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Role of physical exercise for the management of arterial hypertension in women ☆

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ABSTRACT

Arterial hypertension (HTN) is a leading cause of morbidity and mortality in the general population, with significant sex and gender-related pathophysiological differences. Women face higher cardiovascular (CV) risk and unfavorable CV remodeling associated with HTN, as compared with men, and have specific risk factors for the development of HTN, i.e. reproductive factors and breast cancer status. Physical exercise (PE) represents a powerful, cost-effective, non-pharmacological treatment for the primary and secondary prevention of HTN. In this regard, much evidence highlighted the potential gender-related differences in terms of exercise-related CV adaptations, along with a significant gender gap concerning adherence to exercise protocols that is significantly lower in women for all age groups worldwide. However, to date, there are no specific, sex-focused recommendations in terms of exercise training in the female population with HTN or at risk of HTN. Given these premises, our review aims to summarize the role of exercise in the management of HTN in women, with a specific focus on pregnancy, menopause and breast cancer scenarios, as well as on cardiac rehabilitation. Our purpose is to underline the need for more sex-specific data to explore the best exercise protocols tailored on each participant's characteristics, to get the greatest benefit and to improve adherence to exercise protocols.

Background

Arterial hypertension (HTN) is one of the most important cardiovascular (CV) risk factors impacting women in all phases of their lifespan, with peculiar sex and gender-related mechanisms and pathophysiological issues. In particular, the CV risk associated with HTN increases at a lower blood pressure (BP) level in women than in men, and women with HTN experience unfavorable CV adaptations more frequently than men, including pathological CV remodeling and heart failure with preserved ejection fraction (HFpEF) [1]. HTN is associated with many traditional and gender-specific risk factors, including, respectively, physical inactivity and reproductive risk factors [2]. Physical inactivity represents a major, modifiable CV risk factor that is more common and alarming in the female population worldwide for all age groups

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[3]. Among reproductive risk factors, both history of pregnancy complications (including gestational diabetes and HTN, preterm delivery, preeclampsia, recurrent miscarriage) and menopausal transition are associated with increased risk of HTN and CV disease (CVD) [2]. Moreover, HTN represents the most prevalent CV comorbidity among women with breast cancer. It can be a pre-existing CV risk factor as well as a side effect of some cancer therapies (i.e., poly[ADP-ribose] polymerase inhibitors, aromatase inhibitors, mTOR inhibitors, radiotherapy) or an indirect effect of cancer itself due to chronic stress, pain, weight gain, sedentarism. In breast cancer patients, HTN is associated with an increased risk of mortality and constitutes the greatest predictor of cardiac events as compared to other CV risk factors, being associated with a higher risk of decline in left ventricular ejection fraction (LVEF) after initiating potentially cardiotoxic chemotherapy [4].

In these complex scenarios, physical activity (PA), defined as any bodily movement produced by skeletal muscles that determine energy expenditure, and physical exercise (PE), a subgroup of PA that is planned, structured and repetitive, aiming to optimize physical fitness, are advocated as powerful non-pharmacological interventions to prevent and treat elevated BP and HTN, as stated by the latest guidelines from the European Society of Cardiology (ESC) in 2024 [2]. According to the most recent data in the literature, aerobic exercise training (AET) is recommended as the first-line exercise therapy for reducing BP in patients with elevated BP and HTN, as it substantially lowers systolic BP (SBP) by up to 7–8 mmHg and diastolic BP (DBP) by up to 4–5 mmHg, with comparable effects between high-intensity interval training and moderate continuous exercise protocols [5]. Resistance training (RT) is associated with clinically significant BP reductions in hypertensive patients; however, more robust data from randomized controlled trials (RCTs) are needed. Nevertheless, for non-White patients with HTN, RT achieves BP reductions equivalent to those achieved with antihypertensive therapy [2]. In patients with high-normal BP, dynamic RT can be recommended, resulting in a BP reduction of -3.0 to -4.7 mmHg in SBP and -3.2 to -3.8 mmHg in DBP. In individuals with normal BP but with risk factors for the development of HTN, isometric RT may be recommended, with an expected BP reduction of -5.4 to -8.3 mmHg in SBP and -1.9 to -3.1 mmHg in DBP [5]. Given these premises, ESC guidelines for the management of HTN recommend that patients with high BP or HTN get involved for at least 150 min/week of moderate-intensity AET (≥30 min, 5–7 days/week) or 75 min of vigorous-intensity exercise per week over 3 days [2]. This protocol should be supplemented by low- or moderate-intensity RT (2–3 times per week), e.g. dynamic RT, starting at 2–3 sets of 10–15 repetitions at 40%–60% of one-repetition maximum or isometric RT with three sets of 1–2 min contractions, such as handgrip, plank, or wall sit [2]. However, the Authors underline the need for sex-specific data on epidemiology, pathophysiology and management of HTN, as well as on gender-driven barriers in accessing medical care and compliance both to pharmacological and non-pharmacological interventions, including PA and PE adherence that is significantly lower in female than in male [2,3]. Furthermore, there is much evidence supporting the role of PA and PE on CV health and outcomes related to cardiac function, HTN and cardiometabolic status in the abovementioned sex-specific pathophysiological settings, i.e. before, during and after pregnancy, in the menopausal transition, in breast cancer population [3,6–8]. Nevertheless, still more data are needed regarding the best exercise protocols, the dose-response relationship of aerobic and muscle-strengthening exercise with CV health, and the potential interaction of race, ethnicity, or socioeconomic status with adherence to PA and PE protocols [3,6]. Finally, cardiac rehabilitation (CR) represents another area in which PE plays a pivotal role and that requires further investigations in terms of sex and gender differences.

Given these premises, we aim to provide an up-to-date review regarding the role of PE in the management of HTN in women, with a specific focus on pregnancy, menopausal transition and breast cancer scenarios, as well as CR, summarizing the available evidence in terms of exercise protocols and their interaction with short and long-term CV outcomes.

Gender differences in arterial hypertension

HTN is one of the primary CV risk factors, characterized by a high prevalence, morbidity, and mortality [9]. Significant gender differences exist in this condition concerning the age of onset, the risk of associated organ damage, and the likelihood of developing subsequent CVD. These gender differences are not only due to hormonal regulation but also to structural and anatomical characteristics, as well as the different prevalence of predisposing comorbidities in both sexes [10–12].

Regarding the age of onset, males tend to develop high BP at an earlier age compared to females. Conversely, women experience a later but more rapid increase from the third decade onward, eventually surpassing men in HTN prevalence from the sixth decade of life [13,14].

This pattern throughout life is largely influenced by the action of sex hormones. Androgens, particularly testosterone, have a pro-hypertensive effect primarily due to their influence on the renin-angiotensin-aldosterone system (RAAS). In fact, it seems that testosterone increases the expression of specific subtypes of angiotensin II receptors (favoring AT1R over AT2R), thereby enhancing the vasoconstrictive action of this hormone and, consequently, promoting the onset of HTN [15].

Estrogens, on the other hand, have a protective effect against HTN by inhibiting the RAAS through multiple mechanisms: they regulate the expression of vasoconstrictors such as angiotensin II, lower blood renin concentration, and decrease the activity of the angiotensin-converting enzyme (ACE) [16,17]. Additionally, progesterone opposes the sodium-retaining effect of aldosterone [18].

Besides RAAS, estrogens also regulate the sympathetic nervous system and enhance nitric oxide bioavailability. With menopause and the subsequent decline in estrogen levels, there is an upregulation of the RAAS and the sympathetic nervous system, along with a concurrent decrease in vascular nitric oxide synthesis. All these changes contribute to an increased prevalence of HTN in this age group [19,20].

Sex hormones also influence the development of CV risk factors that predispose individuals to high BP. High testosterone levels or, conversely, estrogen deficiency promotes a pro-atherogenic lipid profile and glucose intolerance [21]. These conditions are, therefore, more common in men or perimenopausal women, making them more susceptible to the development of HTN.

BP is highly heritable, and the genetic contribution varies between men and women. Twin and family studies indicate that men experience a stronger genetic effect at younger ages, whereas in women this effect becomes more pronounced after menopause due to a decline in protective hormonal influences.

Kauko et al. analyzed genetic and clinical data from 218,792 Finnish adults in the FinnGen cohort to determine whether genetic risk for developing HTN differs by sex. The Authors calculated sex-specific polygenic risk scores (PRS) for SBP using previously published genome-wide association study data and assessed the predictive value of these scores for incident HTN in women and men separately. The results indicated that genetic risk predicted HTN more strongly in women than in men, with each standard deviation increase in PRS associated with a 42% higher risk of HTN in women than a 27% higher risk in men. This sex difference was most pronounced for early-onset HTN, where polygenic risk scores increased HTN risk by 56% in women and 35% in men per standard unit increase [22]. Large genome-wide association studies have also identified sex-specific genetic loci that may contribute to these differences. Variants near angiotensin-converting enzyme, angiotensinogen, and cytochrome P450 17A-1 exhibit stronger effects in men, whereas variants associated with immune regulation and endothelial function demonstrate stronger effects in women [23].

During menopause, hormonal and body composition changes are associated with greater visceral adiposity, which is strongly associated with HTN independently of body mass index. Obesity is a stronger risk factor for HTN in women than in men, with females frequently experiencing higher odds ratios for developing high BP across BMI categories. It seems that obesity-related HTN develops more readily in women, particularly due to metabolic dysfunction, associated with a worse lipid profile, and to leptin-mediated vascular damage [24].

Lifestyle factors such as psychosocial stress, PA, and diet influence HTN risk differently by sex and gender, with evidence suggesting greater salt sensitivity and stress-related BP responses in women, and earlier lifestyle-driven hypertension onset in men. About psychosocial issues, women cope with chronic stress from caregiving, work–family conflict, and lower socioeconomic status, whereas men generally experience relevant stress burden associated with workplace and financial issues. Moreover, sex differences in physiological stress response pathways exist and could influence how stress affects BP regulation [25]. To date, data on the link between stress and behavioral risk factors for HTN and CVD are still limited, but it seems that stress could influence sleep and engagement in PA more significantly in men than in women, and that associations between stress and diet appear to be greater among women [26]. Moreover, beyond its influence on behavioral risk factors for CVD, stress, especially chronic stress, acts throughout maladaptive immune and metabolic pathways, with sex differences in terms of hypothalamic-pituitary-adrenal axis activation and more significant stress-induced cortisol release in men than in women [27].

Gender differences in diet quality and HTN risk exist, and it seems that women may benefit more than men from healthy dietary patterns (e.g., whole grains, legumes, lower sodium) in reducing HTN risk, possibly due to differences in vascular responses and hormonal influences [28]. In this respect, it is well known that women of all ethnicities are more salt-sensitive than men, both premenopausal and postmenopausal. Menopause exacerbates the severity and prevalence of salt-sensitive blood pressure (SSBP), suggesting that female sex increases the prevalence and susceptibility of SSBP, and sex hormones may exert antagonistic effects in the development of the female heightened SSBP. In particular, females exhibit enhanced and inappropriate activation of the aldosterone-endothelial cell mineralocorticoid receptor axis, which, in turn, is associated with vascular dysfunction. Furthermore, they face a more pronounced adrenal response to angiotensin than males, along with higher endothelial cell mineralocorticoid receptor expression and activation of the endothelial sodium channel, both of which, in turn, are associated with endothelial dysfunction [29]. In this scenario, PA is significantly, independently, and inversely related to SSBP and may be notably effective in lowering BP among salt-sensitive individuals, as demonstrated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study. In this study, the Authors found an inverse correlation between the amount of PA and the increase in SBP after high sodium intake (∼5.2 to ∼3.9 mmHg from lowest to highest PA levels), with greater activity being associated with lower odds of being classified as salt sensitive (∼OR 0.66 for the highest vs lowest activity quartile). These effects are mediated by exercise's role in improving vascular endothelial function via increased nitric oxide, reducing sympathetic nervous system overactivity, and lowering insulin resistance and associated sodium retention. However, the Authors did not report differences by sex, and no other large clinical trial has yet reported whether exercise's protective effect against salt sensitivity differs meaningfully between women and men. A noteworthy limitation of the GenSalt Study is its lack of sex-specific analysis, leaving a gap in understanding how exercise affects salt sensitivity differently across genders. Further research is needed to determine these effects in men and women independently, providing more comprehensive insights into personalized interventions for salt-sensitive HTN [30,31]. The abovementioned evidence highlights the role of diet both in terms of primary and secondary prevention of HTN, as it has long been recognized as an important modifiable risk factor for HTN. While in men, HTN risk is driven earlier by higher sodium, alcohol, and processed food intake, in women, hormonal changes and salt sensitivity make diet especially critical after menopause. Furthermore, women experience a more pronounced protective association between a healthier dietary pattern and lower risk of HTN than men do [32].

Women also have sex-specific risk factors for the development of HTN. The onset of pregnancy-related disorders such as gestational HTN and preeclampsia increases the risk of subsequent development of chronic HTN [33,34]. Conditions that alter the hormonal balance, such as polycystic ovarian syndrome (PCOS), are also associated with a higher risk of HTN, including hypertensive disorders during pregnancy (HDPs) [35].

Although HTN is an earlier CV risk factor in men than in women, the risk of developing HTN-related diseases is higher in women and appears to begin at lower BP thresholds in females compared with males. First, women develop concentric left ventricular hypertrophy more easily and quickly, which is also less frequently reversible with antihypertensive therapy [36]. This difference is due to smaller vessel size and greater wall stiffness, as demonstrated in the PARAMOUNT study, which is responsible for earlier wave reflection leading and increased afterload, consequently favoring a concentric remodeling pattern [37,38]. Alongside concentric hypertrophy, another cardiac modification more commonly associated with HTN in women due to the same mechanisms mentioned above is left atrial dilation, which leads to a higher risk of atrial fibrillation and ischemic events [39]. Consequently, the thickening and stiffening of the left ventricle make women more likely to develop diastolic dysfunction and HFpEF, also favored by HTN-related microvascular inflammation [40].

Additionally, women have smaller heart chambers than men, resulting in a lower stroke volume. With HTN-related cardiac changes and, consequently, increased wall stiffness, combined with a reduced contractile and chronotropic reserve in women, there is a more frequent occurrence of reduced exercise tolerance, with a lower peak VO2 [41].

Moreover, during PE, hypertensive women experience an earlier loss of ventriculo-vascular coupling due to arterial stiffness, which is not adequately compensated by an appropriate increase in cardiac output [42].

Exercise types in women to improve blood pressure management

It is well known that both males and females achieve the primary health benefits when PA improves from sedentary to low-intensity levels. Nevertheless, when PA increases beyond low intensity, significant gender differences occur, as males seem to benefit more from vigorous PA (>6 METS), whereas females gain relevant health improvements even from low-to-moderate intensity (3-6 METS) activities [43]. A recent prospective study by Ji et al. on 412,413 U.S. adults demonstrated that women, compared with men, experience a greater improvement in terms of all-cause and CV deaths from equivalent amounts of PA, compared with inactiv-

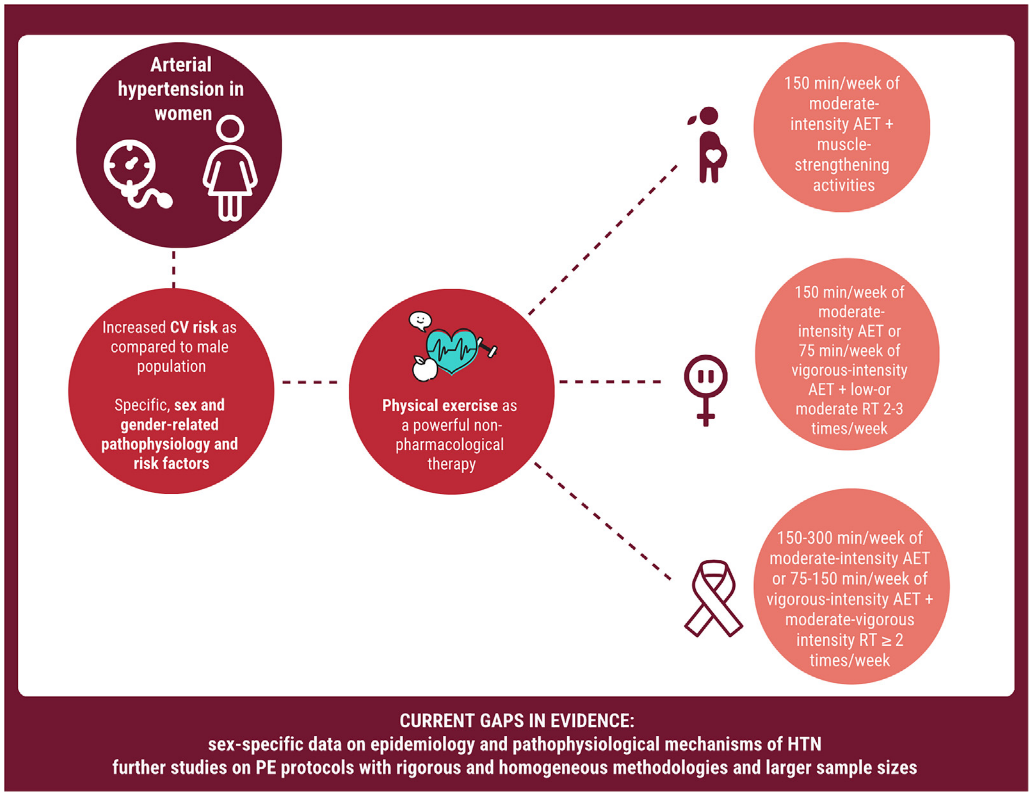

Fig. 1. Physical exercise for the management of HTN in women, with specific reference to exercise protocols in pregnancy, menopause and breast cancer scenarios.

ity (respectively, 24% for women and 15% for men), with men gaining the maximal survival benefit from 300 min/week of moderate-to-vigorous PA (HR 0.81), and women gaining similar benefit for 140 min/week of PA and reaching the maximum survival benefit at 300 min/week (HR 0.76). No differences in exercise protocol (AET or RT) were documented [44]. Regarding the effects of PA and PE on BP, a large-scale systematic review and network meta-analysis of 270 randomized controlled trials, including 15,827 participants, demonstrated that AET, RT, combined training, high-intensity interval training and isometric exercise training are all effective in reducing resting SBP and DBP. Overall, isometric exercise training is the most effective type of exercise in reducing both SBP and DBP, and no specific results regarding the female population were reported [45].

Although much evidence supports the role of sex and gender in CV adaptations and outcomes in response to different PE protocols, even in terms of benefits on BP, there is still a paucity of data specifically focused on the role of different PE protocols on BP in the female population (Fig. 1). The most relevant international guidelines, including the 2020 ESC guidelines on sport cardiology and exercise in patients with CVD, do not recommend any sex-specific exercise protocols in patients with HTN [46].

CR is an established, cost-effective and patient-tailored model for secondary prevention of CVD and represents another scenario in which PE plays an essential role. It encompasses multidisciplinary intervention, including management and control of CV risk factors and structured exercise training, and it constitutes a relevant and effective therapeutic intervention even upon adherence to recommended medical and Interventional therapies. Due to its outstanding benefits in terms of reduction of all-cause and CV mortality and morbidity and risk of cardiac hospital readmissions, as well as in increased quality of life and exercise capacity, CR has been classified by the ESC and the American Heart Association/American College of Cardiology as a therapeutic intervention with the highest level of recommendation in the treatment of multiple CV conditions [47,48]. However, despite these advantageous clinical outcomes, CR uptake remains suboptimal worldwide, and significant sex disparities exist in CR adherence [49].

The prevalence of HTN in patients enrolled in CR is about 60-70%, with an increasing trend over the past two decades. At CR enrollment, women are typically older and generally have a higher prevalence of HTN and comorbidity burden than men, with menopausal status playing a substantial impact. Research on sex-specific BP responses to CR is still limited, and findings vary depending on program type and patient characteristics. Turk-Adawi et al found a statistically significant, although trivial, reduction in SBP in females (−1.6 mmHg), but not in males following CR, while both groups exhibited similar reductions in DBP (−0.5 to 1 mm Hg) [50].

Much evidence highlight that women are less likely to be referred to and attend these programs than men, despite the increase in research to identify the unique needs of women and investigate potential interventions to reduce gender-based disparities in CR participation [51].

In this regard, in the last years many women-focused CR programs have been developed, including specific forms of physical activity (e.g. combined high intensity interval training-RT) and unconventional exercise regimens (e.g. yoga, pilates, Tai-Chi). However, significant gender-based disparities in CR utilization and outcomes still exist and further data are needed to quantify the physical and psychological benefits of these initiatives [52].

Protocols for pregnancy and postmenopausal arterial hypertension

Pregnancy

During pregnancy, substantial adaptations in maternal CV physiology occur, with a significant increase in blood volume, resting heart rate and cardiac output and a concomitant decrease in systemic vascular resistance. The changes in endocrine and neurohormonal function, as well as the CV adaptations, represent a stress test for the maternal CV system, and a preexisting maternal unfavorable cardio-metabolic phenotype can uncover both adverse pregnancy outcomes (APOs) and the subsequent development of CV risk factors during and after pregnancy. Moreover, the maternal environment can affect offspring's short and long-term CV health through a multifaceted mechanism called developmental programming [53]. Among APOs, HDPs represent the second leading cause of pregnancy-related maternal and fetal morbidity and mortality and are related to a substantial risk of short and long-term adverse CV outcomes, both in women and in their offspring; moreover, persistently elevated SBP during pregnancy, even below the diagnostic threshold for HTN, is associated with adverse fetal outcomes, in terms of risk of preterm delivery and low birth weight. BP generally decreases during early pregnancy, with a nadir in mid-pregnancy; it then progressively increases by approximately 8% from the second trimester until delivery and returns to pre-pregnancy levels during the early postpartum period. If BP remains below 130/80 mmHg, the pregnancy is normotensive, whereas a BP threshold $\geq$140/90 mm Hg defines HTN in pregnancy. About 10% of pregnancies are complicated by HDPs, which include chronic HTN, gestational HTN, preeclampsia/eclampsia, and preeclampsia superimposed on chronic HTN [54,55]. PE is advocated as a powerful, non-pharmacological intervention to counteract CV risk factors before, during and after pregnancy, normalize BP levels, and reduce the risk of HTN and pre-eclampsia by 30 and 40%, respectively [3,37]. In this regard, a meta-analysis by Zhu et al., including 18 RCTs and 2,930 pregnant women, highlighted significant differences in BP between physically active pregnant women and sedentary ones, with SBP and DBP of the intervention group being, respectively, 3.19 mmHg and 2.14 mmHg lower than that of the control group. Moreover, the Authors found that, as long as healthy pregnant women participated in exercise, their BP could be slightly regulated, while HTN susceptible pregnant women significantly lowered BP [56].

Given these premises, the 2020 World Health Organization guidelines on PA recommend that all pregnant women, without contraindication, should practice at least 150 min of moderate-intensity aerobic PA throughout the week, with a variety of aerobic and muscle-strengthening activities, replacing sedentary time with PA of any intensity, including light intensity [57]. Moreover, many governments have developed guidelines for PA during pregnancy, as summarized by Hayman et al., highlighting the significant concordance in the recommendations offered worldwide [58]. The latest ESC guidelines concur with previous recommendations and reinforce the importance of low-to-moderate-intensity exercise, particularly when supervised and initiated during the first trimester of pregnancy, to reduce the incidence of gestational HTN, and encourage participation in exercise programs for all pregnant women [2]. In addition to moderate-intensity aerobic and muscle-strengthening activities, high-intensity interval training may be recommended to prevent HDPs. However, more data is needed to support its safety and efficacy [59]. Furthermore, we must consider that a substantial mismatch exists in the current literature as the available papers have not systematically explored BP responses across various maternal health disorders, gestational ages, and specific components of exercise protocols. A recent systematic review and meta-analysis by Pongpanit et al., which included 20 RCTs and a total of 1,221 women, synthesized the effects of PE training during pregnancy and the postpartum period, compared with non-exercise interventions on maternal vascular health, BP and vascular structure. Exercise training, initiated from week 8 during gestation or between 6 and 14 weeks after delivery and lasting for a minimum of 4 weeks up to 6 months, showed no significant impact on vascular structure and function in terms of pulse wave velocity (PWV) and flow-mediated dilatation, whereas it determined a significant reduction in SBP [mean difference (MD): −4.37 mmHg; 95% confidence interval (CI): −7.48 to −1.26; $P = 0.006$] and DBP (MD: −2.94 mmHg; 95% CI: −5.17 to −0.71; $P = 0.01$), with a consistent trend across different gestational stages, types of exercise, weekly exercise times, and training periods [60].

Similarly, Chen et al. explored the impact of different types of PE on health outcomes in a cohort of 40 pregnant women with HDPs and well-controlled BP, who were randomly assigned to a $\geq$ 4-week intervention with AET, RT and AET+RT protocols. They found a significant improvement in PA status, sleep quality, morning BP, lipid profiles, urinary microalbumin-to-creatinine ratios, and pregnancy outcomes, especially in the AET + RT group [61]. A meta-analysis by Corso et al. confirmed that structured AET and RT protocols are reliable and safe strategies for preserving BP at optimal levels during pregnancy [62]. Finally, it seems that a combination of AET and RT has a greater beneficial effect than performing AET only [63]. However, structured and well-designed RCTs with larger sample sizes and rigorous blinding procedures are needed to tailor the best exercise based on individual characteristics, including maternal health condition, gestational age and/or postpartum period, and exercise preferences.

Menopause

As already mentioned, menopause represents one of the emerging, non-modifiable CV risk factors in women, being associated with a decline in ovarian hormone concentrations and endothelial dysfunction that leads to noticeable changes in cardio-metabolic health and immune-neuroendocrine profile. In particular, the incidence of HTN doubles in postmenopausal women as compared with premenopausal ones. Furthermore, the co-existence of sleep breathing disorders, which have a prevalence of about 60% in postmenopausal women, represents a risk factor for the development of resistant HTN, along with the female sex itself [64]. PA represents a valuable tool to counteract these unfavorable adaptations and maintain adequate physical and mental performance, especially if women exercise with a high level of adherence to a fitness program [3,8]. The 2020 WHO guidelines on PA and SB recommend that adults and older adults with chronic conditions, i.e. HTN, should perform at least 150–300 min of moderate-intensity aerobic PA or at least 75–150 min of vigorous-intensity aerobic PA or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for substantial health benefits. However, the Authors do not address any sex-specific advice [57]. Similarly, the 2024 ESC guidelines on the management of HTN do not recommend any specific protocol for the prevention and management of HTN during menopause [2].

In this regard, Loaiza-Betancur et al. found, in a meta-analysis including 75 studies with a sample of 4,179 menopausal and postmenopausal participants, that PE results in a clinically significant reduction in SBP, DBP and MBP (respectively: -3.43 mmHg, -2.25 mmHg and -3.48 mmHg). However, it appears that AET alone does not result in a significant reduction in BP, whereas combined training yields a noteworthy improvement in BP [65]. Similarly, a meta-analysis by Zhou et al., including 729 postmenopausal women, confirmed that exercise decreased SBP, DBP and aortic PWV by 6.74 mmHg, 4.73 mmHg, and 0.79 m/s, respectively. In particular, AET can significantly decrease SBP and DBP by 7.79 mmHg and 5.97 mmHg, respectively, whereas RT can significantly decrease SBP, DBP and aortic PWV by 5.62 mmHg, 1.87 mmHg, and 0.67 m/s, and AET and RT can significantly decrease SBP by 5.42 mmHg. Furthermore, the Authors concluded that the efficacy of mind-body exercise (i.e., Tai Chi/Yoga) on SBP, DBP, and aortic PWV remains to be confirmed ($p > 0.05$) [66]. Finally, a subsequent meta-analysis by et al., which included 22 RCTs and a total of 1,978

Table 1
Studies about gender differences in HTN.

Studies about gender differences in HTN, with a focus on pregnancy and menopause

References	Type of article	Total pts (n)	Population	Aim	Results
Zhou, B. et al. *The Lancet* 394, 639–651 (2019) [11].	Observational study	526,336	Adults aged 40–79 years in 12 high-income countries.	To compare levels and temporal trends in HTN and its pharmacological control.	Better BP control in women than in men in industrialized countries, with similar prevalence.
Ji, H. et al. *JAMA Cardiol* 5, 255 (2020) [14].	Observational study	32,833	Adults and youth (aged 5–98 years) from four community-based U.S. cohort studies, 54% women.	To assess potential sex differences in blood pressure changes over the lifespan.	Women reach men's BP levels and surpass them (in rate of increase) earlier and more rapidly.
White WB et al. *Hypertension*;48(2):246-53 (2006) [20].		750	Postmenopausal women aged 45–75 years, all with stage 1 or 2 HTN, receiving hormone replacement therapy containing drospirenone and estradiol.	To evaluate the efficacy and safety of drospirenone plus estradiol in reducing blood pressure in postmenopausal women with HTN.	The drospirenone–estradiol combination produced a dose-dependent reduction in BP with a good safety profile.
Riise, H. K. R. et al. *Int J Cardiol* 282, 81–87 (2019) [33].	Observational study	617589	Norwegian women who gave birth between 1967 and 2012, categorized by the presence or absence of gestational HTN or preeclampsia.	To determine whether women with gestational HTN or preeclampsia have a higher risk of developing CVD.	Women with gestational HTN or preeclampsia showed a significantly higher risk of developing CVD in adulthood (mainly CAD, stroke, and HF), even after adjusting for preexisting risk factors.
Honigberg, M. C. et al. *J Am Coll Cardiol* 74, 2743–2754 (2019) [34].	Observational study	220,024	Middle-aged women (40–69 years) with a documented history of pregnancy, grouped by presence or absence of HPDs.	To determine whether HPDs are associated with increased CV risk in later life.	Women with a history of HDPs had a significantly higher risk of developing various CV conditions, including CAD, HF, aortic stenosis, mitral regurgitation, AF, stroke, PAD, and DVT, even after adjustment for conventional CV risk factors.
Boomsma, C. M. et al. *Hum Reprod Update* 12, 673–683 (2006) [35].	Observational study	720	Women of reproductive age with clinically or sonographically diagnosed PCOS (n=720) compared to women without PCOS (n=4505).	To evaluate the incidence of obstetric and neonatal complications in women with PCOS compared with controls.	Increased risk of HDPs and neonatal complications (high birth weight, NICU admission, perinatal mortality) in women with PCOS.
Gerdts, E. et al. *Hypertension* 51, 1109–1114 (2008) [36].	RCT	863	Hypertensive patients aged 55–80 years with ECG-detected LV hypertrophy, enrolled in the LIFE study and treated with losartan or atenolol for a mean of 4.8 years.	To assess sex differences in left ventricular structure and function during antihypertensive therapy.	Women had higher indexed LV mass, greater prevalence of residual LV hypertrophy, less regression of hypertrophy, but better systolic function.

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Table 1
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Studies about gender differences in the effects of exercise on CV outcomes and HTN, with a focus on menopause, pregnancy and BCS					
Ji, H. et al. *JACC* 83:783-93 (2024) [44].	Prospective study	412,413	U.S. adults (55% female, age 44±17 years)	To evaluate whether PA derived health benefits may differ by sex	Women have greater improvement than men in terms of all-cause and CV deaths from equivalent amounts of PA, compared with inactivity (24% for women and 15% for men). Women gain the maximal survival benefit from 140 min/week of PA and reach the maximum survival benefit at 300 min/week (HR 0.76). No differences in exercise protocol were documented
Edwards, J. et al. *Br J Sports Med* **57**:1317–26 (2023) [45].	Systematic review and meta-analysis (270 RCTs)	15,827	Adults of all genders, race/ethnicities and socioeconomic levels, undergoing an exercise intervention of ≥2 weeks	To perform a large- scale pairwise and network meta- analysis on the effects of all relevant exercise training modes on resting BP to establish optimal antihypertensive exercise prescription practices.	AET, dynamic RT, combined training, HIIT and IET are all significantly effective in reducing resting SBP and DBP. IET remains the most effective mode.
Zhu, Z. et al. *BMC Public Health* 22:1733 (2022) [56].	Meta-analysis (18 RCTs)	2930	Pregnant women from high-income countries	To evaluate the effects of PE intervention on BP during pregnancy	Physically active pregnant women have better BP profile than sedentary ones (SBP - 3.19 mmHg, DBP -2.14 mmHg).
Sun, J. et al. *Scientific Reports* 14:27975 (2024) [59].	RCT	54	Caucasian women in uncomplicated, singleton pregnancies (age 32±4 years, 22±4 weeks of gestation)	To compare an 8-week HIIT program to self-performed moderate-to-vigorous PA (EDU) among pregnant women by evaluating changes in BP after a maximal CPET performed at pre-intervention and post-intervention time points	No significant differences in either group between resting or post-CPET BP. Both groups showed decreases in resting SBP and DBP. HIIT significantly decreased DBP and improved cardiorespiratory fitness, whereas EDU decreased SBP.
Pongpanit, K. et al. *Eur J Prev Cardiol* 20;31(13):1606-1620 (2024) [60].	Systematic review and meta-analysis (20 RCTs)	1221	Pregnant women from Europe, America and Asia	To assess the effects of PE during pregnancy and the postpartum period on maternal vascular health and BP	PE, initiated from week 8 during gestation or between 6 and 14 weeks after delivery, with the program lasting for a minimum of 4 weeks up to 6 months, showed no significant impact on PWV and FMD. It determined a significant reduction in SBP and DBP, with consistent trends across different gestational stages, types and times of exercise and training periods.
Chen, C. et al. *J Matern Fetal Neonatal Med.* 37(1):2421278 (2024) [61].	RCT	40	Chinese women with HDPs	To explore the impacts of different types of PE (AET, RT, AET+RT) on health outcomes of individuals with HDP.	In the three exercise groups, significant improvement in PA status, sleep quality, morning BP, lipid profiles, urinary microalbumin-to-creatinine ratios, and pregnancy outcomes were found. All differences were most pronounced in the AET + RT group.
Corso, M. et al. *Front Physiol.* 13 (2022) [62].	Systematic review and meta-analysis (20 studies)	846	Pregnant women	To compare the effects of different PE modalities (AET, RT, AET+RT) on SBP and DBP of pregnant women	Structured AET and RT programs are reliable and safe strategies for maintaining BP at optimal levels during pregnancy. The combination of AET + RT determines the best results in terms of control of DBP.

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Table 1
(*continued*)

Studies about gender differences in the effects of exercise on CV outcomes and HTN, with a focus on menopause, pregnancy and BCS

Danielli, M. et al. *J Clin Med* **11**:793 (2022) [63].	Systematic review and meta-analysis (16 RCTs)	5939	Pregnant women	To investigate the effects of a supervised exercise protocol during pregnancy compared to standard antenatal care or unsupervised exercise on the development of HDP	Supervised exercise protocol significantly reduced the risk of developing HTN; a combination of AET and RT, or yoga alone, had a greater beneficial effect compared to performing AET only.
Loaiza-Betancur, A.F. et al. *Maturitas* **149**:40–55 (2021) [65].	Systematic review and meta-analysis (63 RCTs)	3831	Menopausal and post- menopausal women	To synthesize the effect of PE on BP in menopausal and postmenopausal women	PE generated small but clinically relevant reductions in SBP, DBP and MAP in menopausal and postmenopausal women, younger or older than 65 years, with prehypertension or HTN. AT did not lead to a clinically relevant improvement in BP, whereas combined training showed the largest reductions in SBP, DBP and MAP.
Zhou, W-S. et al. *Exp Gerontol* **171**:111990 (2023) [66].	Systematic review and meta-analysis (26 RCTs)	729	Postmenopausal women	To compare the efficacy of different exercises on BP and aortic PWV in postmenopausal women.	PE significantly improved SBP, DBP, and aortic PWV. AET decreased SBP and DBP. RT decreased SBP, DBP, and aortic PWV.
Yang, D.et al. *Syst Rev* **13**:169 (2024) [67].	Systematic review and meta-analysis (22 RCTs)	1978	Postmenopausal women	To assess the effectiveness of PE on AS and BP among postmenopausal women with elevated BP	PE ameliorates AS and reduces BP in postmenopausal women with elevated BP.
Nagy, A. C. et al. *Neoplasma* 64, 92–100 (2017) [74].	Prospective study	55	BCS treated with anthracyclines, divided by PA level: 36 active (mean age 49.2 years) and 19 inactive (mean age 50.1 years).	To assess the effect of regular PA on diastolic function and late HF symptoms in anthracycline-treated BCS.	Regular PA appears to delay the onset of diastolic dysfunction (E/A and E/e′ parameters) and reduce the frequency of HF symptoms.
Kirkham, A. A. et al. *Int J Cardiol* 245, 263–270 (2017) [75].	RCT	24	Adult women with early-stage BC undergoing doxorubicin chemotherapy.	To evaluate whether a single session of acute aerobic exercise 24 h before doxorubicin administration reduces cardiotoxicity markers and improves cardiac function.	Lower NT-proBNP increase and higher LVEF and LV strain in patients who exercised before doxorubicin treatment.
Kirkham, A. A. et al. *Breast Cancer Res Treat* 167, 719–729 (2018) [76].	RCT	24	Adult women with early-stage BC undergoing doxorubicin chemotherapy.	To evaluate whether a single AET session 24 h before each doxorubicin treatment reduces subclinical cardiotoxicity and related symptoms.	An acute AET session 24 h before each doxorubicin treatment had beneficial effects on hemodynamics, musculoskeletal symptoms, mood, and body weight.
Howden, E. J. et al. *Eur J Prev Cardiol* 26, 305–315 (2019) [77].	Controlled clinical trial	28	Adult women with early-stage BC treated with anthracycline chemotherapy, half enrolled in a structured exercise program.	To assess whether a structured PE program reduces functional capacity loss and enables early detection of cardiac dysfunction using exercise imaging.	The PE group showed a significantly smaller reduction in peak VO_2 than controls, supporting structured exercise for preventing cardiac dysfunction. No significant effects were seen on LVEF or biomarkers.
Molassiotis, A. et al. *Support Care Cancer* 23, 1637–1645 (2015) [81].		30	Patients with thoracic malignancies and dyspnea.	To evaluate the efficacy of resistance inspiratory muscle training (RIMT) for improving breathlessness.	RIMT was feasible and safe in patients with thoracic malignancies, significantly improving perceived dyspnea and respiratory functional capacity compared to controls.
Díaz-Balboa, E. et al. *Prog Cardiovasc Dis* 85, 74–81 (2024) [82].	RCT	150	Women with BC undergoing chemotherapy and at risk for cardiotoxicity.	To evaluate the efficacy of PE-based cardio-oncology rehabilitation in preventing CTRCVT.	The PE program significantly reduced cardiotoxicity indicators (smaller LVEF decline) and improved functional capacity and QoL.

HTN, hypertension; BP, blood pressure; CVD, cardiovascular disease; CAD, coronary artery disease; HF, heart failure; HDPs, hypertensive disorder of pregnancy; AF, atrial fibrillation; PAD, peripheral artery disease; DVT, deep vein thrombosis; PCOS, polycystic ovarian syndrome; NICU, neonatal intensive care unit; BCS, breast cancer survivors; LV, left ventricle; RCT, randomized controlled trial; BC, breast cancer; PA, physical activity; PE, physical exercise; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; CPET, cardiopulmonary exercise test; FMD, flow mediated dilatation; AET, aerobic exercise training; RT, resistance training; HIIT, high intensity interval training; IET, isometric exercise training; NT-proBNP, N-terminal pro B-type natriuretic peptide; PWV, pulse wave velocity; AS, arterial stiffness; CTRCVT, cancer therapy related cardiovascular toxicity; LVEF, left ventricular ejection fraction; QoL, quality of life.

participants, confirmed that PE ameliorates arterial stiffness and BP in postmenopausal women with HTN, especially in those with stage 1 HTN. However, the Authors underlined the significant heterogeneity in the characteristics of the studies, especially in terms of PE protocols and country selection, as well as the prevalence of AET in the majority of the obtained RCTs, thus suggesting the need for more methodologically robust RCTs to determine causal links between PE and the benefits of vascular health, as well as to define the best PE protocol in this clinical scenario [67]. Table 1 summarizes the principal studies about gender differences in HTN.

Exercise prescription to prevent cardiotoxicity in breast cancer patients

According to the most recent statistics, breast cancer is the most diagnosed carcinoma worldwide [68]. Thanks to advances in early diagnosis and therapeutic strategies, it is also one of the most treatable, with mortality rates progressively decreasing [69]. However, current therapies increase the risk of developing CVD, partly due to the intrinsic cardiotoxicity of these drugs. The 2022 ESC guidelines on Cardio-Oncology address this issue, examining the concepts of cancer therapy-related cardiovascular toxicity (CTRCVT) and cancer therapy-related cardiac dysfunction (CRTCD). European and American guidelines define CRTCD as a relative reduction in LVEF and/or global longitudinal strain of $>15\%$ with an increase in cardiac biomarkers compared to baseline [70]. Anthracyclines and anti-HER2 antibodies are cornerstone drugs in the treatment of breast cancer: both are associated with a risk of newly onset left ventricular dysfunction and heart failure. Hormonal therapies, such as selective estrogen receptor modulators (e.g., Tamoxifen) and aromatase inhibitors, lead to alterations in glucose and lipid metabolism, increasing the risk of developing metabolic syndrome, diabetes, dyslipidemia, and consequently, HTN, atherosclerosis, and coronary syndrome.

A correlation between specific chemotherapy regimens—such as those including doxorubicin, docetaxel, and cyclophosphamide—and the new onset of HTN has been reported in the literature. These agents appear to impair endothelium-dependent vasodilation mediated by nitric oxide (NO), thereby contributing to microvascular dysfunction, which plays a central role in the pathophysiological mechanisms underlying the development of HTN [71].

Conversely, pre-existing HTN—particularly when severe—appears to be associated with a greater decline in LV function in women with breast cancer undergoing potentially cardiotoxic treatments [72]. Moreover, therapies for ovarian function suppression, estrogen receptor down regulator and cyclin-dependent kinase inhibitors are associated with an increased risk of HTN [73]. Several studies have demonstrated the benefits of PE in preventing CTRCVT. A prospective study conducted on 55 women with breast cancer and no CV risk factors also showed a delayed onset of diastolic dysfunction and a lower incidence of HF symptoms in the group of patients who engaged in PA five years after anthracycline treatment [74]. Furthermore, in 2018, Kirkham et al. demonstrated a significant attenuation of NT-proBNP levels 24-48 h after the first anthracycline cycle in the group of patients who performed 30 min of vigorous-intensity treadmill exercise 24 h before each treatment cycle [75,76]. In 2019, Howden et al. confirmed the value of PE in breast cancer patients undergoing chemotherapy, noting a smaller reduction in functional capacity, measured by peak VO2, in women who exercised [77]. In the same year, the American Cancer Society and the American Heart Association developed the concept of Cardio-Oncology Rehabilitation (CORE), a multimodal program designed to prevent CVD in high-risk cancer patients, with a focus on PA. The PA recommended by this rehabilitation program includes a personalized plan for each patient, incorporating exercises supervised by certified oncology fitness instructors [78]. Although AET has been shown to have greater effectiveness in preventing and treating cardiac damage caused by HTN [79], both AET and RT have been demonstrated to improve outcomes in cancer patients. Endurance training has been found to possess greater CV protection properties, as well as anti-inflammatory effects, although it can be more challenging for this type of patient. For this reason, starting with RT could be a valid strategy. In RT exercises, it is recommended to perform sets of 8-12 repetitions at a moderate to slow speed to promote muscle hypertrophy. The number of sets should be adjusted based on the onset of muscle fatigue and progressively increased: it seems that protein synthesis is more stimulated by the volume of load (the number of repetitions) rather than by intensity (determined by the weight used). The recommended AET, on the other hand, should preferably be performed at moderate or vigorous intensity. To define the training intensity for each patient, the most accurate methods are the lactate test and the cardiopulmonary test: they allow the determination of the aerobic and anaerobic thresholds and thus the prescription of the heart rate range to be maintained during AET. It would be ideal to combine these two modes of training, performing 150-300 min per week of moderate-intensity AET or 75-150 min per week of vigorous-intensity AET along with moderate-vigorous intensity muscle-strengthening activities at least twice a week. In addition to this type of training, it would be beneficial also to include flexibility exercises (e.g., stretching) and respiratory muscle exercises at least two or three times a week. The latter allows for the strengthening of the inspiratory muscles, leading to a significant improvement in peak VO2, maximum inspiratory and expiratory pressures, reducing dyspnea and improving the functional capacity of cancer patients [80,81]. Based on the proposal of this rehabilitation program, the randomized controlled trial ONCORE, conducted on a population of women with early-stage breast cancer undergoing chemotherapy with anthracyclines or anti-HER2 antibodies, compared a group of patients undergoing physical activity as part of usual care with a group of patients following the exercise program outlined by CORE. During this study, both groups showed a decline in left ventricular function after chemotherapy, which was less pronounced in the CORE group, with evidence of a statistically significant lesser decline in LVEF. However, no significant differences were found in global longitudinal strain [82]. A study conducted on postmenopausal women with breast cancer undergoing adjuvant treatment with aromatase inhibitors demonstrated a significant reduction in both systolic and diastolic blood pressure in the group that participated in a combined program of supervised PE and health education sessions, compared to the control group [83]. These findings suggest that PE may play a crucial role in preserving CV health in patients undergoing chemotherapy, not only by improving BP control but also by potentially mitigating CTRCVT.

Conclusions

PE represents an effective, non-pharmacological therapy to prevent and treat HTN in the general population, as well as in women, especially at certain stages of life and in the specific setting of CTRCVT. However, as underlined by the latest ESC guidelines, more sex-specific data on the epidemiology and pathophysiological mechanisms of HTN are needed, as well as information regarding the role of gender in modulating individual responses to pharmacological and non-pharmacological therapeutic interventions [2]. In this regard, further investigations using rigorous and homogeneous methodologies and larger sample sizes are needed to increase our understanding and define tailored, individualized protocols for patients (Fig. 2). This could enhance adherence to training and max-

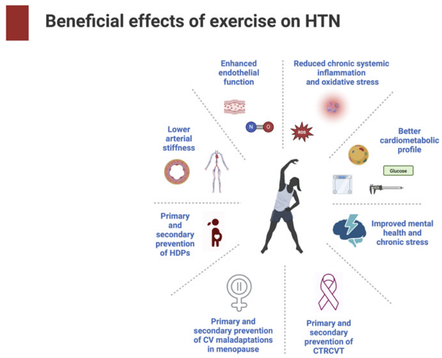

Fig. 2. Summary of the beneficial effects of PE on women with HTN.

imize the benefits of exercise in the female population, including those with or at risk for HTN.

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Declaration of competing interest

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CRediT authorship contribution statement

Valentina Bucciarelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Maria Concetta Pastore:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Elvira Delcuratolo:** Writing – review & editing, Writing – original draft. **Francesco Bianco:** Writing – review & editing, Visualization. **Susanna Sciomer:** Writing – review & editing, Validation. **Federica Moscucci:** Writing – review & editing, Visualization. **Francesco Angeli:** Writing – review & editing, Visualization. **Flavio D'Ascenzi:** Writing – review & editing, Visualization. **Stefania Paolillo:** Writing – review & editing, Visualization. **Pasquale Perrone Filardi:** Writing – review & editing, Visualization. **Sabina Gallina:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Matteo Cameli:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Anna Vittoria Mattioli:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization.

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