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Sex differences in cardiometabolic disorders

Eva Gerdts[1]* and Vera Regitz-Zagrosek[2,3]

The prevalence of cardiometabolic disorders in both women and men has increased worldwide and is linked to a rise in obesity and obesity-associated associated clustering of other cardiometabolic risk factors such as hypertension, impaired glucose regulation and dyslipidemia. However, the predominance of common types of cardiometabolic disorders such as heart failure, atrial fibrillation and ischemic heart disease is sex specific, and our identification of these and the underlying mechanisms is only just emerging. New evidence suggests that sex hormones, sex-specific molecular mechanisms and gender influence glucose and lipid metabolisms, as well as cardiac energy metabolism, and function. Here we review sex differences in cardiometabolic risk factors, associated preclinical and clinical cardiac disorders and potential therapeutic avenues.

Because of the established health risks and substantial increases in prevalence, obesity has become a major global health challenge[1–3]. Obesity is associated with clustering of other cardiometabolic risk factors, such as hypertension, impaired glucose regulation and dyslipidemia, which contribute to the obesity-associated damage of the heart and arteries. Several meta-analyses have demonstrated the equivalence of blood pressure, cholesterol and body mass index (BMI) in contributing to the relative risk of coronary heart disease and stroke in women and men[4–6], while diabetes mellitus confers a higher risk in women[7]. Yet the impact of these risk factors on preclinical cardiac disease and other common cardiometabolic disorders, such as heart failure and atrial fibrillation, differs by sex[8,9]. Stronger consideration should be given to understanding these sex differences and how to integrate them into therapeutic approaches. Thus, the current review gives an update on sex differences in cardiometabolic risk factors and associated preclinical and clinical cardiac disorders, focusing on the diverse diagnostic findings and clinical implications in women and men.

Sex differences in cardiometabolic risk factors

Obesity. According to the World Health Organization (WHO), in 2018 11 % of men and 15% of women worldwide above 18 years of age were obese (BMI ≥30 kg/m^2) when assessed by body mass index (BMI). Worldwide, the prevalence of obesity has tripled since 1975. The National Health and Nutrition Examination Survey (NHANES) from 2013–2014 in the United States reported higher prevalence of obesity in women than in men (40.5 vs. 35.2%)[10] (Table 1). While the obesity prevalence in women steadily increased in the period 1980–2014, no further increase was observed in men after 2006[10]. In NHANES, obesity was more prevalent in subjects of Hispanic origin in both sexes, in current smoking men, and in women with less than high school education[10]. Data from the European Social Survey Round 7, performed in 20 European countries, found on average 15.9% (range 11–20%) of both women and men to be obese (Table 1)[11]. In both sexes, obesity was more common in older subjects compared to middle-aged and younger subjects[11]. Furthermore, regional differences in obesity prevalence were demonstrated; obesity prevalence was highest in the United Kingdom and East European countries, and lower in Central and Northern European countries[11].

Sex differences in body fatness and regional adipose tissue distribution are well documented[12]. Women are generally characterized by greater body fat mass and preferential accumulation of adipose tissue in the gluteofemoral region, whereas men are more prone to abdominal fat deposition, particularly around the abdominal internal organs, referred to as visceral obesity[13–15]. In the Jackson Heart Study, 55% of both sexes were obese (Table 1)[15]. Women had higher subcutaneous adipose mass than men (2,659 vs. 1,730 cm^3), while men had higher visceral adipose mass than women (873 vs. 793 cm^3), measured by computed tomography[15]. Visceral adipose mass was associated with higher odds ratios for hypertension, diabetes and metabolic syndrome than subcutaneous adipose mass in both sexes[15], reflecting the higher metabolic activity of visceral compared to subcutaneous fat. The association of visceral adipose mass with prevalent hypertension and metabolic syndrome differed between women and men (odds ratios 1.62 [95% confidence intervals 1.4–1.9] in women vs. 1.55 [1.3–1.8] in men for hypertension and 3.34 [2.8–4.0] in women vs. 3.46 [2.8–4.3] in men for metabolic syndrome, both $P < 0.001$ for sex interaction) after multivariable adjustment, while no sex difference in the association with prevalent diabetes was demonstrated[15].

Hypertension. According to the WHO, in 2015 one in four men and one in five women worldwide had hypertension, identified as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg. In the United States, the hypertension prevalence has remained the same among adults since 1999, on average 30.2% in men and 27.7% in women ($P < 0.05$ between sexes)[16]. In the NHANES survey in 2015–2016, men had a higher prevalence of hypertension than women among adults aged 18–39 (9.2 vs. 5.6%) and 40–59 years (37.2 vs. 29.4%), while hypertension was more common in women among adults aged 60 years and over (66.8 vs. 58.5%)[16]. In older subjects, isolated systolic hypertension is the most common type of hypertension in both sexes, pointing to the importance of arterial stiffening and aging for development of hypertension[17]. Obesity is generally associated with a threefold higher prevalence of hypertension compared to that in normal weight subjects[3].

Socioeconomic factors. The Australian Longitudinal Study on Women's Health reported that presence of overweight or obesity, low educational level and low income were the key risk factors associated with development of multimorbidity, including arthritis, hypertension, diabetes and depression, in middle-aged women (Table 1)[18]. In the Berlin Female Risk Evaluation (BEFRI) study, designed to evaluate women's estimation of their subjective risk for cardiometabolic disease, the subjective underestimation of this risk was higher in women >50 years of age and in those with joblessness or clustering of social risk factors (Table 1)[19]. An extensive evaluation of the role of gender (the sociocultural dimension of sex) in patients with acute coronary syndromes participating in the

[1]Department of Clinical Science, University of Bergen, Bergen, Norway. [2]Berlin Institute for Gender in Medicine, Charité Universitätsmedizin, Berlin, Germany. [3]DZHK, partner site Berlin, Berlin, Germany. *e-mail: eva.gerdts@med.uib.no

Table 1 | Studies elucidating sex differences in cardiometabolic disorders

Study name	Study acronym	Country/Region	Type of study	Sex-specific outcome
National Health and Nutrition Examination Survey	NHANES	US	Longitudinal, population based	Hypertension more prevalent in men; obesity more prevalent in women
European Societal Survey 7		Europe	Longitudinal, population based	Obesity equally prevalent in both sexes
Jackson Heart Study		Jackson, Mississippi, US	Longitudinal, population-based study in African Americans	Women have higher abdominal subcutaneous adipose mass; Men have higher abdominal visceral adipose mass; visceral adipose mass closer associated with cardiometabolic risk factors in both sexes
Australian Longitudinal Study on Women's Health	ALSWH	Australia	Longitudinal survey, Australian women born 1946–1951	Increased BMI and low socioeconomic position predict risk for multimorbidity in women
Berlin Female Risk Evaluation	BEFRI	Berlin, Germany	Cross-sectional, population based	Joblessness, clustering of social factors and older age is associated with underestimation of personal risk for cardiometabolic disease in women
Gender and sex determinants of cardiovascular disease: from bench to beyond—premature acute coronary syndrome	GENESIS-PRAXY	Canada	Prospective cohort study; acute coronary syndrome patients <55 years of age	Feminine sociocultural variables are closer associated with cardiometabolic risk factors and outcome than sex
Strong Heart Study	SHS	Arizona, Oklahoma, South and North Dakota, US	Longitudinal, population-based survey of Native Americans	In obesity, women have higher prevalence of LVH and MetS than men; men have higher prevalence of left ventricular systolic dysfunction
FAT-associated cardiovascular dysfunction study	FATCOR	Bergen, Norway	Cross-sectional, cohort with increased BMI	Women have higher prevalence of left atrial dilatation; men have higher prevalence of LVH
Losartan Intervention For Endpoint reduction in hypertension study	LIFE	Nordic countries and US	Prospective randomized clinical trial in hypertension, 4.8 years duration	Women have higher prevalence of LVH; women have less regression of LVH during drug treatment
Campania Salute Network Project	CSN	Campania, Italy	Prospective cohort study in hypertension	Women have higher prevalence of LVH; women are more prone to develop LVH despite drug treatment
Dallas Heart Study		Dallas, Texas, US	Prospective, population-based multiethnic	Women have higher plasma NT-proBNP level than men; men have higher prevalence of high plasma hs-cTnT level
Framingham Heart Study	FHS	Framingham, Massachusetts, US	Prospective, cohort study	HFpEF is twice as common in women than men; HFrEF is more common in men;
A systems biology study to tailor treatment in chronic heart failure	BIOSTAT-CHF	Europe	Prospective, observational study of patients with HFrEF	Women with HFrEF need lower doses of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers than men for improved prognosis
Women Ischemia Symptom Evaluation	WISE	US	Prospective cohort study, women with suspected IHD	Women have higher cardiometabolic risk factor burden; women have more non-obstructive CAD
Tromsø Study		Tromsø, Norway	Prospective, population-based study	Men have higher incidence of myocardial infarction; hypertension confers higher risk for atrial fibrillation in women
Atherosclerosis Risk in Communities	ARIC	US	Prospective cohort study; European and African-American ancestry	Men had higher incidence of AFib than women; 57% of AFib risk was attributed to cardiometabolic risk factors
Women's Health Study		US	Prospective cohort study of female health professionals	Left atrial dilatation explains much of the increased AFib risk in obese women
Coronary CT Angiography Evaluation for Clinical Outcomes: an international multicenter registry	CONFIRM	Europe, US, Canada, South Korea	Prospective, international registry of patients who underwent coronary computed tonometry angiography	Obstructive CAD was more prevalent in men; non-obstructive CAD was associated with increased risk for combined death and myocardial infarction in both sexes

BMI, body mass index; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTnT, high sensitive cardiac troponin T; IHD, ischemic heart disease; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Box 1 | Glossary of preclinical and clinical cardiometabolic disease terms

Term	Explanation
Preclinical cardiac disease	
Dilated left atrium	A left atrium that is ≥34 ml/m^2 bsa based on echocardiography
Left ventricular hypertrophy	A left ventricular mass that is >47 g/m body height$^{2.7}$ in women or >50 g/m body height$^{2.7}$ based on echocardiography
Left ventricular systolic function	Measure of left ventricular ejection. Most common measure is ejection fraction. Normally ≥52% in men and ≥54% in women. Other common measures are midwall shortening and global longitudinal strain
Left ventricular diastolic function	Measure of left ventricular relaxation and filling
Left ventricular filling pressure	Measure of left ventricular diastolic function. Can be estimated by echocardiography from the ratio between mitral blood flow velocity and mitral annulus velocity in early diastole (*E*/*e*′ ratio)
Cardiometabolic diseases	
Ischemic heart disease	Heart disease that causes reduced blood flow to the myocardium (heart muscle)
Heart failure with preserved ejection fraction	Heart failure symptoms despite a left ventricular ejection fraction ≥50%
Heart failure with reduced ejection fraction	Heart failure symptoms and left ventricular ejection fraction <40%
Heart failure with midrange ejection fraction	Heart failure symptoms with left ventricular ejection fraction 40–49%
Atrial fibrillation	Disorganized electrical rhythm in the atria. Loss of atrial pump function

bsa, body surface area.

GENESIS PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond—Premature Acute Coronary Syndrome) study underlined the high impact of sociocultural variables on cardiometabolic risk factors and outcomes in patients with acute coronary syndromes (Table 1)[20,21].

Type 2 diabetes mellitus. Obesity and hypertension are both strongly associated with insulin resistance and type 2 diabetes mellitus (T2DM). The prevalence of diabetes was estimated to be 8.8% of the world population in 2017, with a slightly higher prevalence among men than women (9.1% vs. 8.4%)[22]. While the risk for coronary heart disease is generally lower in women compared to men, this sex difference disappears when T2DM is present[7]. In fact, women with T2DM had a 44% higher relative risk of coronary heart disease and a 27% higher relative risk of stroke, but a comparable absolute risk for these diseases compared to men affected with T2DM[23]. A higher comorbidity burden, including the clustering of hypertension, obesity and elevated triglycerides, the possible contribution of hormonal differences, and sex differences in the prescription of and adherence to pharmacologic treatment in women with T2DM, may all contribute to the higher relative risk for coronary heart disease and stroke[24,25].

Metabolic syndrome. Clustering of cardiometabolic risk factors such as obesity, hypertension, impaired glucose regulation and dyslipidemia is often referred to as the metabolic syndrome[26]. Although women have higher fat mass than men, the prevalence of metabolic syndrome is lower in premenopausal women, but higher in postmenopausal women compared to that in men at a similar age[27]. Glucose and lipid metabolism are directly modulated by estrogen and testosterone. A lack of estrogen or a relative increase in testosterone induces insulin resistance and a proatherogenic lipid profile[27]. NHANES reported that the prevalence of metabolic syndrome in US adults is greater than 30%[28]. A much higher prevalence of metabolic syndrome was reported in the Strong Heart Study in Native Americans from North America aged 40–49 years (44% in men vs. 57% in women, $P < 0.001$ between sexes) (Table 1)[29]. Metabolic syndrome is also associated with lower socioeconomic status and with older age, the latter probably explained by sedentary life style and disabilities[28,30].

Sex differences in preclinical cardiometabolic disease

Diagnosis of preclinical cardiac disease. Preclinical cardiac disease refers to structural and/or functional changes in the heart in asymptomatic subjects that precede incident morbid cardiometabolic events (Box 1)[31]. Preclinical cardiac disease may be diagnosed by non-invasive cardiac imaging methods such as electrocardiography, echocardiography, cardiac magnetic resonance imaging (CMR) or cardiac computed tomography. Echocardiography is by far the most utilized imaging method based on its high availability and prognostically validated measures of cardiac structure and function[32–35]. However, complementary information may be obtained by these different methods.

Impact of cardiometabolic risk factors on prevalent preclinical cardiac disease. Cardiometabolic risk factors such as obesity, hypertension, T2DM and metabolic syndrome are all associated with increased prevalence and incidence of preclinical cardiac disease[32,33,35–39]. Obesity promotes preclinical cardiac disease through a number of hemodynamic and non-hemodynamic effects, including combined pressure and volume overload and biological actions in visceral adipose tissue[40]. A number of these changes are sexually dimorphic. In the Fat-Associated Cardiovascular Dysfunction (FATCOR) study in Norwegian middle-aged subjects with increased BMI and without known coronary artery disease, preclinical cardiac disease was diagnosed by echocardiography in 77% of women and 62% of men ($P < 0.01$ between sexes) (Table 1)[36]. The type of preclinical cardiac disease differed by sex: a dilated left atrium was more prevalent in women while left ventricular hypertrophy (LVH) was more prevalent in men (Box 1)[36]. Also, in older patients with moderate hypertension participating in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study undertaken in the United States and Northern Europe, left atrial dilatation was more common in women, found in 56% of women vs. 38% in men ($P < 0.01$ between sexes) (Table 1)[41]. In the LIFE study, women had a significantly higher prevalence of LVH both at baseline (80% in women vs. 70% in men) and after 4.8 years of systematic antihypertensive treatment (50% in women vs. 34% in men, $P < 0.001$ between sexes)[42]. Obesity was identified as the main factor associated with lack of LVH regression. In the American Strong Heart Study, LVH was also more common in women than in men (36 vs. 23%, $P < 0.001$ between sexes)[43]. At a four-year follow-up examination, regression of LVH was rare, seen in only 3% of men and 10% of women ($P < 0.0001$

between sexes). Furthermore, new-onset LVH was diagnosed in a comparable 14% of men and 15% of women[43]. Higher BMI and urinary albumin/creatinine ratio were identified as the most important confounders of lack of LVH regression in the Strong Heart Study in both sexes[43]. In another publication from the same cohort, obesity assessed by fat mass and waist/hip ratio was associated with higher left ventricular mass in women, but not in men[44]. In treated hypertensive patients in the prospective Italian Campania Salute Network project, new-onset LVH was seen in 21% of people during 16 years of follow-up, and particularly more common in women than men and in obese people (Table 1)[45]. Despite the higher prevalence of LVH, several studies in hypertension have reported that women have better left ventricular systolic function (Box 1)[42,46]. In the Strong Heart Study, reduced left ventricular systolic function was more common in obese men compared to obese women (6.2 vs. 2.9%, $P < 0.001$), independent of the co-incidence of other cardiometabolic risk factors such as hypertension and diabetes[47].

We recently demonstrated in the Campania Salute Network project that women with treated, uncomplicated hypertension had a 35% lower risk of major cardiovascular events than their male counterparts ($P < 0.01$ for sex interaction)[33]. However, when hypertension was complicated by LVH, this sex difference in cardiometabolic risk disappeared[33]. Taken together, these reports demonstrate that LVH is more common and less modifiable in women. Furthermore, when T2DM or LVH is present in women, their risk for cardiometabolic disease is similar to that observed in men[25,33].

Circulating biomarkers of preclinical cardiac disease. Clinical use of non-invasive cardiac imaging in cardiometabolic disease prevention is recommended by the European Society of Cardiology and European Society of Hypertension current joint guidelines for management of hypertension[31,48]. However, non-invasive cardiac imaging may be costly and have limited availability, particularly in the case of CMR and computed tomography. To simplify diagnosis of preclinical cardiac disease, measurement of circulating biomarkers of myocardial damage such as high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) has been suggested[49]. Recent data from the Dallas Heart Study, a multiethnic population-based study, found that plasma levels of NT-proBNP and cTnT differ between women and men (Table 1)[49]. Circulating NT-proBNP, a marker of cardiomyocyte stretch, was significantly higher in women than men (39 pg/ml in women vs. 17 pg/ml in men, $P < 0.0001$), even after sex differences in body composition and heart size were considered. Older women had lower NT-proBNP levels than premenopausal women[49]. The prevalence of increased plasma level of hs-cTnT (≥3 ng/L), a marker of cardiomyocyte injury, was less prevalent in women than in men, found in 14% of women vs. 42% of men ($P < 0.0001$ between sexes), independent of the smaller female heart size[49]. These biomarkers are important in the clinical management of cardiometabolic disorders such as ischemic heart disease (IHD) and heart failure (Box 1). However, sex-specific cut-off values for these biomarkers that may be used for simplified diagnosis of preclinical cardiac disease are still lacking.

Sex differences in cardiometabolic disorders

Heart failure. Heart failure is a common complication in women and men who have clustering of cardiometabolic risk factors. Heart failure symptoms and signs may be particularly difficult to interpret in obese subjects[50,51]. Heart failure diagnosis requires typical symptoms in combination with an elevated circulating NT-proBNP level or detection of cardiac dysfunction on a non-invasive cardiac imaging test[50]. In left-sided heart failure, typical findings on echocardiography include LVH or atrial enlargement with elevated filling pressure (Box 1). NT-proBNP rises to a lesser degree in women than in men with heart failure[52].

Heart failure may be divided into two main types according to reduced or preserved left ventricular ejection fraction (Box 1)[50]. Worldwide, heart failure with reduced left ventricular ejection fraction (ejection fraction <40%; HFrEF) is more common in men and typically caused by previous myocardial infarction or dilated cardiomyopathy, conditions that are more prevalent in men (Box 1)[53]. The Framingham Heart Study found heart failure with preserved ejection fraction (ejection fraction ≥ 50%; HFpEF) to be twice as common in women (Table 1)[53].

Cardiometabolic heart failure caused by hypertension, obesity, T2DM or metabolic syndrome is more common in women, and more often of the HFpEF type[54,55]. Cardiometabolic heart failure is characterized by myocardial lipid accumulation and lipotoxic damage[56]. Increased myocardial triglyceride content has been demonstrated both in women with HFpEF and in IHD[57,58]. Increased myocardial triglyceride content in these subjects is thought to reflect a shift in energy substrate, and has been related to inflammation and contractile dysfunction[58]. Unlike the healthy myocardium, which primarily utilizes free fatty acids as energy substrate, the ischemic myocardium preferentially oxidizes glucose, leaving free fatty acids unoxidized. This surplus of unoxidized free fatty acids are then converted to triglyceride droplets in the cytosol of the cardiomyocytes[58]. CMR spectroscopy can be used to detect increased myocardial triglyceride content, reflecting myocardial steatosis, in patients[59]. Recent CMR studies using spectroscopy have documented that epicardial adipose volume is increased in obesity[59,60]. In a small CMR study in women with HFpEF, higher epicardial fat volume was associated with increased triglyceride content in the myocardium and reduced left ventricular diastolic function (Box 1)[61].

The goals of treatment in patients with heart failure are to improve their clinical status, functional capacity and quality of life, and to reduce mortality[50], which has primarily been achieved for patients with HFrEF. International guidelines on heart failure diagnosis and therapy recommendations do not differ by sex[50,51]. However, a pharmacokinetic modeling and simulation study suggest that the optimal effect of metoprolol may be achieved with lower doses in women than in men: a 50 mg metoprolol dose in adult women provides an approximately similar drug exposure to a 100 mg dose in adult men[62]. Furthermore, a recent post hoc analysis in the BIOSTAT-CHF study (a systems biology study to tailor treatment in chronic heart failure), performed in 11 European countries, suggested that, for optimal effects, women with HFrEF might need lower doses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers than men[63]. No therapy so far has been shown to reduce mortality in patients with HFpEF.

In the Euro Heart Survey, objective diagnostic tests such as echocardiography were used less often in women with heart failure[8]. Furthermore, women were less represented (about 20% of the individuals studied) in most of the clinical studies on heart failure that underpin current treatment recommendations, and treatment effect in women is therefore less documented[8]. A recent report on adverse reactions to guideline-recommended drug therapy in 155 randomized heart failure clinical trials found that only 7% of the trials (11 of 155 publications) reported adverse events separately for women and men, even though it is well known that women have more adverse events[64]. In patients with HFrEF and conduction delay, some studies have reported more benefit from resynchronization treatment in women than in men[65,66]. Women with HFrEF are less likely to be referred for implantable cardioverter defibrillator therapy, and they suffer more complications related to the implantation, but have similar survival benefit to men[67]. Whether sex differences in treatment decisions reflect patient preferences or treatment biases needs further research. Improved understanding of cardiometabolic heart failure is necessary to identify new treatment targets for HFpEF.

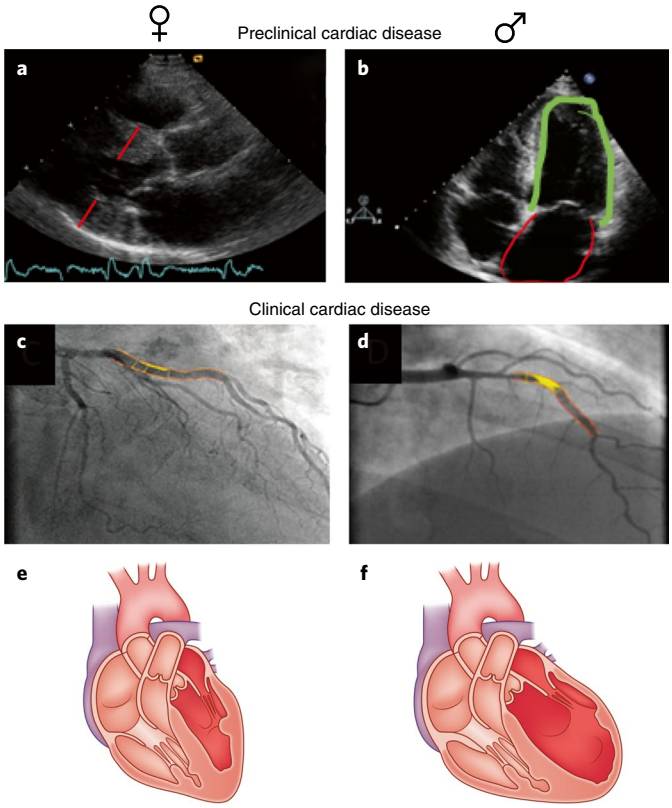

Fig. 1 | Characteristics of preclinical and clinical cardiometabolic disorders in women and men. CAD, coronary artery disease; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MINOCA, myocardial infarction without obstructive coronary artery disease. **a**, Echocardiographic image of concentric LVH. **b**, Echocardiographic image of dilated LA and LV. **c**, Angiographic image of non-obstructive coronary artery disease. **d**, Angiographic image of obstructive coronary artery disease. **e**, Schematic drawing of HFpEF, heart failure with preserved ejection fraction. **f**, Schematic drawing of HFrEF, heart failure with reduced ejection fraction. Credit: Debbie Maizels/Springer Nature.

Atrial fibrillation. The diagnosis of atrial fibrillation (AFib) requires rhythm documentation using an electrocardiogram showing irregular RR intervals and no distinct P waves[68]. The risk of AFib is 1.5–2.0 times higher in men and increases with age and BMI. In the Norwegian community-based Tromsø Study, AFib was prevalent in 15% of women and in 19.5% of men aged 70–79 years ($P < 0.01$ between sexes) (Table 1)[69]. It is well documented that women with AFib have higher risk of stroke, myocardial infarction and heart failure than their male counterparts[8]. In the Tromsø Study, uncontrolled systolic hypertension was a stronger risk factor for incident AFib in women than men, associated with a twofold increased risk for incident AFib in women, compared to a 30–60% increased risk in men[9]. In the Atherosclerosis Risk in Communities (ARIC) study, 57% of incident AFib at 17 years follow-up was attributed to cardiometabolic risk factors, particularly hypertension (Table 1)[70]. A meta-analysis involving more than 600,000 subjects demonstrated that a 5-unit increment in BMI confers a 19–29% increased risk for incident AFib[71]. Furthermore, progression from paroxysmal to persistent or permanent AFib is influenced by obesity[72]. In the Women's Health Study, presence of a dilated left atrium explained the association of obesity with incident AFib, while the association of hypertension with incident AFib was independent of the presence of preclinical cardiac disease (Table 1)[73]. Compared to men, postmenopausal women with AFib had higher epicardial adipose volume—in particular, periatrial adipose tissue, which was associated with reduced atrial voltage and transport function—by computed tomography[74]. These findings point to the potential of body weight control for prevention of AFib[69]. Among patients with AFib, women have a higher symptom burden compared to men[75]. International guideline recommendations for treatment of AFib is the same for both sexes and focuses on rate or rhythm control and stroke prevention[68,76]. AFib treatment includes pharmacological treatment, electrical cardioversion and catheter or surgical ablation therapy. Despite the documented higher symptom burden, it has been well demonstrated that women with AFib are still less likely to receive modern rhythm control antiarrhythmic drug therapy, electric cardioversion or catheter ablation compared to men[67]. In the German AFib registry, women were older, were more likely to have paroxysmal AFib and complications related to catheter ablation (1.9% in women vs. 0.8% in men, $P = 0.023$), and had higher recurrence of AFib within 1 year after the procedure (50% in women vs. 45% in men, $P = 0.017$)[77]. Better results from catheter ablation therapy can be expected in younger patients with a shorter AFib duration, as well as in the absence of structural cardiac disease, factors more commonly found in men. The CHA_2DS_2-VASc score is recommended for stroke risk prediction in AFib patients. This score assesses stroke risk based on presence of the following factors: congestive heart failure (C), hypertension (H), age above 75 years (A_2), diabetes (D), prior stroke or thromboembolism (S), history of vascular disease (V), age 65–74 years (A) and sex (Sc). Age above 75 years, prior stroke or thromboembolism and female sex add 2 points, the other factors 1 point if present. Men who score 2 or more and women who score 3 or more points are recommended to have oral anticoagulant therapy for stroke prevention[68,76].

Ischemic heart disease. IHD may be caused by obstructive and non-obstructive atherosclerotic coronary artery disease (CAD), or myocardial ischemia caused by coronary microvascular dysfunction, endothelial dysfunction, vasomotor abnormalities, spontaneous coronary artery dissection and stress-induced cardiomyopathy[78]. Women with IHD are characterized by a higher prevalence of angina, a higher burden of cardiometabolic risk factors, and a higher prevalence of non-obstructive CAD on angiography compared to men (10–25% in women vs. 6–10% in men)[79,80]. Diagnostic workup in women with suspected IHD should therefore not be limited to routine coronary angiography, given the multifactorial etiology of IHD in women without obstructive CAD. Presence of LVH and increased arterial stiffness may contribute to myocardial ischemia in patients with stable angina and non-obstructive CAD[81,82].

The Tromsø Study demonstrated that myocardial infarction occurs more often in men throughout their lifespan, although the sex difference diminishes with increased age (Box 1)[83]. In general, women with myocardial infarction are less likely to present with classical chest pain and more likely to present with a range of atypical symptoms, including dyspnea, fatigue, nausea and weakness[78,84]. Women also have lower awareness of their subjective risk for IHD, probably contributing to delayed presentation in the emergency room of many women with acute myocardial infarction[8,19]. In Norway, as in many other Western societies, the number one cause of death in women is myocardial infarction, while cancer is the most common cause of death in men[85]. Measurement of cTnT or cTnI are, together with clinical symptoms and the electrocardiogram, mandatory for the clinical diagnosis of acute myocardial infarction. Implementation of sex-specific cut-off values for increased cTnT and use of cTnI rather than cTnT may contribute to reducing the documented underdiagnosis of myocardial infarction in women[86].

Among patients without known cardiovascular disease included in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) Registry (Table 1), women and men with cardiometabolic risk factors such as hypertension or increased BMI had increased presence, extent and severity of

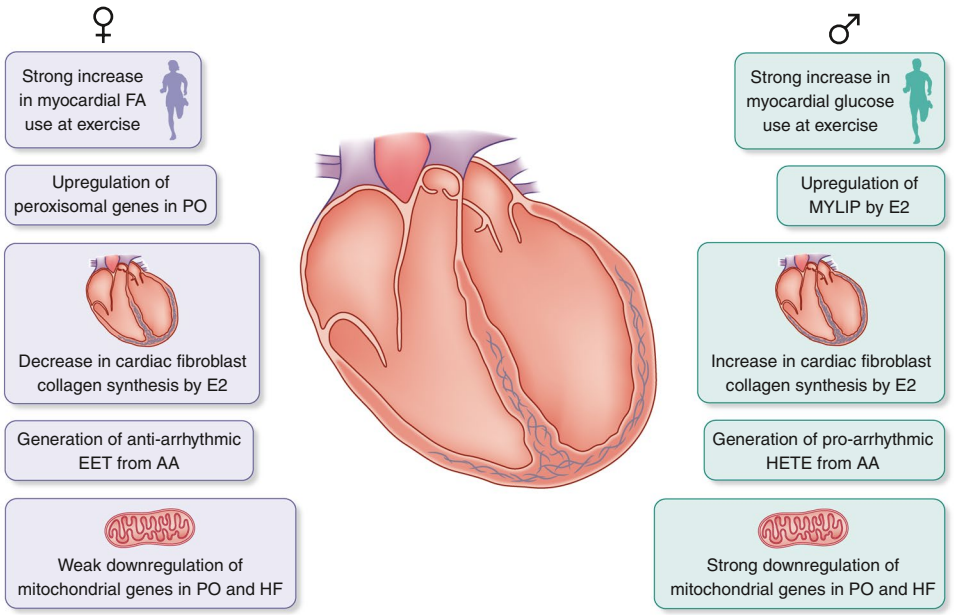

Fig. 2 | Sex-specific features in cardiometabolic disorders. Several mechanisms can be shown to occur predominantly in women or men and to contribute to these disorders predominantly in one sex. AA, arachidonic acid; E2, estradiol; EET, epoxyeicosanoids; FA, fatty acids; HETE, hydroxyeicosatetraenoids; HF, heart failure; MYLIP, myosin regulatory light chain interacting protein; PO, pressure overload. Credit: Debbie Maizels/Springer Nature.

coronary atherosclerosis by computed tomography angiography[87]. During follow-up, increased BMI was also associated with higher mortality in both sexes. In the CONFIRM registry, a comparably increased mortality was found in both women and men with non-obstructive CAD compared to individuals with normal computed tomography angiography[88]. Among 329 patient with suspected IHD who underwent coronary angiography and myocardial ischemia testing with positron emission tomography perfusion imaging, the main prognostic factor in men was the severity of CAD, while in women the presence of reduced coronary flow reserve was the most important predictor of adverse outcome[89]. Taken together, among patients with IHD, women have higher prevalence of cardiometabolic risk factors, different symptoms and less obstructive CAD than men. Further research is warranted to determine the optimal management of women with IHD (Figure 1).

Molecular mechanisms of sex differences in cardiometabolic disorders

Even though a wealth of data exists regarding phenotypic differences between women and men in cardiometabolic disorders and their underlying risk factors, mechanistic understanding is still scarce (Fig. 2). The complex interplay of effects of female and male sex hormones (such as estrogens and androgens and beyond), sex-specific gene expression and gender was recently reviewed[90]. The effect of estrogens on glucose and lipid homeostasis and diabetes received recently more attention, and it was shown that genetic mechanisms contribute to body fat distribution in women and men[91]. Women and men store fat differently. Women store fat preferentially in subcutaneous adipose tissue, which is more suitable for longer storage and may serve as a source of energy in critical periods, and in brown adipose tissue, which is metabolically active and flexible. Men store fat preferentially in the visceral and white adipose tissue. White adipose tissue is particularly active in generating adipokines and cytokines and metabolizing sex hormones[12]. Aromatase activity in the white adipose tissue increases estrogen levels in elderly or obese men above those in women[92]. These estrogens are important to cardiometabolic disorders in men. In HFrEF, men with estrogen levels in the highest quintile had poorer outcomes than those with normal estrogen levels[93]. A mechanistic link may be the myosin regulatory light chain interacting protein (MYLIP). After ex vivo estradiol exposure of human heart tissues from women and men, the *MYLIP* gene was only induced in tissues of men[94]. Exposing isolated mouse cardiomyocytes to estrogen led to impaired contractile function in male cardiomyocytes only. Further analysis showed that MYLIP expression levels rose with increasing age in hearts of men, potentially leading to dysregulation of myosin regulatory light chain function and contributing to poor outcomes of cardiometabolic HF in men. Moreover, MYLIP has a completely independent second function—it acts as an inducible degrader of the LDL receptor[95]. The LDL receptor is a critical factor in the regulation of blood cholesterol levels, which are altered in different human diseases. Both mechanisms may be related to the development or progression of cardiometabolic disease in elderly and obese men, and MYLIP may even offer a novel treatment target.

In pressure overload, downregulation of lipid and energy metabolism-related genes is more pronounced in male than in female hearts from mice and humans[96,97]. During pressure overload, female, but not male, human hearts exhibit an upregulation of peroxisome-dependent lipid-utilization genes, which may represent an alternative pathway to meet a greater energy demand[98]. Similar observations are made in the mouse model, where female animals are better at maintaining cardiac mitochondrial function under stress[96], such as pressure overload[97], than males. Estrogens are involved in this process and stimulate mitochondrial respiration in female and male hearts. In humans, estrogen treatment reverses the mitochondrial dysfunction associated with menopause[99,100]. Mechanisms of estrogen protection of mitochondria include increased expression of proteins that are part of the respiratory chain or the tricarboxylic citric acid cycle[90,101,102]. Estrogen receptors can directly bind to mitochondrial DNA to regulate mitochondrially encoded genes[101,103]. These protective mechanisms are not only active in pressure overload but also in ischemia/reperfusion injury[104,105] and injury induced by oxidative stress[106–108]. Maintaining mitochondrial function under stress requires dealing

more efficiently with the free radicals resulting from high oxidative phosphorylation. Higher amounts of proteins that can capture free radicals have already been documented in the female heart[109]. Estrogen increases expression of the antioxidant enzyme glutathione peroxidase, stimulates the activity of the mitochondrial antioxidant manganese sodium dismutase in the hearts of ovariectomized animals, and represses superoxide generation in neonatal rat cardiomyocytes subjected to oxidative stress[110,111]. Reduced production of reactive oxygen species and subsequent cardioprotection in females can also be achieved by phosphorylation of aldehyde dehydrogenase-2, a key mitochondrial regulatory protein[112].

Further sex differences in lipid metabolism are important for arrhythmia and its treatment. In women, arachidonic acid is metabolized to epoxyeicosanoids (EETs) under the influence of estrogen, whereas in men, it is metabolized to hydroxyeicosatetraenoic acid (HETE) under the influence of androgens. EETs are antiarrhythmic and cardioprotective, whereas HETE is proarrhythmic. EET analogs have now been developed for use in human AFib. Thus, a protective mechanism in females is being used to treat men and women[113,114].

Sex differences in lipid metabolism are also important in the skeletal muscle, and these differences may be reduced by diabetes. A recent landmark study showed that in the skeletal muscle, high-density lipoprotein (HDL) stimulates mitochondrial respiration via its major protein component apolipoprotein AI[115]. HDL levels are higher in premenopausal women than in age-matched men, but the physiological role of this difference for energy metabolism has not yet been fully elucidated. Women with diabetes have lower HDL than those without or men, and they may lose this stimulatory function of estrogen. The decrease in estrogen after menopause leads to a decrease in women's HDL and predisposes women to sarcopenia and frailty. In the Strong Heart Study, sarcopenic women had greater probability of hypertension and abnormalities of glucose metabolism compared to women with normal fat-free mass[116].

Sexual dimorphisms exist not only in cardiac energy metabolism but also in its link to obesity-mediated LVH. A high-fat diet seems to have a sexually dimorphic effect. Male mice on a high-fat diet exhibited a stronger increment in left ventricular mass than females[117]. The mRNA expression of adipocytokines in epicardial adipose tissue after 25 weeks of high-fat diet showed higher levels of adiponectin, leptin and vaspin, which induces cardiac fibroblast proliferation in male mice compared with female mice. This points to a sex-dependent regulation of diet-induced LVH that associated with sexual dimorphic expression of adipocytokines in epicardial adipose tissue, and also a link to tissue fibrosis.

Myocardial fibrosis is a hallmark of cardiac dysfunction, contributes to left ventricular systolic and diastolic dysfunction and is activated in almost all forms of cardiometabolic disorders (Box 1). Myocardial fibrosis affects males to a greater degree than females[118,119]. This may partially be due to greater induction of renin-angiotensin-system (RAS)-related genes in human male than in female myocardium[94]. Or it may be due to dampening of the RAS by estrogens in women[120]. After exposure to pressure overload, men and male mice activate more profibrotic genes and generate more collagen and fibrous tissue in the myocardium than women or female animals[118]. This difference is partly due to the effects of estrogens: they stimulate collagen synthesis in male cardiac fibroblasts from different species, including human, mouse and rat, and inhibit collagen synthesis in the female cells and in engineered connective heart tissues[121]. More precisely, both estrogen receptors (ERα and ERβ) are phosphorylated differently and at different sites in the male and female cells. Once phosphorylated, they bind to the collagen promoters in a sexually dimorphic manner. To simplify, ERα represses and ERβ induces collagen synthesis. In engineered connective heart tissues, estradiol via ER modulates cardiac tissue function in a sex-dependent manner. Engineered heart tissues from male cells show an increased condensation and stiffness upon E2 treatment, as analyzed by rheological measurements, whereas impaired condensation is found in females.

The role of JunD in cardiometabolic disorders. A recent landmark publication identified JunD, a direct target of miR-494 and activator of peroxisome proliferator-activated receptors (PPARs), as a key player in mice with diet induced obesity[56]. Since the results were only obtained in male mice, and sex was not indicated for the confirmatory analysis in the human heart, it remains to be shown whether this mechanism in male mice applies to women. We recently showed that some microRNAs in the human heart that are related to mitochondrial function are regulated by ERβ[122]. Thus, the sex-specific regulation of these miRNAs and corresponding downregulation of downstream protein targets may contribute to sex-specific remodeling in pressure-overload-induced LVH[122]. Moreover, downregulation of microRNA-494 in obesity is associated with upregulation of JunD. Previous studies in a monocytic line showed that estrogen decreases the activity of the Jun N-terminal kinase, leading to lower production of JunD[123]. Thus, women may be less affected by the proposed mechanism for cardiometabolic disorders since estrogen may prevent the increase in JunD.

Further signaling in the proposed pathway leads to activation of PPARs. PPAR coactivation is controlled by PPAR-γ coactivator-1α or 1β (PCG-1), which is regulated by estrogen. In a model of histone deacetylase 5 overexpression that was able to produce a decrease in PCG1, cardiomyopathy, mitochondrial dysfunction and death occurred in male mice only[124]. Female mice survived without mitochondrial damage, suggesting that female mice maintain their PGC-1α levels by some as yet unknown, potentially estrogen-dependent mechanism.

Future directions

Several facts lead to the belief that pathophysiologic mechanisms in diet-induced obesity and cardiometabolic disorders affect women's and men's heart differently. Stronger consideration should be given to understanding these sex differences and to integrating them into diagnostic and therapeutic approaches of cardiometabolic diseases. Particularly, development of circulating biomarkers for simplified diagnosis of preclinical cardiac disease in women and men with cardiometabolic risk factors is called for. Furthermore, a sex-specific algorithm to guide non-invasive imaging testing in IHD is needed. Finally, improved understanding of cardiometabolic heart failure is necessary to identify new treatment targets for HFpEF.

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E.G. and V.R-Z. both drafted and contributed to the manuscript and approved the final version.

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Additional information

Correspondence should be addressed to E.G.

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