Gender issues in cardiovascular diseases. Focus on energy metabolism

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Abstract

It is increasingly recognized that sex and gender differences (S&G) influence cardiovascular diseases (CVD), greatly impacting disease management. In terms of definition, sex refers to biological aspects, gender effects being mainly related to socio-cultural factors. Both sex and gender are interpenetrated in humans and difficult to separate. This is more clearly feasible in animal models were sex effects largely predominate. As alterations in energy metabolism are essential features of cardiovascular diseases, sexual dimorphism of energy metabolism and more specifically mitochondria occupies a place of choice. This review presents the basis of sex and gender differences in the cardiovascular pathophysiology, and how it mainly affects woman diseases, effectiveness of therapies and clinical outcome. These differences rely on complex molecular mechanisms that are still poorly understood because of the under-representation of females/women in experimental and clinical studies. Finally, the differing psychological and biological phases of woman's life are largely underestimated. This review presents an overview of the field with focus on differences in cardiac energy metabolism, which are illustrated with specific examples.

Introduction

It is increasingly being recognized that sex and gender (S&G) differences influence cardiovascular diseases (CVD), greatly impacting disease management. Increasing evidence indicates that alterations in metabolism are essential features of cardiovascular diseases as well as of S&G differences of CVD. In terms of definition, sex refers to biological aspects, gender effects being mainly related to socio-cultural factors. While sex differences are present in animals, gender aspects are more specific to humans. Both intervene in the pathophysiology of cardiovascular diseases, are interrelated and difficult to distinguish properly [1]. These S&G effects affect epidemiology, prevalence, clinical manifestations, pathophysiology as well as medical approaches; they also impact effectiveness of therapies, their possible side effects and finally outcome of diseases. This interrelation between biological factors and social ones like nutrition, environment life style and cultural aspects is operative from the germ cells and throughout life. This review is not intended to exhaustively cover all the aspects of S&G in the cardiovascular field; it will present an overview of the field with the help of a few examples. For comprehensive and exhaustive recent reviews, refer to [1-3].

Men and Women differences in cardiovascular diseases

S&G differences in cardiovascular diseases are particularly well-reported because there is strong epidemiological evidence that men and women face different risks and have different outcomes [4]. The annual number of adults having diagnosed with a heart attack or fatal coronary heart disease (CHD) increases with age, with an under representation of women that vanishes with ageing. In a middle age population, men develop heart failure more frequently and at a younger age than women. Thus women are less susceptible to undergo cardiovascular diseases during the pre-menopausal phase of life. Moreover, the Euro Heart Failure survey has established that among hospitalized patients suspected to have heart failure, the distribution of the severity of left ventricular systolic dysfunction shows that it is higher in men than in women with 61% of men but only 35% of women having moderate to severe systolic dysfunction [5]. The manifestation of heart failure also

differs between men and women. Independently of age, women develop more frequently heart failure with preserved ejection fraction (HFpEF), *i. e.* diastolic dysfunction, while men develop more heart failure with reduced ejection fraction (HFrEF). At present there is no specific treatment for HFpEF.

A sexual dimorphism is also evident in cardiac remodeling with women exhibiting a more concentric form of myocardial hypertrophy and less fibrosis, than men [2].

Concerning ischemic heart disease, it occurs three to four times more often in men under 60 years of age and develops 7-10 years later in women, while after 75, women are the majority of patients [1]. S&G are also a major determinant of the incidence, etiology, and clinical presentation of arrhythmias, as well as in access and response to arrhythmia therapies [3]. The prevalence of the different forms of arrhythmias exhibit an important sexual dimorphism with, for example, increased prevalence of Brugada syndrome in men (1F/9M) and of long QT syndrome in women (3F:1M). Incidence and prevalence of atrial fibrillation (AF) is lower in women than men but atrial fibrillation is a much higher risk factor for cardiovascular disease and death in women while at present causality is not obvious [4]. Female sex has now been included as an additional and independent risk factor in the calculation of the risk of stroke in AF (CHA2DS2-vasc score) [5]. A recent analysis of patients undergoing AF ablation based on the United States Nationwide Readmissions Database, between 2010 and 2014 concluded that independent of age, co-morbidities, and hospital factors, women have higher rates of complications and readmissions following AF ablation than men [6].

Heart disease is the leading cause of death among diabetic patients. Diabetes and mainly type 2 diabetes mellitus (T2DM) increases the risk of CVD by three to four times in women and two to three times in men, after adjusting for other risk factors [7]. Numerous studies have documented worsened cardiac outcomes for women [8, 9]. Thus everything goes as if women with T2DM loose the "*female advantage*" of premenopausal women [7]. The reasons for this sexual dimorphism in the cardiovascular consequences of diabetes between genders are not clear. If both genetic and hormonal factors are involved, it is also possible that gender effects play an important role. Possibly women arrive later and in worse conditions to the diagnosis of diabetes, receive less diagnostic and therapeutic support and, finally, reach therapeutic goals recommended by guidelines to a lesser extent [10].

Finally it should be acknowledged that CVD are the leading cause of death in women. Although the mortality rate declines regularly with time for men, the decline is slower in women [11]. It may thus be that the treatment strategies are maybe not as efficient in women as in men.

As a result, the prevalence and outcome of CVD present gender specificities (Table 1). While a "female protection" against CVD is clearly evident before menopause, CVD is the leading cause of mortality for women. These S&G specificities, although known and recognized, did not yet result in sufficient clinical trials and guidelines.

Women and men differences in pharmacology and therapies

Differences in efficacy of treatments and in the occurrence of side effects have been noted between men and women [12]. This sexual dimorphism in drug effects has been noted for different drug classes among which cardiovascular oriented drugs like diuretics, anticoagulants, β-blockers digoxin, and ACE inhibitors [13-16]. Despite recognition of these facts, specific pharmacology and guidelines that would differentiate treatments between men and women are largely lacking. Usually guidelines recommend identical doses for men and women. However, it is well established that women have increased risk of experiencing adverse drug reactions compared with men, these adverse events being more serious in women than in men [14]. For example, 60% of patients hospitalized for adverse effects of drugs are women and they have 50 to 70% more risk of side effects than men. A recent study shows that, in patients with HFrEF, there are striking sex differences in the optimal dose levels of the main cardiovascular drugs like angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers and β-blockers [17]. Women have the lowest risk of death or hospitalization for heart failure at half the guideline-recommended doses compared with men while risk increases with the dose [17]. Moreover, the occurrence of adverse drug reactions increases the risk of discontinuing the medication, thus loosing the potential benefit.

These adverse effects could originate from both S&G. A recent position document of the Working Group on Pharmacology and Drug Therapy of the European Society of Cardiology has highlighted that S&G differences in pharmacokinetics could be caused by sex

specific oral bioavailability, amount and distribution of body fat, clearance, volume distribution, absorption, plasma protein binding, urinary excretion, and metabolism [14]. As an example, female liver cells have more cytochrome P450 CYP3A compared with male liver cells [18]. Such differences in CYP3A expression between male and female hepatocytes have important clinical consequences, as the actions of CYP3A account for the metabolism of half the drugs in the pharmacopeia. Additionally, risk factors for adverse drug events may be related to polytherapy, higher age or depression that all are more frequent in women. It is urging that these facts are taken in consideration, and both proportionate representation of women in HF trials, and sex-specific reporting of efficacy and safety, are necessary to improve the quality of HF treatment [15].

In summary, women are relatively protected from HF until menopause, however the incidence of chronic disease is elevated after menopause and mortality from cardiovascular disease is higher in women. Cardiovascular diseases affect men and women differently. Women develop more HFpEF than men and have more microvascular defects. Treatments are less effective for women and side effects are more important.

Mechanisms of S&G effects

Gender effects

Gender effects could be defined as masculine or feminine behaviors determined by socio-cultural aspects like gender representations, life style including nutrition and stress, education or experience, behavior, and psychological factors. These gender issues will in different ways influence the outcome of pathologies. For example, patient/caregiver relationship will be sensitive to gender stereotypes. Socio-cultural factors such as inequality of training (knowledge of pathologies), inequality of wages between sexes (effect of poverty and precariousness on health), or stress associated with dual occupancy (work and family) participate in the gender issue of CVD. Moreover, differing manifestations of pain and symptoms, lifestyle (effect of stress, nutrition, and addictive behaviors), sedentarity are also factors that aggravate the sexual dimorphism. For example, the double exposure to stress from work and family is accompanied by the highest risk and the worst prognosis in

women's coronary disease [19]. Bias in the diagnosis and management of coronary artery disease arises from stereotypes; for example women are most likely to receive a mental health diagnosis than men [20]. In medicine these factors are entangled with purely biological factors.

Sex: biological differences

Biological differences between males and females can be categorized in genetic, epigenetic and hormonal factors (Figure 1).

Genetic factors

Males and females differ by their sex chromosomes. While male cells possess XY chromosomes, females are characterized by two X chromosomes. The X chromosome encodes for about 1500 genes involved not only in sexual function but also in heart, immune system and brain. Because of the presence of two X chromosomes, one copy of each gene should be inactivated. However, it appears that 10 to 15% of these genes escape inactivation in a tissue and in a gene specific manner. This leads to twice as much X chromosome gene products as in males for 10 to 15% of X genes in females. The Y chromosome meanwhile encodes 78 genes involved in sexual function.

Our knowledge of the sex chromosomes is poor as the majority of genome wide association studies (GWAS) omit the sex chromosomes [21]. Given that the X chromosome represents ~5% of the genes in the human genome, taking into account the X chromosome in GWAS would reveal many interesting biological insights [21].

Recent studies suggest that sex-specific genetic architecture influences human phenotypes, including reproductive, physiological and disease traits [21].

Epigenetic marks

Sexual dimorphisms take place due to a combination of genetic determinants and environmental cues which are frequently transmitted by epigenetic regulation. A substantial proportion of dimorphic gene expression might be under the control of sex-specific epigenetic marks. Epigenetics refers to functionally relevant changes to the genome that do not involve a change in the nucleotide sequence. Examples of mechanisms that produce such changes are DNA methylation and histone modification like methylation, acetylation, phosphorylation, ubiquitination as well as non-coding RNAs. These epigenetic marks

determine S&G interactions. Epigenetic marks will reflect life style, nutrition, stress, hormonal status, drugs and medication and will influence protein expression in a S&G specific manner [22].

Sex hormones

While female hormones are mainly represented by estrogens and progesterone and the main male hormone is testosterone (or its more active metabolite dihydrotestosterone, DHT), these hormones are actually present in both sexes but in different doses. Estradiol (E2) is the principal estrogen. Estrogen effects are mainly mediated through estrogen receptors (ERs). ERs belong to the family of steroid hormone receptors. Three estrogen receptors have been described: estrogen-receptor alpha (ERα), estrogen receptor beta (ERβ) and the plasma membrane-associated one, the G-protein coupled estrogen receptor (GPER), with specific tissue and intracellular locations. ERα and ERβ have also been localized in different cellular compartments among which mitochondria. Estrogens may have genomic and non-genomic effects because ERs may function as nuclear receptors and transcription factors and as signaling molecules in the cytosol and plasma membrane. Progesterone has also a nuclear progesterone receptor (PR). In contrast, only nuclear localization has been shown for the testosterone/DHT receptor (androgen receptor, AR).

An important point to be taken into account is that androgen and estrogen receptors are present in males and females and in practically all cell types although in varying quantities which means that all organs are potentially sensitive to circulating or paracrine sex hormones. Sex hormones exhibit a peak early after birth and attain their maximum at puberty. While male hormones will decrease slightly after 50, the rapid fall in estrogen at menopause in women will be of importance in the manifestation of pathologies in the postmenopausal women (Figure 1).

Sex specificity of gene expression

All these factors combine to explain the sexual dimorphism in gene expression. The fluctuating amount of circulating hormones together with genetic and epigenetic factors will determine the sex specificity of protein expression.

For example the liver appears to exhibit the higher proportion of sexually dimorphic genes with as high as 72% of genes differentially expressed in mice; the proportion being

68% for adipose tissue, 55% for muscle and 13.6% for brain [23]. The number of sexually dimorphic gene expression in human shows that they are related to various biological systems, and suggests new insights into the pathophysiology of diverse human diseases [24]; for example more than a hundred genes are differentially expressed between men and women left ventricle.

Sex differences in experimental studies

Mechanistic pathways involved in sex differences in cardiovascular diseases have been excellently reviewed recently in depth [2]. Male and female hearts respond differently to experimentally-induced cardiac diseases. For example, rat hearts exhibit sex differences when subjected to aortic constriction; while males have early and pronounced cardiac dysfunction, females have delayed cardiac dysfunction but increased left ventricular hypertrophy [25]. Cardiac transcriptomics also revealed sex differences, with increased protein synthesis capacity and deregulation of matrix remodeling in male hearts and less downregulation of metabolic genes in female hearts [26]. Similar pattern was also observed in humans [27]. Thus energy metabolism and extracellular matrix seem to be more preserved in females following aortic constriction.

With the development of genetically modified organisms, in particular mice, it had become evident that males and females often respond differently to loss or gain of function experiments. We will take few examples of genetically modified animals with sex differences in the field of cardiac energy metabolism. One of the first examples is the mice knocked-out for the peroxisome proliferator-activated receptor alpha (PPARα), a nuclear receptor implicated in the control of cellular lipid utilization. In these mice, inhibition of cellular fatty acid flux caused massive hepatic and cardiac lipid accumulation, hypoglycemia, and death in 100% of male, but only 25% of female PPARα-/- mice [28]. This effect was reversed in males by treatment with estrogen, showing an interaction between lipid metabolism and sex hormones. Conversely, mice expressing a cardiac specific dominant-negative form of the cyclic nucleotide regulatory element binding-protein (CREB) transcription factor, demonstrated a significantly higher mortality in females compared to males. These females exhibited decreased cardiac content of peroxisome proliferator-activated receptor-gamma

coactivator-1alpha (PGC-1α) and estrogen-related receptor-alpha (ERRα) content, two factors essential for mitochondrial biogenesis, increased oxidative stress, decreased mitochondrial content and exacerbated mitochondrial dysfunction, suggesting sex-related effects on cardiac mitochondrial function [28]. However, in general, male mice appear more sensitive to genetic interventions than females, since female animals display a lower mortality, less severe hypertrophy, and better preserved function than males [2].

The expression profile of myocardial genes involved in lipid metabolism was studied in male and female non-obese diabetic and Goto-Kakizaki rats. The analysis revealed strikingly significant sex differences in the expression of a broad range of genes involved in transport, activation, and utilization of lipids. While diabetic male rats exhibited a significant increase in the expression of genes involved in beta-oxidation compared to controls, diabetic female hearts displayed reduced expression of genes involved in fatty acid activation and acylcarnitine metabolism [29]. This result underlines that the cardiac metabolic signature of diabetes differs between males and females and could be of therapeutic significance with regard to the greater sensitivity of women to CVD induced by diabetes.

Finally it is known that females live longer than males. In aging monkeys for example, changes in glycolytic and mitochondrial metabolic pathways with aging were more prominent in males than females. Protection of cardiac energy metabolism can thus participate in explaining gender differences in the aged heart [30].

Cardiotoxicity is a hallmark of many anticancer therapies. A remarkable sexual dimorphism was observed in the response of male and female rats to the anti-cancer drug doxorubicin. Male rats exhibit an exacerbated mortality and major cardiac dysfunction compared to females. Energy metabolism, AMP-activated protein kinase (AMPK) pathway, cardiolipins, and mitochondrial dysfunction appear as critical sites of sex differences in cardiotoxicity and are involved in the protective effects against anthracyclines cardiotoxicity in female rats [31, 32]. Likewise, adult tumor-bearing male spontaneously hypertensive rats (SHR) were shown to be more cardiosensitive to doxorubicin than females, an effect that was attributed to the greater activation of oxidative stress and apoptosis in male SHRs without differences in tumor volume regression [33]. Data for anthracycline cardiotoxicity in humans are still lacking.

Animal studies can help to decipher the role of gender versus sex effects in pathophysiology as sex effect is largely more prevalent in experimental species.

Role of mitochondria in sex differences

Sex specificity of mitochondria

It becomes apparent that energy metabolism is central in cardiac cell pathophysiology. As cardiac muscle relies for more than 90% on oxidative phosphorylation for energy utilization, mitochondria play a central role in cardiac energy metabolism. Many examples have provided evidence that they are also involved in sex differences [34-36].

This could be at first surprising as mitochondria are exclusively maternally inherited. As such, natural selection on mitochondria operates only in females. Indeed, according to the endosymbiotic theory, mitochondria arise from archeobacteria that have colonized ancient eukaryotic cells some 1.45 billion years ago. Mitochondria thus possess their own circular DNA, coding for 13 proteins of some complexes of the respiratory chain, 2 ribosomal and 22 transfer RNAs. However, during the course of mitochondrial genesis, many genes were transferred from the genome of the mitochondrial endosymbiont to the genome of the host. In mammals, the mitochondrial proteome contains more than 1000 proteins, not counting a wide array of splicing and post-translational variants that are encoded by the nuclear genome [37]. Thus the possible sex- (and tissue-) specificity of mitochondria derives from the fact that the vast majority of proteins are encoded by the nucleus, translated, and imported in mitochondria by specific transport mechanisms. As such, mitochondria are under the influence of genetic, epigenetic and hormonal factors known to influence sex specificity. Moreover, the mitochondrial biogenesis machinery is governed by nuclear co-activators and transcription factors that control replication and transcription of the mitochondrial genome and are responsive to steroid hormones. Thus mitochondria are under the control of the nucleus and are influenced by sex in a tissue-dependent manner.

Estrogens modify mitochondria by genomic and non-genomic effects [35]. Estrogens regulate nuclear gene transcription by binding and activating the classical genomic estrogen receptors (ERα and ERβ) and by activating plasma membrane-associated ERs, and GPER. Non-genomic effects involve rapid, signaling actions through activation of membrane-

associated ERs and GPER and subsequent activation of signaling pathways like extracellular signal-regulated kinase 1 and 2 (ERK1/2), increased phosphorylation of c-Jun-NH2-terminal protein kinase (JNK), phosphoinositide 3-kinase (PI3K), protein kinase B (PKB), glycogen synthase kinase3β (GSK3β), β-catenin, calcineurin, mechanistic target of rapamycin (mTOR), p38 mitogen-activated protein kinase (MAPK), and others [2, 38].

Finally, it is now well established that mitochondria contain steroid hormone receptors. ERβ seems to be the main estrogen receptor present in mitochondria as demonstrated by immunohistochemistry, immunocytochemistry and immunoblots using a large panel of antibodies and mechanisms of ERβ import have been studied (see [39] for review).

Mitochondrial function and biogenesis can directly and indirectly be regulated by estrogens/ERs (for extensive reviews see [40, 41]). Estrogens activate mitochondrial biogenesis by increasing the expression of PGC-1α and of its downstream targets [26]. Increased mitochondrial biogenesis is mediated by ERα and also by the presence of an estrogen responsive element (ERE) in the promoter of the nuclear respiratory factors (NRFs) [42]. E2 favors the interaction of ERs with the mitochondrial transcription factor TFAM and other factors in mitochondria and stimulates mtDNA transcription. Moreover, in vascular smooth muscle cells E2/ER regulates the expression and activity of superoxide dismutase (SOD), thereby diminishing the production of ROS and being vasoprotective [43]. Expression of the cardiac mitochondrial MnSOD was also shown to be enhanced in neonatal rat cardiomyocytes by an E2/p38 MAPK interaction [44].

Depending on the tissue, sex-specificity has been described for main mitochondrial pathways like mitochondrial capacity (number and specific activity), production of reactive oxygen species and antioxidant defenses, calcium handling, lipid oxidation and apoptotic signaling [34].

Examples of sex-specificity of mitochondria

Mitochondrial dysfunction is an important factor for a large panel of pathologies including neuromuscular disorders, encephalopathies, cardiovascular diseases, metabolic disorders, neuropathies, renal dysfunction etc. Many of these pathologies present S&G

specificity. It is thus not surprising that the sexual dimorphism of mitochondria takes part in the sex specificity of aging and of important pathologies like CVD [34].

Female rats live longer than male rats. An inverse relationship is observed between longevity and oxidative stress that involves mitochondria. Mitochondria of female liver and brain produce less H_2O_2 and have much more antioxidant defenses like MnSOD, glutathione peroxidase, and reduced glutathione, suggesting a protective role of mitochondria in females [45]. Cardiac mouse mitochondria have the same oxidative capacity in male and female hearts but the female ones produce less reactive oxygen species (ROS) whether on normal or high fat diet [46], 45].

Interestingly female hearts exhibit less injury following ischemia/reperfusion (I/R) induced by *in vivo* left coronary artery ligation. They have decreased infarct size and better recovery of cardiac function. This female protection is accompanied by a lower mitochondrial production of H_2O_2 attributed to increased phosphorylation and activity of the detoxifying enzyme aldehyde dehydrogenase-2 [47]. Another important specificity of female cardiac mitochondria is their participation in calcium homeostasis. Female mitochondria have lower net calcium uptake [48] and less calcium-induced mitochondrial swelling [49] than their male counterpart rendering them less prone to undergo opening of the permeability transition pore and apoptosis. The lower Ca^{2+} uptake rates and the maintenance of mitochondrial membrane potential under conditions of high Ca^{2+} in female rat cardiac mitochondria have been attributed to modulation of the calcium uniporter [48].

Thus the better resistance of female cardiomyocytes to ischemia/reperfusion injury, heart failure or cardiotoxicity could be the combination of maintained mitochondrial mass, decreased calcium uptake, decreased ROS production and increased anti-oxidant defenses.

Sex/Gender studies in clinical and basic science

The few examples presented in this review were aimed at presenting the different facets of S&G differences, in health and disease. Although protected in their reproductive period, women still suffer from inadequacy of care, lower effectiveness of therapies and poorer outcome. Despite the increase in indubitable reported facts, S&G differences are still poorly acknowledged and taken into account in medical practice. Guidelines continue to

ignore the distinction between men and women in manifestation and treatment of diseases. The awareness is slow but anyway progressive although largely insufficient. What are the reasons for these facts?

One important factor is the lack of knowledge of the normal female pathophysiology. As reported by previous authors, in biomedical studies males still dominate [50] the research field. Among research studies utilizing male and/or female animals from published journals with specified biomedical subfield in 2009, 8 over 10 biological disciplines presented a male bias which was more pronounced in neurosciences (M/F ratio: 5.5), physiology (M/F 3.7) and pharmacology (M/F 5/1) [51]. A substantial number of studies do not even mention the sex of animals at all. Such a sex bias has been also reported for surgical research, showing for female prevalent diseases, 44% did not specify the sex of animals studied and among those that specified the sex, only 12% studied female animals [52]. These male biases explain the lack of knowledge of female biology and physiology.

Concerning studies using cells, 75% of articles among a random selection from AJP-Cell Physiology in 2013 did not mention the sex of the cell lines; and yet, nearly all biochemical, signaling, and trafficking pathways elucidated for mammalian cells have been obtained from studies using cell lines [53]. However, the sex of cells matters for example in cell therapy. Muscle-derived stem cells transplanted into dystrophic (mdx) mice efficiently regenerate skeletal muscle. A good example of the importance of cell sex origin is the observation that muscle tissue regeneration was more efficient when the origin of cells was female and this was independent on the sex of the recipient [54]. Thus cell sex is a variable that considerably influences stem cell regeneration abilities, whatever the sex of the recipient [54]. It becomes apparent that conclusions derived from such studies ignoring sex may be specific to only one sex, *i.e.* the male sex.

Concerning clinical trials, enrollment of women has increased over time but remains low relative to their overall representation in patient populations. The percentage of women in randomized clinical trials is in general much lower for any pathology than the percentage of women among population having the disease or the percentage of women among deaths attributable to a specific disease [55]. This shows that the level of women representation is not adequate to ensure evidence-based sex-specific recommendations. The low number of women in clinical trial precludes that appropriate and statistically sound conclusions can be

made in analyses by sex. It is not surprising in this case that therapeutics is not as efficient in women as in men.

Conclusion

A large amount of experimental as well as clinical studies converges to confirm the existence of S&G differences in the physiology and pathophysiology of cardiovascular diseases. Despite this evidence, gender differences are still poorly taken into account in the majority of the experimental and clinical researches. The mechanisms are still poorly understood, largely because of a lack of experimental and clinical studies specifically devoted to the understanding of female sex and gender. Apart from comparisons between males and females, there is a crucial need for studying the female physiology and woman pathology. In particular the biological step that constitutes menopause in women appears to be the border between “female protection” and “female susceptibility” to cardiovascular diseases and needs to be deciphered further (Figure 1). This would help to understand human physiology in general and to properly take care of female and male patients. This is warranted to enter the era of personalized medicine and to develop personalized therapeutic strategies.

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Conflicts of Interest

No potential conflicts of interest to be disclosed.

List of abbreviations

ACE : angiotensin converting enzyme

AF: atrial fibrillation

AMPK: adenosine monophosphate-activated protein kinase

AR: androgen receptor

CHD: coronary heart disease

CREB: cyclic nucleotide regulatory element binding-protein

CVD : cardiovascular disease

CYP3A: Cytochrome P450 3A4

DHT: dihydrotestosterone

DNA: deoxyribonucleic acid

E2: estradiol

ER: estrogen receptor

ERK1/2: extracellular signal-regulated kinase 1 and 2

ERRα: estrogen-related receptor-alpha

GSK3β: glycogen synthase kinase3β

GWAS: genome wide association studies

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

I/R: ischemia/reperfusion

JNK: c-Jun-NH2-terminal protein kinase

MAPK: mitogen-activated protein kinase

mTOR: mechanistic target of rapamycin

NRFs: nuclear respiratory factors

PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator-1alpha

PI3K: phosphoinositide 3-kinase

PKB: protein kinase B

PPARα: peroxisome proliferator-activated receptor alpha

PR: progesterone receptor

RNA: ribonucleic acid

ROS: reactive oxygen species

S&G : sex and gender differences

SHR: spontaneously hypertensive rats

SOD: superoxide dismutase

T2DM: type 2 diabetes mellitus

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Table 1. Cardiovascular diseases in men and women

Cardiovascular diseases	Men	Women
Coronary heart disease	More frequent	Frequency increases with age
Heart failure	More frequent Develop at younger age	Develop later
LV systolic dysfunction	Severity is higher	
Heart failure	More HFrEF	More HFpEF
Cardiac remodeling	More fibrosis More dilatation	Concentric hypertrophy
Ischemic heart disease	More frequent	Develops 7-10 years later
Arrhythmias		
Brugada syndrome	Increased prevalence	
Long QT syndrome		Increased prevalence
Atrial fibrillation	Higher incidence and prevalence	Higher risk factor for CVD and death
Diabetic cardiomyopathy		Increased risk of CVD

For references see text.

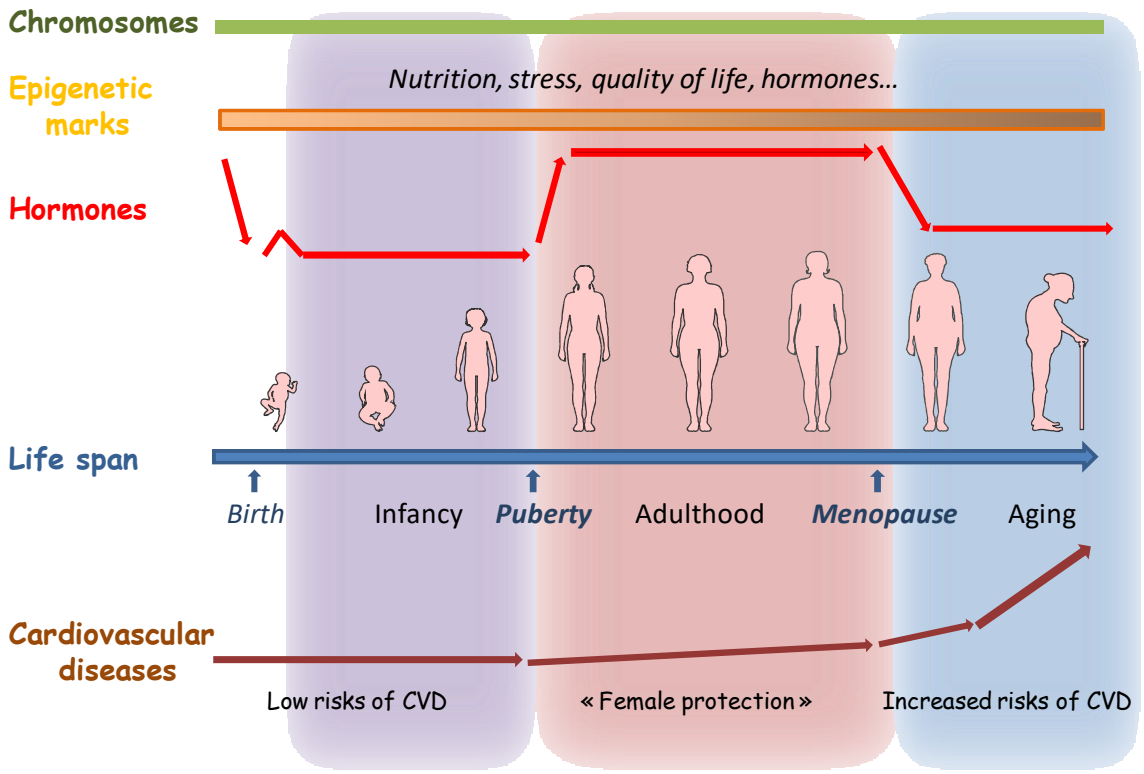

Figure 1. **Woman life and cardiovascular health are temporally determined**. Chromosomes, epigenetic marks and hormonal status determine woman specificity. These factors are inter-related and influence the health status throughout life. The woman's life includes three main periods that differ in cardiovascular risks.

Graphical abstract