Sex Differences in Prevalent Cardiovascular Disease in the General Population

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Abstract

In this chapter, we provide latest insights about sex differences in prevalent cardiovascular diseases (CVD) in the general population. CVD is considered as one of the most prevalent diseases and the leading cause of death in both men and women. Sex-related factors have an important impact of the differences in the

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development, the presentation of symptoms, the awareness for the disease, and the progression and management of CVD. Common CVDs in the general population such as ischemic heart disease, atrial fibrillation, and heart failure demonstrate the importance of sex-specific approaches that have an effect on clinical outcomes. The relationship between sex-specific attributable risk factors and the development of CVD often pass unnoticed. However, differences in classical risk factor distribution can only partly explain observed sex differences. Genetics may contribute to the understanding of sex differences in CVD. Existing and emerging technologies take genetic examinations at increasingly high resolution at the population level.

12.1 Introduction

When discussing the differences in the development of cardiovascular disease (CVD) in women and men, two terms need to be defined: "sex" and "gender." The term "sex" summarizes the biological differences between men and women. This sex-differentiation is characterized by the structure and function of the cardiovascular system. This includes chromosomes, sex organs, and hormonal contributions among others [1]. Whereas the term "gender" summarizes psychosocial and behavioral factors for women and men in the context of their cultural and societal role [2].

It is very likely that the combination of "sex" and "gender" have an impact on the development, progression, and management of CVD and are both of importance (Fig. 12.1) [3].

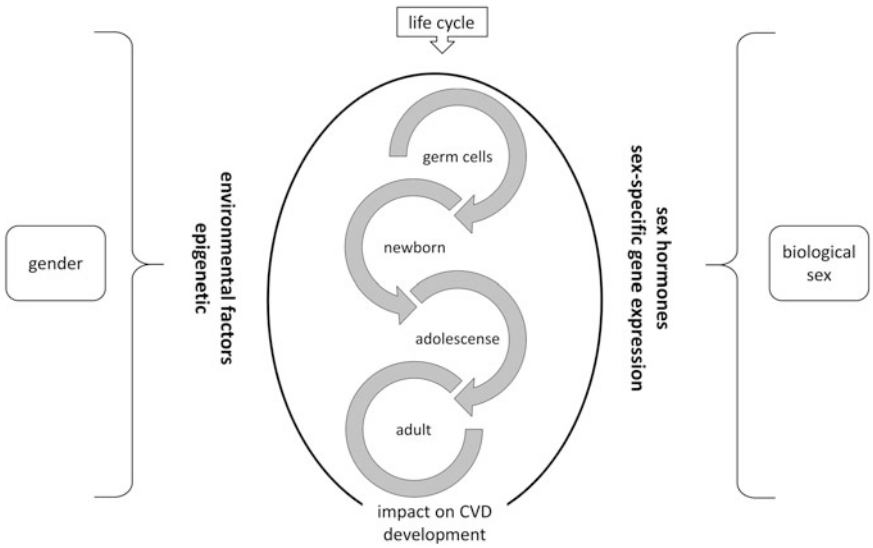

Fig. 12.1 Interaction between sex and gender over a lifetime and their impact on CVD development in the general population

For both men and women, CVD is the leading cause of death worldwide. A further increase of mortality due to CVD is observed at a global level [4]. According to the recent report of the European Heart Network, CVD in women is responsible for 2.1 million deaths (49% of all deaths), while CVD in men accounts for 1.8 million deaths (40% of all deaths) in the European population [5]. This divergence in death rates can be partly explained by a higher risk of competing events, i.e., the risk of men dying from other causes [6]. Men have earlier onset of CVD compared to women [7]. Women lose fewer years of life due to CVD as they develop the disease approximately 7 to 10 years later [8].

Despite these facts, CVD has often been stereotyped as a men's disease. Differences in risk factor profile, clinical presentation, and disease perception may play a role here. For instance, women are considerably more likely than men to present with atypical symptoms (e.g., fatigue, sleep disturbance, nausea, and abdominal, neck, jaw, or shoulder pain) and absence of typical chest pain [9]. These differences of clinical presentation therefore turn into behavioral differences between men and women if they experience a CVD event. In the past, research showed that the delay in seeking CVD treatment in women is significantly longer than men. This time loss may worsen the outcome of the disease [10, 11].

The knowledge about sex differences between the female and male heart such as the difference of physiological and pathophysiological conditions increasing constantly. These differences can be found in all domains of cardiovascular health and disease, including coronary disease, heart rhythm, and heart failure. With regard to the epidemiology, pathophysiology, presentation, and outcomes of CVD, one can determine different clinical characteristics between the sexes [12]. Sex differences in the cardiovascular system can be summarized by general differences with regard to the following factors:

Cardiovascular system: sex-related characteristics in the prevalent general population	
Physiology	• Sympathetic activity in women is reduced. • Parasympathetic activity in women is enhanced. • Plasma concentrations of norepinephrine in women is lower.
Anatomy	• Women's vs men's anatomic dimensions on average (age and race adjusted): – Left ventricular mass: men > women, – Ventricular wall thickness: men > women, – Atrial and ventricular dimensions: men > women, – Vessel size: men >women.
Cardiovascular function	• Stroke volume in women is 10% less on average and thus women have lower cardiac output. • Higher pulse rate in women (3–5 beats/minute). • Higher ejection fraction in women.
Electrocardiographic and electrophysiologic indices Electrocardiographic and electrophysiologic indices	• Women on average have a longer corrected QT interval and a shorter sinus node recovery time. • Drug-induced torsades de pointes is more common in women.

(continued)

	• Sudden cardiac death and atrial fibrillation are more common in men.
Hormonal status	• Estrogen and progesterone represents the most important sex hormones in women; testosterone have a decisive importance in men. • The menstrual cycle can affect hematologic and electrocardiographic indices.
Cardiovascular adaptive mechanisms	• In response to stress: – By increasing the pulse rate, women more strongly regulate the cardiac output. – Due to an increased vascular resistance, men develop an increased blood pressure. • Orthostatic hypotension and syncope is more related to women.
Hematologic indices	• Women have a lower hematocrit, due to a lower number of circulating red blood cells per unit volume of plasma. • Women have a reduced capacity for carrying oxygen due to a lower of hemoglobin. • The consumption of oxygen in women is lower.

Note: Modified with permission from Fink, S. W. Cardiovascular Disease in Women. In: Richardson M, Chessman KH, Chant C, et al. (Eds.). Pharmacotherapy Self-Assessment Program, seventh Edition. Book 1: Cardiology. Lenexa, Kansas City: American College of Clinical Pharmacy, 2010; 182

Multiple variables such as the societal roles and behaviors, biological and physiological characteristics, genes, epigenetics, gene expression, and hormonal status may have sex-specific interactions that determine the pathogenesis and course of the disease.

Over the last decades, research and clinical practice have improved in their focus on sex differences in CVD. Although many of the basic mechanisms underlying sex differences in CVD remain unknown, epidemiological data have clearly shown that there are sex differences in the community. This overview provides insights into the sex differences in risk factors and CVD distribution in the general population.

12.2 Sex and Cardiovascular Risk Factor

12.2.1 Risk Factors in General

Numerous large-scale epidemiological studies (e.g., Framingham Heart Study, INTERHEART, etc.) showed that more than 90% of all cardiovascular events could be attributed to a relatively small number of often modifiable risk factors. These risk factors include: smoking, hypertension, dyslipidemia, diabetes, abdominal obesity, high-risk diet, psychosocial factors, lack of physical activity, and alcohol abstinence compared to moderate consumption [13–15].

In general, the association of these major risk factors with CVD do not differ between the sexes in their direction but may have different magnitude and significance. Also, there are significant sex interactions [6]. For instance, women with diabetes have more than 40% higher risk of incident coronary heart disease (CHD) than men with diabetes [12, 15]. Pregnancy-related hazards such as gestational hypertension [16], as well as frequently occurring endocrine disorders, e.g., polycystic ovary syndrome (PCOS) in women of reproductive age, are accompanied by an increased risk of developing CVD in later life [17]. A recent Norwegian cohort study that included over 15,000 pregnant women confirms the previous findings. Women who experience hypertension in pregnancy have a twofold to threefold higher risk of increased systolic blood pressure in the future. Furthermore, they experience significantly higher body mass index and wider waist circumference compared to women with normal blood pressure during pregnancy [16]. Over the last decades, there have been mixed trends in CVD risk factors for both women and men. On the one hand, there is a decrease in the prevalence of very high levels of cholesterol; on the other hand, a dramatic increase in the prevalence of obesity, particularly among women, has been observed. The proportion of women with high blood pressure increased, whereas it decreased among men [18].

12.2.2 Blood Pressure and Hypertension

One in three adults worldwide have hypertension (hypertension as systolic pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg) [19]. In general, the differences between women and men the prevalence of the disease seems to be equally distributed. A recent systematic analysis of population-based studies from 90 countries showed an age-standardized prevalence of hypertension in adults aged $\geq$20 years in 2010 was 31.9% in men and 30.1% in women [20]. In younger age groups, the incidence rate of hypertension in men is higher than in women (18–29 years: women = 1.3%; men = 8.3%) [21]. Men experience hypertension more often and also have higher low density lipopotein (LDL) cholesterol levels than similar aged women in premenopausal status [22]. In older age groups (> 65 years) the disease is more prevalent in women [23, 24].

In women, white coat hypertension appears to be more frequent. Men show a higher proportion of masked hypertension [25]. The most common type of hypertension in old women is isolated systolic hypertension. Women with hypertension present with stiffer myocardium and vessels compared to men at old age. These conditions may be a possible link to a higher prevalence of heart failure with preserved ejection fraction (HFpEF) in women [26]. Potential sex differences in the pathophysiology of hypertension have been highlighted. The regulation of arterial pressure and renal function by the renin-angiotensin system (RAS) is noticeably different between the sexes [27]. The RAS regulates extracellular fluid homeostasis through renal function and arterial pressure. Several studies show that premenopausal women as compared to aged-matched men are more protected from hypertension due to a differential balance in the RAS [28, 29]. Despite such

differences in the pathophysiology of hypertension, there is no sex-specific approach in the treatment of hypertension yet [26].

Based on the attributable risk of hypertension for myocardial infarction in the INTERHEART study, normalization of blood pressure values can decrease the risk of disease in both sexes. In men, the risk can be reduced by 15.7% compared to women in whom a reduction by 25.4% could be calculated [30]. At the population level, the awareness and knowledge of high blood pressure is limited. An ongoing US national health and nutrition examination study, shows a low rate of awareness with regard to hypertension treatment and control among both sexes [31]. It induces the need to improve health education in both men and women. It remains to be shown whether sex-specific strategies are needed for this purpose.

12.2.3 Diabetes Mellitus

The pathophysiological consequences of diabetes mellitus extend to all components of the cardiovascular system: the microvasculature, the larger arteries, the heart, as well as the kidneys [32]. Diabetes mellitus, type 1 and type 2, is an established risk factor for CVD that harbors a significant increase in CVD mortality [32]. About 70% of all deaths in patients with diabetes are related to CVD [33]. New estimates indicate a total number of individuals with diabetes will rise from 6.4%, 285 million adults, in 2010 to 7.7%, 439 million adults, by 2030 [34]. On a global scale, the overall prevalence of diabetes is somewhat higher in men than in women. In particular, age is an important factor of sex-specific difference in the prevalence of diabetes. Whereas men have a higher prevalence of diabetes in the age group of $<$60 years, women have a significantly higher number of the disease in the older age group [35]. Consistent evidence exists that women with this condition experience a greater relative risk for CVD events and CVD death compared to their male counterparts [36]. Framingham Heart Study data showed a twofold increased risk of CVD in men with diabetes and a more than 3.5-fold higher risk in women [37]. An excess risk in women with diabetes has also been observed for heart failure, and peripheral artery occlusive disease. Data of the INTERHEART study confirm that diabetes was more strongly associated with a risk of myocardial infarction in women with a relative risk of 4.26 versus 2.67 in men [38]. A recent meta-analysis of prospective population-based studies also reported a 44% higher relative risk in women compared to men [14]. More than 15% excess risk of fatal coronary heart disease is also observed among women with type 1 diabetes compared to men [39].

12.2.4 Body Mass Index and Obesity

The development of CVD is associated with obesity and overweight. However, the development of obesity and overweight differ between men and women due to the manifestation of obesity-related conditions such as hyperlipidemia, insulin resistance, and type 2 diabetes mellitus. For instance, weight gain occurs differently in

men and women. Men generally have higher body weight than women, but the proportion of fat is greater in women.

According to the data of the global burden of disease (GBD), the prevalence of obesity (BMI $\geq$30 kg/m^2) has more than doubled worldwide since 1980 and is now 5% in children and 12% in adults [40]. Two billion adults (>18 years) worldwide are overweight whereof 39% men and 40% of women (>18 years) are overweight (BMI $\geq$ 25 kg/m^2) and 11% of men and 15% of women were obese [40]. In the western societies, the rates of overweight and obesity have dramatically increased in the recent decades for both men and women [41]. Associations can be seen between a high value of BMI in individuals and the gross domestic product (GDP) level of a respective country. The prevalence of obesity in upper middle income counties (24%) in both sexes is more than threefold higher compared to lower middle income countries (7%). Several overlapping physiological systems and processes predict the development of CVD related to overweight and obesity which includes sex differences. In the Framingham Heart Study, obesity increased the relative risk of coronary artery disease (CAD) by 64% in women as opposed to 46% in men [42].

12.2.5 Cholesterol

In general, there is no sex difference in the prevalence of elevated total cholesterol worldwide [43]. Among adults, 37% men and 40% women present with elevated cholesterol levels. On a global scale, the mean total cholesterol changed little between 1980 and 2008, falling by less than 0.1 mmol/L per decade in men and women [44]. The lipid profiles of young women tend to be more beneficial compared to men. High-density lipoprotein cholesterol concentrations are higher on average whereas low-density lipoprotein cholesterol is lower in women compared to men. However, with age this advantage diminishes, in part due to hormonal changes after the menopausal transition of women [45]. In a meta-analysis of 55,000 participants a decrease in total cholesterol by 1 mmol/L was associated with about lower ischemic heart disease mortality in both sexes in all age categories [46]. In contrast, a recent meta-analysis of 97 cohort studies with over one million participants showed that there is evidence of a small but significantly stronger effect in men (Cl = 95%; RR = 1.24) compared to women (Cl = 95% CI; RR = 1.20) with raised cholesterol to develop coronary heart disease [47]. A systematic work-up of potential sex-specific effects of major lipids on cardiovascular risk is missing [6].

12.2.6 Smoking and Alcohol Intake

Smoking and alcohol intake are common in many populations. However, the consumption characteristics vary considerably between sexes. On a global level, the prevalence of smoking is much higher in men (48%) than it is in women (10%) [48]. In general, women smoked fewer cigarettes than men and tended to start smoking later in life. However, women and men who start smoking cigarettes

nowadays smoke nearly the same number of cigarettes and take up smoking at the same age. Multiple studies have shown a stronger association in women between long-term smoking and the risk of developing CVD than in men [49–51]. A meta-analysis by Huxley and Woodward which included about four million individuals and at least 67,000 coronary heart disease events from 26 prospective trials found that women had a 25% increased risk related to cigarette smoking compared with men [39]. Both the change of smoking patterns in women over the last century and the higher risk of CVD when smoking may therefore result in increasing numbers of smoking-related CVD compared to men. Considering the population attributable risk to develop ischemic heart disease, it seems to be possible that the prevalence of ischemic heart disease will particularly increase in the future for this target group [52].

The reasons for the differential associations of smoking may include sex hormones. Combined use of contraceptives and smoking pose a significant risk of ischemic heart disease [39, 51]. In a small cohort study of 346 women with PCOS, including 98 smokers and 248 non-smokers, an increased level of fasting insulin, free testosterone, and free androgen index was observed in women with PCOS who smoke [53]. These increased levels may enhance insulin resistance that potentially results in a cardiovascular health risk. Another possible association is shown due to differential gender effect of smoking and arginine vasopressin (AVP) [54]. AVP has a direct impact of the cardiovascular system [55]. A small study observed a higher level of AVP in smoking in women that could contribute to negative effect on cardiovascular health in women [55]. These hormones possibly lead to a higher risk of CVD [54, 55]. However, it should be considered that these findings are only based on limited data and need validation. Therefore, the current understanding of the negative impact of smoking on CVD in females needs further investigation.

Besides smoking, alcohol intake is also a relevant risk factor for the development of CVD for both men and women. Alcohol consumption in the population is attributed to 3.3 million deaths per year and men have a higher mortality rate attributed to alcohol (7.6%) compared to their female counterparts (4.0%). In general, the intake of alcohol is described with a U-shape association. Both very low or high alcohol consumption are negative for CVD health whereas moderate alcohol consumption appears to be beneficial, except for atrial fibrillation for which a linear relation has been shown consistently. Several studies demonstrated that consuming moderate amounts of alcohol has been associated with reduced risk of coronary heart disease, stroke, and congestive heart failure. There are speculations on sex differences in alcohol intake and CVD risk. However, due to diverse study results about general alcohol consumption there is no scientific certainty whether women or men have a different risk of CVD development related to alcohol consumption [56, 57].

12.2.7 Psychosocial Factors

Psychosocial factors are well established for CVD risk. Depression is known for the adverse effects on CVD risk factors including hypertension, obesity, and smoking. According to the World Health Organisation (WHO) at a global scale, more women are affected by depression than men and have an earlier age of onset [58, 59].

In fact, all of them predict the development of CVD. Recent studies report that more than 300 million people of all ages experience depression worldwide. Women show twice the rates of stress-related psychiatric disorders, including posttraumatic stress disorders and depression, compared to men [60]. Several studies have identified psychosocial factors (e.g., depression, perceived stress at home or work, low amount of control, and major life events) as predictors of future cardiovascular events in initially healthy populations [61–63]. A large case control study showed that women with psychosocial or mental health problems also have a 40% higher population attributable risk to develop myocardial infarction compared to women without these conditions. In contrast, men with psychosocial problems have a population attributable risk of 25% to develop myocardial infarction [30]. Furthermore, half of the women aged <55 years who overcome a myocardial infarction experience or already had a history of depression [64]. The cardiovascular risk increases almost twofold in women with depression [65]. In a follow-up of a community-based survey, the risk of women aged >40 years with depression to develop CVD is reported significantly higher than in men in the same age group [60].

Physical and sexual abuse and child neglect are determined as significant risk factors for the development of CVD. Affected individuals in the general population are mostly women. Independent of other risk factors, individuals with a history of child abuse have a 50% increased risk of CVD [66]. It seems that young women who experienced sexual abuse have a greater risk of developing CVD than men [67].

Furthermore, sex differences in CVD have been, at least in part, related to environmental and social differences between men and women (e.g., occupational hazards, habits, social stress) [68, 69]. The combination of work stress and private difficulties has also been associated with an increased risk in CVD events in women [70]. A recent review of Varianaco and Bremers describes that young women are disproportionally vulnerable to the adverse effects of marital stress and the risk of CVD [59].

In addition to long-term mental health predictors of CVD, acute stressors can also contribute to CVD onset. An acute stress situation reduces the perfusion of the epicardial coronary arteries. This mental stress-induced myocardial ischemia has been associated with adverse prognosis in patients with coronary artery disease [71]. Few studies of patients with coronary artery disease or a history of myocardial infarction report an approximately twofold higher incidence rate of mental stress-induced myocardial ischemia in women compared to men [72, 73]. However, for the general population psychosocial factors have rarely been evaluated for their ability to explain sex differences in CVD.

12.2.8 Risk Factors Unique to Sex

Today, increased attention is given to sex-specific risk factors of CVD such as hypertensive disorders of pregnancy (HDP) and gestational diabetes. The American Heart Association declares "HDP as a major risk factor for the development of the disease" [74]. The two types of HDP manifestation are gestational hypertension and preeclampsia. The prevalence of hypertensive disorders in pregnancy is between 2.8% and 5.2% in Europe [75]. A prospective cohort study ($n = 15{,}000$) from Magnusson et al. confirms that gestational hypertension in women that recurs during several pregnancies is significantly associated with a higher blood pressure later in life [76]. Therefore, one can assume that women with a history of hypertensive disorders in pregnancy, and particularly women with recurrent pregnancy disorders, should be followed closely and treated as necessary to prevent premature CVD [76]. Several studies had already shown that the risk of developing CVD later in life is two times greater in pregnant women with preeclampsia [77–79]. To date, it remains largely unknown whether HDP is an independent risk factor for CVD or whether the frequent co-existence of classical cardiovascular risk factors are responsible for the associations. Further epidemiological research will be needed to elucidate the mechanisms of both pathways of HDP and possible causal relations including genetic predispositions.

The other well-known pregnancy-associated risk factor is gestational diabetes that significantly increases the risk of developing future CVD. The prevalence of gestational diabetes is associated ethnic differences. For instance, in Europe, gestational diabetes is more common in women with an Asian background compared to women with a European background [80]. In a population-based matched case–control study with 2600 women with a cardiovascular event, the odds ratio of CVD in women with gestational diabetes was 1.51-times higher [81]. Recent population-based studies that examined the association between gestational diabetic women also report a more than twofold risk to develop CVD compared to women without diabetes in the pregnancy [82, 83]. But the mechanisms contributing to the vascular dysfunction seen in gestational women remain uncertain.

Menarche, menopause, and the length of the reproductive period appear to play a role for CVD risk. Early menarche (10 years or younger) has been identified as a risk factor for developing CVD in women. A recent cohort study ($n = 1.2$ million) that included women with no known CVD at follow-up demonstrated that women aged 10 years compared to their counterparts aged 13 years had an approximately 30% higher risk of developing CVD [84]. In a meta-analysis, every 1 year increase in age at menarche was associated with a 3% reduction in CVD-related mortality [85]. Women aged <44 years who experience early natural menopause have an increased CVD risk. In a recent meta-analysis with over 300,000 women, the findings indicate a two times higher risk of coronary heart disease, a 25% higher risk of CVD mortality, and overall mortality in women who experience premature menopause (before age 45) as compared to women in whom menopause occurs later [86]. Menopause per se may not be directly related to an increase in CVD risk after menopause, but the prevalence of CVD risk factors and co-morbidities rises in the

postmenopausal phase. The risk factor distribution in women and men becomes similar. A prospective cohort of 34,000 individuals in Norway observed a decline in the gender gap of CVD with age in part due to an increasingly similar risk factor profile in post-menopausal women and middle-aged men, e.g., for hypertension and dyslipidemia [87].

12.2.9 Sex-Specific Biological Factors

The difference between men and women in the epidemiology, pathophysiology, clinical manifestations, effects of therapy, and outcomes of CVD can partly be explained by differences related to sex chromosomes. According to the current state of the scientific knowledge, XX and XY zygotes differ only in their sex chromosomes. This genetic disposition predisposes to sex differences between men and women [88]. The prediction of mechanisms like the gonadal effects of Sry, non-gonadal effects of Y genes, X gene dosage, and imprinting of X genes are associated with sex differences in the development of CVD [89]. One of the key players seems to be the sex-determining region on the Y chromosome (Sry). This region acts within gonadal primordia and leads to organ differentiation into testes. Afterward, the cardiovascular system is exposed to a lifelong difference in the levels of gonadal hormones, e.g., testosterone, estradiol, and progesterone [88]. Male-specific nongonadal effects of the Y chromosomes are, for instance, the expression of Sry in catecholaminergic cells which results in a predisposition to the development of hypertension in men [90]. Further explanation that causes sex differences in the expression of specific X genes could possibly be the mechanism that XY cells receive a maternal imprint on X genes and XX cells receive imprints from both parents. This imbalance in parental imprinting seems to be a possible cause of the difference in the expression of specific X genes that enhance differences in the development of the disease in men and women [89]. Recent research also demonstrated potential sex differences in the phenotype caused by X chromosomal genes due to sex-specific dose and X escape [91].

12.3 Differences in Disease and Outcomes

This chapter focuses on three major sex-specific differences in CVD area—ischemic heart disease, atrial fibrillation, and heart failure that are common in the general population (Fig. 12.2).

12.3.1 Ischemic Heart Disease

Ischemic heart disease is a complex, multifactorial disease and is defined as “an impairment due to ischaemia in the myocardium, which can arise from stenosis of the major coronary arteries, impaired microcirculation, or a demand/supply

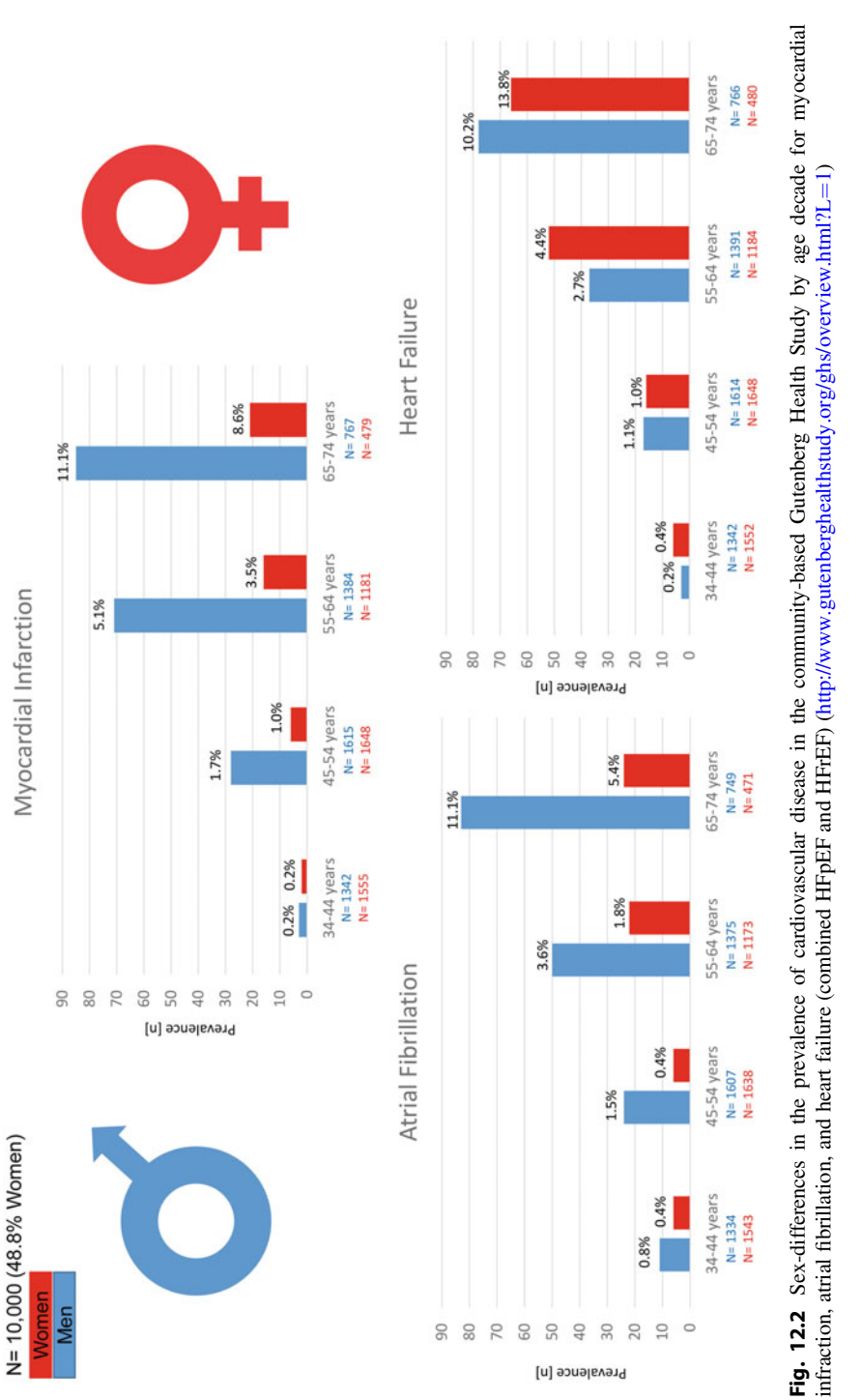

Fig. 12.2 Sex-differences in the prevalence of cardiovascular disease in the community-based Gutenberg Health Study by age decade for myocardial infraction, atrial fibrillation, and heart failure (combined HFpEF and HFrEF) (http://www.gutenberghealthstudy.org/ghs/overview.html?L=1)

imbalance." Ischemic heart disease is the leading cause of cardiovascular death in both men and women in the western societies [12].

Coronary artery disease (CAD) is the most common type of ischemic heart disease. On a global scale, it is the leading cause of death for both men and women. The worldwide mortality rate is about 7.2 million deaths per year as a result of an atherosclerotic process of the epicardial coronary arteries. Recent report present almost the same coronary artery disease prevalence for men (6.3%) and women (5.3%) aged 40 to 59. However, men experience coronary artery disease more often if they are aged between 60 to 79 years compared to their female counterparts (19.9% vs 9.7%).

Ischemic heart disease results in myocardial ischemia and injury, most prominently myocardial infarction [92]. Men experience myocardial infarction (ST-elevation and non-ST-elevation) and acute coronary syndromes three to four times more frequently than women below the age of 60. However, if an ischemic heart disease event occurs after the age of 75 the majority of the patients are women [93]. Ischemic heart disease develops on average 7–10 years later in women compared to their male counterparts. In 20–30% of typical infarction emergencies, women presented a pathophysiological obstruction or a lack of microvascular vessel extension of the heart. Compared to men (5–10%), the prevalence of these causes seems to be doubled in women [94]. Usually, these syndromes are diagnosed by the measurements of perfusion and coronary flow. But these measurements are not part of the CVD standard diagnostic [95]. However, in the recent decade the diagnostic possibilities to clarify the coronary microcirculation have improved. Women more frequently present non-obstructive coronary artery disease that is not related to atherosclerotic plaques. Acute coronary syndrome pooled trials already show that women have a 7% higher risk of non-obstructive coronary artery disease [62]. Besides plaque erosion and calcific nodule, plaque rupture is the most common cause of fatal myocardial infarction for both women (55%) and men (76%). The recent PROSPECT study can confirm that women present 10% less plaque rupture than men if they have an acute coronary syndrome [96]. Clinical manifestations such as angina pectoris, myocardial infarction, and sudden cardiac death reveal sex differences in the progression of the disease [97]. A recent study reports significant sex-differences in coronary atherosclerosis progression due to a higher score in the progression rate of severe proximal plaque, segment stenosis, and segment involvement in men compared to women with suspected coronary artery disease [98]. A possible explanation for the differences in ischemic heart disease progression lies in the higher incidents of comorbidities such as obesity and inflammation as well as more adverse changes in the coagulation in women [99]. Furthermore, the endothelial function may lead to a greater cardio metabolic risk in women with diabetes. In a meta-analysis by Hemingway et al. which included more than 14,000 angina patients from 31 countries, the prevalence of angina was similar or slightly higher in women and up to 20% higher in pre- and postmenopausal women [100]. Life-threatening conditions of acute coronary artery disease (myocardial infarction; sudden cardiac death) increase with age for both men and women. However, a recent meta-analysis revealed that young women (30–54 years) with acute myocardial infarction have

more comorbidities, a longer hospital stay, and higher in-hospital mortality compared to men of the same age [101].

Chest pain is the predominate presentation of the acute coronary syndrome for both men and women. However, there are possible gender differences in symptom presentation of the acute coronary syndrome. It seems that men with acute coronary syndrome are more likely to present chest pain and discomfort, whereas women with acute coronary syndrome present more atypical symptoms such as dyspnea, weakness, fatigue, and indigestion compared to men [9]. However, there is inconsistency in the findings reported in the literature on whether women present with chest pain as a symptom of acute coronary syndrome less frequently. There is scientific evidence that the symptom of chest pain in acute coronary syndrome declines considerably with age which may account for lower chest pain frequency in women because they usually present at older age [21]. However, in current chest pain unit cohorts, the distribution of typical chest pain is fairly comparable between both sexes. Prior reports showed significant sex differences in outcomes after acute coronary syndrome, with adverse prognosis in women which had been explained by older age and more co-morbidities. In the meantime, the short-term outcomes have become similar in men and women in contemporary chest pain unit cohorts although therapeutic strategies remain different. For example, invasive therapy is more commonly used in men. Future changes in awareness and treatment of ischemic heart disease can be expected.

12.3.2 Atrial Fibrillation

The worldwide prevalence of atrial fibrillation in the general population is on average higher in men (approximately 596 per 100,000) compared to women (373 per 100,000) [102]. In the last decades, one can observe a decrease of atrial fibrillation–associated mortality rate in men compared to women. The higher mortality in women in the developing countries is responsible for the overall higher atrial fibrillation–related mortality among women compared with men. In both sexes, an increase in atrial fibrillation prevalence and also in the incidence has been documented due to a better awareness of the disease, the use of routine electrocardiography, and extended electrocardiographic monitoring in the community among other factors. On a global scale, many individuals remain undiagnosed due to the intermittent and often asymptomatic nature of the disease. Thus, it can be assumed that the true prevalence is likely to be substantially higher [103].

In general, atrial fibrillation is associated with a significantly increased risk of morbidity and mortality. Causes of morbidity and death are due to a fivefold increased risk of stroke and a doubled risk for myocardial infarction compared to the population without atrial fibrillation. A recent meta-analysis of 30 population-based cohort studies with approximately four million participants report that atrial fibrillation is a stronger risk factor for all-cause mortality, stroke, cardiovascular mortality, cardiac events, and heart failure in women compared to men [104].

Cohort data of the Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium reported significant sex differences in the risk of developing atrial fibrillation. BiomarCaRE is a population-based and longitudinal study design with long-term follow-up information that has good power to examine gender interactions. Fewer atrial fibrillation cases were observed in women (4.4%) than in men (6.4%) over a median follow-up of more than 12 years. Cumulative incidence increased markedly after the age of 50 years in men and about a decade later, after 60 years, in women. The lifetime risk of atrial fibrillation accumulates to more than 25–30% in both sexes. Obesity and hypertension range among the most important modifiable risk factors. BMI appears to be more strongly related to atrial fibrillation in men compared to women [105]. The occurrence of atrial fibrillation is accompanied by a poor prognosis for cardiovascular outcomes and mortality. The BiomarCaRE data provide evidence that differences in atrial fibrillation incidence observed by gender may be explained by gender-specific distribution of risk factors and by differential associations of traditional risk factors. A substantial proportion of the atrial fibrillation burden can be explained by classical cardiovascular disease risk factors in both genders. While blood pressure, smoking, alcohol consumption, and prevalent cardiovascular disease are largely similar predictors of incident atrial fibrillation in both genders, total cholesterol concentrations may show gender differences. A higher BMI and obesity are significantly more hazardous for the development of atrial fibrillation in men and need better awareness and targeted intervention. Observed gender differences in the association of BMI and total cholesterol with atrial fibrillation need to be evaluated for their pathophysiology and relevance in gender-specific prevention strategies [105].

12.3.3 Heart Failure

Heart failure results from different pathological processes. According to the European Society of Cardiology (ESC), heart failure can be defined as "a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra cardiac pressures" [106]. Left-sided heart failure can be differentiated as heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF) due to ischemic or non-ischemic genesis. The frequency of HFpEF conversion into HFrEF in the general population is unknown and a topic of ongoing studies. Most population-based studies report an increasing incidence of heart failure [4] and a new epidemic has been predicted while the incidence of HFrEF appears to be deceasing [107]. A recent meta-analysis of 25 different western populations (>60 years) reports a prevalence of 4.9% of HFpEF compared to 3.3% that have HFrEF. The prevalence of HFrEF in men is higher compared to women and the prevalence of HFpEF in the population increases with age and is less common in men. Due to the onset of heart failure in later life, one can expect that women have a higher probability to experience the syndrome [62]. In younger age groups HFpEF is rare (almost 0.1% in men and about 1% in women).

For older individuals (>80 years), the prevalence of HFpEF in men is 4–6% and for women it is 8–10% [108]. In the population-based Gutenberg Health Study, sex differences in the prevalence of the two heart failure subtypes are clearly visible (Fig. 12.3).

Heart failure with HFpEF accounts for 50% of all heart failure cases and is characterized by diastolic dysfunction and high prevalence of left ventricular hypertrophy. The manifestation of HFpEF in older men and women (>60 years) differs in clinical outcomes. In a sample of approximately 4000 patients of the I-PRESERVE study, men with HFpEF had significantly less chronic kidney disease and hypertension than women. However, men experience more ischemic events and have an increased risk of atrial fibrillation [109]. Under stress conditions, the remodeling of the ventricles is different. Whereas women with the combination of the risk factors obesity and hypertension experience central (concentric) hypertrophy, men with the same risk factors tend to develop eccentric hypertrophy [110].

Women are more likely to develop HFpEF due to the specific risk profile of HFpEF. In addition, in female patients, HFrEF caused by non-obstructive coronary disease is more common whereas in men atherosclerotic coronary artery disease prevails in the causal chain [107]. The most common risk factors for the development of HFpEF are hypertension, diabetes, and obesity [111]. In the general population, hypertension has the highest attributable risk for heart failure among women. Pregnancy and cancer treatment for breast cancer are sex-specific risk factors for the development of HFrEF triggered by non-ischemic events. Hypertension may also be associated with peripartum cardiomyopathy. HFrEF occurs in the terminal phase of pregnancy or shortly after birth and its cause remains unclear. A combination of environmental and genetic factors has been suggested. Recent evidence suggests that inflammation may play a relevant role in the development of peripartum cardiomyopathy [112]. Furthermore, anthracyclines (type 1) and potentially reversible toxicity (type 2) are determined as possible risk factors for the development of cardiomyopathy due to toxic chemotherapy treatment against breast cancer [113]. Chemotherapy treatment such as anthracyclines (type 1), for breast cancer, and newer targeted agents such as trastuzumab (type 2) have established risks of cardiotoxicity [114]. In women, 8% of all acute heart failure cases are attributed to the takotsubo syndrome. It is characterized by acute and profound, but transient, regional left ventricular dysfunction in the absence of obstructive coronary disease and is commonly associated with emotional or physical stress [115]. About 90% of the patients are women and most of them experience psychological stress. The mortality rate is around 5% and the recurrence of the disease is about 10% [116].

A major issue of the sex difference of heart failure patients is that women who experience heart failure have a higher rate of adverse drug events compared to men, in particular for diuretics, anticoagulants, digoxin, and angiotensin-converting enzyme inhibitors which show that sex-specific treatment and management of the disease may be needed [117].

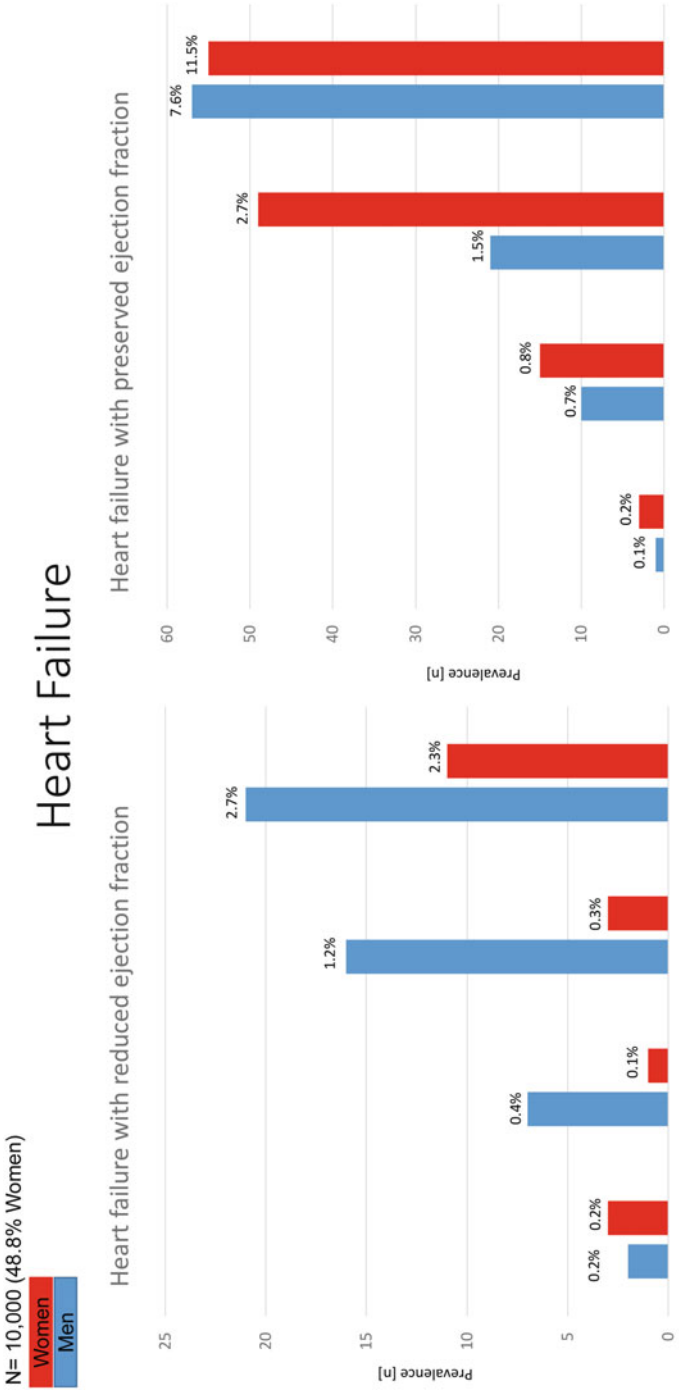

Fig. 12.3 Prevalence of heart failure in the community-based Gutenberg Health Study by age, decade, and sex for heart failure with reduced ejection fraction (HFrRF) and heart failure with preserved ejection fraction (HFpEF) (http://www.gutenberghealthstudy.org/ghs/overview.html?L=1)

12.4 Sex Differences in CVD Prevention

In the past, the importance of prevention in women with cardiovascular disease was underestimated and women were largely underrepresented in CVD clinical research [118]. Only in the last decades, the practice of CVD prevention in women has been transformed. As an example, the data release of the Women Health Initiative (WHI) in particular addressing hormone replacement therapy reported that menopausal hormone therapy did not prevent incident coronary heart disease and increased the risk of stroke in healthy women [119].

There are also general behavioral factors that may have impact on the prevention of CVD in men and women. Women tend to be more aware of a healthy lifestyle and they are more focused on healthy behaviors. At the same time, the risk of CVD is still underestimated by women and their treating physicians, which is a serious misperception that hampers CVD prevention [94]. In particular, for very young and very old women this circumstance results in a poor emergency management in women [94]. There is a strong need to investigate lifestyle methods to prevent CVD effective, in particular, approaches with long-term sustainability among diverse groups of women. An increase of sex-specific data will inform future guidelines and enhance the translation of research findings into practice. Gender disparities in preventive care need to be overcome. For instance, the number of individuals that participate in secondary prevention programs, such as heart rehabilitation, is on average lower in women compared to men. These gender disparities can partly be explained due to personal barriers such as lack of time and family obligations [120]. Many studies have investigated gender disparities in the acute management of cardiovascular disease with less emphasis on disparities in cardiovascular prevention [121]. For instance, women are less likely to receive electrocardiography when presenting to the emergency departments [122]. Screening for smoking status and education on cessation are important for lowering cardiovascular risk for all patients, but particularly for women.

In conclusion, understanding the gender differences CVD risk and risk factors is essential for developing long-term preventive measures to reduce mortality, public health burden, and healthcare costs related to CVD in both women and men [123].

12.5 Challenges in Research on Sex Differences

Crucial in future sex-specific research in CVD at the population and patient level is to collect sex-specific information and evaluate it in adequately powered studies. In the past, women have been underrepresented in diagnostic, prognostic, and therapeutic CVD studies [26]. That means that more women need to be enrolled in clinical trials or need to be over-sampled and results of those investigations need to be reported by sex. A separate monitoring of both sexes in studies does not appear to be sufficient. According to the recommendations of the EU-funded project EUGenMed (www.eugenmed.eu/), there is a broad range of possible strategies and methods to target sex and gender-specific issues in CVD research [124]:

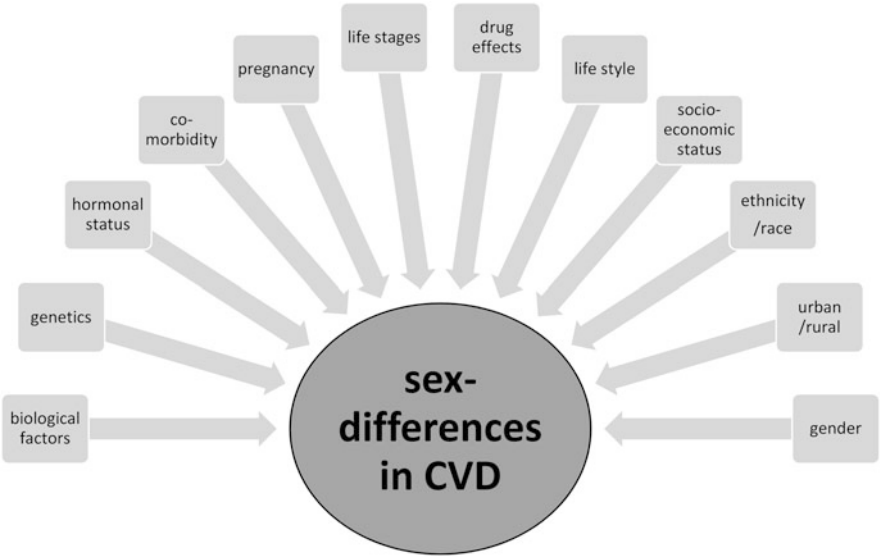

Fig. 12.4 Holistic view on sources of the sex differences in CVD in the general population

- Oversampling one sex
- Stratification
- Prospective planning for meta-analyses based on stratified patient data
- Studying interactions of risk factors with multilevel Cox regression models
- Planning of robust study designs that take into account relevant covariates from the beginning to avoid inefficient data collection

More extensive information needs to be gathered to better understand sex differences in CVD in the general population using a holistic approach (Fig. 12.4). Current efforts of publishing women-specific guidelines have been successful in increasing awareness and improving treatment and prevention of CVD risk in women. Differences in classical risk factor distribution can only partly explain observed sex differences. Genetics may contribute to the understanding of sex differences in CVD. Existing and emerging technologies take genetic examinations at increasingly high resolution at the population level. They are promising tools and may provide novel insights into the biology of sex differences of CVD in the community beyond classic epidemiology.

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