Supplement submission

Italian Federation of Cardiology

Cardiovascular prevention in women: an update by the Italian Society of Cardiology working group on ‘Prevention, hypertension and peripheral disease’

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The recent pandemic has substantially changed the approach to the prevention of cardiovascular diseases in women. Women have been significantly impacted by the changes that occurred during the pandemic and the quarantine adopted to prevent the spread of the disease. Changes involved prevention both through the reduction of visits and preventive screening and through social and economic changes. It is necessary to adopt new cardiovascular prevention approaches focused on returning to healthy lifestyles, reducing stress and depression also using modern tools such as telemedicine, mobile phone applications and the web. These tools convey messages in a persuasive way especially in young and adult women. There is less impact of these new tools on older women towards whom it is important to adopt a more traditional approach. This review focuses on the new approach to cardiovascular prevention in women in light of the lifestyle changes recorded during the pandemic and which led to an increase in obesity examines the effects on the cardiovascular system induced by stress and depression and analyses the new high blood pressure guidelines and indications that are specific to women.

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The recent pandemic has substantially changed the approach to the prevention of cardiovascular diseases. Major factors affecting cardiovascular prevention include not only the inability to offer routine clinic visits and to enforce preventive actions during the years of the pandemic but also the changes that have occurred in the exposure to risk factors. To prevent, diagnose and treat cardiovascular disease (CVD) in women, it is essential to collect precise and updated data at regional and country levels.[1]

The recent guidelines endorsed by the European Society of Cardiology on cardiovascular prevention recognize the importance of integrating sex, gender and gender identity considerations into the risk assessment and clinical management of individuals and populations.[2] According to the WHO, sex ‘refers to the different biological and physiological characteristics of females, males, and intersex persons, such as chromosomes, hormones and reproductive organs’.[3] This is to be distinguished from gender, which ‘refers to the characteristics of women, men, girls and boys that are socially constructed. This includes norms, behaviours and roles associated with being a woman, man, girl or boy, as well as relationships with each other. As a social construct, gender varies from society to society and can change over time’.[3] The Global Health 50/50 definition further states that gender refers ‘to the socially constructed norms that impose and determine roles, relationships, and positional power for all people across their lifetime’.[4]

Healthy lifestyle and adherence to guideline-based care can effectively prevent CVD.[5,6] However, several known

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factors widen gender disparities in the prevention of CVD: adoption of unhealthy lifestyles by women, underestimation of female risk categorization and the inability to identify early and treat properly CVD in women.[7] Women tend to have a longer life expectancy; however, while living longer, they generally have worse health status and higher rates of chronic diseases than men.[8] As nutrition is directly related to a higher risk of developing chronic disease, it is essential to understand how this modifiable factor affects health status.

The aim of the present manuscript is to update the previously published narrative review on cardiovascular prevention in women, also in view of the SARS-COV-2 pandemic.[9]

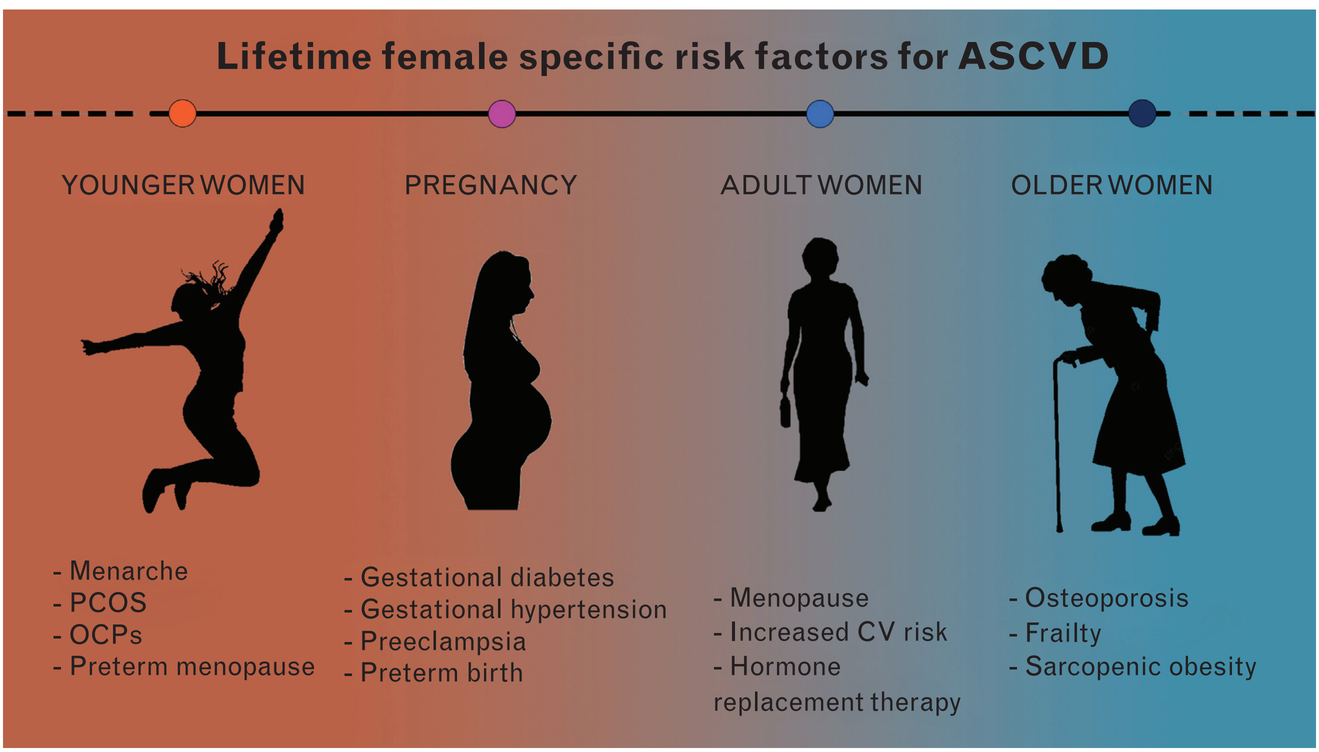
Traditional cardiovascular risk factors in women: the central role of obesity

It is increasingly accepted that several genetic variations and biological differences influence cardiovascular risk and the pathogenesis of CVD in women.[10,11] Specific sex differences in physiology and pathophysiology could be related to both endogenous and exogenous reproductive hormones, although contemporary data question the protective role of synthetic estrogens.[12] It is controversial whether exogenous oestrogen therapy used for contraception and menopause lowers the CVD burden.[13,14]

In recent years, various specific risk factors for women have been identified (Fig. 1) and several studies have investigated their impact on the development of CVD in women. Increasing amounts of evidence underline that traditional and well known risk factors such as dyslipidaemia, hypertension and diabetes exert different effects in women than men.[9,15] Obesity is a modifiable risk factor that represents a central underlying disease of many cardiovascular risk factors: sedentary behaviour, fat- and sugar-rich diet, reduced physical activity, prediabetes and hypertension. Globally, obesity is more prevalent in women than in men,[16] although this varies by country, and, in the UK and USA, it is more prevalent in men.[17,18]

Adipose tissue is an active organ that dynamically reacts to the metabolic state of the body and changes over the course of life, especially in women in response to hormonal changes. Whole body AT can be divided into two main deposits – subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) – and several minor AT deposits (epicardial, perivascular, perirenal, intraosseous, intraarticular and so on). Visceral obesity, which is mainly present in the mesentery and omentum, contains a large number of metabolically active and insulin-resistant adipocytes.[19,20] In the presence of long-term overweight and obesity, immune cells initially react with changes in the expression profile of adipocyte hypertrophy (typically by

Fig. 1



Cardiovascular risk factors in women during their lifetime.

increasing leptin, TNFα, IL6 and decreasing adiponectin production) to counteract inflammation; with the prolongation of the state of obesity, the original regulatory reactions and the immune cells themselves, under the influence of cytokines and chemokines produced by the adipocytes, are overexpressed and begin to contribute to the inflammatory environment, creating a vicious circle.[21]

In premenopause and menopause, there is a significant increase in total and intra-abdominal fat mass, which is associated with the so-called 'sarcopenic obesity' linked to the decrease in muscle mass.[22–25] These two conditions of excess fat accumulation are related to several chronic diseases, including CVD, diabetes, hypertension and some types of cancer.[26,27]

A strong association between obesity and invasive breast cancer has been described; the relationship is mediated by an increase in oestrogen production by adipocytes, inflammation and insulin resistance in peripheral tissues.[28] Therefore, the development of weight management strategies is a major public health priority in the women with obesity also in order to reduce the risk of breast cancer.[28–30]

Several diets have been tested to facilitate weight reduction in women, starting from the basic knowledge that underlines how the absorption and bioavailability of food is different in women and men also due to the effect of oestrogens on the intestinal microbiota.[31,32]

The gut microbiota, also referred to as the hidden organ, or the organ within an organ, includes tens of trillions of microorganisms resident in the human intestine, which are important for metabolic health of the same organs that support them. Its role in the development of metabolic diseases, diabetes and cardiovascular diseases is well supported by studies in both humans and animals.[32]

Karlsson *et al.*[33] reported compositional changes linked with T2D in a Scandinavian cohort of postmenopausal women. Authors characterized the faecal metagenome of 145 European women with normal, impaired or diabetic glucose control and observed compositional and functional alterations in the metagenomes of women with T2D. Interestingly, when they applied their model to a Chinese cohort, they found that the discriminant metagenomic markers for T2D differ between European and Chinese individuals.[33,34]

The important and reciprocal impact of sex hormones on gut microbiota has been identified as 'microgenderome'. This refers to sex-specific characteristics of microbiota and to the different interaction with sex hormones and immune systems.[35]

Diet and diet components are the dominant contributing factors influencing gut microbial composition.[32,36] However, it is very difficult to determine the extent to which dietary factors affect gut microbiota composition, aside from genetic factors.

Polyphenol is an umbrella term that includes several food compounds containing several phenolic groups that exert an antioxidant effect.[37] It is abundant in vegetables, fruits, plants and nuts, and more than 8000 types have been identified.[38–40] Polyphenols have antioxidant and anti-inflammatory effects, promote angiogenesis, improve vascular endothelial function, inhibit platelet aggregation and reduce insulin resistance. Several studies have reported its favourable effects in the prevention and treatment of cancer, hypertension, CVD, and type II diabetes.[38,40] Less than 10% of the total polyphenol intake is absorbed in the small intestine; the remaining accumulates in the large intestine and, by the action of intestinal microbiota enzymes, is transformed into smaller, low molecular weight phenolic metabolites, which can then be absorbed in the body.[41]

The recent DIRECT-PLUS (Dietary Intervention Randomized Controlled Trial PoLyphenols UnproceSsed) weight-loss trial evaluated 294 participants randomized to healthy dietary guidelines (HDG), Mediterranean Diet (MED) or green-MED diets, all combined with physical activity. The MED groups consumed 28 g/day of walnuts (+ 440 mg/day polyphenols). The green-MED group further consumed green tea (3–4 cups/day) and Wolffia globosa (duckweed strain) plant green shakes (100 g frozen cubes/day) (+ 800 mg/day polyphenols) and reduced red meat intake. Both MED diets reached similar moderate weight (MED: −2.7%, green-MED: −3.9%) and waist circumference (MED: −4.7%, green-MED: −5.7%) reduction, whereas the green-MED dieters doubled the visceral adipose tissue loss (HDG: −4.2%, MED: −6.0%, green-MED: −14.1%; $P < 0.05$). These results suggested that the green-MED diet might be more effective in visceral adipose tissue reduction compared with traditional MED diet.[42] This reduction was associate with Wolffia globosa and walnut intake, decreased red meat consumption and improved serum folate. Moreover, the loss of visceral fat was also associated with a higher intake of green tea and dietary fibre.[43] Wolffia globosa is an aquatic plant rich in polyphenols and high-quality protein with beneficial effects on postprandial and fasting glycaemic control, known to provide bioavailable essential amino acids, iron and available B12 vitamin.[43] The beneficial effects of the green-MED diet on visceral adiposity loss might be explained by polyphenols.[42] In foods and beverages, phenolic compounds are mainly stored as a glycone or, mostly, as glycosidic conjugates. In the organism, they are widely metabolized due to enzymes that are differently expressed in men and women.[31,32]

The diffusion of technologies applied to monitoring and education in the field of prevention has proven to be of great importance in programmes aimed at reducing weight.[44,45] Medical nutrition treatment for weight loss using telemedicine may be effective for weight loss in adults; telemedicine interventions are recommended for at least 6 months and the importance of postintervention follow-up should be emphasized. The recent Chinese guidelines indicate an Evidence level B, strong recommendation, with 93.7% agreement.[46]

Telemedicine-driven medical nutritional weight loss can provide a variety of interventions for a wide range of populations.[44,46,47] Tarraga Marcos *et al.*[48] evaluated two groups of obese individuals: the study group received intervention in primary care centres with a telematic platform support and the control group was provided constantly with guidelines to lose weight and follow-up in primary care centres. Participants from both groups had a reduced BMI after 12 months; the test group had a mean weight loss of 4.3 kg, whereas the control group lost 1.8 kg.[48]

Several applications for mobile telephones have been developed to increase adherence to a healthy lifestyle. The use of apps will be of undoubted usefulness in young and adult individuals but are of little use in the elderly individual who needs a more traditional approach for education and prevention.[49]

Impact of the pandemic on socioeconomic status

The pandemic has generally led to negative changes in nutrition towards the intake of unhealthy calorie-dense foods rich in fats and sugars, driven psychologically: boredom, fear, stress induced by lockdowns and social isolation acted as triggers.[50–52]

As highlighted by the 'The Lancet women and cardiovascular disease Commission', [1] the pandemic has led to profound changes also in the socioeconomic status of minorities and frail individuals. Specifically, women, have been particularly severely hit by the pandemic on the one hand as a consequence of the economic crisis, which has affected sectors that predominantly involve women and, on the other hand, because of their social role as a caregiver of the fragile people of the family and children, according to an established stereotype of at least several countries.[52,53] Socioeconomic deprivation substantially contributed to the global burden of CVD in women.[1] Caring for the elderly requires a commitment of both time and effort. In many cases, women were forced to leave work to meet family needs.[54,55] Similarly, distance learning imposed a further burden, predominantly taken by women, to follow the children in regular learning activities.[56] These constraints have affected women's daily lives, leading to an additional burden to the already increased stress induced by the pandemic. Women reaction was varied, but, as highlighted by several reports in populations with different origins and cultures, the net result was a tendency towards the adoption of worse habits and lifestyle.[1,51,56]

Stress and depression

Stress may exert a different sex impact, as the strategies used to cope are generally different between men and women.[57,58] A representative example is the attitude to practice relaxation techniques such as yoga, which in the western world are practiced by a greater number of women than men.[59]A recent editorial underlines that, despite the stressful times, we would all like to be seen as exemplary human beings caring for our families, our jobs and our civic responsibilities.[59]

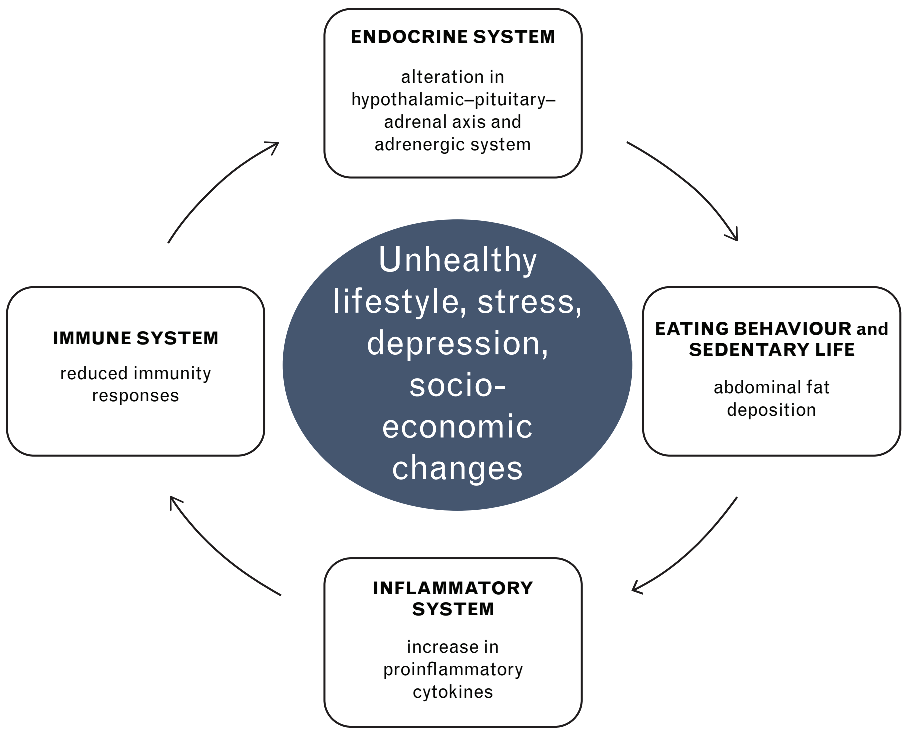
The author suggests 12 possible actions and activities that are possibly helpful in staying balanced during times of crisis.[59] The majority of these actions encourage the adoption of a healthy lifestyle. However, women are less likely to adopt a healthy lifestyle despite being aware of what good practice would be for a healthy life.[60,61]

A healthy lifestyle includes not only healthy eating and regular physical activity, but also good stress management and good sleep quality.[59,62] The WHO also supported relaxation techniques in its statement 'stay-physically-active-during-self-quarantine' published during the pandemic.[63] It is well known that scientific studies evaluating the effects of yoga and relaxation techniques on CVD are scarce and characterized by small groups of patients, not randomized and lack objective biomarkers for evaluating efficacy.[64] However, it has to be noticed that women are under-represented in clinical trials, especially in those evaluating cardiovascular end points, which might explain the lack of validated data. This point is of great importance, and it has to be addressed by the scientific world, which will have to change its approach to diseases taking into account the impact of gender differences. Moreover, stress impacts on women's habits. Stress profoundly influences the development of diseases, specifically CVD both with direct action through endothelial dysfunction and the development of atherosclerosis and with an indirect effect mediated by less favourable lifestyle habits in terms of diet, physical activity, sedentary behaviour and poor sleep quality.[65,66]

There is a different response between the sexes regarding stressful situations. These differences are influenced by psycho-social environmental factors, as reported during the recent pandemic, and change throughout the lifespan of women.[1,61] Women are more likely to cope with stress through emotional eating and are more prone to developing food cravings.[67–72]

The effects of stress on endothelial dysfunction have been studied. Stress acts by increasing system adrenergic tone, which determines a reduction in the production of nitric oxide and induces the secretion of pro-inflammatory cytokines.[73,74] Furthermore stress, depression and anxiety are associated with depression of the immune system[73–75] (Fig. 2).

Fig. 2



Effects of cardiovascular risk factors in women during their lifetime.

Stress plays an important role as a trigger of acute disease for individuals who already have atherosclerosis plaques. It correlates with an increased risk of negative clinical outcomes for those with preexisting CVD.[76] A recent meta-analysis showed that stress was as a predictor of CVD and mortality,[76] underlining that the link between stress and cardiovascular events is moderate in the general population, while strong links are found in high-risk groups experiencing anger, despair, bereavement and emotional instability.[77,78]

The same mechanisms are activated by depression. A recent review by Bucciarelli *et al.*[79] nicely described the effects of depression on cardiovascular risk burden. Depression is more prevalent in women than men, especially in later life, affecting nearly 20–25% of women who go through depression during their life.[80] Similarly, COVID-19 symptoms had been associated with depression; a recent study showed that 52.4% of the individuals who experienced acute coronavirus disease 2019 (COVID-19) symptoms subsequently met the criteria for moderate or greater symptoms of major depression.[81]

Women involved in healthcare (HCW identifies all people engaged in actions whose primary intent is to enhance health) were more likely to experience psychological stress and burnout compared with men involved in HCW. More specifically, young women HCWs and mid-career women HCWs were more likely to experience emotional and mental health issues due to COVID-19.[82,83]

Lockdowns imposed under COVID-19 reduced physical activity and favoured sedentary behaviour in both sexes. In addition, mental health has been both a motivation and a barrier to physical activity, and women who engaged in lower physical activity due to COVID-19 reported significantly lower mental health scores, and lower social, emotional and psychological well being.

Maintaining and improving participation in physical activity programmes have been shown to mitigate the mental health consequences of COVID-19.[84] Therefore, given the numerous physical and mental benefits of physical activity, public health strategies should include the creation and implementation of interventions that promote physical activity especially in women. Women are less focused on physical activity than on diets as a strategy for good health and longevity; however, the two lifestyle components perform synergistic actions and act favourably on cardiovascular prevention.[84–87]

Women and hypertension

Data are available that sex chromosomes and sex hormones differently influence blood pressure (BP) regulation, distribution of cardiovascular risk factors and comorbidities in women and men with essential arterial hypertension. There is clear evidence that the risk for cardiovascular disease increases at a lower BP level in women than in men, suggesting that sex-specific thresholds for diagnosis of hypertension may be considered. However, limited evidence is available on whether hypertension should be differently managed in women and men, including treatment goals and choice and dosages of antihypertensive drugs. A consensus paper coordinated by the Council on Hypertension of the European Society of Cardiology has recently provided a comprehensive overview of current knowledge on sex differences in essential hypertension, including BP development over the life course, development of hypertension, pathophysiologic mechanisms regulating BP, interaction of BP with cardiovascular risk factors and comorbidities, hypertension-mediated organ damage in the heart and the arteries, impact on incident cardiovascular disease and differences in the effect of antihypertensive treatment.[88] This study, while demonstrating how our knowledge about sex differences in hypertension has improved over the past decades, clearly emphasizes the need for having such an improved knowledge implemented in clinical practice. Indeed, better implementation of sex differences in BP development, regulation and cardiovascular risk factors in prevention tools might allow major progress in improving cardiovascular disease prevention in women. There is also a need for better communication of known sex differences in the efficacy and adverse effects of antihypertensive drugs to healthcare providers aimed at optimizing treatment and improving patient adherence to daily pill intake. The 2022 ESC consensus document also highlights areas in which more research is needed to further improve sex-specific prevention and management of hypertension.[88] There is in particular a need to fill some gaps in knowledge related to sex-specific incidence of hypertension-mediated organ damage, to sex-related BP threshold values and antihypertensive treatment targets, aimed at improving hypertension-related cardiovascular disease prevention.

Women and heart failure

Chronic heart failure represents the final evolution of many chronic CVDs and is often secondary to preexisting conditions, including ischemic heart disease, systemic diabetes mellitus and arterial hypertension.[89–91]

The lifetime risk of heart failure is comparable between sexes; according to the Framingham Heart Study, its prevalence was estimated at 21% for men and 20% for women at the age of 40 years in the Framingham Heart Study, and 33% for men and 29% for women at the age of 55 years in the Rotterdam Study.[89,90]

Moreover, the estimate of the impact of heart failure in women has been underestimated for many years, mainly because of a believed better prognosis, and of an objective delayed onset in the life compared with men.[91]

Although the incidence of heart failure is similar for women and men, sex differences are seen in specific heart failure phenotypes [e.g. heart failure with preserved ejection fraction (HFpEF) is more common in women while heart failure with reduced ejection fraction HFrEF is more common in men].[91–95]

In the USA, among patients with incident HFpEF, women outnumbered men by approximately 2 : 1.[96] Epidemiological data for incident heart failure cases occurring between 2000 and 2010 showed an increase in the overall proportion of HFpEF relative to HFrEF, from 48% in 2000–2003 to 52% in 2008–2010.[96]

Interestingly, the incidence of HFrEF decreased more sharply than that of heart failure with HFpEF in women (−61% in 2000 vs. −27% in 2010), but not in men (−29% in 2000 vs. −27% in 2010).[97]

A UK population study investigating heart failure outcomes between 1998 and 2017 reported an increase in hospitalization rates and a slower decrease in mortality in women compared with men.[97] The authors suggested that these patterns could reflect an absence of effective therapies for HFpEF in women compared with men. Although there are multiple drug and device therapies for the treatment of HFrEF, few drugs are effective for HFpEF. Furthermore, most studies include more men than women, although this trend seems to have recently declined.[97] There are several pathophysiological hypotheses to explain this difference in incidence, including the difference in anthropometry, a different shape of the left ventricle in healthy men compared with women, the role of oestrogen, differential gene expression, and the different tendency to maintain systemic inflammation.

All of these factors can work together and influence microvascular coronary inflammation. Furthermore, despite the fact that sex-specific differences in natriuretic peptide levels have been detected, these differences have not been included in diagnostic or risk prediction models.[98]

Several studies have demonstrated significant gender disparities in pharmacokinetics and pharmacodynamics in heart failure patients. A 2.5-fold higher concentration of ACE inhibitors, angiotensin receptor blockers and beta-blockers has been reported in women than in men, at dose equipoise.[98,99] This can be explained by considering the lower renal and hepatic metabolism in women.[100,101] Furthermore, most of the efficacy studies are carried out predominantly in male populations leading to a knowledge gap regarding the use of the same drugs in women.[102–104] Similarly, a fixed dose of beta blockers resulted in a greater reduction in heart rate and BP in women than in men.[105]

Future perspectives

The COVID-19 pandemic has changed the approach of healthy subjects to CVD prevention. In particular, women were deeply affected from a socioeconomic and psychological point of view. This has resulted in a slowdown of public prevention actions because governments were focused on fighting the virus. Following the pandemic emergency, it will be necessary to set up necessary actions to favour a return to a correct lifestyle and to resume educational campaigns to stimulate the fight against modifiable risk factors. Women must be encouraged to take care of their own health.

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Conflicts of interest

There are no conflicts of interest.

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