	HR ^b	HR ^c	HF (n)	HR ^a	HR ^b	HR ^c
Q1 (n = 1319)	21	Reference	Reference	Reference	25	Reference	Reference	Reference
Q2 (n = 1218)	26	1.22 (0.69–2.18)	1.22 (0.68–2.18)	1.19 (0.65–2.16)	34	1.33 (0.79–2.22)	1.29 (0.77–2.17)	1.25 (0.73–2.14)
Q3 (n = 1141)	27	1.30 (0.73–2.31)	1.29 (0.72–2.30)	1.20 (0.66–2.20)	32	1.26 (0.75–2.14)	1.26 (0.74–2.15)	1.15 (0.67–2.00)
Q4 (n = 1083)	34	1.85 (1.07–3.20)	1.85 (1.04–3.31)	1.64 (0.90–3.00)	38	1.69 (1.02–2.80)	1.62 (0.95–2.76)	1.41 (0.81–2.45)
Total (n = 4761)	108				129			
P value for trend		0.027	0.039	0.114		0.062	0.101	0.302

^aHazard ratio (HR) adjusted for age and sex.^bHR adjusted for age, sex, history of CAD, SBP, use of blood pressure-lowering medication, diabetes mellitus, waist circumference, smoking habits, high alcohol consumption, low physical activity, marital status, education level, haemoglobin, and leucocyte count.^cHR adjusted for age, sex, history of CAD, SBP, use of blood pressure-lowering medication, diabetes mellitus, waist circumference, smoking habits, high alcohol consumption, low physical activity, marital status, education level, haemoglobin, leucocyte count, plus cystatin C, log-transformed NT-proBNP, and hsCRP. CI, confidence interval.

The mechanism underlying the relationship between RDW and HF is unclear. It has been shown that activation of the renin–angiotensin system is associated with increased erythropoiesis,^{23,24} which also increases the RDW. Increased neuroendocrine activation is also associated with cardiac arrhythmia, and it is an important feature of HF and atrial fibrillation.²⁵ Hence, one could speculate that a possible link between RDW and HF could be increased levels of angiotensin or adrenergic hormones,²⁶ which could increase RDW and reduce cardiac function.

Red cell distribution width has been associated with low-grade systemic inflammation.²⁷ In our study, RDW was associated with leucocyte counts and hsCRP, e.g. classic markers of inflammation which have previously been associated with incidence of HF.²⁸ However, the relationship between RDW and risk of HF hospitalizations remained unchanged when leucocytes or hsCRP were taken into account. This suggests that inflammation is not the major mechanism for the increased incidence of HF in the present study. Red cell distribution width was associated with

several other risk factors, e.g. age, waist circumference, smoking, high alcohol consumption, diabetes, blood pressure, history of CAD, leucocyte count, and being unmarried. However, RDW remained significant after adjustment for these risk factors, and there was no interaction between RDW and other risk factors on incidence of HF. Malnutrition and deficiency of vitamin B₁₂ and folic acid are other factors that are associated with high RDW, because of their role in erythropoiesis.⁶ We did not have information on plasma levels of these vitamins, and it therefore remains unclear as to whether these factors contributed to the relationship between RDW and incident HF in our study.

N-terminal pro-B-type natriuretic peptide is produced mainly in the cardiac ventricles and is involved in body fluid homeostasis and blood pressure control.^{29–32} Cystatin C is a marker of renal function that predicts cardiovascular events.^{20,33,34} In the present study, both NT-proBNP and cystatin C were significantly associated with RDW. Adjustment for cystatin C and hsCRP only marginally affected the RDW risk for incident hospitalization due to HF, when NT-proBNP was also taken into account, the point estimate for individuals in the top quartile decreased from 1.85 (95% CI: 1.04–3.31) to 1.64 (95% CI: 0.90–3.00). However, the analysis of the MDC-CC was based on a substantially smaller sample and it is likely that the absence of a significant relationship could be explained by low statistical power.

Strength and limitations

The study cohort included large numbers of subjects and events during a long follow-up period.^{12–14} The cardiovascular endpoints were retrieved from national registers covering all hospitalizations in Sweden. Validation studies of cases retrieved from the SHDR have shown a 95% validity of HF as the primary diagnosis, irrespective of clinic type,²¹ and 94% sensitivity and 86% positive predictive value for MI.²² We were unable to detect cases of HF that were diagnosed in the out-patient setting. Thus, our results do not allow conclusions about less severe cases. Since all cases were treated in-hospital and had a primary diagnosis of HF, we can assume that the diagnosis was valid and that the HF was quite severe in most cases.³⁵ A previous study showed that inclusion of subjects, who died outside hospital with HF as the underlying cause of death, as potential HF cases, only marginally affected the results.³⁶

The MDC is a population-based study with an attendance rate of 40%. Similar to most population-based studies, the incidence of disease in the MDC was higher in non-participants. The incidence of first hospitalization due to HF in the present study (subjects aged 45–73 years and 60% women) was 2.0 per 1000 person-years (2.9 for men and 1.44 for women), which is almost 50% less than what was found during 17 years of follow-up of all individuals aged 45–73 years living in the city of Malmö in 1990.³⁶ Retrieval, ascertainment, and definition of HF cases were identical in that study as compared to the present one. It is well established that high-risk individuals are less likely to participate in population-based studies.^{37,38} Thus, a potential underestimation of first hospitalization due to HF in the present study could be explained by the so-called 'healthy cohort effect'. However, it seems less likely that these effects would be differential based on RDW measured here, but would more likely bias our study to the null.

Another main limitation of the present study is lack of information on type and cause of HF. Furthermore, biomarker data were only available for a subgroup of subjects. However, this sub-cohort was randomly selected and should be regarded as representative for the whole MDC cohort in distribution of age, sex, traditional biological and lifestyle cardiovascular risk factors, and socio-economic circumstances.¹³

In conclusion, RDW among middle-aged subjects was associated with long-term incidence of first hospitalization due to HF. The possible mechanism underlying the association between RDW and incident HF needs further investigation.

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