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Research Paper

Teaching gender medicine can enhance the quality of healthcare

Anna Vittoria Mattioli [a,*], Valentina Bucciarelli [b], Sabina Gallina [c]

[a] University of Bologna- Alma Mater Studiorum, Bologna, Italy
[b] Cardiovascular Sciences Department-Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy
[c] Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

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ABSTRACT

Teaching gender and sex differences is fundamental in medical classes because it has a strong impact in reducing disparity in treatment, in defining effective and personalized therapies that respect the different physiology and pathophysiology of women. Furthermore, it is the prerequisite for the pharmacoequity.

1. Introduction

Gender medicine is indeed a crucial field that recognizes the impact of biological sex and gender identity on health and healthcare [1]. By incorporating the analysis of sex and gender differences into medical education, healthcare providers can gain a more comprehensive understanding of the diverse health needs and risks associated with different sexes and genders [2–5]. Advancing gender medicine through education and training is crucial for enhancing the quality of healthcare. It not only benefits individual patients by addressing their unique health needs but also contributes to a more inclusive and informed healthcare system overall.

What are the main gaps in knowledge that reduce the effectiveness of gender cardiovascular medicine and that could be addressed by adequate training?

Although there is a good knowledge of the differences between the sexes in terms of anatomy and physiology, there is still a gap in knowledge of the cardiovascular pathophysiology of atherosclerosis and vascular response [2–5].

An adequate therapeutic approach must know that most clinical studies have been conducted in males and that women are underrepresented [2–5].

Knowledge of these gaps is a good starting point for solving them but above all it can determine an accurate evaluation of cardiovascular disease in women and a good risk stratification.

2. Cardiovascular risk factors and diseases: Differences between the sexes

It is known that there are important differences between the sexes in cardiovascular anatomy and physiology. Several underlying mechanisms contribute to sex disparities in cardiac remodeling and response to stressor, including alterations in calcium signaling, electrophysiology, metabolism, inflammation, fibrosis, apoptosis, and sex hormone regulation [6–8]. Innate genetic variations stemming from X and Y chromosomes play a role. Sex-specific differences extend to the cellular makeup of the heart, with distinct genetic enrichment patterns and functions observed between male and female cardiac cell types [8].

For a long time, females were frequently regarded as essentially smaller versions of males; however, it's now evident that this is not true. Various sex-dependent disparities have been identified concerning fundamental cardiovascular structure and function. Men typically have larger hearts both in terms of absolute size and relative to body size, thicker ventricular walls and chamber dimensions compared to women, resulting in higher stroke volume in males. Despite this, cardiac output is comparable between the sexes, primarily due to increased heart rates in females induced by hormonal factors [9,10]. Additionally, the shape of the heart may differ slightly between men and women, with women often having a more rounded heart shape [11].

Differences in blood pressure have been observed between the sexes and crucial factors appear to be both body weight and sex hormones, but not heart mass. Males show higher systolic and diastolic blood pressures than females [12,13]. The contribution of the X and Y chromosomes to blood pressure variations has recently been highlighted. Preclinical

* Corresponding author at: University of Bologna-Alma Mater Studiorum, Bologna Italy.
E-mail address: annavittoria.mattioli@unimore.it (A.V. Mattioli).

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studies demonstrated that angiotensin II-mediated increases in blood pressure were more pronounced in XX mice [14]. Additionally, women's vessels may exhibit greater vascular reactivity and responsiveness to vasoactive substances. This effect is mediated by hormone particularly estrogens. Estrogens promote vasodilation, reduce inflammation, and improve lipid metabolism [15–18].

Women may experience different symptoms of heart disease compared to men. While chest pain is a common symptom in both genders, women may also present with atypical symptoms such as shortness of breath, fatigue, nausea, and back or jaw pain [19,20].

Women are exposed to CV risk factors like men, but female-specific risk factors have been identified and play a role in the development of cardiovascular diseases [21]. Women specific risk factors include pregnancy-related complications (such as hypertensive disorders and gestational diabetes), the use of oral contraceptives, menopause and hormone replacement therapy, stress and depression. These factors contribute to an increased risk of acute coronary syndromes and cardiovascular events as women age [21–23]. As menopause sets in, women gradually approach the CVD risk levels observed in men, and in some cases, may even exceed them [24].

In addition to its established significance in bone health and muscle function, vitamin D has attracted growing interest concerning cardiovascular well-being. Vitamin D plays a crucial role in calcium absorption and bone metabolism [25]. Inadequate vitamin D levels increase the risk of osteoporosis and bone fractures, especially in postmenopausal women who are already at risk due to declining estrogen levels [26,27].

Several observational studies have explored the relationship between vitamin D levels and cardiovascular diseases (CVDs). While findings exhibit some variability, they consistently underscore a negative correlation between vitamin D status and the likelihood of developing CVDs [28]. A recent study analyzed data from the NHANES (2001–2018) to examine associations between serum vitamin D and all-cause mortality, cardiovascular mortality, and cancer mortality in 8865 postmenopausal women. Authors found that higher serum vitamin D levels were associated with a decreased mortality risk from all-cause, CVD and cancer [29]. Emerging research suggests a potential link between vitamin D deficiency and cardiovascular disease risk factors, such as hypertension, dyslipidemia, and insulin resistance, which are prevalent in women [30–32].

Indeed, research has consistently shown that men and women may respond differently to stress, and the COVID-19 pandemic has brought attention to these gender-specific responses. The differences go beyond just anatomy and physiology, extending to psychological and behavioral aspects [21,23,33].

Men and women can exhibit variations in the physiological response to stress. For instance, the release of stress hormones, such as cortisol, may differ between genders. Women often show a stronger physiological response to stress, which could be influenced by hormonal fluctuations related to the menstrual cycle and pregnancy [33–36].

Similarly, the psychological response to stress can vary. Studies suggest that women may be more prone to experiencing symptoms of anxiety and depression in response to stressors. Social and cultural factors, as well as differences in coping mechanisms, can contribute to these variations [37].

Notably, instances where women exhibit heightened susceptibility to CVD often coincide with the decline in estrogen associated with menopause or periods of emotional stress [38].

The recent COVID-19 pandemic has highlighted disparities in how stress affects men and women. Women have reported higher levels of stress, anxiety, and depressive symptoms during the pandemic. Women, particularly those in caregiving roles, have faced increased challenges due to the pandemic's impact on childcare, remote learning, and healthcare responsibilities. Economic stressors, such as job loss or financial strain, have also affected women disproportionately in certain sectors [38–40]. Tailored mental health strategies that consider the unique needs and challenges faced by both men and women are needed.

Furthermore, sex disparities in the occurrence, manifestation, and consequences of cardiovascular disease (CVD) are well-documented (Fig. 1).

Compared to men, premenopausal women exhibit a decreased risk of developing obstructive coronary heart disease, myocardial infarction, genetic cardiomyopathies such as hypertrophic cardiomyopathy and dilated cardiomyopathy, Long Covid Syndrome and heart failure with reduced ejection fraction (HFrEF) [19,41–44]. Women are more likely to developing heart failure with preserved ejection fraction and diastolic dysfunction, whereas men are more inclined towards heart failure with reduced ejection fraction and systolic dysfunction [44–46].

This discrepancy likely stems from the tendency for men to develop macrovascular dysfunction while women tend to experience microvascular dysfunction.

Additionally, women are more susceptible to spontaneous coronary artery dissection, which can affect both pre- and post-menopausal women, occurring after episodes of stress, both emotional and physical and presenting symptoms similar to MI [47,48].

Postmenopausal women are at an increased risk of developing Takotsubo cardiomyopathy, often triggered by emotional stress leading to elevated stress hormone levels and subsequent cardiovascular dysfunction [49].

The recognition of these differences is essential for accurate diagnosis and the development of effective treatment plans. For example, understanding that women are exposed to specific risk factors and that some diseases, such as autoimmune diseases, increase cardiovascular risk, allows us to adopt a different diagnostic approach in women and men. It also allows you to adequately stratify cardiovascular risk in women based on specific cardiovascular risk factors [11,21,50].

Despite the importance of gender medicine, there's a need for a significant shift in the clinical approach, which includes proper training for healthcare professionals. Many existing clinical guidelines may only marginally address sex and gender differences, indicating a gap that needs to be filled [51,52].

This shift also has broader implications for research, as studies that consider sex and gender differences can lead to more personalized and effective medical interventions.

3. Response to drugs: Sex-related differences

Although the concept of differences between the sexes in cardiovascular anatomy and physiology has been acquired, little is applied in clinical studies. Historically, medical research has often focused on male subjects, assuming that findings and treatments would be equally effective for both sexes [53,54]. However, this approach neglects the fact that women may experience different symptoms and respond differently to treatments than men [53–55].

In clinical trials for heart failure, women make up about a quarter of patients with heart failure with reduced ejection fraction (HFrEF) and more than half of those with heart failure with preserved ejection fraction (HFpEF). However, epidemiological data indicate a significantly higher proportion of women affected by the disease in real-world settings [56].

It is becoming increasingly apparent that many of these treatment regimens may not be optimal for women. Recent findings suggest that females may require a reduced dose of Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers to effectively lower all-cause mortality in heart failure settings [57].

Determining medication dosage for women with heart failure (HF) can be further complicated due to the higher prevalence of heart failure with preserved ejection fraction (HFpEF) among women. Effective treatments and dosage guidelines for HFpEF are often lacking [56,57].

Sex disparities are also evident concerning the efficacy and survival rates of non-pharmacological heart failure treatments, such as heart transplantation and implantable defibrillators [58]. Research indicates disparities in arrhythmic risk and complications related to implantable

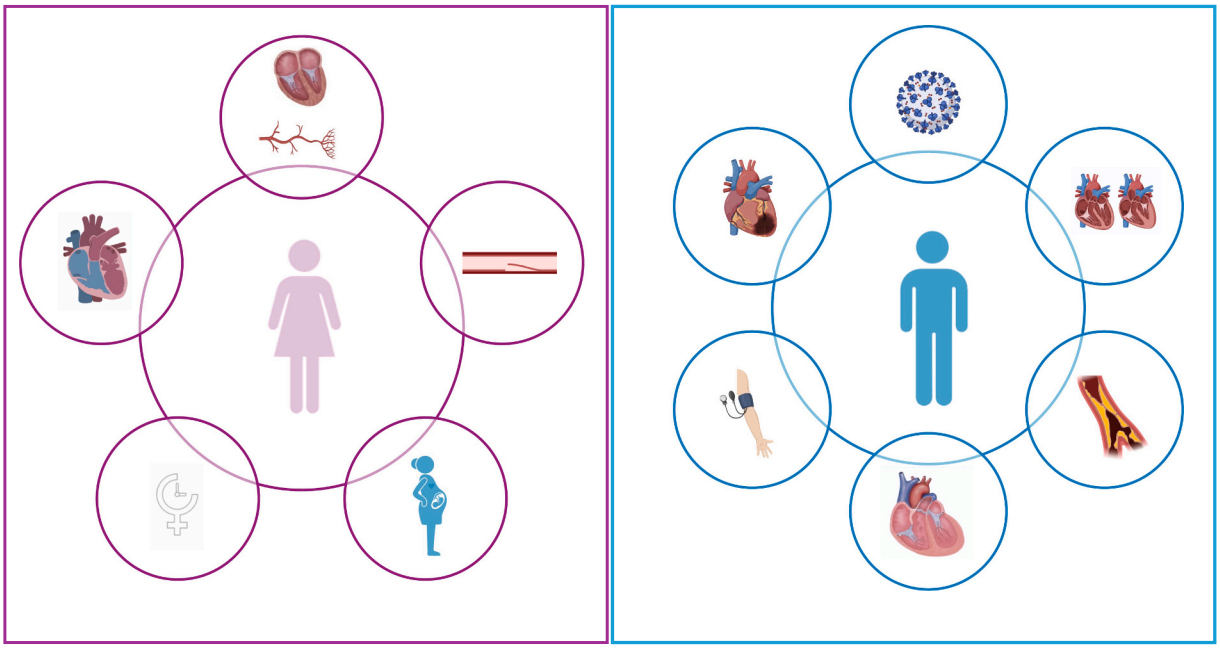

Fig. 1. Differences in CVD according to sex categories. Women (left) are more prone to the development of CVD associated with gender-specific risk factors, e.g. hormonal status and emotional triggers (namely, pregnancy and menopause-related CVD, takotsubo syndrome); furthermore, they generally experience coronary events related to microvascular dysfunction and spontaneous coronary dissection. On the other hand, men (right) are more prone to the development of coronary artery disease, macrovascular dysfunction, heart failure with reduced ejection fraction; recently, it has been demonstrated that they are likely to experience more severe long-COVID complications as compared to female population.

cardioverter-defibrillator (ICD) use between sexes [58]. Despite this, there remains a risk of sudden death in women with heart failure (HF) and reduced left ventricular ejection fraction (LVEF) that may be mitigated by ICD implantation. However, careful and personalized assessment is essential to identify patients who would derive the greatest benefit from this treatment [58].

These observations underscore the need for additional optimization in the treatment of CVD in females.

Furthermore, sex-dependent differences in the pharmacokinetics of calcium channel blockers have been observed. In women, the oral clearance of verapamil and amlodipine is accelerated compared to men, attributed to the higher activity of CYP3A4 and lower activity of P-gp [59].

Recently, several studies have revealed differences in platelet reactivity and clinical treatment outcomes, suggesting that antiplatelet therapy in women may not be as beneficial as in men [60].

Disparities depend on sex, defined as biological and physiological characteristics but also on gender – the social construct that reflects cultural norms. Lifestyle, socio-economic class and many other external factors have a crucial impact on CVD and its pathophysiology [61–63].

The sex differences in platelet reactivity observed between individuals with metabolic diseases and cardiovascular diseases (CVD) may result from the different pathophysiological response. Women show favorable characteristics in atherosclerotic plaques, including lower total plaque volume, lower plaque burden, and smaller volumes of fibrous tissue, fibro-adipose tissue, necrotic core [64].

In contrast, men more frequently develop vulnerable plaques and obstructive structural lesions in the epicardial coronary arteries. Furthermore, endothelial dysfunction can overstimulate platelets in men, leading to reduced platelet reactivity [65].

Comorbidities such as diabetes mellitus (DM), which promotes platelet aggregation, are more prevalent in women than men with CVD, potentially contributing to greater platelet reactivity in women [66]. Additionally, women tend to show increased platelet reactivity during treatment with antiplatelet agents. However, it remains uncertain whether this is due to disparities in baseline platelet reactivity or a weaker response to therapy [67].

The historical focus on male physiology in medical research has indeed contributed to a significant gap in knowledge regarding how medical treatments and interventions may affect women differently [68]. For many years, research studies primarily involved male subjects, leading to an incomplete understanding of the nuances of female physiology and health [54,55,68].

This gender bias in research has had far-reaching consequences, as it can result in medical practices and treatments that are less effective or appropriate for women. Biological differences, hormonal fluctuations, and other factors unique to female physiology can influence the efficacy and safety of medical interventions, making it crucial to include both sexes in research studies [33,34].

In the context of cardiovascular disease, managing therapy requires careful consideration of sex-specific differences in drug bioavailability and effects. Studies have shown that sex differences exist in drug bioavailability, with women often having faster absorption rates for drugs than men. This difference can be attributed to factors such as body composition, hormones, and other variables [69,70].

The variation in drug bioavailability can have significant implications for dosage recommendations. Women may require higher doses of certain drugs to achieve the same therapeutic effect as men, or conversely, lower doses to avoid side effects [70–73].

4. Pharmacoequity and underrepresentation of women in clinical trial

"Pharmacoequity" is a term, introduced first by Amin and coworkers, that emphasizes the critical need for ensuring equal access to high-quality, guideline-based therapies for treating medical conditions, irrespective of various demographic factors [74]. The term underscores the importance of eliminating disparities in access to medications and healthcare interventions among different populations. These disparities may be related to factors such as gender, race, ethnicity, age, rurality (urban or rural residence), or socioeconomic status [74].

The concept of pharmacoequity aligns with broader efforts to

promote health equity and reduce healthcare disparities. It recognizes that certain groups of individuals may face barriers to accessing appropriate and effective treatments due to systemic and structural factors. These barriers can contribute to variations in health outcomes and exacerbate existing health disparities [75,76].

Key considerations within the realm of pharmacoequity may include accessibility and health system policies. Addressing issues related to the availability and affordability of medications to ensure that patients can access necessary treatments without facing undue financial burdens and advocating for policies that prioritize equity in healthcare delivery, including pharmaceutical access, and working to eliminate systemic barriers.

In terms of training healthcare personnel, it is mandatory to acquire skills to recognize and address factors that can influence individuals' healthcare decisions, preferences and adherence to treatment plans.

A key point of pharmacoequity is determined by guidelines [77,78]. The guidelines are based on clinical evidence studies, however it is known that the percentage of women enrolled in the studies is much lower than the percentage of men. All patients, regardless of demographic factors, should receive treatments consistent with established medical guidelines and evidence-based practices. However, the underrepresentation of women constitutes a gap in pharmacoequity [77,78].

Since 1993, the National Institutes of Health (NIH) has introduced various initiatives and mandates aimed at incorporating women into research [3,5]. These efforts focus on improving reproducibility by promoting rigor and transparency. Researchers are now required to consider sex as a biological variable in the design, analysis, and reporting of both human and animal studies. Similar requirements have been implemented by other government-based international research funding agencies, such as the Canadian Institutes of Health (CIHR) and the European Commission (EC), which mandate the integration of sex and gender into biomedical research [79,81].

Current guidelines are based on data derived primarily from men, as women are generally underrepresented in trials [52,79–82].

This underrepresentation is influenced by historical biases, gender stereotypes, and concerns related to potential risks and side effects [22,54,55].

There are various reasons why women may be less likely to volunteer for clinical trials, including concerns about potential risks and side effects. This hesitancy to participate in research studies can lead to a lack of diverse data on how medical treatments specifically impact women [82,80].

The increased inclusion of women in clinical trials over the last two decades is a positive development, attributed in part to the implementation of laws, regulations, and guidance aimed at addressing gender disparities. However, despite these improvements, significant gaps persist in the representation of women in clinical research [81,82].

These gaps can be observed when trials are analyzed based on therapeutic area, race and ethnicity, age, and geographical location outside of the United States. The underrepresentation of women in clinical trials is a multifaceted issue, and various factors contribute to this disparity [83,84].

The data from 2015 to 2016 highlight notable disparities in the representation of women in clinical trials, both within the United States and internationally. While the overall percentage of women participants was essentially equivalent to men in the U.S. (49 % women, 51 % men), there were significant variations outside the U.S., with women comprising only 40 % of the overall population and showing wide variation by country (ranging from 13 % to 100 %) [83,85,86].

The disparities become even more pronounced when evaluating by therapeutic area, especially in the context of cardiovascular disease (CVD). Drug Trials Snapshots and other reports consistently indicate an underrepresentation of women in clinical trials focused on cardiovascular disease across all geographies. This is a concerning trend given that CVD is a major health concern for both men and women, and understanding how treatments affect both genders is crucial for developing effective interventions [85–87].

The underrepresentation of women in cardiovascular trials raises important questions about the generalizability of study findings to the broader population. It also underscores the need for targeted efforts to address these disparities and promote more inclusive research practices.

The observed variations in the representation of women in clinical trials from 2005 to 2015 highlight the complexity and heterogeneity of participation across different therapeutic areas [86].

Specifically, during this period women were adequately represented in trials related to hypertension and atrial fibrillation. This suggests a relatively balanced inclusion of both genders in studies addressing these conditions. Similarly, women were significantly underrepresented in trials related to heart failure and ischemic heart disease. This underrepresentation is concerning given that heart failure and ischemic heart disease affect both men and women, and understanding gender-specific responses to treatments is crucial [87,88]. The underrepresentation of women in trials related to heart failure and ischemic heart disease may have implications for the generalizability of study results to female patients, potentially leading to suboptimal and less effective healthcare practices for women with these conditions [89,90].

On contrary, women were overrepresented in trials focused on pulmonary arterial hypertension. The reasons for this overrepresentation could be multifactorial, including the prevalence of the condition among women or deliberate efforts to include a diverse participant pool.

These findings underscore the need for a more nuanced approach to clinical trial design and recruitment to ensure adequate representation of diverse populations [7,40].

Geographical and cultural differences can impact the opportunity for women to participate in clinical trials [88–90]. The willingness or ability to volunteer for research endeavors may vary based on cultural norms, accessibility to healthcare, and awareness of clinical trial opportunities [90]. Addressing these challenges is not only crucial for public health but also for social justice, recognizing the importance of equitable access to medical research opportunities.

Ensuring diverse representation in clinical trials is essential for several reasons. Firstly, it allows researchers to understand how medical treatments and interventions may impact different demographic groups, including women, leading to more effective and personalized healthcare practices. Secondly, it contributes to the generalizability of research findings, ensuring that the results are applicable to a broader population.

Efforts have been made to address these disparities and enhance the representation of women in clinical trials. Recognizing the importance of including diverse populations in research studies, regulatory agencies and researchers have worked towards ensuring greater gender balance in clinical trial participation.

Several newer approaches have been suggested to improve the enrollment of women in clinical trials including gender-specific recruitment strategies. Tailored recruitment strategies that specifically target women, such as outreach through women's health clinics, social media campaigns, and community organizations, can help increase participation. Similarly, collaboration with patient advocacy groups focused on women's health issues can help raise awareness about clinical trials and encourage women to participate. Given that one of the reasons for the poor participation of women in clinical studies is the lack of time, it would be recommended to implement study designs that meet the specific needs and preferences of women, such as flexible scheduling, child support and transportation assistance. Involving women in the design and implementation of clinical trials ensures that their perspectives and preferences are taken into account, leading to more relevant and attractive studies. To date, there are very few women present as leaders in study design [91].

Between 2014 and 2018, over half of cardiovascular trials published in three high-impact factor journals did not include women investigators on their executive committees [92]. Furthermore, no more than 10 % of

publications stemming from these trials were led by a woman investigator. The lack of representation of women is even more noticeable in leadership positions within CV clinical trials compared to U.S. academic cardiology (17 %) or cardiology fellowship programs (25 %) [93]. This disparity is particularly prominent in procedural CV specialties, highlighting the significant gender gap in procedural subspecialties [94].

5. How teaching gender medicine can help reduce the gender gap

Teaching gender medicine can play a crucial role in reducing the gender gap in healthcare in several ways: 1. increased awareness; 2. improved diagnosis and treatment; 3. reduced health disparities; 4. advanced of medical research by encouraging the inclusion of diverse populations in studies and clinical trials; 5. promoting gender equity in healthcare.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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