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Cardiovascular prevention in women: a narrative review from the Italian Society of Cardiology working groups on 'Cardiovascular Prevention, Hypertension and peripheral circulation' and on 'Women Disease'

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Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in women.

Some authors highlighted that the female risk profile consists of traditional and emerging risk factors. Despite the lower prevalence of type 2 diabetes, years of life lost owing to the disease for women are substantially higher compared with men. In addition, pregnancy complicated by gestational diabetes, represent a risk factor for CVD. Women with gestational diabetes have a higher prevalence of coronary artery disease that occur at a younger age and are independent of T2DM.

Hypertension is an important cardiovascular risk factor in women. Estrogens and progesterone, known to have an impact on blood pressure levels, have also been proposed to be protective against sleep-disordered breathing. It is very difficult to understand whereas obstructive sleep apnea in women is independently associated with hypertension or if many confounders acting at different stages of the woman lifespan mediate this relation.

The cardioprotective effect of physical activity in women of all ages is well known. Women are generally more physically inactive than men. During and after menopause, most women tend to reduce their physical activity levels and together with the reduction in basal metabolic rate, women experience loss of skeletal muscle mass with a negative change in the ratio of fat-to-lean mass.

In conclusion, sex differences in cardiovascular system are because of dissimilarities in gene expression and sex

hormones; these results in variations in prevalence and presentation of CVD and associated conditions, such as diabetes, hypertension and vascular and cardiac remodeling.

Changes in lifestyle and increase of physical activity could help in prevention of cardiovascular disease in women.

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Cardiovascular risk factors: sex differences

Despite significant advances in our knowledge about pathophysiology and prevention in cardiovascular diseases (CVD), they still remain the leading cause of morbidity and mortality in women worldwide.^{1,2}

During the last quarter of century, a continued decrease of mortality for heart disease on both men and women have been observed, especially in elderly. Actually, it seems to be a slowdown or even a stop in the decrease of

morbidity and mortality of ischemic heart disease (IHD), especially among younger women (<55 years) compared with both young men and older women.³

Significant gains in research-based treatments have been reached, but this problem remains understudied, under diagnosed and undertreated (Table 1).⁴ IHD is widely spread in female population, and it is often cause of death because the very often 'atypical' clinical presentation makes symptoms difficult to be recognized.⁵ A recent

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About other vascular diseases in women

In USA, 55 000 more stroke events occur in women than in men; furthermore, women have an increased lifetime incidence of stroke compared with men, because of an increased lifetime prevalence of stroke risk factors, including hypertension, abdominal obesity and metabolic syndrome, especially in postmenopausal women;

Incidence of atrial fibrillation is lower in women than in men; however, women with atrial fibrillation show a higher incidence of stroke and a higher relative risk of all-cause mortality, cardiovascular mortality, cardiac events and heart failure compared with men;

Heart failure with preserved ejection fraction (HFpEF) occurs in women in older age and with less ischemic causes. Women are approximately two times more likely than men to develop HFpEF, its pathophysiology is because of impairments in cardiac reserve, vascular and peripheral function caused by aging, adiposity, hypertension and metabolic stress, and these conditions are more frequent in elderly women.

study has shown that women with myocardial infarction suffer from higher excess mortality compared with men, attenuated after adjustment for the use of guideline-indicated treatments.⁶ Thus, the awareness of female patients and even of clinicians about this problem has a dramatic role in the appropriate management of CVD in women.

We need to improve early diagnosis and treatment of acute coronary syndromes on women, through a better recognition of signs and symptoms, especially atypical chest pain, for a better outcome. Atypical presentations more prevalent in women, include: myocardial infarction with nonobstructive coronary arteries (MINOCA), that in a recent systematic review suggests a prevalence of 40% of women; spontaneous coronary artery dissection (SPAD) 80% of patients are women and 20–25% of cases occurring in peripartum period; stress-induced cardiomyopathy (Takotsubo Syndrome) that mainly affects postmenopausal women.^{5,7,8}

The fundamental differences in clinical presentation and outcomes arise from peculiar pathophysiology vessels damage. In fact, women show less coronary artery calcification than men.⁹ Notwithstanding, this evidence remains effective until 75 years old,¹⁰ when sex differences in CVD seem to decrease. The hypoestrogenemia and endothelial changes, which start even years before the menopause itself,¹¹ constitute sex-specific precursors that could merge with other proatherogenic factors (traditional cardiovascular risk factors, i.e. hyperlipidemia, smoking, hypertension, metabolic dysfunction) and accelerating factors (i.e. early menopause). These factors promote microvascular disease throughout endothelial dysfunction, which often cohabits with nonobstructive atheroma in the coronary vessels. For these reasons, female patients could experience shortness of breath, unusual fatigue and more prolonged symptoms more frequently than myocardial infarction classic patterns.¹² Through advanced imaging modalities like magnetic resonance (MR) perfusion or positron emission perfusion study, the subendocardial or epicardial ischemia, more likely peculiar of microvascular damage, could be

Table 2 Traditional and nontraditional cardiovascular risk factors that can contribute to worsening risk factor profile in women

Traditional
Dyslipidemia
Diabetes
Hypertension
Obesity
Physical inactivity
Stress
Nontraditional
Depression
Menopause
Breast cancer treatment
Autoimmune disease
Hypertensive disorders of pregnancy
Preterm delivery
Gestational diabetes

identified. In addition to traditional cardiovascular risk factors,^{13–15} there are sex-specific risk factors, which contribute to risk profile in women (Table 2).

The turning point in the female risk profile is menopause.¹¹ Compelling evidence supports the idea that the different impacts of CVD and the differences in vascular biology in men and women may be, at least in part, related to the cardiovascular and metabolic effects of sex steroid hormones. Estrogens exert potential beneficial effects on the cardiovascular system in both sexes.

Pimenta¹⁶ has shown that in 2025, hypertensive women are going to overtake the number of hypertensive men. Although intrinsic mechanisms that regulate arterial blood pressure (BP) are similar in men and women, marked variations exist at the molecular, cellular and tissue levels. Key systems that are important in the development of hypertension and CVD, including the sympathetic nervous system, the renin–angiotensin–aldosterone system and the immune system, are differentially activated in men and women.^{17–19}

Furthermore, sex hormones, such as estrogen and testosterone as well as sex chromosome complement likely contribute to sex differences in BP and CVD.¹⁹ Moreover, dyslipidemia has the highest population-adjusted risk among women (47.1%, compared with all other known risk factors). This risk factor is typically not observed before menopause, even if cholesterol levels are elevated. Primary prevention guidelines for statin initiation have recently been tailored to be sex-specific, with inclusion of sex in the American Heart Association (AHA)/American College of Cardiology (ACC)-pooled cohort formula for CVD risk determination.²⁰

A big lack concern the lower chance for postmenopausal woman to be treated with statins and aspirin if compared with a man at similar cardiovascular risk, the same happens regarding therapeutic lifestyle changes.^{21,22} And even when drugs are prescribed, the treatment often is less aggressive and does not achieve optimal targets, as hypertensive postmenopausal women often do not meet a good control of their blood pressure levels,

hypercholesterolemic women do not receive statins therapy and diabetic women had high levels of glycated hemoglobin. These suboptimal treatment pattern leads to higher mortality, and poorer CVD outcomes compared with men.^{21,22}

Alongside the above mentioned, there are sex-specific risk factors, that are dramatically important, as well as the traditional one. In fact, there are some pathological conditions, more frequent in women that could increase CVD risk. Autoimmune disorder, and in particular, rheumatoid arthritis and systemic lupus erythematosus²³ determine a dramatic predisposition to CVD. Moreover, cardiotoxicity of immunosuppressive drugs is a well recognized burden to the cardiovascular organs.²⁴ The anamnesis of these patients should include this important pathological datum; otherwise the underestimation of the cardiovascular risk profile is evident.

Another important aspect to deal with is the possible previous breast cancer treatment, with chemotherapy or radiotherapy. In the first case, some cardiotoxic drugs (such as anthracycline or trastuzumab) could have been administered to the patient, who retains cardiovascular risk for even 10 years after treatments.¹²

In the second case, the exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose.²⁵

Diabetes: sex differences and prevention

There is no significant sex-related difference in the incidence and prevalence of diabetes mellitus. According to the IDF, the prevalence of diabetes for women aged 20–79 years is estimated to be 8.4%, which is even slightly, lower than that of men (9.1%) with 17.1 million more men than women with diabetes (221.0 million men versus 203.9 million women).²⁶ Despite the lower prevalence of type 2 DM (T2DM), years of life lost owing to the disease for women are substantially higher compared with men (6.8, 6.4, and 5.4 years of age in women versus 6.3, 5.8, and 4.5 in men at 40, 50, and 60 years, respectively) with vascular death accounting for the majority of premature deaths.²⁷ This sex difference also applies to type 1 DM (T1DM) in which women bear a 37% higher excess risk of all-cause (in particular, vascular) mortality compared with men. In addition, the risk of incident major cardiovascular events in women with T2DM is anticipated by 20–30 years (whereas in men it is by 15–20 years) attenuating the premenopausal advantage in the onset of CVD. Additionally, diabetic women experience a 30% greater risk of stroke than men.^{28,29}

In addition, pregnancy complicated by gestational diabetes, represent a risk factor for CHD. Women with GDM have a higher prevalence of coronary artery disease and/or stroke that occur at a younger age and are independent of T2DM.³⁰

Moreover, a recent study showed that GDM is associated with angina pectoris, myocardial infarction and hypertension within the 7 years postpartum, regardless of subsequent diabetes.³¹

Indeed, one of the reasons accounting for the worse cardiovascular outcome in women with diabetes mellitus relies in the different cardiovascular risk profile. Women with T2DM are less likely to achieve target values for SBP, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)-cholesterol, fasting plasma glucose and HbA1c. As for treatment, women are more likely than men to take insulin, alone or in combination with oral hypoglycemic drugs, to be under antihypertensive treatment, whereas the use of lipid lowering drugs is similar in men and women.³² In women with T2DM from the ‘The Renal Insufficiency And Cardiovascular Events (RIACE)’ cohort, a more adverse CVD risk profile and a higher likelihood of failing treatment targets, compared with men, were not associated with treatment differences. In keeping with these data, female patients with diabetes mellitus had significantly higher LDL-cholesterol levels than male counterparts, regardless of statin therapy. Similar data apply for T1DM in which a lower likelihood to reach a good metabolic control for women was shown.³³

The pathophysiologic mechanisms underlying this excess in cardiovascular risk and differences in cardiovascular risk factors are still partly unknown; however, disparities in accessibility and quality of care do not seem to contribute. Quality-of-care summary score (*Q* score) – calculated based on a combination of process and outcome indicators – is similar in men and women with type 1 diabetes mellitus and T2DM.³⁴ Psychosocial factors might be taken into account. The so-called ‘allostatic load,’ that is, the imbalance between the ability to adapt to environmental demands and overexposure to environmental stress is higher in women, particularly middle-aged, leading to increased risk of cardiometabolic diseases via insulin resistance, neuroendocrine, autonomic and immune mediators.³⁵ Women are less represented in randomized controlled trial (RCT) in diabetes mellitus (relative to their overall representation in disease populations); adherence to therapy is consistently lower in women compared with men with diabetes mellitus.³⁶ Importantly, sex differences in treatment modalities and metabolism of drugs (sex-specific cytochrome expression) have to be considered, that is, as in the case of statin therapy in which female sex is one of the major risk factors that predispose patients to myopathy.²⁰

However, sex-related difference might play a predominant role. In sex dimorphism in diabetes risk factors, adiposity has a central impact as diabetic women showed greater relative differences in abdominal adiposity and consequently in the downstream insulin resistance-associated cascade leading to more unfavorable lipids (low

HDL cholesterol), DBP, inflammation, endothelial dysfunction and coagulation profile than men with diabetes mellitus.³⁷

Indeed, psychosocial and sex-related disparities (and their correlated implications, i.e. the impact of level of education, income, social support on body composition), cooperate in determining a more detrimental cardiovascular risk profile in women compared with men with diabetes mellitus.^{38,39} There are marked sex differences among people with depression and those with CVD. It is well known that depression is more prevalent in women.^{38,39} This is especially true during periods of hormonal transition. Findings of elevated rates of depression during the perinatal and perimenopausal periods suggest that steroid hormones (17- β -estradiol and progesterone) may be involved. Such evidence suggests that the co-occurrence of depression and CVD may be amplified in women.

Hypertension and sleep-related breathing disorders

The occurrence of a relationship between sleep disorders, in particular, obstructive sleep apnea (OSA), and hypertension has been extensively explored, both in men and women, in the frame of several longitudinal studies and in different cohort of subjects.^{40,41}

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Although most studies have provided evidence of a significant association between OSA and hypertension in a general population, the interference by sex-related determinants, such as the hormonal status and the lower prevalence of obesity, has made the investigation of this relationship much more complex amongst females.

Women are continuously under the influence of hormonal changes from menarche to menopause. It's known that both estrogens and progesterone have an impact on blood pressure levels. Some authors suggest that hormonal levels are protective against sleep-disordered breathing. In fact, it seems that progesterone is a ventilatory drive stimulant. It would dilate the upper airways increasing the genioglossus muscle's activity.⁴² Furthermore, OSA is more prevalent in postmenopausal than in premenopausal women and estrogens, when administered as hormone replacement therapy, are associated with a lower prevalence of sleep apnea in postmenopausal women.⁴³

However, it is important to underline that OSA in women is often under diagnosed both for 'social' reasons and also because OSA symptoms are less 'typical' in women than in men with a predominance of sleep fragmentation and mood alterations over choking, abrupt awakenings and motor activity during sleep, which are conversely more often reported by men.

Another factor, which contributes to make the whole picture even more puzzling, is pregnancy. The female

body undergoes significant changes in the physiological and hormonal homeostasis during pregnancy, such as gestational weight gain, pregnancy-associated nose-pharyngeal edema, decreased functional residual lung capacity and an increased frequency of arousals from sleep can contribute to the likelihood of developing OSA.⁴⁴

For all these reasons, it is very difficult to understand whereas OSA in women is independently associated with hypertension or if is mediated by the many confounders acting at different stages of the woman lifespan.

Continuous positive airway pressure (CPAP) is, thus far, the most effective treatment for OSA by delivering positive pressure into the patient's airway in order to keep it patent, and therefore, to avoid its obstruction at night. Its beneficial, although mild, effect on blood pressure has been demonstrated in several trials in both patients with essential and resistant hypertension.⁴⁵

However, most of the studies published so far were conducted mainly in cohorts of male patients and a recent meta-analysis of seven studies with a total of 794 patients reported that all the OSA trials predominantly recruited male patients (74%).⁴⁶

A recent randomized controlled study showed that in women with moderate-to-severe OSA, CPAP treatment for 12 months determined a significant reduction of DBP but not SBP (-2.04 mmHg, 95% CI -4.02 to -0.05 ; $P=0.045$ and -1.54 mmHg, 95% CI -4.58 to 1.51 ; $P=0.32$, respectively) with no changes in terms of metabolic profile, compared with conservative treatment.⁴⁷

This again raises the question of whether or not CPAP is effective in reducing blood pressure and the overall cardiovascular risk profile in patients with OSA.

In pregnancy, one of the most serious complications and the leading cause of maternal death is preeclampsia, characterized by severe arterial hypertension and proteinuria with kidney damage. Although the pathogenesis of preeclampsia is still not clear, Yinon *et al.* found that in a group of 17 women with preeclamptic toxemia the respiratory disturbance index (RDI), a surrogate of the apnea hypopnea index, was higher than in a control group of nonpreeclamptic pregnant women [18.4 (8.4) versus 8.3 (1.3)/h, $P<0.05$]. Moreover, blood pressure levels correlated with RDI values and with indices of endothelial function.⁴⁸

With regards to preeclampsia treatment, there are several case reports and case series in the literature showing that CPAP can help controlling blood pressure in such patients.⁴⁹ However, the lack of large prospective studies in patients with or at risk of preeclampsia make it difficult to recommend such treatment not only to reduce BP but also to improve maternal outcomes in these patients.

Other than OSA, other sleep disturbances are thought to be associated with hypertension in women. Insomnia is

the most frequent sleep disorder affecting almost 20% of the general population. Li *et al.* demonstrated that in a large cohort of patients, insomnia with short sleep duration (<6 h) was associated with incident hypertension.⁵⁰ However, very few studies in women have been conducted on this topic, although insomnia is more frequent in women.

Lastly, it is worth mentioning that both the quantity and quality of sleep might predict the development of hypertension in women. The detrimental effects of sleep restriction and lack of sleep are well known in the literature: in the First National Health and Nutrition Examination Survey, men and women who reported typical sleep durations of 5 h or less per night were at increased risk for incident hypertension over an 8–10-year follow-up period, after adjusting for sociodemographic factors, health behaviors, obesity and diabetes mellitus.⁵¹

Interestingly, in the Whitehall II Study short duration of sleep (less than or equal to 5 h per night) was associated with higher risk of hypertension compared with the group sleeping 7 h, among women (odds ratio: 1.72; 95% CI: 1.07–2.75), independent of confounders, with an inverse linear trend across decreasing hours of sleep ($P=0.037$). No association was detected in men suggesting a sex difference in the association between sleep duration and hypertension.⁵²

However, none of the above-mentioned studies assessed sleep by means of full polysomnography, thus not considering sleep characteristics but only self-reported sleep quantity.

Matthews *et al.* showed that in 355 women, followed up for 4.5 years, low NREM delta power, which indicated a reduction in deep sleep, was associated with the development of hypertension whilst sleep duration and sleep efficiency were unrelated to BP either cross-sectionally or longitudinally in multivariate models.⁵³

It highlights the importance of sleep assessment in the evaluation of sleep alteration effects. This idea would be supported by some polysomnographic exams in women with sleep breathing disorders – for example, hypopneas and REM-related breathing alterations. This would be of great interest as breathing disorders can affect the cardiovascular system. Thus, there is still a need of larger studies exploring the complex link between sleep disorders and hypertension in women. Moreover, these studies should include more frequently full polysomnography in large samples of female patients, in order to investigate more in depth the possible sleep-related mechanisms involved in hypertension development among women.

Prevention through physical activity and exercise

Physical activity (PhA) is inversely associated with all-cause mortality in both sexes, although the relationship is

stronger in women than in men after adjustment for demographic and behavioral risk factors. Moreover, mortality risk reduction is greater in women than in men for any given level of physical activity.⁵⁴ The American College of Sport Medicine (ACSM) recommends that most adults engage in ‘moderate-intensity cardiorespiratory exercise training for ≥ 30 min/day on ≥ 5 day/week for a total of ≥ 150 min/week, or vigorous-intensity cardiorespiratory exercise training for ≥ 20 min/day on ≥ 3 day/week (≥ 75 min/week).⁵⁵ However, it is important to recognize that the two terms of PhA and Exercise, both key components of energy expenditure and balance, should not be confused with each other and shall be defined in a different way. PhA is defined as any movement (or force) exerted by skeletal muscles that results in an expenditure of energy higher than in the resting state, including occupational, leisure and daily activities. Exercise is usually described as a subcomponent of PhA that is planned and/or structured^{56,57} to improve or maintain fitness and health. All the components are important to reduce the risk of chronic diseases. Sedentary behavior, defined as an energy expenditure of 1.0–1.5 metabolic equivalent tasks (METs), is recognized as a distinct construct beyond lack of leisure-time physical activity, having independent effects on human metabolism and health outcomes.⁵⁸ It is well known that cardiovascular events, in the vast majority, occur in adult women, nevertheless, lifestyle and dietary behaviors are established during childhood and adolescence. A sedentary behavior, as well as a wrong diet or smoking in a girl, are intended to persist in subsequent years and predict cardiovascular risk in adult women.^{57,59} Moreover, it has been clearly demonstrated a direct relationship between time spent sitting, the overall volume of physical activity and the risk of CVD in postmenopausal women, independent of leisure-time physical activity.⁵⁸ Prolonged sitting time determines many detrimental adaptations, such as increased energy intake and suppression of skeletal muscle lipoprotein lipase activity that might explain its role on cardiovascular risk factors.^{59,60}

Studies over the last year confirmed the cardioprotective effect of physical activity in women of all ages and pointed out the evidence that the elderly age is not a limit for the beginning of a correct physical training program.⁶¹

Females are generally more physically inactive than men. During and after menopause, most women tend to reduce their physical activity levels and together with the reduction in basal metabolic rate, women experience loss of skeletal muscle mass as well as loss of bone mineral density, with a negative change in the ratio of fat-to-lean mass. Unfortunately, during perimenopause period, fat deposition shifts to favor the visceral depot that, in addition to the decreased protective effect of estrogen, contributes to abnormality of fatty acid metabolism, insulin resistance, endothelial dysfunction, inflammatory state, all markers and causes of female CVDs.⁶²

Both aerobic and strength exercise is capable to produce several beneficial effects such as a favorable alteration of the metabolism of carbohydrates and lipids, a better distribution of adipose tissue, a reduction of hematic levels of lipoprotein and adipokines. The muscle activity influences adipose tissue, both acutely and in the longer term. A single session of exercise stimulates adipose tissue, blood flow and fat mobilization, resulting in delivery of fatty acids to skeletal muscles. Regular physical activity produces changes in the physiology of adipose tissue, with a heightened capacity to mobilize fat after each training session. In addition to the regulation of fat mass, exercise training contributes to the metabolic health benefits through dynamic changes within the adipose tissue.⁶³ Although cardiometabolic effects of physical exercise depend on its intensity, duration and type, however, regular physical activity in postmenopausal women have been associated with positive changes in skeletal muscle mass, percentage fat distribution and body composition variables.⁶⁴

Exercise increases the ability of skeletal muscles to utilize lipids as opposed to glycogen, thus, reducing a number of negative influences of physical inactivity on lipid profile in menopause. Vigorous exercise training is required in eliciting the reduction in low-density lipoprotein and triglycerides.^{64,65}

The effect on HDL may be less prominent in women, given that this lipoprotein component is on average higher in female sex. Regular, long-term aerobic exercise, more than resistance training, induces an increase of insulin sensitivity and glucose profile, helping to improve the control of T2D; moreover, also regular habitual physical activity, specifically walking 6000 or more steps daily is associated with a decrease risk of diabetes in middle-age women, independent of menopause status.^{65,66} Menopause is also associated with adverse changes in both coagulation and fibrinolysis. The training carried out in a tailored and progressive way decreases the risk of thrombosis, especially by reducing the plasma concentration of fibrinogen. Despite its positive effects above mentioned, the vigorous physical activity is not recommended in completely untrained individuals, because of the possibility to inducing acute ischemic events. This is especially true for women, in relation to their susceptibility to thrombosis plaques and to coronary dissection.⁶⁷

Evidences have underscored the relationship among metabolic syndrome, inflammation and oxidative stress in postmenopausal women. Current data support that exercise training, such as aerobic and resistance exercise, reduces chronic inflammation, and this effect is independent of the exercise-induced weight loss.^{58,68} Moderate aerobic training improves serum/plasma oxidative stress and inflammatory biomarkers in women with metabolic syndrome.⁶⁸

There are several mechanisms through which exercise training reduces chronic inflammation, including improvement of endothelial function, the capacity to regenerate endothelial cell after injury, increase laminar shear stress. It is well known that impaired vascular endothelial function, higher vascular resistance, intrinsic arterial stiffness and sympathetic tone activity are mechanisms leading to increased hemodynamic load, higher ventricular elastance and cardiovascular adaptation. Arterial stiffness may play a relevant role in the female predominance of several diseases, such as arterial hypertension, heart failure with preserved ejection fraction. Healthy postmenopausal sedentary women demonstrated significantly higher levels of aortic pulse-wave velocity and carotid augmentation index compared with premenopausal women; however, this dynamic adaptation did not occur in physically active women.⁶⁹ Acute bout during exercise leads to a larger stretch on the arterial wall, increasing arterial pressure, but it is associated with antioxidant effects when performed regularly at moderate intensity levels. Thus, the increase of antioxidant defenses may itself contribute to decreased arterial wall thickness.^{70,71} Moreover, exercise also increases the sensitivity of beta-adrenergic receptors, reducing the release of catecholamine. It is well known that long-term aerobic exercise results in significant reduction in resting blood pressure in postmenopausal women affected by high normal resting BP or by stage I essential hypertension.⁷²

Recent studies, indeed, have shown that not only endurance program but also a combination of circuit resistance and endurance training is effective to improve arterial stiffness, hemodynamics and arterial hypertension in postmenopausal women.⁷³

Menopausal transition may represent a period of higher depressive vulnerability.³⁹ Randomized trials found that aerobic and strength training improved mood symptoms in women affected by depression. In addition, the moderate levels of physical activity seem to be the specific target capable to assure mental health benefits in women.⁷⁴

The importance of increasing women's level of PhA is well recognized as a priority to reduce the risk of CVD. However, the application of PhA programs needs to be adapted to the specificity of female sex, as the cardiovascular risk profile changes during life course. More studies need to understand whether and which type of PhA and exercise intervention or characteristic of exercise (frequency, intensity, time or duration and volume) would yield more benefit in achieving cardiovascular health in women.

Sex-specific risk factors

There are risk factors related to women's gynecological history: that is, polycystic ovary syndrome (PCOS),

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premature ovarian failure (POF), surgical and natural menopause and obstetric conditions, such as complications of pregnancy, that is, gestational diabetes, preeclampsia, intrauterine growth restriction (IUGR), miscarriage and preterm birth (PTB). These specific risk factors in addition to the traditional cardiovascular risk factors described in this article, are associated with the development of CVD later in life. Recently, some studies have suggested that these relatively frequent conditions taking place during the fertile years and around menopause represent early markers of future CVD and provide a unique opportunity for healthcare professionals to attempt early identification of women who may be at risk of developing CVD.⁷⁵

PCOS is characterized by both endocrinological and metabolic alterations involving both the hypothalamic–hypophysis–ovary–adrenal axis and adipose tissue: hyperandrogenism with hirsutism, acne, alopecia, obesity and insulin resistance with compensatory hyperinsulinaemia. PCOS is an independent risk factor for metabolic syndrome. It is associated with diabetes, atherosclerosis, hypertension autonomic dysfunction and preclinical chronic inflammation. Visceral obesity in PCOS influences the release of proinflammatory cytokines, which in turn contribute to the development of inflammation and increase free radical production. All these cardiovascular risk factors synergistically contribute to the activation of the endothelium with increased intima–media carotid thickness and the development of preclinical atherosclerosis in young women.^{76–78}

However, PCOS is an independent risk factor for coronary heart disease (CHD) and stroke and may exert a causal effect on CVD.⁷⁹ In addition, PCOS is a common cause of infertility and spontaneous abortion that are predictive of future CVD. All these pathological features promote coronary artery disease (CAD), stroke and cardiovascular mortality in women with PCOS in the perimenopausal years.⁷⁹

Pregnancy complications, affecting the mother but also the fetus, are now considered as early markers to identify high-risk women for CVD: gestational diabetes, preeclampsia, intrauterine growth restriction, miscarriages and preterm birth, may affect the onset, clinical picture and prognosis of CVD later in women's lives. These pathological conditions that develop during the fertile period of life have been suggested to be early markers of future CVD.

Pregnancy can, therefore, be considered to be an opportunity to identify, at an early stage, women who may be at increased risk for CVD and who might benefit from early preventive measures.⁸⁰

Menopause, early and surgical menopause should be considered to be early markers of future CVD and may represent a unique opportunity for the early

identification of women who are at increased risk of developing CVD. These imply the loss of the protective effects of endogenous estrogen and ovarian steroids, therefore, hormonal deficiency leads to abnormalities in different organs and systems, including central nervous system, endothelium, bones and liver-inducing significant functional and metabolic changes.^{81,82} Obesity, high blood pressure, dyslipidemia, diabetes, metabolic syndrome and atherosclerosis may occur or exacerbate in peri-menopausal years.^{82,83}

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Similarly, early menopause is independently and positively associated with an increased risk of stroke and CAD independent even of traditional CVD risk factors.⁸³

Women who experienced premature or early-onset menopause had a greater risk of CHD, CVD mortality and all-cause mortality.⁸⁴

In addition, Saha *et al.*⁸⁵ showed that menopause leads to changes in metabolism and lipid status by increasing total and LDL cholesterol and by reducing HDL cholesterol in Bangladesh.

In conclusion, menopause, surgical and early menopause, PCOS and other pathological conditions in pregnancies, such as GDM, preeclampsia, SGA and miscarriage represent sex-specific risk factors. The identification of these women's peculiar CVD risk factors should be considered by health practitioners and used for CVD risk calculation and CVD prevention programs.^{38,86}

Conclusion

Sex differences in cardiovascular system are because of dissimilarities in gene expression and sex hormones, these results in variations in prevalence and presentation of CVD and associated conditions, such as diabetes, hypertension and vascular and cardiac remodeling. Sex differences instead arise from behaviors, environment, lifestyle and nutrition factors. It is evident that there is a need for the physician who approaches the female patient to stress main anamnestic and sex-specific data concerning also hormonal life starting from menarche, through pregnancy, until menopause. Menopause, in particular, represents a turning moment: the modifications age-related and menopause-related facilitate the onset of a series of diseases, such as CHD and stroke, diabetes, osteoporosis and cognitive decline. It becomes particularly important during this period of potential vulnerability across a woman's lifespan to identify the risk factors in order to establish the most effective and prompt preventive and therapeutic strategies. Furthermore, we need to recognize those aspects of IHD among women in absence of obstructive artery disease angiographically assessed, because a more aggressive lifestyle and medical preventive treatment may contribute to reduce sex-based mortality gap. The importance of increasing women's level of physical activity is a priority to reduce the risk of CVD.

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Conflicts of interest

AQ10 None declared.

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<AQ14>	Please provide caption for Table 1.	AQ 14: Additional cardiovascular disease in women